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SCHOOL OF ENGINEERING AND SLOAN SCHOOL OF MANAGEMENT

ECONOMIC MODELING OF A HYALURONIC ACID SUPPLY CHAIN TO HELP EVALUATE, PLAN AND IMPROVE MANUFACTURING STRATEGY

By

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EXECUTIVE SUMMARY

This study contains an in depth study of the Hyaluronic Acid supply chain for the Genzyme Corporation. A series of static, dynamic, deterministic and stochastic models were generated to quantify the economic value of the business. Strategic level qualitative analysis was also conducted to analyze long term opportunities for this part of the corporation.

Based on the quantitative analysis of the Hyaluronic Acid supply chain, it was concluded that Genzyme should remain in the business. The expected net present value, over a five year time horizon with a discount rate of 15%, was determined to be $100 million. Approximately 90% of this value derived from the sale of Product A. Monte Carlo analysis showed an 87% probability of achieving a net present value between $60 million and $180 million.

Economic breakeven for the supply chain was determined to occur in year 4 of the analysis under a likely case scenario. This calculation includes marketing, product development, manufacturing and capital plant improvement costs as well as a 15% discount rate. Expected value for the internal rate of return for the business was determined to be 65%. It was also calculated that there is a very high (>98%) probability that the internal rate of return will be greater than 15%. In other words, this is a good business for the company to be in.

Qualitative analysis of the strategic options for Genzyme resulted in the conclusion that the company should remain in the upstream manufacturing of Hyaluronic Acid in the short term. However, it is expected that a competitive market will begin to develop over time. As this occurs, the company should assess options to leave upstream manufacturing after securing fixed contracts with a reliable supplier. This will allow Genzyme to focus on the high margin end use medical products that presently account for 95% of the supply chain revenue stream.

Finally, it was recommended that the economic modeling tools developed in this study be used to periodically assess the value of the business for Genzyme and to help senior management make strategic decisions in the presence of ambiguity and uncertainty.

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1.0 Introduction

Biotechnology is the integrated use of biochemistry, microbiology and engineering sciences to achieve technological application of microorganisms and cells for a particular human need [18]. Ancient Sumerians and Egyptians used biotechnology in ca. 6000 B.C. and ca. 4000 B.C., respectively, for an area of particular interest to the author: beverage brewing applications. This process was further advanced by Chinese scientists in ca. 14 A.D. by the addition of a distillation process.

However, it was not until 1865 that Pasteur showed that microorganisms were active agents in brewing, wine making and food spoilage that the science began to be understood. Since Pasteur's work, many developments have occurred in this area leading to great advances in human health. One of the most important breakthroughs was the discovery of the recombinant DNA process which allow in vitro manipulation of genetic material.

This development effectively removed the limit of obtaining raw materials for many products due to their origins in finite stocks of animals and plants. Genentech's successful experiments in isolating, converting, cloning and expressing insulin in 1977 was the first time a human protein had been expressed in bacteria. This was the beginning of the commercialization of the biotechnology industry [32]. In the present case, fermentation technology is applied to the practical application of making Hyaluronic Acid (HA) for sale as a specialty chemical as well as downstream use in surgical products.

This study analyzes the economics of the manufacturing supply chain for HA and its derivative products at Genzyme Corporation. This product is sold to the market place for end uses in ophthalmic treatments as well as for the treatment of osteoarthritis. Development is underway for use in surface coating of surgical instruments as well as the topical medical market, for use in wound dressing and actinic keratosis. Genzyme uses HA as a raw material for a variety of surgical adhesion prevention products. These are discussed in the following sections.

The primary aim of this study is to provide quantification of the economic value of the HA business to Genzyme with the end goal of facilitating the strategic decision making process for this part of the corporation. An important question considered in the study is whether Genzyme should stay in the business, or look to outsource sections of, or the entire, HA supply chain.

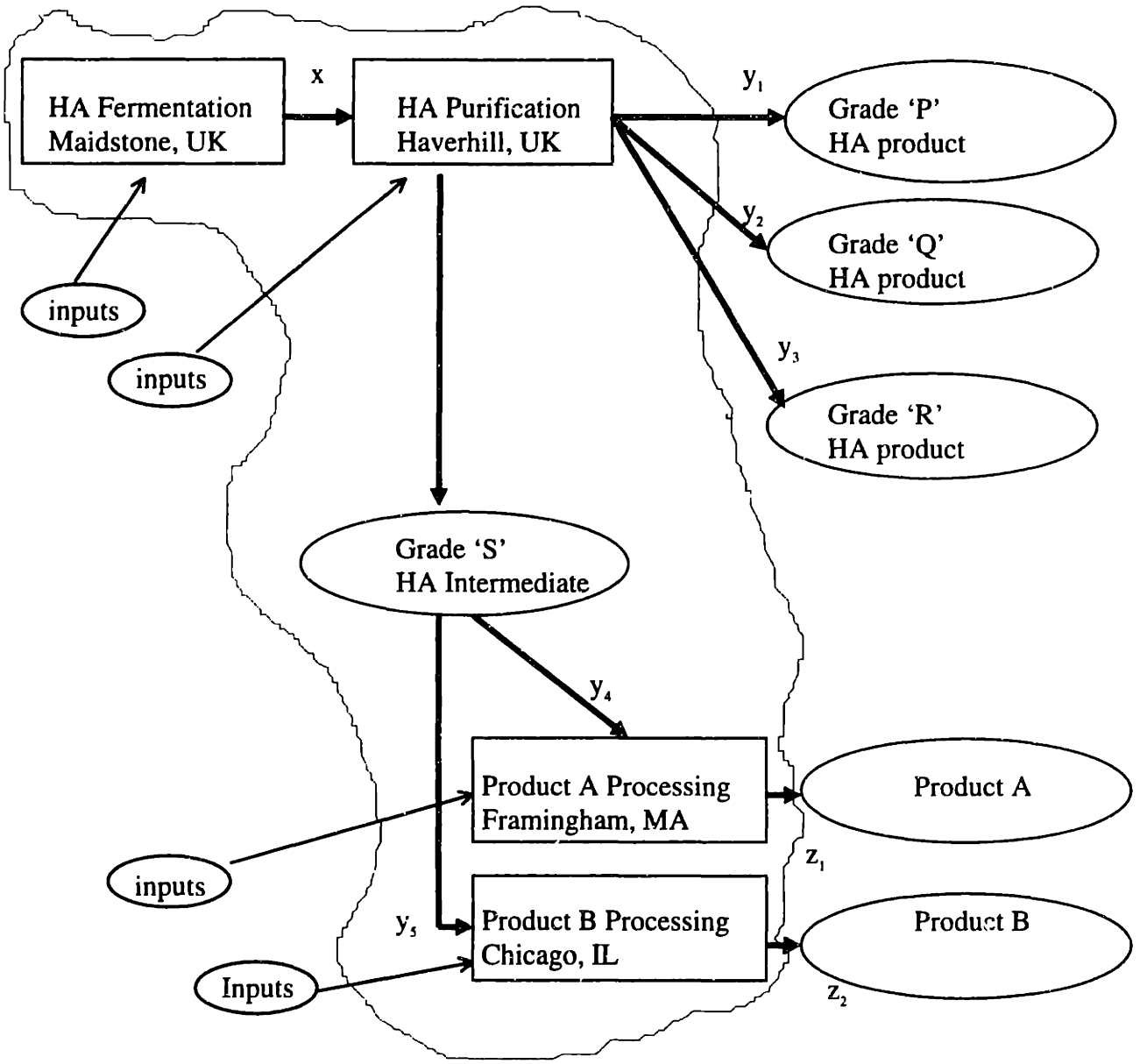
Important quantitative parameters behind such decisions are the net present value of the business and the internal rate of return. These parameters, combined with qualitative areas such as strategic vertical integration, consistency and quality of supply as well as organizational structure modification issues, form the basis of the business decision.

Primary focus will be placed on the quantitative measures in this study; although there is some discussion of qualitative information.

An economic control space has been drawn around the HA supply chain: inflows and outflow of resources through this control space are measured (see Figure 1). Labor, capital and technology inputs are modeled at each step of the supply chain. Demand forecasts for intermediate and end products are simulated from normal randomization of sales and marketing projections. Mean figures and standard deviations were determined based on historical projection accuracy and a 95% confidence interval between best and worst case scenarios. A probabilistic analysis has also been conducted through a Monte Carlo simulation of the various inputs into the model.

The remainder of the introduction outlines a background of surgical adhesions, a brief competitive analysis as well as a description of HA and its derivative products. An overview of the manufacturing process is also provided. An outline of the manufacturing challenge faced by Genzyme in this business as well as a discussion of potential solutions is presented in Section 2. Various models that have been established are discussed in Section 3: from simple unit material cost models to an overall economic model of the product supply chain.

Experiments and sensitivity analyses are discussed for best case, likely case and worst case scenarios in Section 4. A probabilistic model using Monte Carlo simulations has been used to take account of some of the uncertainty associated with market forecasts. Conclusions from the analysis and recommends actions for the company are given in section 5.



——— indicates the Genzyme Corporation profitability control space

Figure 1: Genzyme Corporation HA Supply Chain Control Space

1.1 Background on Surgical Adhesions

Surgical adhesions are attachments between skin layer tissues or between tissues and internal organs after surgery. When tissues undergo trauma through incision, cauterization, suturing and other standard operating processes, fibrous strands of scar tissue heal by fusing together, sometimes resulting in abnormal surgical adhesions. These usually occur within five days after surgery [2].

Complications from adhesions vary from small bowel obstructions to chronic pelvic pain and even to female infertility. Different types of operations result in varying incidence of adhesion. General surgery has been estimated at 40% of the total incidence followed by gynecology at 38%, orthopedic surgery at 13% and cardiac surgery at 9% [1].

Alternatives to adhesion prevention are presently being investigated in the latter area: minimally invasive techniques may be able to eliminate the cause of the problem for cardiothoracic surgery. Adhesions have been determined to occur in more than 90% of patients following major abdominal surgery [3] and pelvic adhesions are associated with female infertility in 15 to 20% of cases [1]. Additionally, it has been estimated that 74% of intestinal obstructions are caused by post surgical adhesions

The economic impact of surgical adhesions has been estimated to be more than $1.2 billion annually in the U.S. [4], excluding outpatient care and lost productivity. Medicare patients (approximately 14% of the U.S. population) are treated for adhesion resulting in over $700 million in hospitalization charges [1]. Adhesion prevention devices are not expected to extract all this potential revenue; it has been estimated that the U.S. market for this area is worth $500 to 600 million [1].

Product A was proven to be a successful product for reducing surgical adhesions late in 1996. Becker et al. [17] showed that for a sample size of 175 patients only five (6%) of 90 control patients had no adhesions, 43 (51%) of 85 patients using the Product A membrane were free of adhesions. This was statistically significant with p less than $1X10^{-11}$. This positive indication resulted in the approval of the product by the FDA in August of that year.

Penetration of Product A into the surgical adhesion prevention market is expected to follow an S-curve model. This model from the literature [30] has been observed in technology industries from electrical power to telecommunications to software (see Figure 2). The vertical axis on the plot is performance, which can be measured by the percentage of patients that do not suffer surgical adhesions and require further operation per sheet of film used. The horizontal axis is effort, which can be measured by the cumulative amount of money invested into research and development of the manufacturing process.

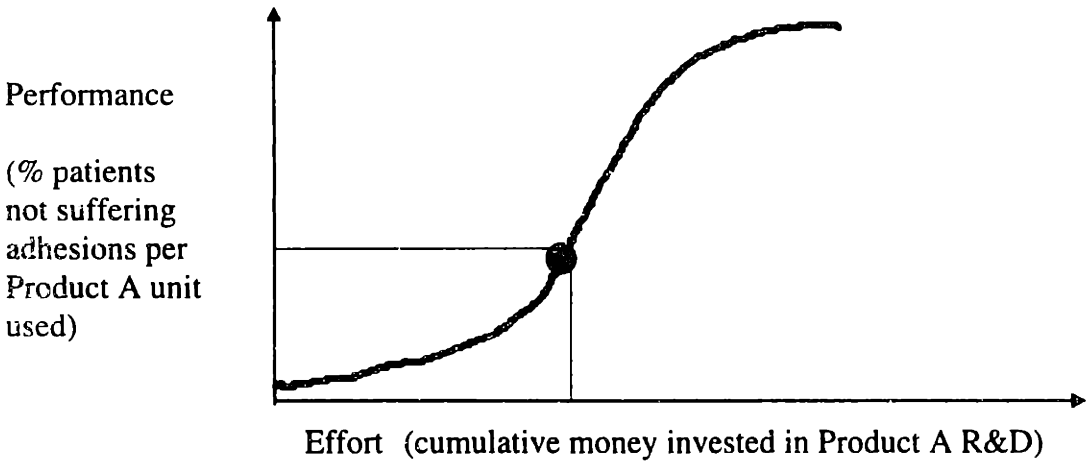


Figure 2: Representative S-curve for Product A

As can be seen in Figure 2, Genzyme is still improving on the product and manufacturing processes as well as the handling characteristics of individual films to better its performance parameter. There are a number of competing companies looking to enter this market working their way up their own S-curves, although Genzyme has the lead in terms of performance and market penetration. Section 1.2 looks at a detailed competitive analysis.

1.2 Competitive Analysis

Porter's five forces framework [11] will be used as a generic system to determine the strength of Genzyme's competitive position, based on data in the literature. The five forces: competitors, new entrants, buyers, suppliers and substitutes will be looked at, in turn. This analysis is used to set a basis from which strategic opportunities for the market can be analyzed (see section 2.2). As Product A is the main revenue source for the supply chain, it will be analyzed in preference to other products.

1.2.1 Competitors

Genzyme's Product A is primarily focused on prevention of abdominal, pelvic and cardiac surgery. The main competitors in these market segments are: Johnson and Johnson, Lifecore Biomedical and Biomatrix. Alliance Pharmaceutical and Life Medical Sciences are focusing on the closely related area of gynecological surgery. Table 1 looks at a number of anti-adhesion products from the literature that are presently in clinical trials or on the market.

The biggest threat of the companies presented in Table 1 is expected to come from the partnership between Lifecore Biomedical and Johnson and Johnson [1]. Their product, Lubricoat, is aimed at the core market of Product A and is backed up by the financial force of Johnson and Johnson. Additionally, there are existing marketing and logistics systems as well as distribution channels that Johnson and Johnson can leverage through their Ethicon division. However, Genzyme can gain an advantage by obtaining market share with their Product A before the Lubricoat product is approved by the FDA. Product C can then be piggy-backed upon the Product A distribution channel to facilitate its penetration of the market.

1.2.2 Buyers

Product A is sold to hospitals based on the recommendations of resident surgeons and outside conferences and symposia. At a meeting of the Society for Colorectal Surgeon in Philadelphia, June Year 1, Product A received a good, but not glowing, report [1]. The investigators reported that the product is challenging to place since it is brittle and sticks to wet surgical gloves. Additionally, each procedure requires an average of three sheets, at a significant cost per sheet. The conclusion was that surgeons should use the product selectively when there is a high degree of probability for re-operation.

This example proves the strong power of buyers of this product. The buyers as a group include a complex and relationship between end use surgeons and health maintenance organizations which now cover the health costs for a majority of people within the United States [33]. Scientific analysis and assessment of performance dramatically govern the proliferation of sales. For this reason a second generation of Product A, which aims to be

more malleable and easier to place after surgery, is currently under development at Genzyme.

Table 1: Some Anti-Adhesion Products [1]

Company	Product	Form	Indication (Surgery Type)	FDA Status
Genzyme	Product A	Film	Abdominal, Pelvic, Gynecological	Approved
	Product C	Gel	Abdominal, Pelvic, Cardiac	Clinical trials (late Year 2)
Alliance Pharmaceutical	Flo-Gel	Gel	Gynecological	Clinical trials
Biomatrix	Hylagel	Gel	Pelvic, Laminectomy, Sinusectomy	Clinical trials
Lifecore Biomedical / Johnson and Johnson	Lubricoat	Gel	Abdominal, Pelvic	Clinical trials
Life Medical Sciences	Repel	Film	Gynecological	Clinical trials

1.2.3 Suppliers

Main raw materials for Hyaluronic Acid and Product A are easily obtainable from the market as commodity chemicals or specialty chemicals. The initiation material for the fermentation of HA is highly specialized, but is sourced by the company internally from derivatives of a master seed stock. Commodity chemicals such as sodium hydroxide, hydrochloric acid, phosphoric acid and Chemical X are easily obtainable and the suppliers have no real market power, due to the large number of competitors.

Suppliers of more specialized inputs, such as filters, do have some market power. When a process is approved by the regulatory authorities with a particular filter type, it is difficult

to change the process. However, despite the presence of these process development and regulatory switching costs, there is sufficient competition in the supply of filters to make the market power of their suppliers moderate, at most.

1.2.4 New Entrants

In addition to those companies mentioned in section 1.2.1, there are a number of companies who are in early stages of developing products that could enter the surgical adhesion prevention market. Examples of such companies, and their potentially competing product in parentheses, are: Anika Research (Incert), Atrix Laboratories (Atrigel) and Gliatech (Adcon-L). These companies are in investigation or preclinical trials phases for applications that may compete with Genzyme's existing area of use.

Given the long lead time to receive regulatory approval and the historical failure rate (~70%) of products to return the company's cost of capital [31], it is expected that one of the competitors in Table 1 will dominate the market rather than one of the new entrants. However, if dramatically greater efficacy is shown by Anika, Atrix or Gliatech, then one of these may make a significant late entry impact on the market.

1.2.5 Substitutes

Presently, there are two alternatives for the prevention of surgical adhesion: film based and gel based products. Both materials are able to meet the end use specification of preventing surgical adhesions; although they are focused on different ranges of market segments, there is some overlap (for example, in abdominal, pelvic and gynecological surgery). Gels have the advantage that they are able to coat the entire surface of an organ before settling to form a thin layer similar in effect to the film technology. Since Genzyme has one foot in each of these markets, it could be argued that the threat of such a substitute is lessened. Although Genzyme was first to market with its film-based product, an important concern is that Lifecore Biomedical has the development lead in gels and thus may gain significant market share before Product C is released.

1.3 Hyaluronic Acid Product Background

Hyaluronic Acid (HA) is an anionic polysaccharide, or complex sugar, which is produced naturally in the human body as a salt: sodium hyaluronate. The chemical structure of HA is represented in Figure 3. This compound is found throughout the body in various tissues, including skin and cartilage. Physiological functions performed by HA include protection and lubrication of cells, maintenance of the structural integrity of cells and transport of molecules within cells.

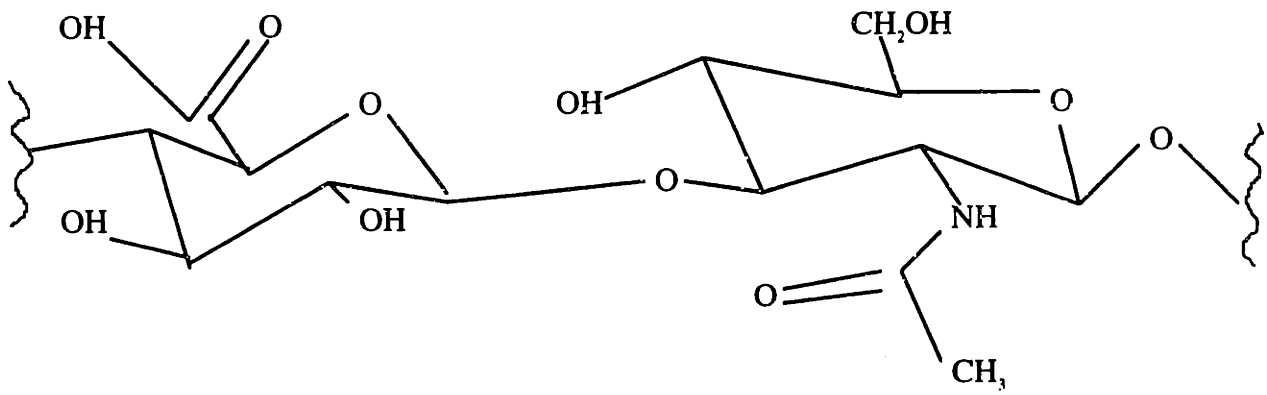


Figure 3: Chemical Structure of Hyaluronic Acid

The primary initial commercial use of HA was in the ophthalmic area, to protect sensitive corneal tissue during cataract surgery. Recently, new applications in treatment of osteoarthritis and during arthroscopic surgery have been developed. Genzyme sells HA powder in three grades: Grade 'P', Grade 'Q' and Grade 'R'. Grade 'P' has the most stringent specifications and Grade 'R' the least stringent.

Due to a combination of its hydrophilic, non-immunogenic and viscoelastic properties, HA is able to coat and lubricate serosal tissue. This makes it an ideal compound from which to make products that reduce surgical adhesions. Genzyme has three products that aim to achieve this: Product A, Product C and Product B. Manufacturing processes associated with HA and Product A are discussed in section 1.3. Product C and Product B are not expected to play a major part in the HA supply chain during the five year time period considered in this study. Regulatory approval and marketing issues associated with these products, resulting in significant manufacturing challenges, are discussed in section 2.1.

1.4 Manufacturing Process Overview

This section outlines the four major manufacturing processes in the production of HA and the Product A derivative product. Product A presently accounts for approximately 90% of the revenues for the product range, and is expected to continue to dominate for the five year time horizon of this study. The first step in the manufacturing process is production of HA via fermentation from seed media; the HA is precipitated to form Chemical Y, which is sent to the second step of the process, purification.

The purified bulk HA can be sold externally or used in Product A, Product B or Product C processes. The Product A process then continues through the third step producing Chemical Y powder. This step consists of the addition of two chemicals to extend the life of the biopolymer on the tissue surface. The fourth and final step is the casting, drying, cutting and packaging of Product A.

The four processes are discussed in detail in the following sections.

1.4.1 Fermentation Process

Seed media for the HA molecule is derived from a working seed stock, on site at the plant in Maidstone, UK. The working stock is, in turn, derived from an original master seed stock stored at the company's headquarters in Cambridge, MA.

The seed media is combined with glucose, yeast extract, deionized water and sodium hydroxide where HA is produced through a fermentation process. Small amounts of other chemicals are also added. The final broth is then passed in batches to two tanks in which another chemical is added and the bacteria are killed.

Cell debris is removed through a series of filters and the filtrate is undergoes further solid liquid separation. The solid product is fed into bags and readied for transport to the purification plant in Haverhill, UK.

1.4.2 Purification Process

Solid HA is dissolved by the addition of sodium chloride and water, forming sodium hyaluronate. This suspension is passed through a processing unit that alters the chemical nature of the product. Chemical X is added to the resultant solution precipitating the product and allowing removal of undesired material in the supernatant.

The product is re-dissolved by the addition of sodium chloride and subsequently another chemical is added to remove impurities in a first stage filtration process. A second precipitation is conducted along with a second filtration process to remove endotoxin material. A final precipitation and wash step with Chemical X follows, before the product

is passed to a dryer. HA powder is removed from the dryer and packaged in gamma radiated bags. This intermediate product is either sold to the market or sent to the US for manufacture into downstream products.

1.4.3 Chemical Y Production Process

HA powder from the UK production plants is transported to Framingham, MA where it is modified into another chemical form. This mixture is filtered to remove any impurities and the filtrate is passed to a reactor where Chemical Z is added. The pH of the reaction is controlled and a complex is formed between HA and Chemical Z.

The reactor product is precipitated with Chemical X and the supernatant is removed. The solids are passed through two further Chemical X washes before drying and grinding into a Chemical Y powder. This material is packaged and stored in Framingham for use in the Product A manufacturing process.

1.4.4 Product A Manufacturing Process

Chemical Y powder is re-suspended in water and passed into a flat casting machine. The re-suspension is spread over the casting plate at a controlled rate allowing a fixed thickness of film to form.

The resulting sheet of film is dried in a controlled atmosphere drying room, peeled from the plate and cut into 13 x 15 centimeter membranes. These are packaged within an inner sleeve and outer trilaminate pouch. The product is gamma radiated to kill any remnant bacteria and stored for sale.

2.0 Broad Case Scenario Analysis

In this section the manufacturing challenge associated with the HA supply chain is presented. Five potential solutions are discussed outlining their respective advantages and disadvantages. A comparison between the possibilities is made before focusing on the economic analysis part of this study.

2.1 Hyaluronic Acid Manufacturing Challenge

Manufacturing facilities for HA were designed on the basis of expected sales of three main adhesion prevention products: Product A, Product B and Product C. Product A received regulatory approval in Europe and the U.S. during 1996, but sales have been growing at a slower rate than originally anticipated. Product B received regulatory approval in Europe, but was not recommended for approval by the U.S. FDA review board. Product C is in preclinical trials; however, the latest candidates have HA reduced or removed from the formulation. The net result of all these factors is that the manufacturing plant has excess capacity and is expected to remain that way for a number of years.

This challenge has prompted the question of whether or not Genzyme should remain in the HA business or look at alternative arrangements. Some of the possibilities considered in this study are:

1. selling HA externally to drive down unit manufacturing costs
2. campaign the HA facilities for a variety of products
3. purchase HA from the market
4. lease the purification facility to a third party
5. remove HA from the supply chain altogether

These five possibilities are looked at in sections 2.2.1 to 2.2.5, respectively.

2.2 Potential Conceptual Solutions

2.2.1 Sell Hyaluronic Acid Externally Case

To drive down unit costs of manufacturing for HA, one possibility is to sell material to the market place for use in various Grade 'P', Grade 'Q' and Grade 'R' applications. Potential customers have been contacted and there appears to be a potential market in this area. There are a number of important advantages and disadvantages for such an approach to the problem.

The primary advantage of selling HA externally is to utilize currently owned assets and maintain cash flow for the business. Another advantage is to leverage a position as one of the few Good Manufacturing Practice (GMP) grade suppliers of HA in the marketplace; presently there are only two producers of this grade material: Genzyme Corporation and Lifecore Biomedical.

Another advantage of selling HA externally is to allow a faster move down the cumulative production learning curve, resulting in lower unit costs. Studies in the chemical processing industry have shown that for each doubling of cumulative output, the production curve is reduced by approximately 25% [13]. Economies of scale in purchase of raw materials would also result due to higher volumes of production.

Genzyme's presence within a relatively low margin specialty chemicals business is a potential strategic disadvantage for a biotechnology firm. However, there are very few players in this emerging market presently; a presence is thus very important in terms of ensuring quality and reliability of supply as well as a reasonable price. There are considerable sales and marketing costs associated with developing the market for HA powder. A cost benefit analysis is required to determine whether or not such an approach is profitable in itself, without the flow on effects discussed above.

2.2.2 Campaign Hyaluronic Acid Purification Facility

Another possibility is to campaign the HA purification facility for a variety of products. The fermentation plant is already campaigned for a variety of products; downstream Product A facilities are highly specialized and not suitable for production campaigns.

Key advantages of this technique are the utilization of existing strategic assets and reduced overhead costs by spreading them over multiple products. Disadvantages of the approach include process qualification and validation of new processes by internal and external regulatory groups. Also, some capital modifications would be required to adapt the existing plant to new processes. Increased scheduling complexity would also result due to the need to balance core HA business with other product campaigns.

2.2.3 Purchase Hyaluronic Acid from Market

The main advantage associated with outsourcing HA manufacture is that it allows Genzyme to leave a market that is expected to become more a focus for specialty chemical companies than biotechnology companies. A secondary advantage in outsourcing is that internal downstream HA demand will not directly affect unit cost, assuming the market is reasonably competitive (although this is not yet the case).

A key disadvantage associated with this option is that specialized capital equipment will need to be written off and the purification facility shut down. Alternately, the equipment could be sold to another company or revalidated for another use.

By leaving the HA market Genzyme is leaving Lifecore Biomedical as a sole supplier of GMP grade material. Although new entrants are beginning to enter the market, it will take some time before they are validated and recognized as GMP suppliers. Providing monopoly status to a competitor is not an advisable approach and Genzyme should probably wait until other players are able to provide the material before considering this option. This is further discussed in section 2.3.

A final disadvantage is that Genzyme would need a fixed price contract with a guarantee of supply. Reliability of supply is very important as there is no direct substitute for HA and downstream products will not meet regulatory or quality standards without it.

2.2.4 Lease Facility to Third Party Manufacturer

Potentially a small and lean organization could target aggressive material reductions and cut overhead costs. A lease agreement would transfer the risk of cost reduction to a third party allowing Genzyme to focus on the task of improving the final product and ramping up ion sales volume. An important question that could be asked is: why would another company be able to do this better than Genzyme?

Key requirements of such a lease agreement would be the maintenance of GMP procedures, as well as a fixed price contract and guarantee of supply for a suitable period: for example, five to seven years. With such an agreement there is the possibility to negotiate a price for HA that would allow Genzyme to make money immediately on downstream products, allowing the lessee to strive for and achieve their own raw material cost savings. Similarly to the outsourcing option, this allows Genzyme to leave a market that is approaching specialty chemical status and focus on the higher value added manufacture of the medical products.

A potential disadvantage is that the loss of control of manufacturing assets may mean a decrease in strategic advantage in terms of security of supply and control of the value chain for downstream products. Additionally, the third party would need to validate the

process and there may end up being a doubling up of regulatory support: at Genzyme and the third party manufacturer. All these costs would be, in effect, passed on to the final product.

2.2.5 Remove Hyaluronic Acid from Supply Chain

There is the possibility that a replacement material could be found for HA for use in the downstream products. A material that is quite similar to HA in both chemical structure and properties is Chemical P. The former presently costs around $'x' per gram; optimistically, this may be reduced to around $'0.5x' per gram when volumes reach 90 throughput index units per year. Chemical P, on the other hand, costs around $'0.005x' per gram and is available from a variety of suppliers. This two order of magnitude reduction is a very promising opportunity.

Such a system would require considerable development work and involve detailed preclinical and clinical trials as well as regulatory application and approval. The costs associated with this work need to be traded off against the fact that HA is approved and downstream products are presently on the market achieving cash flow. Long lead time to market and development costs make this option seem less viable on a first pass analysis.

Another disadvantage associated with this option is that, as with the purchase from the market possibility, the HA purification facilities would have to be written off accounting books, or sold. The specialized nature of the assets makes sale difficult.

2.3 Comparison of Conceptual Solutions

In the following, the five scenarios are compared and contrasted. Conclusions are drawn from this discussion regarding an appropriate strategy for Genzyme.

Removing HA from the supply chain has a long lead time for implementation due to the highly regulated state of the biotechnology industry. Ideally, the cost of development of a non-HA based adhesion prevention product should be compared to the cost advantages, given an assumed development time. Due to the high level of uncertainty associated with development and obtaining regulatory approval for this change, detailed analysis has not been conducted in this study.

The need for new versions of products, given customer demands for a more easily handled and less brittle product, are being pursued by development staff within the organization. Along with this development work, candidates with less HA are being investigated along with other candidates. This approach of pursuing a reduction or elimination of HA from adhesion prevention products in parallel with other projects is a useful technique. It also allows the company to pursue other options in the short run to hedge future profitability.

Leasing of the HA purification facility to a third party would introduce considerable regulatory difficulties. By introducing a new organization into the operation, regulatory staff would be required both within Genzyme and at the third party company. Additionally, the equipment and staff operating it are quite specialized and would probably remain quite similar; although, some cost cutting measures could be taken by a new owner. The primary disadvantage highlighted in the previous sections, is that Genzyme would lose control of the upper portion of the supply chain. This is not advisable until a competitive market for GMP grade HA has developed.

Purchasing HA from the market has similar problems: losing control of the supply chain and leaving a market that has only two players. Allowing a competitor to have a monopoly and sole supplier status is definitely not advisable. As a competitive market for GMP grade HA develops, however, and the product moves into the specialty chemical market segment, then prices will be driven down - approaching marginal cost. At this point, Genzyme should look at leaving the HA business to focus on their core competency of developing, manufacturing and marketing high value added products which serve an unmet medical need.

Campaigning of HA production with other purification processes is a potential solution to the high unit cost problem at low volumes. Presently, there are no candidate processes within Genzyme that could easily be adapted; although there are some potential deals underway which could utilize the facilities. As possibilities come up, the cost of modifying the plant should be compared to the returns received from processing the new material and the reeducation in overhead costs associated with the HA process. Such an

analysis is not conducted here due to the confidential status of such projects and the uncertainty associated with their pursuit by the company.

Selling excess capacity HA powder to the market place makes the most sense in terms of a directly applicable strategy that can have benefits in the relatively short term. The solution would allow the company to maintain cash flow and develop the process, moving down the cumulative production cost curve.

Additionally, Genzyme can control supply of this material in an oligopolistic market. Given that pursuit of this idea is a valid proposition, the question of which grades of HA to focus on for external sales is introduced. A back of the envelope analysis of the profit and loss for Grade 'Q' versus Grade 'R' shows that Grade 'Q' should be pursued on a strictly economic profit basis (see Appendix D). Grade 'R' material would then be only produced as a lower grade of material from development trials for the higher grade products.

Potential concerns with this model are that firstly, it will be difficult to retain customers with erratic supply based on a development program. One technique would be to try to smooth development trials over time to allow a regular supply for customers. The other important concern is that low end producers will gain expertise in producing low grade HA and then leverage their learning and cash flow from these businesses to take the higher end markets.

Examples of such a bottom up entrance to a market have been seen in a variety of industries: Honda's entrance into the US automobile industry and Canon's entrance into the previously Xerox dominated photocopying industry [11]. One potential rebuttal of the argument is that, as the HA market becomes more competitive and margins are reduced, Genzyme would want to leave upstream processing anyway (as outlined previously) - specialty chemical manufacturing is not one of Genzyme's core competencies. It is thought that the latter argument is most likely and that Genzyme should focus on high value added upstream HA manufacture as long as it is high value added, but maintain primary focus on biotechnology innovation and development of medical products that serve an unmet patient need.

3.0 Economic and Process Models

In this section of the study, three models are presented which look at the Hyaluronic Acid supply chain at different levels of abstraction. The idea behind multiple models is to provide a realistic basis for models with progressively greater broader coverage of the business. Thus, lower level models can provide physical and technological constraints that act as boundary values in higher level models. Before discussing the models in detail, some modeling theory from the literature is provided (section 3.1).

The first model (section 3.2) is a microanalysis of one of the manufacturing processes: it looks at individual unit operations and how they combine to purify the product in a single operating plant. The second and third models (section 3.3) look at a combination of fermentation and purification over two manufacturing plants, with a focus on unit manufacturing costs as affected by technology and throughput variables, respectively. These models are designed to complement the scientific basis of the first model with economic considerations. The final model (section 3.4) looks at the complete supply chain for this product from raw materials to the five products sold to the marketplace. This model builds on the three other models and uses them to generate boundary values for the Monte Carlo simulation.

An overview of the history and specific theory of Monte Carlo modeling is presented in section 3.5, setting the scene for a presentation of experimental results from the various case scenarios. These and the output from the Monte Carlo analysis are discussed in section 4.

3.1 Modeling Theory

Rosenbluth and Wiener [15] stated in 1945 that:

"No substantive part of the universe is so simple that it can be grasped and controlled without abstraction. Abstraction consists of replacing part of the control space under consideration by a model of similar but simpler structure. Such models are a central necessity of scientific procedure."

Mankiw [16] outlined economic models more simply: he defined them as theories that summarize, in mathematical terms, relationships among economic variables. There is a certain difficulty in applying the scientific method to the uncertain area of business and economics. There is a great deal of ambiguity and uncertainty in market forecasts, which introduces significant sources of error into any such model. This study attempts to deal with such ambiguity by the use of three case scenarios and the Monte Carlo analysis technique.

Rubinstein [6] outlined a number of advantages and disadvantages of mathematical models. These are presented in Table 2. Despite the key disadvantages of uncertain accuracy and the potential for self delusion, the simplicity of the mathematical models presented and the low cost of operating them argue for their use in this study.

Additionally, the supply chain model is a predictive tool; in this case there is no way of actually testing the system without waiting for the next five years of sales data at which point the model would be redundant. To paraphrase Judy Lewent, CFO of Merck, such predictive tools which combine economic constraints, pricing and selling costs are ideal for analysis and are integral to the strategic decision making process [31].

A final important aspect of theoretical modeling is to ensure that assumptions are documented and stated explicitly in conjunction with any conclusions. Recommendations based on a model are only valid if the assumptions hold; decision makers need to be aware of these assumptions so that their validity can be assessed. The assumptions behind the supply chain model are shown in section 3.4.1.

Models can be split into divisions of being static or dynamic as well as deterministic or stochastic. Within this framework, a two by two matrix can be derived outlining the basis of the four models analyzed in this section (see Figure 4). This diagram seeks to show how the lower level models (the left quadrants and upper quadrants) feed physical and technological constraints to the models at a higher level of abstraction. This is represented by information flow lines in Figure 4. Thus, a more informed basis is provided for the broad level Monte Carlo simulation based upon the output from the other three models.

Table 2: Advantages and Disadvantages of Mathematical Models

Advantages	Disadvantages
Enable investigators to organize their theoretical beliefs and empirical observations to deduce logical implications	No guarantee of accurate and useful output a priori - this may even be difficult to assess ex post
Lead to improve knowledge of a given system	Modelers tend to believe the output from their models too much
Bring in to perspective the need for detail and relevance	Extrapolation of the model beyond its bounds can introduce errors
Expedite an analysis	Need to make simplifying assumptions
Provide a framework for testing proposed system models	
Provide easier manipulation than a real world system	
Permit control over sources of variation to measure effects of singular variables	
Generally costs less than analyzing the real world system	

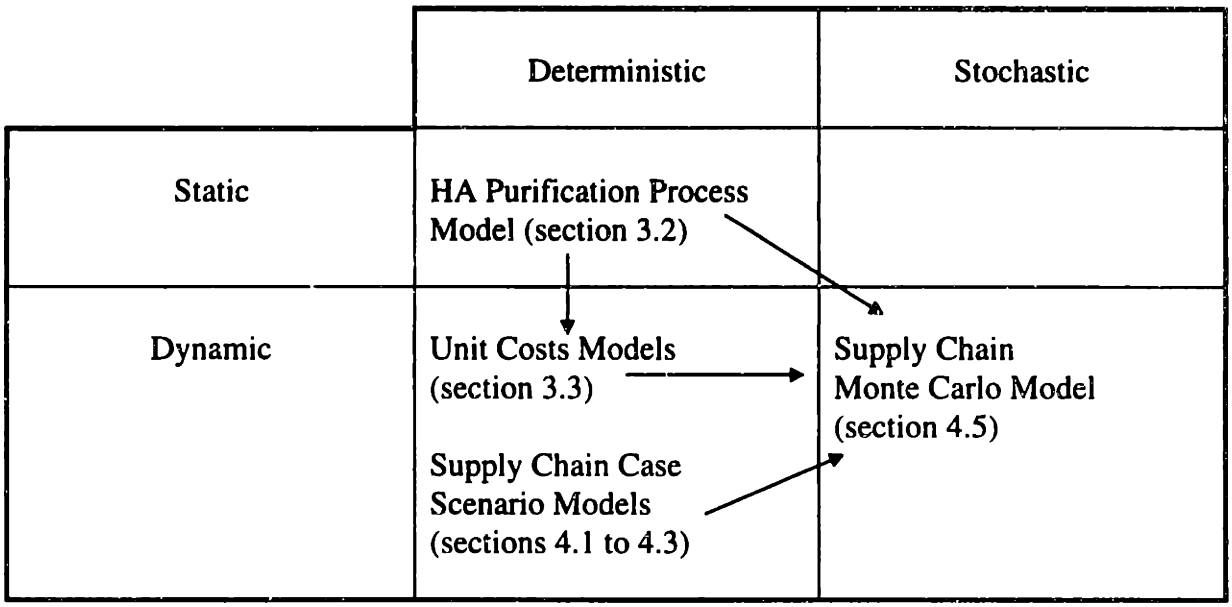


Figure 4: Conceptual Framework and Information Flow for Created Models

3.2 Process Model of HA Purification

BioPro™, a commercially available bio-simulation software licensed from Intelligen, Inc. by Genzyme, was used to model the HA purification process. This process is a critical step in the supply chain and is thus a good basis from which to build higher level models. Figure 5 shows the process flow diagram that was modeled; this figure has been removed as it contains proprietary information. The flow of the purification system is represented by individual unit operations for every step of the process. If a piece of equipment conducts multiple steps, then it is represented on the process flow diagram by a new unit process for each step.

The main purpose of the process model is to provide process development engineers with a first pass simulation of the potential effects of a proposed change on the overall system. It is noted that such simulations are only preliminary and bench scale as well as pilot plant results provide a far more accurate representation of the real world system. Due to the relative inaccuracy of the simulation as a predictive tool for effects of process changes on product quality (compared to the accuracy of Aspen™ software, say, in chemical processing), it is recommended that this model be used as a first pass analysis tool to help guide the decisions of engineers and scientists in both development and operations.

Appendix A includes a detailed printout from the model including mass balances and a reasonably detailed economic analysis. As discussed previously, to model successive unit processes that occur in one physical unit, multiple units must be added to the BioPro™ process flow diagram. This introduces a significant error when calculating the capital and operating costs and thus makes the economic analysis of the actual physical system flawed. Additionally, the BioPro™ software includes depreciation of capital equipment which, although included in an accounting sense, should not be analyzed for the purposes of forward looking economic business decisions. For these reasons, BioPro™ was used as a process modeling tool and not for detailed economic analysis: section 3.3 outline the cost models that were developed as part of this study.

3.3 Manufacturing Process Economic Models

3.3.1 Technology Adjusted Unit Cost Models

Simple models were developed to determine the unit costs of various modifications to the HA manufacturing process. These models complement the process model previously developed, focusing on the economic aspects of the system rather than the biochemistry and material balances. The modifications considered vary from simple alterations, such as removing or replacing one unit process, to major re-formulations of the production system. Additionally, alterations of the amounts of components as well as the removal of raw materials was considered.

These unit cost models are then used as an input into the Monte Carlo model as a technology input. As new technology is applied, the production process can be improved and the unit cost of production correspondingly reduced. More than 10 different cases were analyzed resulting in technology that is expected to encompass developments over the next 3 to 5 years. Output data from these models are included in Appendix B.

3.3.2 Throughput Adjusted Unit Cost Models

Relationships were established between plant throughput and the unit cost of production to determine the relative profitability under various case scenarios. Three different technology inputs were used in the analysis to additionally examine the effect of process development work on unit cost. Figure 6 shows a plot of the three cases.

It is interesting to note that the relative effect of technology improvements on cost reduction is far greater at higher production volumes. For example, at a throughput of 20 index units, moving from current production technology to phase 2 technology saves just 3% on the unit cost of production; while at a throughput of 90 index units, the same technological improvement achieves 20% unit cost improvement. The conclusion from this simplified analysis is that technological improvements become far more important if we are able to move down the production quantity curve.

Realistic assessments of the aggregate market demand have to be made to determine whether or not production levels are going to be at '20' or '90' throughput index units. If it is the latter, Genzyme should assign people to process development work; if the former, then a direct quantitative cost benefit analysis should be conducted: it is quite possible their talents could be used more profitably elsewhere in the company. Assessments of market demand variability are made in the Monte Carlo analysis (see section 4.5).

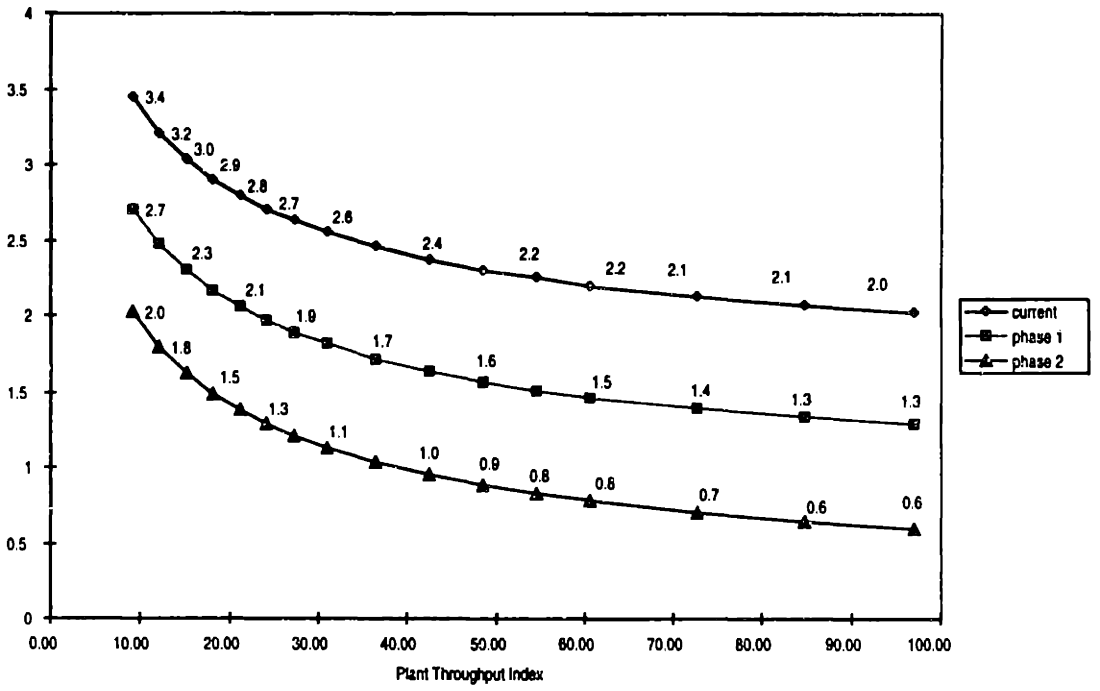


Figure 6: Plot of the Logarithm of Unit Cost Index versus Plant Throughput Index

3.4 Supply Chain Economic Model

This model builds upon the scientific and economic basis provided by the previously presented models by using them to formulate labor, capital and technology constraints. Details behind these labor, capital and technology inputs as well as fundamental assumptions made are discussed in the following (sections 3.4.1 to 3.4.9). Case scenarios, sensitivity analyses and probabilistic models are discussed in section 4. A printout from the model is provided in Appendix C. Before discussing the model in detail, the structure and basis of the model will be presented.

A profitability control space was drawn around the Genzyme Corporation (see Figure 1). Fixed and variable costs were used for each step in the HA supply chain based on budget data and scalability assumptions. Important fixed costs modeled include rent as well as depreciation of capital equipment and capitalized validation costs. Variable costs modeled include raw materials and utilities as well as support from QA, QC, engineering, R&D, management, production labor, manufacturing technical support, facilities, regulatory among others.

Organizational costs associated with entering an emerging market and moving down the cumulative production cost curve were also included. Support of sales, marketing and management groups for the entrance to an emerging market were accounted for by allocating full time equivalents (FTEs) and a marketing budget for focused customer campaigns. Development of the manufacturing process was accounted for by allocating FTEs for the technology development, quality assurance, quality control, regulatory and management groups involved in improving the HA process. A capital budget was also allowed for investments in bench scale, pilot plant and materials for full scale engineering trials.

Revenues obtained from product sales along the supply chain were obtained by estimating the market demand. Main products from the Genzyme HA supply chain are: Product A and Product B as well as Grade 'P', Grade 'Q' and Grade 'R' HA. Estimates from Genzyme's marketing group were used as a starting point for demand estimates; expected ranges of market demand were derived from these values with historically based adjustments for the various case scenarios and probabilistic models.

3.4.1 Assumptions

The following assumptions were made in designing the model:

- straight line depreciation of plant capital costs - not adjusted for plant utilization - this is conventional accounting practice
- fixed:variable overhead split is 70%:30% ; this is based upon historical budget data and industry norms [34]
- Year 1 process qualification certified manufacturing technology was used for Grade 'P' and Grade 'Q' HA
- Year 1 process qualification certified manufacturing technology at 'Y' times the concentration of the Grade 'P' process was approved for Grade 'Q' HA
- Year 1 process qualification certified manufacturing technology at 'Z' times the concentration of the Grade 'P' process was approved for the Grade 'R' HA
- transportation costs were not included in the model
- sales, marketing and management support for entrance to an emerging market was estimated to be 'X1' full time equivalents (FTEs) from Year 1 to Year 3 and 'X2' FTEs for Year 4 and Year 5
- marketing budget for focused customer campaigns were established at approximately 10% of best case HA powder product revenues
- technology development, manufacturing technical support, quality assurance, quality control and regulatory were estimated to account for 'Y1' FTEs for Year 1 to Year 3 and then 'Y2' FTEs for Year 4 and Year 5
- capital spending in development for bench scale and pilot plants as well as training associated with personnel was estimated at $'Z1'/year for Year 1 to Year 3 and $'Z2'/year for Year 4 and Year 5
- FTEs were valued at $150K per year fully loaded
- nominal discount rate was set at 15% per year
- duration of estimate for NPV calculations was 5 years
- results are presented in Year 1 US$

3.4.2 Model Inputs

Inputs into the model were split into those affecting revenues and those affecting costs. As outlined previously, revenues included sales of intermediate HA products as well as Product A and Product B. Costs included both fixed and variable elements as well as accounting for market and process development support. These are each described, in turn, in the following sections.

3.4.3 Revenue Inputs - Market Demand

The following products constituted revenue input data for the model in order from most value added to least:

- Product A
- Product B
- Grade 'P' HA powder
- Grade 'Q' HA powder
- Grade 'R' HA powder

Forecasts for sales of Product A and Product B were obtained from marketing management in the Surgical Products division. Forecasts for sales of the various grades of HA powder were obtained from marketing management at the pharmaceuticals division. These data were incorporated into the best, likely and worst case scenarios discussed in section 4.

Grade 'P' and Grade 'Q' customers are being pursued by focused marketing campaigns; the Grade 'R' market will be used as an outlet for the material produced in development trials. It is noted that it may be a challenge to maintain a presence in the Grade 'R' market with erratic supply of material.

Product A sales were shown to be the key driving factor behind revenues for the whole supply chain. This indicated that it should be the core focus of people throughout the group to ensure high quality and regular supply of material for end use in Product A.

3.4.4 Revenue Formula

$$\mathcal{R} = y1*\mathcal{F}1*\mathcal{P}1 + y2*\mathcal{F}2*\mathcal{P}2 + y3*\mathcal{F}3*\mathcal{P}3 + z1*\mathcal{F}6*\mathcal{P}4 + z2*\mathcal{F}7*\mathcal{P}5$$

where ...

R	is the total revenue for the HA supply chain at Genzyme
y1	is the mass flow of Grade 'P' HA sales
y2	is the mass flow of Grade 'Q' HA sales
y3	is the mass flow of Grade 'R' HA sales
z1	is the mass flow of Product A sales
z2	is the mass flow of Product B sales
P1	is the sales price for Grade 'P' HA
P2	is the sales price for Grade 'Q' HA
P3	is the sales price for Grade 'R' HA
P4	is the sales price for Product A
P5	is the sales price for Product B
F(i)	is a unit conversion factor for the given product, i=1,2,...,7

3.4.5 Cost Inputs - Foreign Exchange and Plant Characteristics

Primary inputs included foreign exchange rates, Maidstone plant input data, Haverhill plant input data as well as manufacturing material cost data. Foreign exchange rate was entered separately into each case spreadsheet: likely, best and worst; this allows the scenario analysis to include variations in the US/UK exchange rate. This same principle was applied to all model input data.

The first Maidstone plant characteristic modeled was the percentage of overhead fixed with respect to production level; the remainder of the budget overhead allocation was variable. The annual variable cost was calculated by multiplying the budget variable cost by the number of actual batches divided by the budget number of batches (see formula below).

Plant yield from Maidstone was also put into the model in kilograms of Chemical Y and HA. The yield of Chemical Y was used in the supply chain mass flow balance which insures that sufficient material was made in Maidstone to meet the market demand. The yield of HA was used in allocating material cost data, which were input in units of dollars per gram of HA.

Material costs data for Maidstone (Cm was the variable name in the model) was based on the phase 1 PQ process. For Grade 'P' and Grade 'S' HA, the phase 1 PQ process uses type 1 yeast extract; for Grade 'Q' and Grade 'R' HA, the phase 1 PQ process uses type 2 yeast extract. To allow for this difference, the additional cost of using type 2 yeast extract was added into the unit costs of purification for Grade 'Q' and Grade 'R' HA (variable names Ch2 and Ch3, respectively). All material costs data was obtained from the unit cost models presented in section 3.3.

The first plant characteristic for Haverhill was the percentage of overhead that is fixed with respect to production level; the remainder of the budget overhead allocation was variable. The annual variable cost was calculated by multiplying the budget variable cost by the number of actual batches divided by the budget number of batches (see section 3.4.6). This was identical to the treatment of overhead for Maidstone in the model.

Plant input for the purification process was set as an input to the model in kilograms of Chemical Y. This was used in the supply chain mass balance (see section 3.4.8). Plant yield for the Grade 'P' process was input to the model in kilograms of HA; yields for Grade 'Q' and Grade 'R' processes are applied as multiples of the Grade 'P' process. The Grade 'Q' material cost was based on the high molecular weight Grade 'Q' phase 1 PQ process from the unit cost models presented previously (see section 3.3). The Grade 'R' material cost was based on the low molecular weight Grade 'Q' phase 1 process as an approximation of the Grade 'R' material. Grade 'R' material will primarily be obtained from trials to improve the Grade 'P' and Grade 'Q' processes: the low molecular weight Grade 'Q' process was a useful approximation.

3.4.6 Cost Inputs - Support Costs

Support costs covered include marketing for the Grade 'Q' product and development of the manufacturing process. The former included staff in sales, marketing and management of the entrance into the emerging Grade 'Q' market. Development support included staff from technology development, quality assurance and quality control, regulatory and management of the process improvement team.

Marketing staff support was set at 'X1' full time equivalents (FTEs) until Year 4, and then increased to 'X2' FTEs. A modest marketing budget for focused customer contact for $'X3' until Year 4, and then increased to $'X4'. Sensitivity analyses were conducted for +/- 50% from these estimates (see section 4.3).

Development staff support was set at 'Y1' FTEs until Year 4, and then decreased to 'Y2' FTEs. The justification behind this reduction was that the process would be sufficiently improved (assuming we will have moved down the steepest slope of the learning curve), such that less development focus would be required. A capital budget of $'Z1' was provided until Year 4, which was then reduced to $'Z2'. This would cover costs associated with running bench scale, pilot plant and engineering trials. Sensitivity analyses were also conducted for +/- 50% from these estimates (see section 4).

3.4.7 Cost Formulae

Fixed Cost Formula:

$$Cfixed = - FCm - FCh - FCf - FCi$$

where ...

Cfixed	= fixed cost of the supply chain
FCm	= fixed cost of the Maidstone HA fermentation plant
FCh	= fixed cost of the Haverhill HA purification plant
FCf	= fixed cost of the Framingham Chemical Y / Product A plant
FCi	= fixed cost associated with the contract Product B manufacturer

Support Cost Formula:

$$Csupport = - FTEm * Sm - FCm - FTEp * Sp - FCp$$

where ...

FTEm	= cost of a full time equivalent in marketing support
Sm	= number of support people in the marketing team
FCm	= fixed cost of the marketing campaign budget
FTEp	= cost of a full time equivalent in process support
Sp	= number of support people developing the process
FCp	= fixed cost of the process development project

Variable Cost Formula 1:

$$Cvar(1) = -Nm / Nm,b * VCm - Nh / Nh,b * VCh - z1 * VCf - z2 * VCi$$

where ...

Nm	= forecast number of batches at Maidstone per year
Nm,b	= budget number of batches at Maidstone per year
VCb	= budget variable cost for a Maidstone batch
Nh	= forecast number of batches at Haverhill per year
Nh,b	= budget number of batches at Haverhill per year
VCh	= budget variable cost for a Haverhill batch
z1	= flow of units of Product A to the market
VCf	= variable cost of producing a Product A unit
z2	= flow of units of Product B to the market
VCi	= variable cost of producing a Product B unit

Variable Cost Formula 2:

$$Cvar(2) = -x*F0*Cm - y1*F1*Ch,1 - y2*F2*Ch,2 - y3*F3*Ch,3 - y4*F4*Ch,4 - y5*F5*Ch,5 - z1*F6*Cf - z2*F7*Ci$$

where ...

x	= mass flow of Chemical Y out of the Maidstone plant
Cm	= material unit cost of HA production at Maidstone
y1	= mass flow of Grade 'P' HA product from Haverhill
Ch,1	= material unit cost of production for Grade 'P' HA at Haverhill
y2	= mass flow of Grade 'Q' HA product from Haverhill
Ch,2	= material unit cost of production for Grade 'Q' HA at Haverhill
y3	= mass flow of Grade 'R' HA product from Haverhill
Ch,3	= material unit cost of production for Grade 'R' HA at Haverhill
y4	= mass flow of Grade 'P' HA product from Haverhill to the Product A process in Framingham
Ch,4	= material unit cost of production for Grade 'P' HA at Haverhill
y5	= mass flow of Grade 'P' HA product from Haverhill to the Product B process in Chicago
Ch,5	= material unit cost of production for Grade 'P' HA at Haverhill
z1	= mass flow of Product A from Framingham
Cf	= material unit cost of Product A production at Framingham
z2	= mass flow of Product B from Chicago
Ci	= unit cost of Product B production at Chicago
F(i)	= unit conversion factor for the given product, i=0,1,...,7

3.4.8 Mass Balance

Maidstone output was used as the basis for the supply chain mass flow balance as every product must pass through this point of the supply chain. Chemical Y was therefore set as the mass flow balance unit. Market demands for each product was set and then converted to an equivalent mass flow of Chemical Y. These equivalent flows were then added up to determine the requirements of the Maidstone plant and to balance the flow of the supply chain.

Unit conversion factors (F0,F1,F2,...,F7) were used for each path in the supply chain. These conversion factors were either in kilograms of HA per kilogram of Chemical Y (F0,F1,F2,...,F5) or units per kilogram of Chemical Y (F6,F7). Apart from use in the material balance, these factors also allowed unit costs to be converted into dollar values in the cost formulae.

3.4.9 Model Outputs

Revenues, Net Income and Discounted Net Income are provided in column charts: see Figures 7, 8 and 9, respectively. These were compiled for the best, likely and worst case scenarios. Net Present Value was also calculated for each of the case scenarios (see Table 3). A five year time horizon and a discount rate of 15% was used in these calculations. Internal Rate of Return values were provided for each of the case scenarios; this was calculated using the Solver function in Excel.

Recognizing the disparity between best case scenario and worst case scenario outputs, it was realized that further analysis was required. Probability theory was seen as a useful tool to help deal with the uncertainty associated with forecasting market demands. Monte Carlo analysis techniques have been used in modeling since the early 1900's, mainly on approximation of mathematical relations, rather than in simulation. Recently, the Monte Carlo analysis has widely been used in simulation, as outlined in the following section.

3.4.10 Uses of the Model

There are two main uses of the model for Genzyme: as a measure of overall HA supply chain economic profitability, and as an analysis tool for the profitability of a specific market segment. Each of these are discussed in the following.

3.4.10.1 Overall HA Supply Chain Profitability

The primary use of the model is as a high level view of the HA supply chain economics. The model provides quantification behind strategic decisions such as whether to maintain a presence in HA manufacturing or to outsource. This model focuses on the quantitative

Figure 7: Five Year Revenue Projection

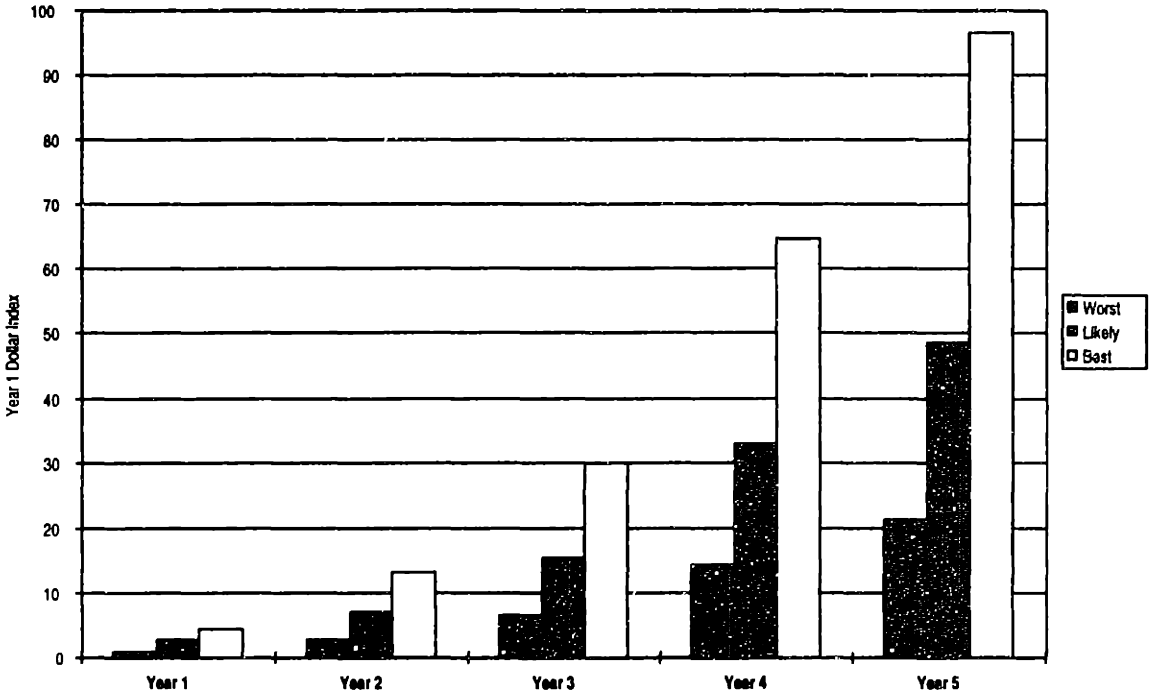


Figure 8: Five Year Net Income Projection

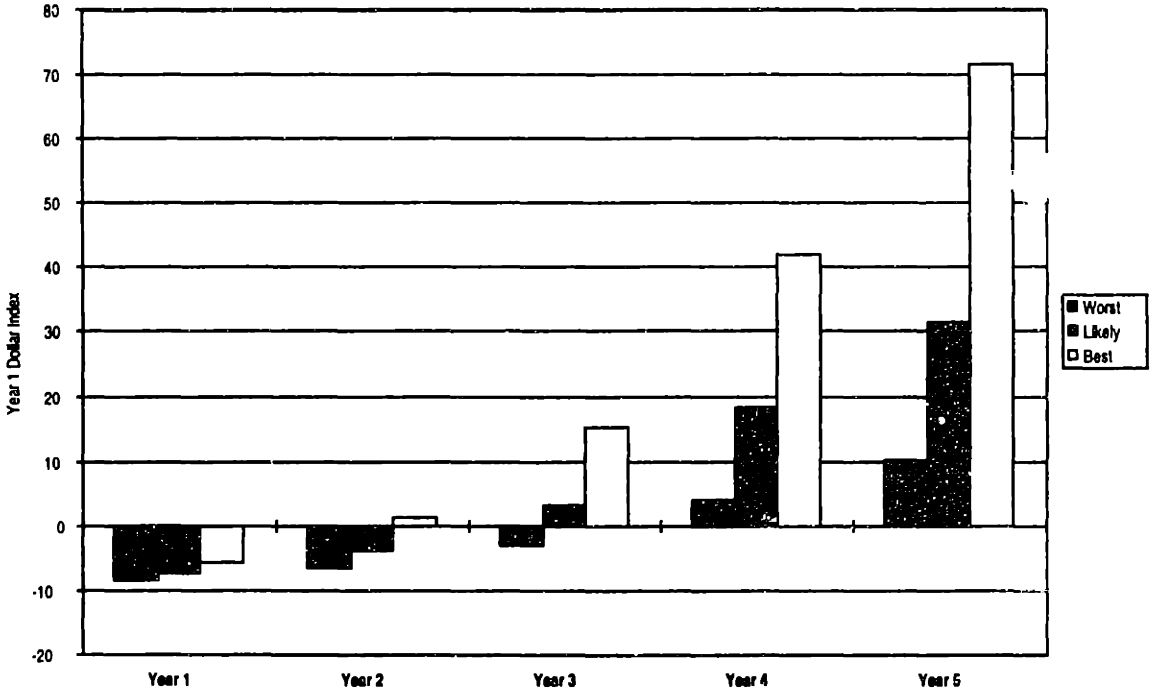
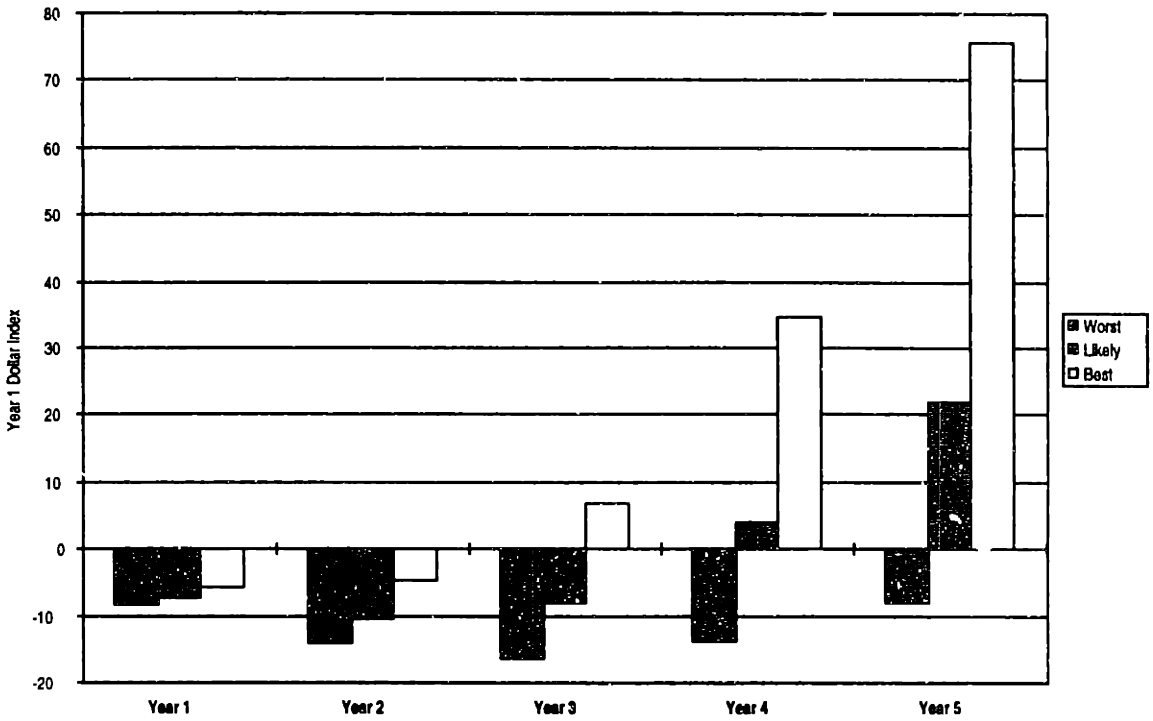


Figure 9: Five Year Cumulative Net Income Projection (with 15% discount rate)



measures: NPV and IRR, as key inputs for management to use in making strategic decisions.

Assumptions behind these figures must be considered carefully when using them for decision making. Some important assumptions are the five year time horizon and the idea that it is likely we will reach 'N'% of our sales forecasts. If the time horizon is extended, NPV will obviously increase, however there is large uncertainty in this market and forecasts beyond five years are very difficult. Additionally, sales forecasts have been getting more and more accurate. Basing a likely case on an average that includes early development stages of the market development is reasonably conservative and could be more optimistically determined.

Qualitative concerns must also be taken into consideration, such as long term strategic areas for the corporation. Not all NPV positive opportunities should be pursued; similarly, not all NPV negative projects should be rejected if there are sufficient non-quantifiable side benefits. The model provides a quantitative basis to analyze the HA supply chain profitability; this must be taken into consideration along with management intuition and the long term strategic goals of the corporation.

3.4.10.2 Specific Market Segment Profitability

The model has demonstrated that approximately 90% of the total supply chain revenues come from Product A: this should therefore be the supply chain path to which all others are subjugated. However, new markets for HA derived products may develop either within Genzyme or in another company, changing internal or external demand. The model provides a tool that will allow a relatively simple 'first pass' analysis of such an opportunity.

For example, if Product B was replaced by a new internally produced HA derived ophthalmic product (say), an analyst could simply adjust the market demand worksheet and input parameters (price, overhead allocation, unit material cost data and unit conversion factor) to simulate the effect on the supply chain. The model will indicate primarily if the product will have a positive or negative effect on profitability. However, other uses such as indicating a potential capacity constraint concern would help focus management attention on this area and other model which have a more operational focus could be employed to investigate these areas.

Another example could be the potential to supply a client with a large amount of Grade 'Q' HA. The model allows simple adjustment of the market demand sheet to help determine whether such a potential contract would be profitable, and if so, how profitable. Again, potential capacity constraints would be indicated by looking at the number of batches required from Maidstone and Haverhill to determine if further in depth analysis was needed.

3.5 Monte Carlo Model Theory

Scientific and economic analysis generally requires that decisions be made without complete information. In such circumstances, analysts like to use tools such as statistical inference to narrow down the decision space. Statistical inference is a method that aims to provide some framework with which to predict the state of a defined control space from available information [12]. Statistical inference is used in generating a simulation for the defined control space.

Simulation was defined by Naylor [19] as "a numeric technique for conducting experiments on a digital computer which involve certain types of mathematical and logical models that describe the behavior of business or economic systems over extended periods of real time". Such simulation is extremely useful if experiments are difficult to conduct or it is very expensive to obtain and measure real data. In the present study, we are trying to model the future for which, presently, there are no techniques at any cost which can produce verifiable data.

Important things to note when looking at results from simulations is that they are imprecise: they provide statistical estimates rather than exact results. The main purpose of a simulation is to compare alternatives rather than determining an absolute optimal one. In contrast to analytical methods, which utilize deductive and logical arguments, simulations provide inductive and probabilistic answers.

Stochastic, or randomized, simulation is often called Monte Carlo analysis. The term Monte Carlo analysis was introduced by Metropolis and Ulam during World War II as a code word for work conducted on neutron diffusion for atomic bomb experiments at Los Alamos [6]. The first published article by Metropolis and Ulam [29] describing the work conducted in this area was released in 1949. Early work using this type of stochastic model was conducted on the Boltzmann equation and, in 1908, Student used this method for estimating the coefficients in his famous t-distribution.

Modern use of the Monte Carlo technique varies from multidimensional integration in physics to radiation transport and river basin modeling. Major pharmaceutical corporations such as Merck [31], among others, have also used the technique for financial modeling and strategic planning. Niederreiter [7] has summarized some applications of Monte Carlo analyses in the literature:

1. Numerical integration in 's' dimensional space [22]
2. Boundary value problems [23]
3. Integro-differential equations (e.g. Boltzmann equation) [24]
4. Numerical solutions of systems of mathematical equations [25]
5. Computational statistics [26]
6. Stochastic algorithms [27]
7. Stochastic optimization [28]

Monte Carlo techniques have been defined as "procedures which enable the economist or statistician to set up a laboratory within which the properties of the econometric estimators may be discerned" [12]. In the present study, Monte Carlo analysis is used to model the economic value of the supply chain for HA and derivative products, including Product A.

Smith [12] defines the Monte Carlo technique using estimation theory: by using a sample of output information we are able to learn something of the nature of an underlying process. The mechanism by which sample outputs are generated is governed by a set of input parameters, or estimates. In the present study these estimates are market forecasts of customer demands.

The methods by which estimates are determined are called estimator processes. Usefulness of estimator processes can only be assessed in terms of the distribution of estimates they will provide. In the present case, 95% confidence intervals between best case and worst case scenarios are the estimator processes. Knowledge of the estimate distribution allows the generation of a probability statement regarding the true value of the parameter of concern. Derivations of estimate distributions for complex economic models have been made in the literature [20] [21].

Smith [12] has defined the steps involved in conducting a Monte Carlo Study as:

1. Specify a true structure for the model of interest and a series of values for the exogenous variables.
2. Generate a series of pseudo-random numbers from a pre-assigned distribution, satisfying the statistical properties of a random variable.
3. Solve the model with the structural parameters and exogenous variables as well as the errors for the endogenous variables for a given sample size.
4. Repeat the process a number of times, changing the errors.
5. Apply analysis techniques to the generated samples and obtain probability distributions for variables.

An important advantage of Monte Carlo over other numerical methods was outlined by Fishman [5]. He observed that, in the absence of exploitable special structure, traditional numerical methods that rely on 'n' point evaluations in 'm' dimensional space have an absolute error of estimation that decreases as $n^{-1/m}$ at best. Whereas, Monte Carlo analyses for the same system have an absolute error that decreases as $n^{-1/2}$.

This gives Monte Carlo analyses significant advantages in terms of lower absolute errors for an identical system and lower computational requirements. The computational cost for Monte Carlo analyses increase as a polynomial function of 'm'; whereas, that for other similar numerical methods increases exponentially or super-exponentially in 'm' [5].

A final note from the literature provides a bit of a reality check on the output from Monte Carlo simulations. Even after employing the best random number generation methods and

the most elegantly designed simulation models, the Monte Carlo method rarely offers more than two or three significant figure accuracy [5]. For further discussion on error in Monte Carlo analysis, a quick look at the Weak Law of Numbers Theorem and Central Limit Theorem is needed.

If we let X_1, X_2, X_3, ... denote a series of mutually independent, uniformly distributed and reproducible random numbers. We then let $Sn = X_1 + X_2 + ... + X_n$. Now, if the expectation $\mu=E(Xi)$ exists then the Weak Law of Numbers [5] states that for every $\mathcal{E} > 0$:

$$\lim (\text{as n approaches infinity}) \Pr (I\, Sn/n - \mu\, I > E\,) = 0$$

If, additionally, the expectation $d^2 = E\,(\,Xi - \mu)^2$ then the Central Limit Theorem [5] asserts that for a fixed a:

$$\lim (\text{as n approaches infinity}) \Pr((S_n - n\mu)/(dn^{0.5}) < a) = 2 * \int_{\text{inf.}}^{a} e^{(-z^2/2)}\, dz$$

The Weak Law of Numbers leads to the conclusion that as the sample size, n, increases, the error in estimating μ by S_n/s becomes smaller and smaller. The Central Limit Theorem then allows assessment of the statistical error for large n [5].

Contradictory to the above, the Monte Carlo method when applied in practice uses pseudo-random number sequences which repeat themselves in a finite number of steps; thus, statistical error is not removed from the analysis. For experiments, such as in the present study, conducted on digital computers, these realities limit the accuracy that can be obtained.

It should be noted that the pseudo-random number sequences generated by the Apple Macintosh PowerBook 5300cs used in this study were randomized before each experiment. This randomization function adjusts the starting point in the pseudo-random number sequence based on the time of the clock. The erratic hours kept by the author of this paper in operating the model ensure that any reduction in randomness due to the time when the simulations were run is minimized.

4.0 Experimental Results and Discussion

In this section a brief outline of the three deterministic cases analyzed in this case was provided as well as a sensitivity analysis to determine the magnitude effect of changing important input variables on the results from the model. Output for the revenues, net incomes and discounted net incomes for these three models were presented in Figures 7, 8 and 9, respectively. These results are summarized in Table 3. For a full printout of the spreadsheet model see Appendix C.

A description of the series of stochastic models used in the Monte Carlo analysis was then provided. Emphasis was placed on the latter for discussion, as it had the most technically challenging characteristics and, more importantly, it also provided the greatest value for Genzyme's senior management in understanding the uncertainty in valuation of the HA supply chain business.

4.1 Best Case Scenario

The best case scenario was based upon achieving the sales forecasts for all products from the HA supply chain. The vast majority of revenues from the supply chain are from Product A. Present forecasts for Product A predict sales of 'A1' units in year 1, raising to 'A2' units by year 5. These forecasts were described by marketing management as "aggressive, but achievable" and were thus set as the best case scenario figures.

Product A and Product B forecast were obtained from leaders of the marketing management team. Grade 'Q' grade HA data were obtained from the drivers of the pharmaceutical division's push into these markets, with some assumptions regarding growth rates of future sales. Grade 'P' HA was assumed to be constant at 'P1' kilograms per year, as per Genzyme's contract with A pharmaceutical customer. Grade 'R' HA was assumed to be constant at 'R1' kilograms per year. This material was produced during development runs for the higher value added HA products.

Table 3: Revenue, Net Income and Discounted Net Income

Net Present Values and Internal Rate of Return

Discount Rate: 15%

Case	*NPV (1997 US$)*	*IRR (%)*
Worst	$ (35,660,795)	< 0%
Likely	$ 98,542,398	65%
Best	$ 340,432,531	176%

Revenue

Case	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Worst	0.8	2.7	6.5	14.4	21.3
Likely	2.6	7.1	15.3	32.8	48.6
Best	4.3	13.3	29.9	64.8	96.4

Net Income

Case	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Worst	-8.4	-6.4	-3.1	4.0	10.1
Likely	-7.2	-3.8	3.3	18.2	31.4
Best	-5.7	1.2	15.3	42.1	71.8

Cumulative Net Income, i = 0%

Case	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Worst	-8.4	-6.4	-3.1	4.0	10.1
Likely	-7.2	-3.8	3.3	18.2	31.4
Best	-5.7	1.2	15.3	42.1	71.8

Cumulative Net Income, i = 15%

Case	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Worst	-8.4	-14.0	-16.3	-13.7	-7.9
Likely	-7.2	-10.5	-8.0	3.9	21.9
Best	-5.7	-4.6	6.9	34.6	75.7

NOTE: NPV data have been normalized around a likely case of $100 million. All other data has been indexed 0 to 100.

4.2 Likely Case Scenario

Based on a first pass analysis of the past quarterly forecasts and actual sales for Product A, an average ratio of actual to forecast sales of N% was determined. It should be noted that these forecasts are becoming more and more accurate over time: choice of the mean figure represents a conservative approach. More rigorous analysis of the uncertainty in forecasting sales data was conducted in the Monte Carlo analysis (see section 4.5) to improve this approximation.

Using this figure, the likely case scenario was assumed to be N% of the forecast sales figure for the four products: Product A, Product B, Grade 'Q' HA and Grade 'R' HA. Grade 'P' HA was assumed to be constant at 'P1' kilograms per year as this was based upon a fixed contract that has already been signed. The assumption was that this contract was extended to year 5. If this does not happen the model will not be greatly adversely effected due to the fact that Grade 'P' HA has less than a 2% effect on the final parameters (NPV, IRR, Revenue, Net Income) produced by the model.

4.3 Worst Case Scenario

In the worst case, Product B may be removed from the market. Additionally, the emerging market of Grade 'Q' HA may prove to be unfruitful and Genzyme may lose their deal with a pharmaceutical customer for Grade 'P' material.

Continuing the pessimistic outlook, Product A could prove to have very slow penetration of the potential market due to problems in convincing surgeons of its usefulness. As a first pass analysis, a worst case assumption of P% of the Product A sales forecasts has been assumed: in this case year 5 sales are approximately 'A3' units.

4.4 Sensitivity Analyses

Sensitivity analyses have been conducted on the main inputs to the model. The most important parameter for sensitivity analysis was the market demand; this was analyzed in the various case scenarios and the Monte Carlo model looked at in other parts of this section. Other parameters from the assumptions that could have varying values were analyzed to determine the magnitude of any effect they would have on the model inputs.

Values were assumed in the assumptions (see section 3.4.1) for three important parameters: the ratio of fixed to variable costs in manufacturing plants, the level of marketing support for the emerging Grade 'Q' HA product market and the level of development support for the Grade 'P' and Grade 'Q' processes. Each of these could vary significantly from the chosen values and thus analysis of the effect of their variance on the model output is needed.

Other inputs such as the annual cost of an FTE or the corporate discount rate applied to investments, have a more assured basis and would not be expected to vary significantly from the assumed values. Additionally, the labor costs and raw materials inputs into the model are reasonably stable and would not be expected to vary significantly from the values used.

The fixed to variable overhead ratio used in the model was 70% : 30%. This assumption was based on Genzyme convention as well as industry norms [34]. When the fixed overhead portion was lowered to 60% the NPV of the likely case scenario was increased by <7%. When the fixed overhead portion was raised to 80%, the NPV of the likely case scenario was reduced by <7%. These data indicate that the model was not highly sensitive to this parameter and that further analysis and refinement of this figure was not needed.

Marketing support for the emerging Grade 'Q' HA product market was varied between 50% and 150% of the values estimated in the model. This includes both the allocation of FTEs and the marketing budget associated with the product. A 50% reduction in staff allocation and marketing budget, with no associated loss in market share, increased the NPV of the likely case scenario by <7%. A 50% increase in the staff requirement and marketing budget, with no additional gain in market share, decreased the NPV of the likely case scenario by <7%. Again the model demonstrates that it was not highly sensitive to this parameter, so detailed refinement of market support estimates was not needed.

Process development support was similarly varied between 50% and 150% of the estimated staffing and capital allocation levels. A 50% reduction in process development support, increased the NPV of the likely case scenario by <7%. A 50% increase in the level of process development support decreased the NPV of the likely case scenario by <7%. Although having a slightly more noticeable effect on the output of the model, the

model was not highly sensitive to this input parameter. Again, detailed analysis and refinement of process development support estimates would not be extremely useful in terms of affecting the model NPV output.

As discussed in the following sections, the main determinant of variation in the model is the market demand. The model is very sensitive to changes in this parameter. The Monte Carlo analysis (see section 4.5) developed as part of this study aims to deal with this uncertainty and provide some quantification of the effect of market demand fluctuations and risk on the profitability of the business.

4.5 Monte Carlo Model

Four Monte Carlo models were developed to analyze the problem. The first model used mutually independent random variables for each of the four markets that were analyzed. This model is based on the premise that there is no relationship between the sales performance of one product on another and no affect of year 'n' sales on year 'n+1' sales.

The second model used a straight run through with directly correlated random variables, such that each of the products in the supply chain were at identical parts of the normal distribution bell curve. The theory behind this model was that the market response to each product was directly related to the others on the market: i.e. if surgeons like Product A, they will like Product B just as much.

Effects of time and market memory were introduced into the third model. This model asserts that the sales performance of year 'n' has a direct effect on the sales in year 'n+1'. A random effect is also introduced each year to weight the market flow one way or another. This is thought to model the inertia of the market place reasonably realistically in terms of upswings or downswings in aggregate demand.

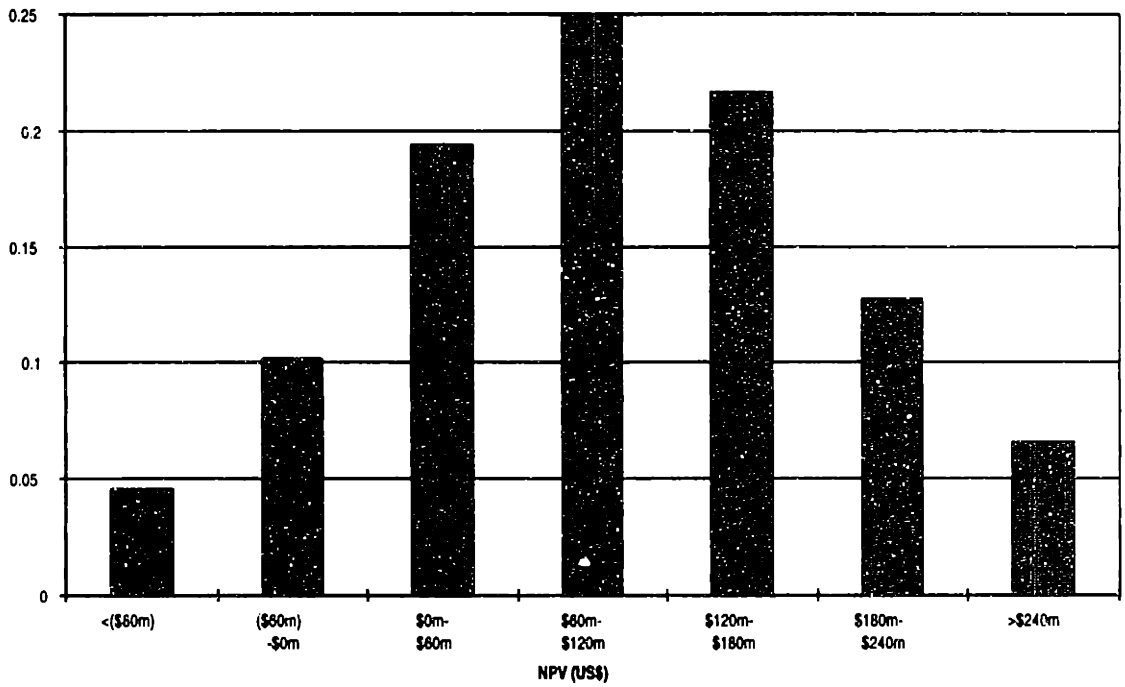
Partially correlated random variables between the two sets of products (Product A and Product B / Grade 'Q' HA and Grade 'R' HA) were established in the fourth model. This model attempted to take account of the differentiation of each of the market sets by customer type and end use. In combination with this a time lag was introduced to reflect the market place inertia described above.

Prior to running the Monte Carlo simulations, a first pass attempt at a probability distribution analysis was made by simply taking the best case and worst case scenario NPVs and applying a normal distribution curve. Assuming a 95% confidence interval between the best and worst case results the mean and standard deviation can easily be derived the results from this simplistic analysis are presented in Figure 10. This output is contrasted with the more rigorous Monte Carlo analyses in section 4.5.4.

4.5.1 Mutually Independent Random Variables (Base Case)

An assumption of mutually independent random variables for each of the four product groups modeled in the supply chain was used in this model. As outlined previously, this model is based upon the idea that each product is totally independent of the performance of other products and not affected by sales of previous years. This implies that information is not transferred within the market or effectively retained from one year to the next. A full printout of the visual basic code operated on the spreadsheet model is provided in Appendix E.

Figure 10: First Pass Analysis - Applied Normal Distribution of Output NPV



The basic operation of the model can be summarized from the following excerpt of the code:

```
Randomize

...

For i = 1 To 5

r1 = Rnd(1)

r2 = Rnd(1)

r3 = Rnd(1)

r4 = Rnd(1)

fo(i) = Application.NormInv(r1, fx(i), fs(i))

co(i) = Application.NormInv(r2, cx(i), cs(i))

hto(i) = Application.NormInv(r3, htx(i), hts(i))

hco(i) = Application.NormInv(r4, hcx(i), hcs(i))

...

Next i
```

This subroutine represents the use of four separate pseudo-random numbers, randomized by the time of modeling, for each of the markets analyzed over a five year time horizon. The sales for each of the markets (Product A, Product B, Grade 'Q' HA and Grade 'R' HA) were determined from a normal distribution of these four mutually independent random variables as well as a mean and standard deviation obtained from the best and worst case scenario analysis. This subroutine was then run 1,000 times and the five year time horizon for each of the four products was reduced down to a single output Net Present Value figure. The raw data output for all the models is provided together in Appendix M.

Probability distribution of the NPV for this case is presented in Figure 11. It can be seen that there is a much narrower spread of NPV output than the first pass case scenario analysis (Figure 10).

Figure 11: Mutually Independent Random Variables - NPV Probability Distribution

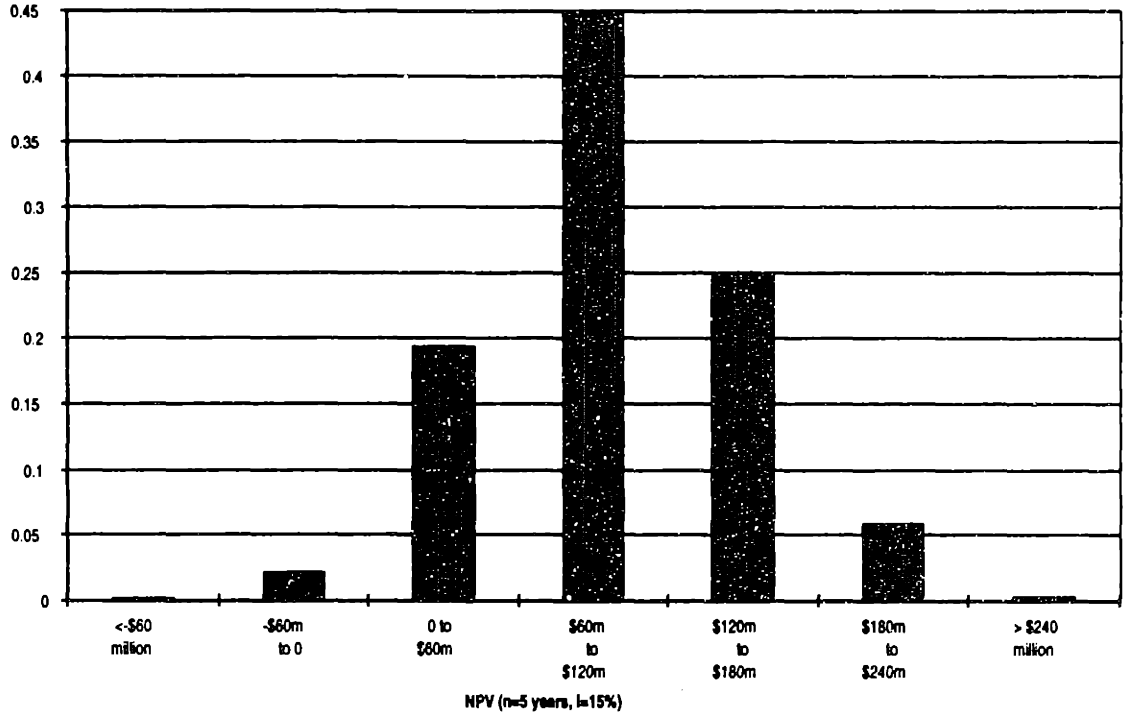
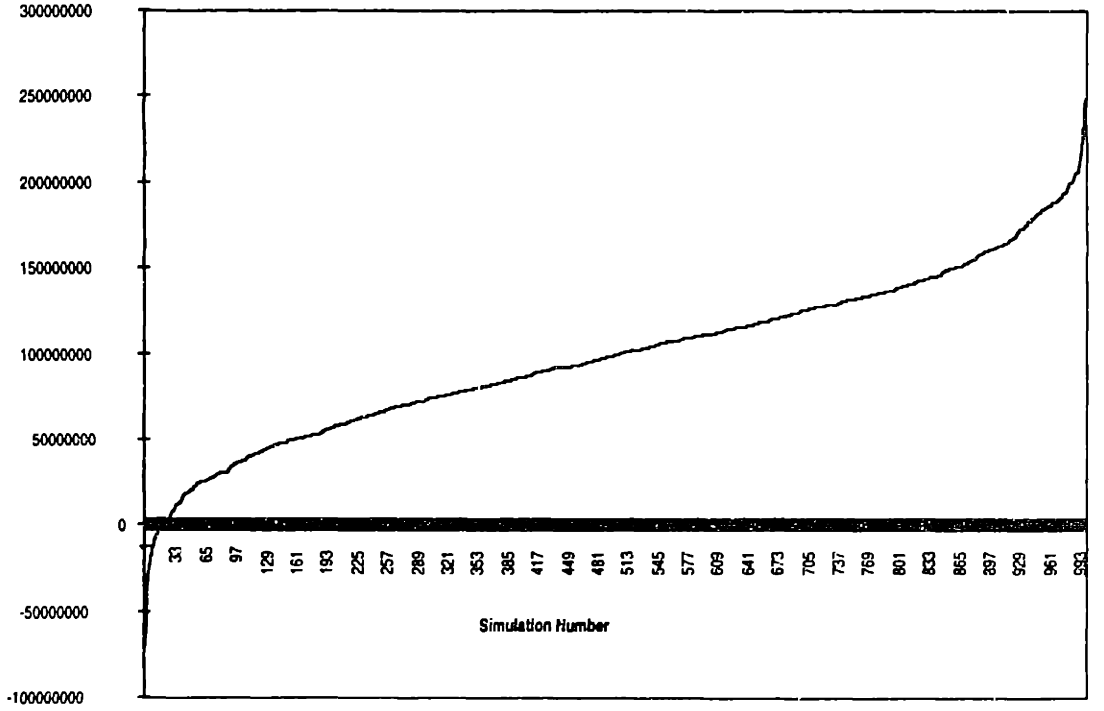


Figure 12: Mutually Independent Random Variables - NPV Data Plot



Statistical analysis on the means and standard deviations was conducted (see Appendix F). The means of the two distributions are *not* statistically different at the 0.05 level of significance. However, the standard deviations of the two distributions *are* significantly different at the 99.999% level of confidence. Figure 12 shows a spread of the NPV data for the analysis; each of the outputs from the 1000 simulations is included in this plot.

4.5.2 Directly Correlated Random Variables

Essentially, this model uses the same random variable for a given year of the analysis and applies it to each of the four products considered. The theoretical basis for this model is that information regarding the efficacy of the products travels fast and that the resulting market perceptions are uniform across the product range. However, like the previous case sales performance of one year has no effect on the following year. This could either mean that the market does not retain information effectively from one year to the next, or that technological improvements of this product (or competitors products) overpowers the time based effect to raise (or lower) sales from the expected value.

A full listing of the visual basic code for this case is provided in Appendix G The code from the previous case is simply adjusted in the following manner:

```
r1 = Rnd(1)

r2 = r1

r3 = r1

r4 = r1
```

Otherwise, the subroutine operates as in the previous case. Figure 13 shows the NPV probability distribution function for directly correlated random variables. Comparison with the base case (Figure 11) reveals that the co-dependability of the random variables for the four products has very little effect on the net distribution of the NPV.

Figure 13: Directly Correlated Random Variables - NPV Probability Distribution

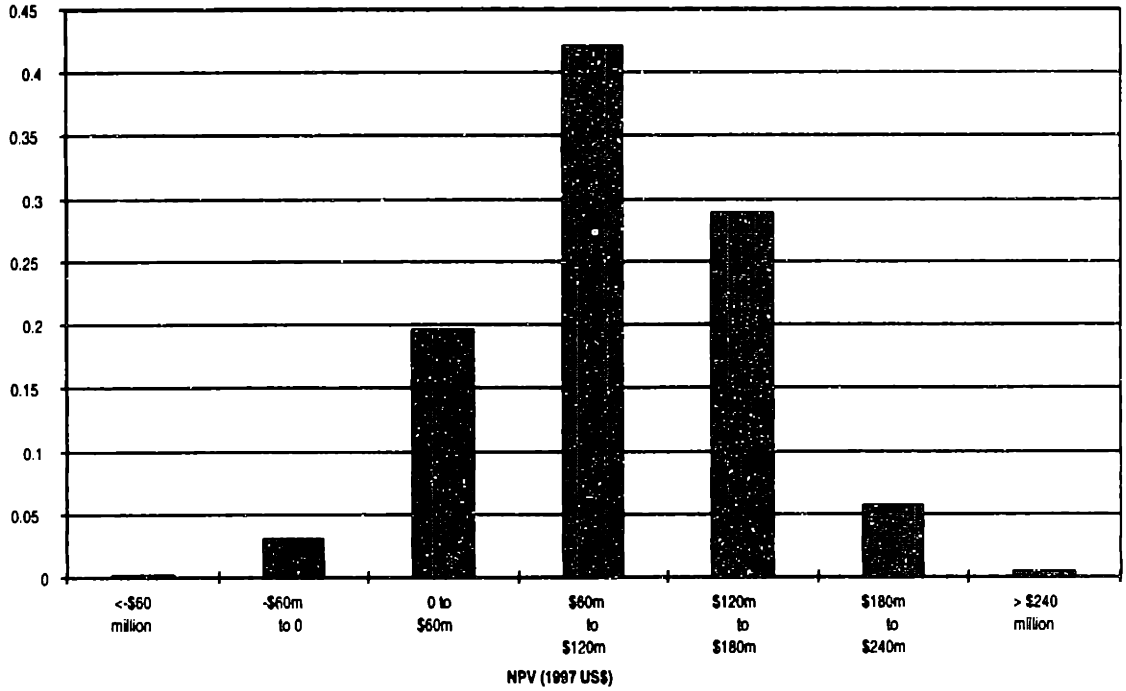
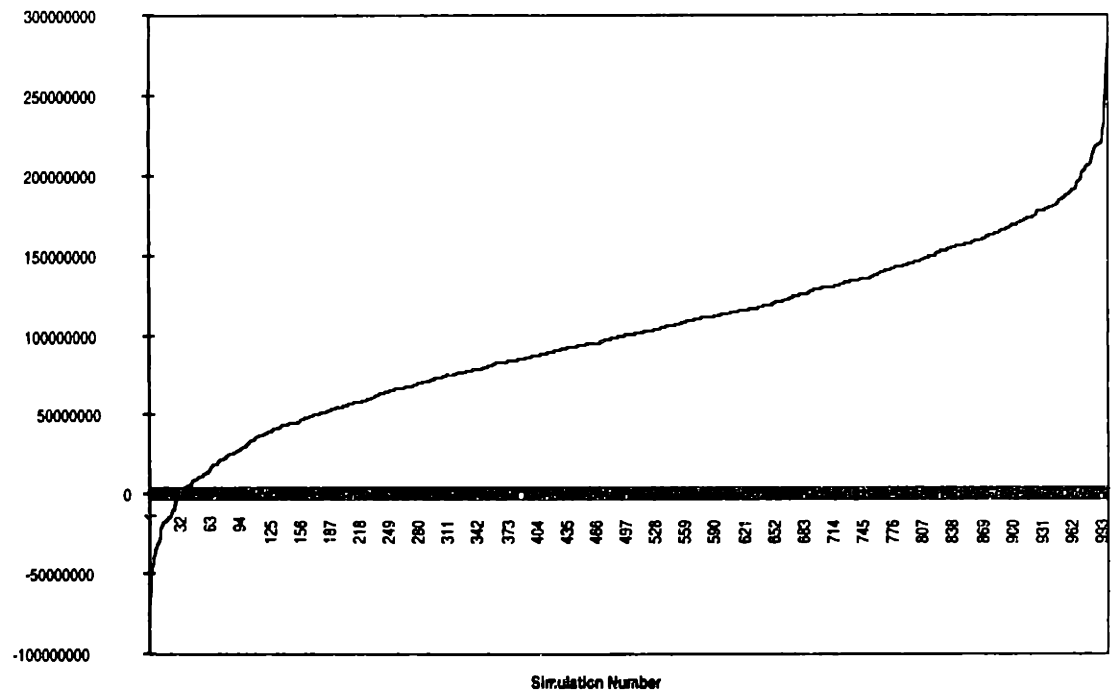


Figure 14: Directly Correlated Random Variables - NPV Data Plot



One reason for this is the fact that the Product A market dominates the NPV output: it has ~90% of the effect on the NPV output. Thus, the dependency, or lack thereof, of the other 10% does not have a dramatic effect on the output. Analysis of the output data from this case and the base case reveals that there is no difference between the means at the 0.05 level of significance. Additionally, the standard deviations of the two cases are *not* statistically significant (see Appendix H) at the 99.999% level of confidence . Figure 14 shows the spread of NPV data from the model for each of the 1,000 simulations.

4.5.3 Mutually Independent Random Variables with Lag Time

Based on the fact that there was no statistically significant difference between the level of interdependence of the four product groups in the previous case, it was decided to set up a model that tested another major parameter involved in the analysis: time. In this model the sales performance of year 'n' has a direct effect on the sales in year 'n+1' along with an introduced random effect.

Input code for the visual basic simulation is provided in Appendix I. A summary of the formulae that were used to capture this follows:

$$(r1)^n = \text{Rnd}(1)$$

$$(r2)^n = \text{Rnd}(1)$$

$$(r3)^n = \text{Rnd}(1)$$

$$(r4)^n = \text{Rnd}(1)$$

$$(r1)^m = 0.5*(r1)^n + 0.5*\{ (r1)^n + (r1)^{n-1} \}/2$$

$$(r2)^m = 0.5*(r2)^n + 0.5*\{ (r2)^n + (r2)^{n-1} \}/2$$

$$(r3)^m = 0.5*(r3)^n + 0.5*\{ (r3)^n + (r3)^{n-1} \}/2$$

$$(r4)^m = 0.5*(r4)^n + 0.5*\{ (r4)^n + (r4)^{n-1} \}/2$$

Figure 15: Mutually Independent Random Variables with Time Lag - NPV Probability Distribution

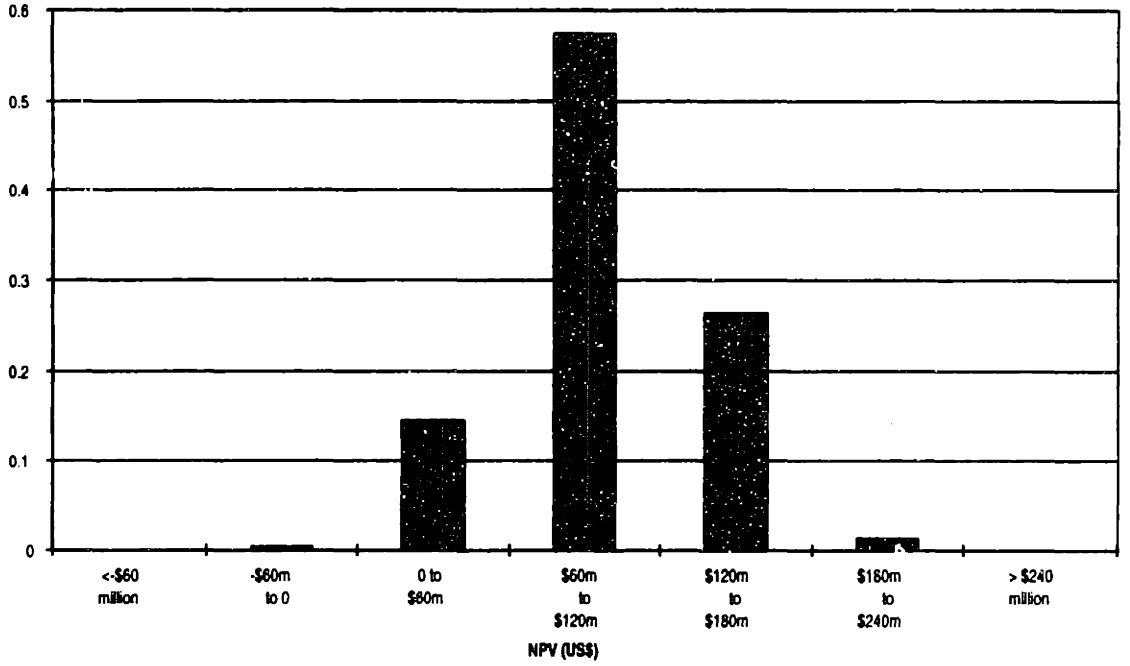
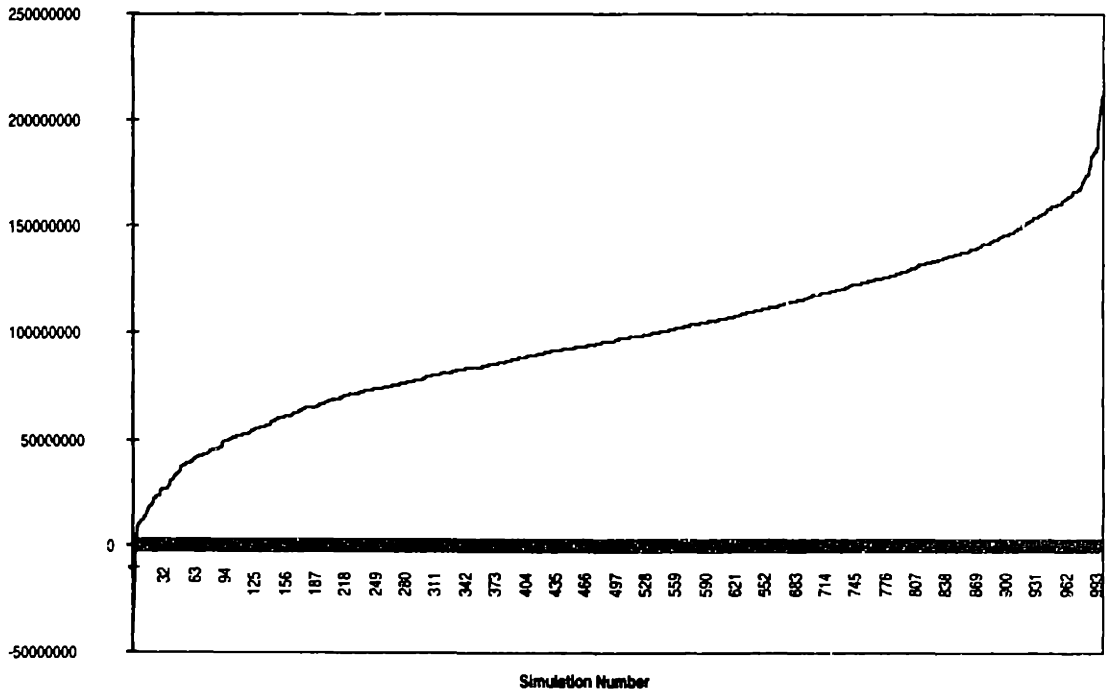


Figure 16: Mutually Independent Random Variables with Time Lag - NPV Data Plot



A summary of the raw data from this model is shown in Figure 15, which is a probability distribution of the NPVs. Comparison with the base case (Figure 11) shows that there is considerable change in the output of model by introducing the inertia effect of prior sales on future sales with lag time. Statistical analysis showed that there is no significant difference between the means of the two models; however, there is a significant difference between the standard deviations at a 99.999% level of significance (see Appendix J).

Figure 16 shows the spread of the 1,000 NPV data points for this case. It can be noticed that there are no incidences of negative NPV values; additionally, there are very few occasions on which the NPV was shown to be greater than $210 million. Thus, the introduction of a time lag effect into the model resulted in a thinning down of the NPV probability distribution and an introduction of more certainty into the prediction of the economic worth of the HA business for Genzyme.

4.5.4 Partially Dependent Random Variables with Lag Time

A simulation was run which contained partially dependent random variables with a lag time. A partially dependent model was chosen as it can represent a realistic combination of the products in terms of customers served and uses of the products: Product A with Product B and Grade 'Q' HA with Grade 'R' HA. Product A and Product B are both sold to hospitals through health maintenance organizations for end use in surgery, while Grade 'Q' HA and Grade 'R' HA are both sold to pharmaceutical and medical device companies for use in downstream processes. On top of these dependencies, a time based effect was again introduced. This is thought to be a realistic representation of the inertia associated with an upswing or downswing in the marketplace.

The input code was modified to incorporate these two factors; a full listing of the input code is provided in Appendix K. A summary of the important formulae follows:

$$(r1)^n = Rnd(1)$$

$$(r2)^n = Rnd(1)$$

$$(r3)^n = Rnd(1)$$

$$(r4)^n = Rnd(1)$$

$$(r1)^m = 0.5*(r1)^n + 0.5*\{ (r1)^{n-1} + (r2)^{n-1} \}/2$$

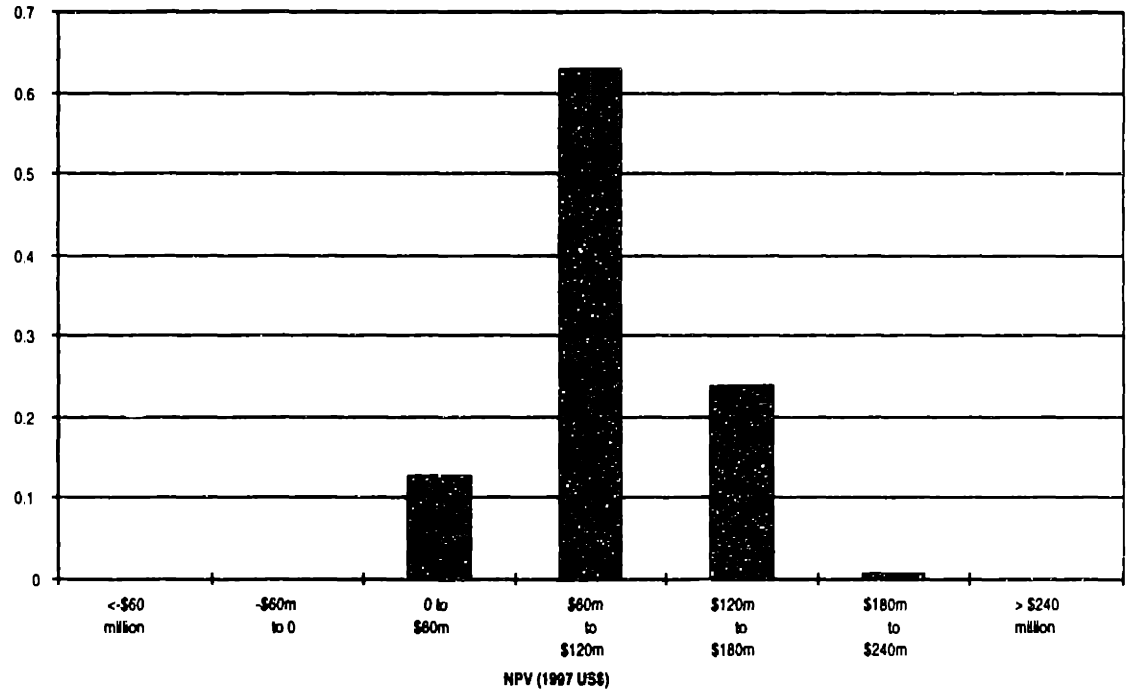
$$(r2)^m = 0.5*(r2)^n + 0.5*\{ (r2)^{n-1} + (r1)^{n-1} \}/2$$

$$(r3)^m = 0.5*(r3)^n + 0.5*\{ (r3)^{n-1} + (r4)^{n-1} \}/2$$

$$(r4)^m = 0.5*(r4)^n + 0.5*\{ (r4)^{n-1} + (r3)^{n-1} \}/2$$

Figure 17 shows a summary of the raw data from this model with a probability distribution plot of the NPV data from the simulation. Significant differences in the spread of the data can be seen between this case and the base case (Figure 11). The means of the two models were not statistically different at the 0.05 level of significance. However, the standard deviations of the two models were shown to be statistically different at the 99.999% level of confidence (see Appendix L). This model is thought to be the most realistic assessment due to its incorporation of product interdependency and the inertia associated with a positive or negative swing in sales of the preceding period.

Figure 17: Partially Dependent Random Variables with Time Lag - NPV Probability Distribution



4.5.5 Discussion of the Monte Carlo Model Results

Prior to conducting the Monte Carlo simulations, it was expected that the first pass analysis which applied a normal distribution to the output data from the model would produce a reasonably accurate picture of the output from a simulation of normally distributed inputs. As was seen in comparing Figure 10 with Figures 11, 13, 15 and 17, there is a marked difference between the approaches.

Summary statistics for the first pass analysis and the four subsequently analyzed cases are shown in Table 4. It can be seen that as more complexity is introduced into the model through codependency of product groups and time inertia, the models become more certain in their predictions. This is an intuitive result.

As we move down the table, the certainty of achieving the expected net present value increases from 25% to 63%. Additionally, the probability of achieving an internal rate of return greater than 15% increase from 85% to 100%. This seems to indicate that the more complex models produce more favorable results. However, the probability of achieving a net present value of greater than $120 million decreases as we move down the table from 41% to 24%. This indicates that along with increasing certainty of achieving a minimum internal rate of return, there is also a decreased probability of achieving excessively high returns in the HA business: i.e. lower risk, lower potential reward.

Table 4: Summary Statistics from Monte Carlo Analyses

Model	Probability of NPV $60m to $120m	Probability of IRR > 15%	Probability of NPV >$120m
First Pass Analysis	25%	85%	41%
Mutually Independent Random Variables (Base Case)	45%	98%	33%
Directly Correlated Random Variables	42%	97%	35%
Mutually Independent Random Variables with Lag Time	57%	100%	28%
Partially Dependent Random Variables with Lag Time	63%	100%	24%

The observation is that the combined effect of introducing multiple simulations of cost and revenue equations and increasing complexity in random number generation, results in a narrow distribution of NPVs around the mean. In statistical terms, the changes transform a mesokurtic distribution into a leptokurtic distribution. Alteration in skewness of the outputs was not observed; however, the kurtosis did vary between the models. Kurtosis was quantified and recorded for each model (see Table 5), from the formula shown below:

$$K = Q_{peak} / (P_{90} - P_{10}) \quad [10]$$

K is the coefficient of kurtosis
Q is the height of the probability distribution peak
P_{90} is the ordinate value at which 90% of the output data is to the left
P_{10} is the ordinate value at which 10% of the output data is to the left

Table 5: Kurtosis values of five output distributions

Model	Kurtosis Value
First Pass Analysis	0.263
Mutually Independent Random Variables	0.750
Directly Correlated Random Variables	0.702
Mutually Independent Random Variables with Lag Time	0.955
Partially Dependent Random Variables with Lag Time	1.05

An important conclusion to draw from Table 5 is that as increased detail is introduced to the model, through the inter-dependability of products on one another and the market inertia effect of year 'n' sales on year 'n+1' sales, the kurtosis of the output similarly increases. Thus, increased detail used in generating the model results in increased certainty about the output; however, the question of whether the net result is *increased accuracy* or simply *increased precision* around an inaccurate mean remains to be answered. (It could be argued that the observed increased kurtosis simply results from the combination of negatively correlated random variables).

Which of these conclusions is correct is by no means certain: critical analysis regarding the validity of each introduced, ostensibly 'more realistic', assumption has to be conducted before it can be concluded that a better model is produced. The partially dependent random variable model proposes that there is interdependence between sales in related end product markets as well as an effective customer memory function in successive time periods. The net result of these assumptions is increased certainty (resulting in increased kurtosis of the output distribution) in the expected value of the business.

An important question is raised: are these assumptions, that have been determined a priori, the best representation of the market? In a time pressured business environment where decisions have to be made, the information inclusion versus exclusion trade-off comes down to a judgement call. The author believes that the partially dependent random variables with lag time model manages the information trade off effectively, using assumptions which are valid in analyzing the underlying business economics. The real test of the model will occur during the five years following this study, as sales data are collected. It is proposed that this model can provide senior management with a realistic forward looking representation of the economic value of the HA supply chain and is a useful tool for making strategic decisions in this part of the company's business.

5.0 Conclusions and Recommendations

Detailed economic analyses of the Hyaluronic Acid supply chain were conducted as part of this study. These analyses included static, dynamic as well as deterministic and stochastic models. Strategic level analysis of the business was also conducted. Michael Porter's five forces technique was used as a generic framework, before analyzing various strategic options for the company.

The most important conclusion from this study is that Genzyme should remain in the Hyaluronic Acid and downstream product business. The expected net present value for the Hyaluronic Acid supply chain over a five year time horizon is $100 million, with a discount rate of 15%. It should be noted that 90% of this value comes from the sale of Product A.

Monte Carlo analysis for a case using partially independent, uniformly distributed random variables with lag time showed a 62% probability of achieving a net present value between $60 million and $120 million. Additionally, the same model showed an 87% probability of a net present value between $60 million and $180 million. This model was concluded to be the most realistic as it incorporated codependent groupings of product sales in terms of customers served and uses of the products. On top of these dependencies, a time based effect was introduced to account for the inertia associated with sales results from one period to the next.

Economic breakeven for the business, including marketing, product development, manufacturing and capital costs was determined to occur in year 4 under a likely case scenario, including a 15% cost of capital. The expected value of the internal rate of return is 65% and there is a very high (>98%) probability that the internal rate of return will be greater than 15%. In other words, this is a good business to be in.

Strategic level analysis resulted in the conclusion that Genzyme should remain in the upstream Hyaluronic Acid business. An important point is that Genzyme should focus on upstream Hyaluronic Acid manufacture only as long as it is high value added. It is expected that a competitive market for Grade 'P' and Grade 'Q' Hyaluronic Acid will develop over time with the result of lowering margins and driving market players down to marginal cost. As this occurs, the company should assess options to leave upstream manufacturing after securing fixed contracts with a reliable supplier. This will allow Genzyme to focus on high margin end use medical products; these presently account for 95% of the revenue stream for the Hyaluronic Acid supply chain. It will further allow the company to focus on their core competency of developing, manufacturing and marketing products that serve an unmet medical need.

Copies of the Hyaluronic Acid supply chain model were provided to personnel from accounting, manufacturing, product development and management. It was recommended that the economic models be used on a quarterly or half yearly basis to reassess the value of the business so that the company can periodically adapt to changes in a fast moving market. Additionally, these quantitative tools should serve as an input to senior management in making strategic business decisions in the presence of ambiguity and uncertainty.

References

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Appendix A - BioPro™ Model Output

NOTE: This section has been removed from the publicly available copy of this study due to proprietary information that is contained within it.

Appendix B - Unit Cost Model Output

NOTE: This section has been removed from the publicly available copy of this study due to proprietary information that is contained within it.

Appendix C - HA Supply Chain Model

NOTE: This section has been removed from the publicly available copy of this study due to proprietary information that is contained within it.

Appendix D - Simplified Profit and Loss for Grade 'R' and Grade 'Q' Grade HA

NOTE: This section has been removed from the publicly available copy of this study due to proprietary information that is contained within it.

Appendix E -Mutually Independent Random Variable Case Visual Basic Code

```
Sub MonteCarlo()

' Monte Carlo analysis randomizing market demand forecasts

'Base Case - Mutually Independent Random Variables

Open "Raw Data" For Output As #1
Open "NPV" For Output As #2

Dim i, x, r, f(5), c(5), ht(5), hc(5), fo(5), co(5), hto(5), hco(5)
Dim fx(5), cx(5), htx(5), hcx(5), fs(5), cs(5), hts(5), hcs(5), Npv, pdp(7)

'Product A sales numbers (#units/year)

f(1) = f1
f(2) = f2
f(3) = f3
f(4) = f4
f(5) = f5

'Product B sales numbers (# units/year)

c(1) = c1
c(2) = c2
c(3) = c3
c(4) = c4
c(5) = c5

'HA Grade 'Q' sales numbers (kg/year)

ht(1) = h1
ht(2) = h2
ht(3) = h3
ht(4) = h4
ht(5) = h5

'HA Grade 'R' sales numbers (kg/year)

hc(1) = hc1
hc(2) = hc2
hc(3) = hc3
hc(4) = hc4
hc(5) = hc5

'Establish means (Ax) and standard deviations (As) for each product line

For i = 1 To 5

fx(i) = f(i) * 0.5
```

```
cx(i) = c(i) * 0.5
htx(i) = ht(i) * 0.5
hcx(i) = hc(i) * 0.5

fs(i) = f(i) * 0.75 * 0.25
cs(i) = c(i) * 0.25
hts(i) = ht(i) * 0.25
hcs(i) = hc(i) * 0.25

Next i

' User inputs the name for the run and the number of simulations

10 NumberSim = Application.InputBox("Number of simulations ?")

If NumberSim < 0 Or NumberSim > 1000 Then GoTo 10

Runname = Application.InputBox("What is the name for this run ?")

Write #1, Runname

Write #2, Runname

Write #1, "Number of Simulations", NumberSim

Write #2, "Number of Simulations", NumberSim

' Randomize pseudorandom numbers by use of the computer clock

Randomize

For i = 1 To 7

pdp(i) = 0

Next i

' Intialize the loop

For x = 1 To NumberSim

Write #1, "Loop Number:", x, "Product A", "Product B", "HA Grade 'Q'", "HA Grade 'R'"

For i = 1 To 5

r1 = Rnd(1)

r2 = Rnd(1)

r3 = Rnd(1)

r4 = Rnd(1)
```

```
fo(i) = Application.NormInv(r1, fx(i), fs(i))
co(i) = Application.NormInv(r2, cx(i), cs(i))
hto(i) = Application.NormInv(r3, htx(i), hts(i))
hco(i) = Application.NormInv(r4, hcx(i), hcs(i))
If fo(i) < 0 Then fo(i) = 0
If co(i) < 0 Then co(i) = 0
If hto(i) < 0 Then hto(i) = 0
If hco(i) < 0 Then hco(i) = 0
Write #1, fo(i), co(i), hto(i), hco(i)
Next i
Worksheets("MarketDemand").Activate
For i = 4 To 8
Application.Cells(17, i) = fo(i - 3)
Application.Cells(20, i) = co(i - 3)
Application.Cells(11, i) = hto(i - 3)
Application.Cells(14, i) = hco(i - 3)
Next i
Worksheets("NPV").Activate
Npv = Application.Cells(7, 2)
' Sort Npv into baskets for the probability distribution plot
If Npv < -60000000 Then pdp(1) = pdp(1) + 1: Write #2, 1, Npv: GoTo 20
If Npv < 0 Then pdp(2) = pdp(2) + 1: Write #2, 2, Npv: GoTo 20
If Npv < 60000000 Then pdp(3) = pdp(3) + 1: Write #2, 3, Npv: GoTo 20
If Npv < 120000000 Then pdp(4) = pdp(4) + 1: Write #2, 4, Npv: GoTo 20
If Npv < 180000000 Then pdp(5) = pdp(5) + 1: Write #2, 5, Npv: GoTo 20
If Npv < 240000000 Then pdp(6) = pdp(6) + 1: Write #2, 6, Npv: GoTo 20
pdp(7) = pdp(7) + 1: Write #2, 7, Npv
```

```
20  ' Collect together and redo the loop

Next x

For i = 1 To 7

a = -20 + (i - 1) * 20

If i < 7 Then Write #2, "pdp basket#", i, "NPV <", a, "m", pdp(i)

If I = 7 Then Write #2, "pdp basket#", i, "NPV > $80m", pdp(i)

Next i

End Sub
```

Appendix F - Statistical Variance from First Pass Analysis to Mutually Independent Random Variable Case

Difference Between Means:

Ho: u1 = u2 ... the means of each data set are not statistically different

u1 = the mean of the first pass analysis
u2 = the mean of the mutually independent random variable case

$X_1 = 32.847$ $S_1 = 31.341$ $N_1 = 25$

$X_2 = 33.018$ $S_2 = 16.177$ $N_2 = 1000$

$\emptyset_{1-2} = (S_1^2/ N_1 + S_2^2/ N_2)^{0.5}$

$= 1.115$

$Z = (X_1 - X_2)/ \emptyset_{1-2}$

$= (32.847 - 33.018)/1.115$

$= -0.153$

since IZI < 1.96 the means are not statistically different at the 0.05 level of significance

Difference Between Standard Deviations:

$\emptyset = S \pm Zc\ S*(2*N)^{-0.5}$

$= 16.177 \pm 4.50 * (2 * 1000)^{-0.5}$

$= 16.177 \pm 1.63$

Since $S_1 = 31.341$, does not fall within this range, the standard deviations are statistically different at a 99.999% confidence level

Appendix G - Directly Correlated Random Variable Case Visual Basic Code

```
Sub MonteCarlo()

' Monte Carlo analysis randomizing market demand forecasts

' Directly Correlated Random Variable Case

Open "Raw Data" For Output As #1
Open "NPV" For Output As #2

Dim i, x, r, f(5), c(5), ht(5), hc(5), fo(5), co(5), hto(5), hco(5)
Dim fx(5), cx(5), htx(5), hcx(5), fs(5), cs(5), hts(5), hcs(5), Npv, pdp(7)

'Product A sales numbers (#units/year)

f(1) = f1
f(2) = f2
f(3) = f3
f(4) = f4
f(5) = f5

'Product B sales numbers (# units/year)

c(1) = c1
c(2) = c2
c(3) = c3
c(4) = c4
c(5) = c5

'HA Grade 'Q' sales numbers (kg/year)

ht(1) = h1
ht(2) = h2
ht(3) = h3
ht(4) = h4
ht(5) = h5

'HA Grade 'R' sales numbers (kg/year)

hc(1) = hc1
hc(2) = hc2
hc(3) = hc3
hc(4) = hc4
hc(5) = hc5


'Establish means (Ax) and standard deviations (As) for each product line

For i = 1 To 5

fx(i) = f(i) * 0.5
```

```
cx(i) = c(i) * 0.5
htx(i) = ht(i) * 0.5
hcx(i) = hc(i) * 0.5

fs(i) = f(i) * 0.75 * 0.25
cs(i) = c(i) * 0.25
hts(i) = ht(i) * 0.25
hcs(i) = hc(i) * 0.25

Next i

' User inputs the name for the run and the number of simulations

10 NumberSim = Application.InputBox("Number of simulations ?")

If NumberSim < 0 Or NumberSim > 1000 Then GoTo 10

Runname = Application.InputBox("What is the name for this run ?")

Write #1, Runname

Write #2, Runname

Write #1, "Number of Simulations", NumberSim

Write #2, "Number of Simulations", NumberSim

' Randomize pseudorandom numbers by use of the computer clock

Randomize

For i = 1 To 7

pdp(i) = 0

Next i

' Intialize the loop

For x = 1 To NumberSim

Write #1, "Loop Number:", x, "Product A", "Product B", "HA Grade 'Q'", "HA Grade 'R'"

For i = 1 To 5

r1 = Rnd(1)

'r2 = Rnd(1)

'r3 = Rnd(1)

'r4 = Rnd(1)

r2 = r1
```

```
r3 = r1

r4 = r1

fo(i) = Application.NormInv(r1, fx(i), fs(i))

co(i) = Application.NormInv(r2, cx(i), cs(i))

hto(i) = Application.NormInv(r3, htx(i), hts(i))

hco(i) = Application.NormInv(r4, hcx(i), hcs(i))

If fo(i) < 0 Then fo(i) = 0

If co(i) < 0 Then co(i) = 0

If hto(i) < 0 Then hto(i) = 0

If hco(i) < 0 Then hco(i) = 0

Write #1, fo(i), co(i), hto(i), hco(i)

Next i

Worksheets("MarketDemand").Activate

For i = 4 To 8

Application.Cells(17, i) = fo(i - 3)

Application.Cells(20, i) = co(i - 3)

Application.Cells(11, i) = hto(i - 3)

Application.Cells(14, i) = hco(i - 3)

Next i

Worksheets("NPV").Activate

Npv = Application.Cells(7, 2)

' Sort Npv into baskets for the probability distribution plot

If Npv < -60000000 Then pdp(1) = pdp(1) + 1: Write #2, 1, Npv: GoTo 20

If Npv < 0 Then pdp(2) = pdp(2) + 1: Write #2, 2, Npv: GoTo 20

If Npv < 60000000 Then pdp(3) = pdp(3) + 1: Write #2, 3, Npv: GoTo 20

If Npv < 120000000 Then pdp(4) = pdp(4) + 1: Write #2, 4, Npv: GoTo 20

If Npv < 180000000 Then pdp(5) = pdp(5) + 1: Write #2, 5, Npv: GoTo 20
```

```
If Npv < 240000000 Then pdp(6) = pdp(6) + 1: Write #2, 6, Npv: GoTo 20

pdp(7) = pdp(7) + 1: Write #2, 7, Npv

20  ' Collect together and redo the loop

Next x

For i = 1 To 7

a = -20 + (i - 1) * 20

If i < 7 Then Write #2, "pdp basket#", i, "NPV <", a, "m", pdp(i)

If i = 7 Then Write #2, "pdp basket#", i, "NPV > $80m", pdp(i)

Next i

End Sub
```

Appendix H - Statistical Variance from Mutually Independent Random Variable Case to Directly Correlated Random Variable Case

Difference Between Means:

Ho: u1 = u2 ... the means of each data set are not statistically different

u1 = the mean of the mutually independent random variable case
u2 = the mean of the directly correlated random variable case

$X_1 = 33.018$ $S_1 = 16.177$ $N_1 = 1000$

$X_2 = 33.346$ $S_2 = 17.741$ $N_2 = 1000$

$\emptyset_{1-2} = (S_1^2/ N_1 + S_2^2/ N_2)^{0.5}$

$= 0.759$

$Z = (X_1 - X_2)/ \emptyset_{1-2}$

$= (33.018 - 33.346)/0.759$

$= -0.432$

since IZI < 1.96 the means are not statistically different at the 0.05 level of significance

Difference Between Standard Deviations:

$\emptyset = S \pm Zc\ S*(2*N)^{-0.5}$
$= 16.177 \pm 4.5 * (2 * 1000)^{-0.5}$
$= 16.177 \pm 1.63$

Since $S_2 = 17.741$, does fall within this range, the standard deviations are not statistically different at a 99.999% confidence level

Appendix I - Independent Random Variables with Time Lag Case Visual Basic Code

```
Sub MonteCarlo()

' Monte Carlo analysis randomizing market demand forecasts

' Mutually Independent Random Variables with Lag Time

Open "Raw Data" For Output As #1
Open "NPV" For Output As #2

Dim i, x, r, f(5), c(5), ht(5), hc(5), fo(5), co(5), hto(5), hco(5)
Dim fx(5), cx(5), htx(5), hcx(5), fs(5), cs(5), hts(5), hcs(5), Npv, pdp(7)

'Product A sales numbers (#units/year)

f(1) = f1
f(2) = f2
f(3) = f3
f(4) = f4
f(5) = f5

'Product B sales numbers (# units/year)

c(1) = c1
c(2) = c2
c(3) = c3
c(4) = c4
c(5) = c5

'HA Grade 'Q' sales numbers (kg/year)

ht(1) = h1
ht(2) = h2
ht(3) = h3
ht(4) = h4
ht(5) = h5

'HA Grade 'R' sales numbers (kg/year)

hc(1) = hc1
hc(2) = hc2
hc(3) = hc3
hc(4) = hc4
hc(5) = hc5

'Establish means (Ax) and standard deviations (As) for each product line

For i = 1 To 5

fx(i) = f(i) * 0.5
cx(i) = c(i) * 0.5
```

```
htx(i) = ht(i) * 0.5
hcx(i) = hc(i) * 0.5

fs(i) = f(i) * 0.75 * 0.25
cs(i) = c(i) * 0.25
hts(i) = ht(i) * 0.25
hcs(i) = hc(i) * 0.25

Next i

' User inputs the name for the run and the number of simulations

10 NumberSim = Application.InputBox("Number of simulations ?")

If NumberSim < 0 Or NumberSim > 1000 Then GoTo 10

Runname = Application.InputBox("What is the name for this run ?")

Write #1, Runname

Write #2, Runname

Write #1, "Number of Simulations", NumberSim

Write #2, "Number of Simulations", NumberSim

' Randomize pseudorandom numbers by use of the computer clock

Randomize

For i = 1 To 7

pdp(i) = 0

Next i

' Intialize the loop

For x = 1 To NumberSim

Write #1, "Loop Number:", x, "Product A", "Product B", "HA Grade 'Q'", "HA Grade 'R'"

For i = 1 To 5

a = r1

b = r2

p = r3

q = r4

r1 = Rnd(1)
```

```
r1 = 0.5 * r1 + 0.5 * (r1 + a) / 2

r2 = Rnd(1)

r2 = 0.5 * r2 + 0.5 * (r2 + b) / 2

r3 = Rnd(1)

r3 = 0.5 * r3 + 0.5 * (r3 + p) / 2

r4 = Rnd(1)

r4 = 0.5 * r4 + 0.5 * (r4 + q) / 2

fo(i) = Application.NormInv(r1, fx(i), fs(i))

co(i) = Application.NormInv(r2, cx(i), cs(i))

hto(i) = Application.NormInv(r3, htx(i), hts(i))

hco(i) = Application.NormInv(r4, hcx(i), hcs(i))

If fo(i) < 0 Then fo(i) = 0

If co(i) < 0 Then co(i) = 0

If hto(i) < 0 Then hto(i) = 0

If hco(i) < 0 Then hco(i) = 0

Write #1, fo(i), co(i), hto(i), hco(i)

Next i

Worksheets("MarketDemand").Activate

For i = 4 To 8

Application.Cells(17, i) = fo(i - 3)

Application.Cells(20, i) = co(i - 3)

Application.Cells(11, i) = hto(i - 3)

Application.Cells(14, i) = hco(i - 3)

Next i

Worksheets("NPV").Activate

Npv = Application.Cells(7, 2)

' Sort Npv into baskets for the probability distribution plot
```

```
If Npv < -60000000 Then pdp(1) = pdp(1) + 1: Write #2, 1, Npv: GoTo 20

If Npv < 0 Then pdp(2) = pdp(2) + 1: Write #2, 2, Npv: GoTo 20

If Npv < 60000000 Then pdp(3) = pdp(3) + 1: Write #2, 3, Npv: GoTo 20

If Npv < 120000000 Then pdp(4) = pdp(4) + 1: Write #2, 4, Npv: GoTo 20

If Npv < 180000000 Then pdp(5) = pdp(5) + 1: Write #2, 5, Npv: GoTo 20

If Npv < 240000000 Then pdp(6) = pdp(6) + 1: Write #2, 6, Npv: GoTo 20

pdp(7) = pdp(7) + 1: Write #2, 7, Npv

20  ' Collect together and redo the loop

Next x

For i = 1 To 7

a = -20 + (i - 1) * 20

If i < 7 Then Write #2, "pdp basket#", i, "NPV <", a, "m", pdp(i)

If i = 7 Then Write #2, "pdp basket#", i, "NPV > $80m", pdp(i)

Next i

End Sub
```

Appendix J - Statistical Variance from Mutually Independent Random Variable Case to Independent Random Variables with Lag Time Case

Difference Between Means:

Ho: u1 = u2 ... the means of each data set are not statistically different

u1 = the mean of the mutually independent random variable case
u2 = the mean of the independent random variable with lag time case

$X_1 = 33.018$ $S_1 = 16.177$ $N_1 = 1000$

$X_2 = 32.687$ $S_2 = 12.379$ $N_2 = 1000$

$$\emptyset_{1\text{-}2} = (S_1^2/ N_1 + S_2^2/ N_2)^{0.5}$$
$$= 0.644$$

$$Z = (X_1 - X_2)/ \emptyset_{1\text{-}2}$$
$$= (33.018 - 32.861)/0.644$$
$$= 0.514$$

since IZI < 1.96 the means are not statistically different at the 0.05 level of significance

Difference Between Standard Deviations:

$$\emptyset = S \pm Zc\ S*(2*N)^{-0.5}$$
$$= 16.177 \pm 4.5 * (2 * 1000)^{-0.5}$$
$$= 16.177 \pm 1.63$$

Since $S_2 = 12.379$, does not fall within this range, the standard deviations are statistically different at a 99.999% confidence level

Appendix K - Partially Dependent Random Variables with Time Lag Case Visual Basic Code

```
Sub MonteCarlo()

' Monte Carlo analysis randomizing market demand forecasts

' Partially Dependent Random Variables with Lag Time

Open "Raw Data" For Output As #1
Open "NPV" For Output As #2

Dim i, x, r, f(5), c(5), ht(5), hc(5), fo(5), co(5), hto(5), hco(5)
Dim fx(5), cx(5), htx(5), hcx(5), fs(5), cs(5), hts(5), hcs(5), Npv, pdp(7)

'Product A sales numbers (#units/year)

f(1) = f1
f(2) = f2
f(3) = f3
f(4) = f4
f(5) = f5

'Product B sales numbers (# units/year)

c(1) = c1
c(2) = c2
c(3) = c3
c(4) = c4
c(5) = c5

'HA Grade 'Q' sales numbers (kg/year)

ht(1) = h1
ht(2) = h2
ht(3) = h3
ht(4) = h4
ht(5) = h5

'HA Grade 'R' sales numbers (kg/year)

hc(1) = hc1
hc(2) = hc2
hc(3) = hc3
hc(4) = hc4
hc(5) = hc5

'Establish means (Ax) and standard deviations (As) for each product line

For i = 1 To 5

fx(i) = f(i) * 0.5
```

```
cx(i) = c(i) * 0.5
htx(i) = ht(i) * 0.5
hcx(i) = hc(i) * 0.5

fs(i) = f(i) * 0.75 * 0.25
cs(i) = c(i) * 0.25
hts(i) = ht(i) * 0.25
hcs(i) = hc(i) * 0.25

Next i

' User inputs the name for the run and the number of simulations

10 NumberSim = Application.InputBox("Number of simulations ?")

If NumberSim < 0 Or NumberSim > 1000 Then GoTo 10

Runname = Application.InputBox("What is the name for this run ?")

Write #1, Runname

Write #2, Runname

Write #1, "Number of Simulations", NumberSim

Write #2, "Number of Simulations", NumberSim

' Randomize pseudorandom numbers by use of the computer clock

Randomize

For i = 1 To 7

pdp(i) = 0

Next i

' Intialize the loop

For x = 1 To NumberSim

Write #1, "Loop Number:", x, "Product A", "Product B", "HA Grade 'Q'", "HA Grade 'R'"

For i = 1 To 5

a = r1

b = r2

p = r3

q = r4

r1 = Rnd(1)
```

```
r1 = 0.5 * r1 + 0.5 * (r1 + a + b) / 3
r2 = Rnd(1)
r2 = 0.5 * r2 + 0.5 * (r2 + b + a) / 3
r3 = Rnd(1)
r3 = 0.5 * r3 + 0.5 * (r3 + p + q) / 3
r4 = Rnd(1)
r4 = 0.5 * r4 + 0.5 * (r4 + q + p) / 3
fo(i) = Application.NormInv(r1, fx(i), fs(i))
co(i) = Application.NormInv(r2, cx(i), cs(i))
hto(i) = Application.NormInv(r3, htx(i), hts(i))
hco(i) = Application.NormInv(r4, hcx(i), hcs(i))
If fo(i) < 0 Then fo(i) = 0
If co(i) < 0 Then co(i) = 0
If hto(i) < 0 Then hto(i) = 0
If hco(i) < 0 Then hco(i) = 0
Write #1, fo(i), co(i), hto(i), hco(i)
Next i
Worksheets("MarketDemand").Activate
For i = 4 To 8
Application.Cells(17, i) = fo(i - 3)
Application.Cells(20, i) = co(i - 3)
Application.Cells(11, i) = hto(i - 3)
Application.Cells(14, i) = hco(i - 3)
Next i
Worksheets("NPV").Activate
Npv = Application.Cells(7, 2)
' Sort Npv into baskets for the probability distribution plot
```

```
If Npv < -60000000 Then pdp(1) = pdp(1) + 1: Write #2, 1, Npv: GoTo 20

If Npv < 0 Then pdp(2) = pdp(2) + 1: Write #2, 2, Npv: GoTo 20

If Npv < 60000000 Then pdp(3) = pdp(3) + 1: Write #2, 3, Npv: GoTo 20

If Npv < 120000000 Then pdp(4) = pdp(4) + 1: Write #2, 4, Npv: GoTo 20

If Npv < 180000000 Then pdp(5) = pdp(5) + 1: Write #2, 5, Npv: GoTo 20

If Npv < 240000000 Then pdp(6) = pdp(6) + 1: Write #2, 6, Npv: GoTo 20

pdp(7) = pdp(7) + 1: Write #2, 7, Npv

20  ' Collect together and redo the loop

Next x

For i = 1 To 7

a = -20 + (i - 1) * 20

If i < 7 Then Write #2, "pdp basket#", i, "NPV <", a, "m", pdp(i)

If i = 7 Then Write #2, "pdp basket#", i, "NPV > $80m", pdp(i)

Next i

End Sub
```

Appendix L - Statistical Variance from Mutually Independent Random Variable Case to - Partially Dependent Random Variables with Lag Time Case

Difference Between Means:

Ho: u1 = u2 ... the means of each data set are not statistically different

u1 = the mean of the mutually independent random variable case
u2 = the mean of the partially dependent random variable with lag time case

$X_1 = 33.018$ $S_1 = 16.177$ $N_1 = 1000$

$X_2 = 32.861$ $S_2 = 10.886$ $N_2 = 1000$

$\emptyset_{1\text{-}2} = (S_1^2/ N_1 + S_2^2/ N_2)^{0.5}$

$= 0.617$

$Z = (X_1 - X_2)/ \emptyset_{1\text{-}2}$
$= (33.018 - 32.861)/0.617$
$= 0.254$

since IZI < 1.96 the means are not statistically different at the 0.05 level of significance

Difference Between Standard Deviations:

$\emptyset = S \pm Zc*S*(2*N)^{-0.5}$
$= 16.177 \pm 4.5 * (2 * 1000)^{-0.5}$
$= 16.177 \pm 1.63$

Since $S_2 = 10.886$, does not fall within this range, the standard deviations are statistically different at a 99.999% confidence level

Appendix M - Raw Data Output From the Monte Carlo Models

NOTE: This section has been removed from the publicly available copy of this study due to proprietary information that is contained within it.