Chapter 1

1.1 Introduction

This thesis is comprised of two papers that assess the potential size and distribution of benefits from the use of transgenic[1] tobacco as a source of therapeutic proteins. The first paper, "Potential Impacts of Pharmaceutical Uses of Transgenic Tobacco: The Case of Human Serum Albumin (HSA)" focuses on the benefits generated from the production of HSA from transgenic tobacco. The second paper, "Potential Impacts of Pharmaceutical Uses of Transgenic Tobacco: The Case of Gaucher's Disease Treatment" assesses the potential benefits from the use of transgenic tobacco for the production of a protein which is used to treat Gaucher's disease.

1.2 Biotechnology and Transgenic Tobacco

The science of biotechnology, now almost two decades old, has long promised the use of plants and livestock for entirely new purposes (Davies and Chambers, 2000). Traditionally, genetic engineering has been used to increase the productive capacity of crops and livestock. But transgenic plants can be generated for a variety of reasons including using plants as bioreactors for the production of therapeutic proteins (Smith and Glick, 2000). Therapeutic proteins are bioactive molecules that have potential applications in medical diagnosis and therapy, and also control of pathogens (Stoger et al, 2002). Transgenic plants have shown great potential as sources for efficient production of therapeutic proteins. The production of human proteins in plants requires the insertion of a human gene into the plant genome. The information contained in the foreign gene makes the plant produce the desired protein.

[1] Genetically engineered

Many companies have been working with transgenic plants for more than a decade now. A few therapeutic proteins derived from transgenic plants are in the last stages of clinical trials. The time when the first transgenically produced pharmaceuticals hit the US market is not far. CaroRX [2] for example is a dental caries preventing treatment and it is the most advanced plant produced medicine, having already been subject to clinical studies in humans with favorable results (Larrick et al., 2001). CaroRX has received European approval and could launch in 2005. The treatment is currently undergoing Phase II clinical trials in the US, and the company plans are to market the drug within 3 years (Planet Biotech, 2002). According to Planet Biotechnology[3], 70% of US dental service expenditures are due to tooth decay and the current preventatives are not effective. Sales of CaroRX are expected to produce revenues from $250 million to $2 billion annually in each, the US and EU market (Sun Mateo County Times, CA, 2004). Hirudin is another protein that is suitable for expression in transgenic plants. Hirudin comes from transgenic oilseed rape and it is an anticoagulant used to threat thrombosis (Giddings et al., 2000). Transgenic oilseed rape was commercially grown for a short period in Canada by SemBioSys but the company ceased production because of the risk of contaminating oilseed rape used for food or feed. Experiments are currently being conducted on a variety of transgenic plants such as tobacco, potato, rice, corn, tomato etc. Examples of other important proteins that have already been produced from transgenic plants include Glucocerebrosidase Enzyme, which is an essential enzyme for treating Gaucher Disease Type 1 patients. Human Serum Albumin is another important protein that is used as a blood volume replacement during shock, surgeries or for people that have experienced serious burns.

[2] CaroRX contains secretory IgA antibody which can be produced in tobacco and is effective in preventing the dental-caries agent, Streptococcus mutans.
[3]Planet Biotechnology (Hayward, CA) is the company that is developing CaroRX.

Tobacco has emerged as a potential agricultural crop that is suitable for mass production of many pharmaceutical proteins and it is currently the subject of intensive research from biotechnology/pharmaceutical companies.

1.3 Problem Statement

Economic studies on transgenic plants related to pharmaceutical protein production so far have been focused on production cost estimates, but the impact of advances in pharmaceutical use for transgenic tobacco will not be captured by the pharmaceutical industry exclusively. The use of tobacco as a source of proteins in the pharmaceutical industry may also have significant impacts on tobacco producers, product consumers and society as a whole.

Methods to produce drugs from transgenic plants can affect pharmaceutical products in two ways. Firstly, they can be applied to produce new products and secondly, they can be applied to more cost effectively produce existing products. Pharmaceutical companies may capture huge benefits from having new or significantly cheaper drugs derived from transgenic plants. Patents will ensure protection of their products for a relatively long period of time (about 10 years). Companies, through patents, can not only recover their R & D costs but can also earn considerable profits. There have always been debates about the high prices of prescription drugs in the market. For established products, considering the great cost reduction that transgenic plants offer, the pharmaceutical companies that adopt this method will surely be able to compete with lower prices. Introduction of significantly lower priced drugs can make pharmaceutical markets more competitive and yield significant benefits for consumers.

Tobacco is an important crop in Virginia, Tennessee, North Carolina, Kentucky and other states. US tobacco producers have been losing their markets during the recent years because of

increased competition from exports, changes in tobacco policy (decline in quotas) increasing health concerns and policies that tend to make people reduce smoking in general. Interviews with US tobacco farmers have shown that they are willing to grow transgenic tobacco, but this willingness is accompanied by uncertainties such as the cost of growing transgenic tobacco, regulations, technology and amount of investment needed (Nevitt, et al., 2003). Alternative uses of tobacco provide tobacco farmers with opportunities for profits, but there is a need to know the magnitude of demand and potential prices for transgenic tobacco. Pharmaceutical companies will most likely contract tobacco farmers since they are experienced and already have some of the infrastructure required to grow transgenic tobacco. Commercialization of transgenic tobacco will create new opportunities to tobacco growers if they are willing to grow the transgenic crop. Recent interviews with tobacco farmers indicate that they have no objections to grow transgenic tobacco if it were profitable (Nevitt, et al., 2003). Transgenic tobacco can also have a broader positive economic impact in those regions where tobacco is an important crop (assuming transgenic tobacco will be cultivated there as well) because it can be a source of income and it will increase farmers' welfare.

Since there is no therapeutic protein from transgenic tobacco in the market, there is an uncertainty about the actual transgenic tobacco acreage that will be used for producing pharmaceuticals. The papers in this study for the two products, estimate acreage of approximately 10,000 acres, which is roughly 2.4 percent of the total tobacco acreage in US in 2003. HSA is considered to be one of the tobacco produced proteins with the largest acreage. Further studies on more pharmaceuticals from tobacco are needed in order to have a better approximation of the transgenic tobacco acreage involved when commercialization time comes.

The results of the present study indicate that the acreage employed to produce pharmaceuticals from transgenic tobacco will result in insignificant gains to tobacco farmers.

Considering the potential cost reduction, lower priced drugs may enter pharmaceutical markets and consumers may be the most important beneficiaries. Adaptations of transgenic tobacco to produce proteins that will provide significantly cheaper drugs in the pharmaceutical markets will have a positive economic impact on the consumers. As mentioned above, transgenic tobacco has the potential to provide cheaper proteins and substitutes for some of the most expensive drugs (such as Cerezyme which is the only treatment for Gaucher's Disease) in pharmaceutical markets. Those drugs will be available in greater amounts and lower prices assuming pharmaceutical companies will compete both on the quality and cost side of their products. Thus, commercialization of pharmaceuticals that contain proteins from transgenic tobacco can have a positive impact on the welfare of consumers, tobacco producers and pharmaceutical companies.

All the 'potential' benefits mentioned above are important and economic analysis to assess and quantify these effects will be useful to policy makers whose decisions are crucial in setting the appropriate regulatory environment for plant-produced pharmaceuticals. Policy makers need a clear understanding of the risks and benefits associated with introducing transgenic plants since this field is relatively new and it is progressing at a fast pace. Transgenic tobacco and its potential use in the pharmaceutical industry have received strong attention from governmental regulatory bodies. Policy makers try to weigh benefits and risks associated with new applications of biotechnology in order to set up the right rules and regulations that will benefit society as a whole. The set of the regulations for the industry on drugs, biologics and medical devices derived from bioengineered plants for use in humans and animals is constantly

being revised to represent the latest decisions of regulatory agencies such as FDA, USDA, EPA, etc. The tremendous progress in research on drugs from genetically engineered plants has led to an informational gap between what's being done and where it may lead. In order to be successful in promoting technological progress to improve human welfare, the right policies and regulations must be in place. An economic analysis on the size and distribution of benefits from introducing transgenic plants as production vehicles for pharmaceutical proteins will provide important economic information to the debate. The general public will also be one of the beneficiaries from these studies as they will help to increase public understanding and awareness on the economic benefits of tobacco biotechnology applications. As the public is the major stakeholder in agricultural biotechnology, a more informed and educated public is able to contribute more in shaping the regulatory process.

In sum, the economic future of the use of transgenic tobacco in the pharmaceutical industry is surrounded by both exciting promises and uncertainty. Unfortunately little information currently exists on the magnitude and distribution of the expected benefits from transgenic tobacco use as a source of inputs for pharmaceutical industry. The goal of this research is to reduce the uncertainty about the expected economic benefits from introducing transgenic tobacco in generating proteins usable by the pharmaceutical industry. The two papers estimate the size and distribution of the expected benefits for two potentially important future applications and thereby provide some economic information to increase public awareness on the role transgenic tobacco can play in improving social well-being.

1.4 Theses Objectives

The specific objectives of this thesis are to:

- Estimate the potential size of benefits coming from transgenic tobacco use as a source of inputs in the pharmaceutical industry.
- Estimate the expected distribution of benefits among pharmaceutical companies and consumers.
- Discuss the appropriate public support for and regulation of transgenic tobacco in light of the magnitude and distribution of potential benefits.

1.5 The Contribution of Each Chapter

Both papers tackle these objectives by applying economic surplus analysis to generate empirical estimates of the potential magnitude of future benefits. Each paper provides a unique contribution to the objectives of the study because each of them analyses fundamentally different product markets. HSA is a protein with a wide usage and its production from transgenic tobacco stands to generate significant benefits. HSA was chosen for this study because it has been the subject of substantial research and it is one of the proteins expected to involve a relatively large acreage in agriculture. Furthermore, HSA is the product of a well-established plasma fractionation industry and the current HSA market is competitive with no price markups charged by plasma fractionators. The Gaucher's disease treatment has a very limited usage (about 3,600 patients worldwide[4]) but it is currently one of the most expensive medicinal products and there is only one company that provides an effective treatment. The current market for Cerezyme is a

[4] This number refers to the people that were receiving the treatment in 2003.

monopoly and the entry of another competitor on the market will result in a shift in market power. Differences in market structure will need to be captured in economic surplus analyses.

1.6 Overview of Theoretical Framework

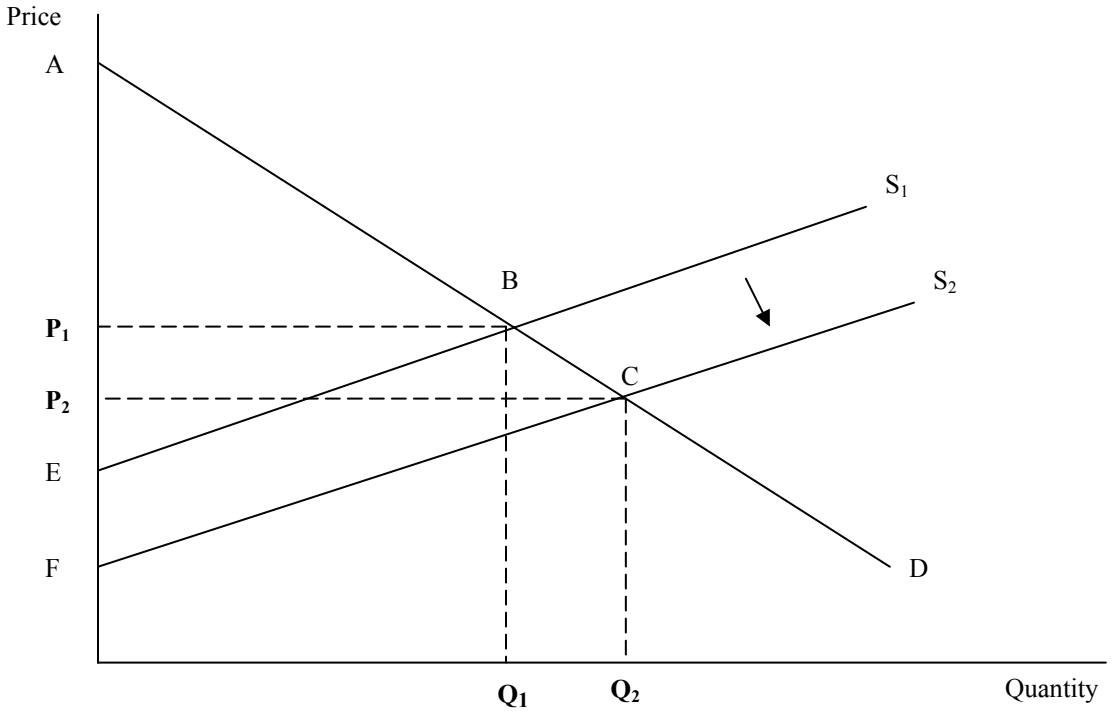
Measures of the size and distribution of research benefits in agriculture have been subject to many studies. In general, innovations cause welfare changes among producers, consumers and innovators and their effects are captured using economic surplus models. Consumer surplus is the difference between consumers' maximum willingness to pay and what they are paying for a product. Producer surplus is the returns to the quasi-fixed factors of production. In a perfectly competitive environment total surplus is the sum of consumer and producer surplus.

Studies conducted on the magnitude and distributions of benefits for agricultural innovations under imperfect competition have represented a research-induced technical change by a shift in agricultural supply. The majority of the studies have used linear supply and demand functions and parallel supply shifts, but pivotal shifts are also commonly used. The induced technical change from agricultural innovation in this study will be presented as a parallel supply shift in the input market, and linear supply and demand functions will be used. A pivotal supply shift will also be employed in order to see how results compare between the two types of shifts.

A simple case of economic surplus analysis under perfect competition for a good is illustrated in figure 4 below. The supply of the good is S_1 and demand is D. The initial consumer surplus is represented by the area of triangle APB, the initial consumer surplus is represented by the area BPE and, equilibrium price and quantity are P_1 and Q_1 respectively. A technology improvement causes a parallel supply shift and the supply of the good shifts to S_2. The new

equilibrium price associated with the shift is P_2 and the new quantity supplied is Q_2. The shift results in changes to the consumer and producer surplus. Consumers gain the area represented by BP_1P_2C and producers gain the area represented by EG P_1F. The supply shift caused by the innovation is not necessarily parallel; it can also be pivotal or convergent. The nature of the supply shift depends on the type of innovation and its relation to the production process.

Figure 1. Change in total surplus with a technical innovation.



Supply shifts in perfect competition do not result in deadweight losses because firms[5] do not have market power and they may not influence price. Recent literature on the industrial organization of markets has revealed that many markets exhibit forms other than perfect competition (Alston, et.al, 1997). A few studies have shown that the magnitude of the benefits from agricultural research and their distribution can differ extensively in cases where imperfect

[5] Assuming that there are many firms.

competition is present. Huang and Sexton used an imperfect competition model for the application of mechanical harvesting of processing tomatoes in Taiwan. They compared their findings to a perfect competition model and found that imperfect competition reduced benefits by 25 % compared to perfect competition. Alston, Sexton and Zhang (1997), Moschini and Lapan (1997), Huang and Sexton (1996) have constructed theoretical models of imperfect competition where the size and distribution of research benefits can be captured.

Protein production from transgenic tobacco is clearly an innovation causing a unit cost reduction for inputs in the pharmaceutical industry. Proteins derived from transgenic plants are estimated to be significantly cheaper than proteins produced using traditional cell culture methods. The magnitude and distribution of expected benefits from the use of transgenic tobacco as a source of inputs in pharmaceutical industry will be examined with an imperfect competition model for the following reasons:

- Private firms carry out the research on transgenic tobacco use. As such, when commercialization time comes, pharmaceutical firms are likely to contract with farmers that are willing to grow transgenic tobacco. The demand for transgenic tobacco in terms of planted acreage is expected to be insignificant (2.4 percent of the total tobacco acreage in the US) compared to the area planted with regular tobacco. In procuring transgenic tobacco as raw material for their drugs, pharmaceutical companies may have flexibility to contract with many farmers and also exhibit buyer's power since there will be just a few buyers in the transgenic tobacco market. Both papers assume that pharmaceutical companies will contract transgenic tobacco farmers and pay them the marginal cost associated with transgenic tobacco production.

- The pharmaceutical industry requires millions of dollars of investment in R & D for new products. In order to promote research and technological progress in the pharmaceutical industry the government applies intellectual property rights (IPR) laws. Patents prevent competitors from entering the market with the same product or a generic product and also allow patent holders to charge price mark ups. As a result, we can expect to encounter monopoly or oligopoly power from the producers of drugs with transgenic tobacco origin. In order to face the competition from the entrants which have lower production costs, current producers will have to decrease their price mark ups and engage in price limiting behavior.

As explained in the two papers, the initial structure of the market prior to the entry of the firm(s) that will offer plant produced proteins is important and influences not only the magnitude of the total surplus, but also the distribution of the benefits among pharmaceutical companies and product consumers. The initial structure of the market differs in the two applications that are presented in this study.

1.7 Structure of Rest of Thesis

The rest of thesis is comprised of chapters 2 and 3. Chapter 2 contains the paper on Human Serum Albumin production from transgenic tobacco. The paper on the case of Glucocerebrosidase Enzyme production from transgenic tobacco follows in Chapter 3.

Chapter 2. Potential Impacts of Pharmaceutical Uses of Transgenic Tobacco: The Case of Human Serum Albumin (HSA)

2.1 Introduction

Transgenic plants and animals have received considerable attention over the last decade as potential production sources for pharmaceutical drugs. Hiatt et al. (1989) were the first to produce antibodies in plants; subsequent experiments demonstrated that transgenic plants and animals can synthesize (at the laboratory scale) many of the proteins that are used by the pharmaceutical industry to produce drugs[6]. With laboratory success, the focus has more recently shifted to safety/efficacy studies (with some proteins currently being tested in human clinical trials), and to developing industrial scale production methods. Although no protein derived from transgenic plants or animals is presently on the market, there are indications that drugs derived from transgenic systems will be available to consumers in the foreseeable future.

Molecular farming (or bio-pharming) is a term used to describe the use of genetically modified plants or animals as production systems for therapeutic proteins. One of the benefits that molecular farming offers is the potential cost advantage, compared to current drug production methods. In fact, some empirical studies have shown that transgenic plants can produce recombinant proteins (proteins produced in the cells of genetically modified organisms) 10-100 times cheaper than cell culture systems[7] (Misson and Curling, 2000: Kusnadi et al., 1997). Moreover, molecular farming with transgenic plants may hold certain advantages over

[6] The term drug here indicates the final product sold in the market, whereas protein refers to the material from which the drug is made.

[7] Cell culture systems refer to bacterial or mammalian cells genetically modified to express a desired protein. Examples are Chinese Hamster Ovary and Escherchica Coli.

protein production using transgenic animals: plants have a greater ability to produce complex proteins, and they do not serve as hosts for mammalian pathogens (reducing the risk of contamination) (Cramer et al., 1996). Across the range of potential transgenic plants, some have suggested that tobacco represents an ideal vehicle for molecular farming because it is not used in the feed or food chain, and it is not highly regulated by food laws.

The purpose of this paper is to assess the potential size and distribution of benefits from molecular farming with (patented) transgenic tobacco. The study examines the case of producing Human Serum Albumin (HSA) out of transgenic tobacco, a protein with widespread use. An economic surplus model is employed that allows for market power associated with the developer holding patent rights. The first section of the paper introduces HSA, its uses, current production methods and market characteristics along with a short description of the HSA production method using transgenic tobacco. The model, including the effects of the patent holder's market power, is then presented in the second section. Data sources and modeling results are given in the third section. The last section summarizes the findings and discusses the implications for fostering the emergence of the bio-pharming industry.

2.2 HSA Production and Market Characteristics

HSA is primarily used for blood volume replacement in medical situations involving severe burns, surgeries, and shock, and is more effective in these scenarios than cheaper, more available (crystalloid and non-plasma colloid) substitutes. It is also used as a stabilizer in pharmaceutical products and as a coating for medical devices. HSA is the most abundant protein

in blood plasma[8], with one liter of plasma containing about 60 percent HSA (approximately 25 grams HSA/liter plasma).

Although blood plasma represents the richest source of HSA, there are problems associated with the purity of HSA obtained from human donor blood, currently the most available source of blood plasma. Donated blood plasma can carry viruses like Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Hepatitis A Virus (HAV), and variant Creutzfeldt-Jakob disease (vCJD). Such viruses must be removed during the process of HSA recovery from donated plasma and, although historically HSA has been a safe product, it is constantly subject to potential risks of contamination.

Recovering HSA from blood plasma requires a series of steps. The most important steps in achieving purity are taken during a process known as Cohn fractionation, which provides semi-purified fractions of plasma that contain HSA (Lin et al, 2000). HSA is not the only protein recovered during the fractionation process; a variety of other therapeutic proteins such as polyvalent intravenous immune globulin (IVIG), Factor IX, Factor XIII, IVIG, Hepatitis B IgG, Rabies IgG, and Thrombin are obtained as well.

Companies that carry out plasma fractionation process millions of liters of plasma per year and provide several plasma-derived therapeutic proteins to the market. Until the early 1990s HSA was the driver of the fractionation industry (with US companies providing nearly 40 percent of the world supply). Since then, IVIG demand has been dictating the fractionation process and capacity (Colgan et al., 2000). In 2002, the world market value of IVIG was more than $2 billion, while the market value of HSA was slightly more than $1.5 billion.

Equivalent blood plasma products using DNA technologies, with recombinant therapeutic proteins, offer several potential advantages over human donor plasma. Most notably, because

[8] Plasma is the portion of blood that remains after red and white cells are removed.

they are expressed in bacteria or animal cells, recombinant proteins are (theoretically) 100 percent risk-free from the viral contaminants that human plasma derived products may contain. But under current technologies production costs are higher (as recombinant proteins are now produced using cell cultures grown in large tanks called bioreactors that are very expensive to built and operate).Currently, some therapeutic recombinant proteins have made it into the market and are competing with their plasma-derived counterparts as safety attributes appear to compensate for higher production costs. For example, Factor VIII and Factor IX are proteins derived from blood plasma that are used to treat hemophilia. Recombinant forms of these proteins became widely available in the early 1990's (O'Mahony, 1999), and since then their market share has been increasing considerably.

Beyond purity/safety issues, consistence of supply is also an important issue in HSA production. The fractionation industry has not always been capable of providing an adequate HSA supply and shortages have been encountered, particularly when there are shortages of donated human blood plasma. To address this issue, pharmaceutical companies have developed some recombinant versions of HSA. Recombumin^{R} is a recombinant albumin produced and patented by Aventis (a US pharmaceutical company), which completed large pivotal phase I clinical trials of the protein successfully in 2002. Recombumin^{R} will be used as a stabilizing agent for pharmaceutical and biologic products (Chuang et al., 2002). Aventis has not, however, pursued a recombinant version of the blood replacement form of HSA, because the product is in its infancy, and the FDA approval process is long and requires a significant financial commitment.

2.3 GM HSA from Transgenic Tobacco

Shortcomings in therapeutic protein production from blood plasma have inspired the production of recombinant proteins. For recombinant HSA production, molecular farming using transgenic tobacco appears to hold great promise. In particular, cost savings associated with the purification process from tobacco are a strong incentive for pursuing GM HSA[9] technologies. Moreover, GM HSA should be free from viral contaminants, and, adjusting the acreages of tobacco planted can control for fluctuations in HSA supply.

The processes that tobacco biomass have to go through in order to achieve purified HSA for commercial purposes are quite different from those used to process HSA from blood plasma. Transgenic tobacco is grown in fields and collected as fresh plant material. To extract the protein from the fresh biomass, transgenic tobacco is ground, and then filtered and centrifuged. (see Millan et al., 2003 and Staub et al., 2000 for a review of the steps involved in obtaining the final product).

Production costs of GM HSA are influenced by two primary factors: protein expression level, and purification yield[10]. Plant cells can be modified to express a foreign protein in various cell structures such as the nucleus, intracellular fluid, oil bodies, or chloroplasts. HSA has been expressed in both the nuclei and chloroplast of transgenic tobacco, although research has shown that chloroplast expression can produce higher expression levels, eases purification, and increases yield, compared to other expression systems (Millan et al., 2003; Staub et. al., 2000). The expression level of GM HSA using chloroplasts can produce 3-4g per kg of fresh tobacco.

[9] GM (genetically modified) HSA in the remaining text refers to HSA from transgenic tobacco.

[10] Expression level is the amount of the targeted protein produced in tobacco leaves. Purification yield is the amount of the targeted protein in its pure form that is recovered at the end of the extraction process.

Purification yield in laboratory levels is about 25 percent of the initial quantity in leaves. Improvement in both expression level and purification yield have a direct impact on GM HSA production costs. The present study assumes that chloroplast expression will be used for commercial GM HSA production[11].

2.4 The Model

Because GM HSA has yet to reach the market, ex-ante welfare benefits are estimated in the present investigation. The majority of studies evaluating the benefits and distribution of technologies developed for agriculture have assumed perfectly competitive markets (see Alston, Norton and Pardey, 1995). However in this case the developer of GM HSA is likely to hold significant market power through its patent rights. Such imperfect competition cases in general fall into two categories: innovations in agricultural inputs that affect agricultural outputs (Moschini and Lapan, 1997; Falk-Zepeda, Traxler and Nelson, 2000); and, innovations in agricultural products that serve as raw materials to other industries (Wohlgenant and Lemieux, 1989; Alston, Sexton and Zhang, 1997; Huang and Sexton, 1996). The models capture research benefits and their distribution among suppliers of the input, producers and consumers. In the case of GM HSA, market power can be exerted by the pharmaceutical firms in both the output (HSA) and input markets (transgenic tobacco). In the output market, given patent protection, pharmaceutical companies are likely to exhibit pricing power in pharmaceutical markets. In the input market, pharmaceutical firms will be able to set the price for transgenic tobacco from farmers. Based on current experimental results, around 10,000 acres of transgenic tobacco could

[11] Personal interviews with representatives from Chlorogen Inc. (a biotech company working with HSA production from transgenic tobacco) have indicated that their efforts are directed that way.

meet the world's demand for HSA. This acreage represents only about 2.4 percent of the total tobacco acreage in the US. Since the tobacco production in the US has been shrinking and the need for transgenic tobacco accounts for a very modest fraction of the total acreage, the study assumes that pharmaceutical companies will contract with the growers and compensate them for their costs of production. As a result, the patent holder is a perfect monopsonist in the input market.

Although the largest five plasma fractionators serve 70 percent of the world plasma product market, currently there is little evidence of a price mark-up for the existing plasma-derived products. However, the firm that succeeds in producing GM HSA, completing safety/efficacy trials and obtaining FDA approval, will be the only provider in the market during its patent period. Therefore, the company can charge a price mark-up. The magnitude of this mark-up will depend on the difference between its marginal cost and the current marginal cost of fractionation industry. Under the assumption that the quality of GM HSA from transgenic tobacco will be the same as that of plasma-derived HSA, the pricing behavior of the firm can be characterized under two different scenarios based on the magnitude of the unit cost reduction. Using the terminology from Moschini and Lapan (1997), the innovation will be *drastic* if the patenting firm can charge its monopoly profit maximizing price ($^{m}P^{0}$ in figure 2) and *non-drastic* if it cannot charge a monopoly price but, given the presence of blood plasma products, must involve a limit pricing rule and price $^{m}P^{1}$ ($^{m}P^{1} < {}^{m}P^{0}$) instead.

Following Moschini and Lapan (1997) we assume that HSA's current production function is $y = f(x_0, z)$ and it can be produced with a new production function using the new technology according to $y = g(x_1, z)$ where $f(.,.)$ and $g(.,.)$ are strictly concave production functions. In our case x_0 represents the old input, blood plasma, and x_1 represents the new input,

transgenic tobacco. Other inputs in the production function are represented by z. It is assumed that the patenting firm has enough capacity (or achieve enough capacity through licensing its technology to other firms) to fulfill demand for HSA in the US market. In order to assess the size and distribution of benefits from transgenic tobacco use as a production vehicle for HSA the following information is needed: linear functional forms of supply and demand for HSA; price and quantity data on HSA production and consumption in the US; and unit production costs of HSA from transgenic tobacco. Surplus benefits are estimated only for the HSA market in the US for a one year period. Research and development costs of GM HSA are considered sunk costs.

Assuming linear functional forms of supply and demand, and having price, quantity, and elasticity information, equations of supply and demand can be easily obtained.

Demand for HSA in quantity dependent form may be stated as

$Q_d = \gamma - \delta P \quad (1)$

Supply of HSA in quantity dependent form may be stated as

$Q_s = \alpha + \beta P \quad (2)$

Price elasticity of demand is

$$\varepsilon = \left[\frac{\partial Q}{\partial P} * \frac{P}{Q}\right] \Rightarrow \frac{\partial Q}{\partial P} = \frac{\varepsilon Q}{P} \quad (3)$$

Under the linear demand assumption, the slope of the demand function is found by substituting the value of ε, ${}^{c}P^{0}$ (initial price), and ${}^{c}Q^{0}$ (initial quantity) in equation (3). The intercept of the demand function is found by substituting the slope, and initial price and quantity into equation (1).

The end result is the linear demand function which can be written in price dependent form as

$$P = \frac{\gamma}{\delta} - \frac{1}{\delta} Q \quad (4)$$

Linear functional form of supply is found following the same procedure. Supply of HSA in price dependent form is

$$P = \frac{\alpha}{\beta} + \frac{1}{\beta}Q \quad (5)$$

Several studies including Alston, Norton and Pardey (1995) have examined the errors due to assumptions made in modeling the size and distribution of research benefits. They state that 'in relation to total benefits, functional forms and elasticities are relatively unimportant compared with the nature of the supply shift', while in relation to the distribution of benefits, the results are very sensitive to elasticity assumptions (Alston, Norton and Pardey, p.208, 1995). In the absence of information on the specific nature of the supply shift, the suggestion is the use of a parallel shift (Alston, Norton and Pardey, 1995).

The parallel outward supply shift is represented as

$$P = \left(\frac{\alpha}{\beta} + k\right) + \frac{1}{\beta}Q \quad (6)$$

Where k is the size of the unit cost reduction expressed as cost savings for each unit of GM HSA produced compared to a unit of HSA from blood plasma.

For comparison a pivotal supply shift for the same unit is also employed and is represented as

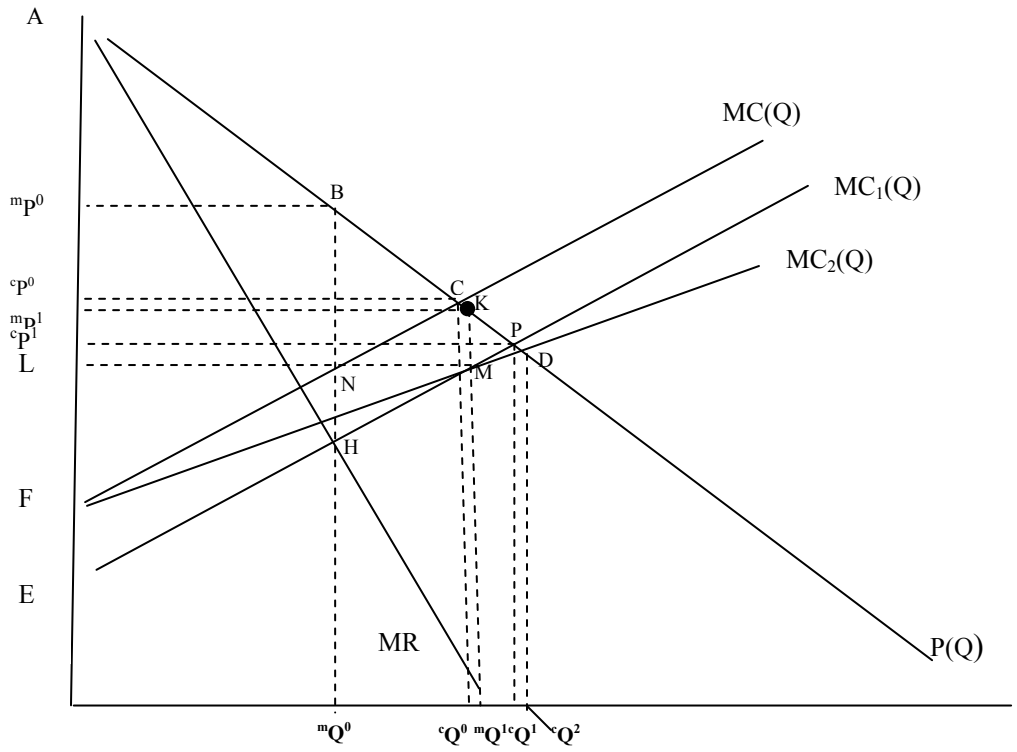
$$P = \frac{\alpha}{\beta} + \left(\frac{1}{\beta} + k\right)Q \quad (7)$$

2.4. A Model of Non-drastic Innovation

The market for HSA in the case of a non-drastic innovation is illustrated in figure 2. Again, the equal quality assumption ensures that consumers' buying behavior will not be influenced by price.

The non-drastic innovation can be represented using a limit price argument. The current HSA market is considered to be perfectly competitive with price reflecting marginal cost of the industry. P(Q) is the demand curve for HSA; MR is the marginal revenue curve that the patenting firm faces. MC(Q) is the current supply curve of HSA market. $MC_1(Q)$ is the new supply curve after the introduction of the innovation, with a vertical parallel shift caused by a unit cost reduction in HSA production and $MC_2(Q)$ is the new supply curve with a pivotal supply shift caused by the same unit cost reduction. Under perfect competition the price of HSA is ${}^{c}P^{0}$ and the quantity supplied is ${}^{c}Q^{0}$. The firm that patents GM HSA production from transgenic tobacco will have lower production costs. In order to maximize its profits the patenting firm's optimal behavior would be to price at ${}^{m}P^{0}$. However, it cannot price above ${}^{c}P^{0}$ because in that case it loses all the market. Thus, the innovation is non-drastic and to maximize its profits the firm will price its product slightly lower than ${}^{c}P^{0}$ at ${}^{m}P^{1}$ and gain all the HSA market. At a price of ${}^{m}P^{1}$ consumers' gains are very small because ${}^{m}P^{1}$ is very close to ${}^{c}P^{0}$.

Figure 2. HSA market with the entry of transgenic tobacco HSA (non-drastic innovation)



To facilitate the analysis, monopoly price $^{m}P^{1}$ is considered the same as $^{c}P^{0}$ and $^{m}Q^{1}$ the same as $^{c}Q^{0}$ since the change in price from $^{c}P^{0}$ to $^{m}P^{1}$ is infinitesimal and does not really affect the quantity sold. Thus, consumer surplus does not change as long as the innovation is non-drastic. Producer surplus also remains the same when the supply shift is parallel because the area of triangle $^{c}P^{0}CF$ that represents the initial producer surplus is equal to the area of triangle LME that is the 'new' producer surplus. The change caused by the vertical parallel shift in this case is in the form of monopoly rents, equal to the area represented by rectangle $^{c}P^{0}CML$. Comparing this scenario to perfect competition there is a deadweight loss equal to the area of triangle CMP in case of a parallel supply shift. The size of the deadweight loss depends on the elasticities of

supply and demand. Deadweight loss is smaller the more inelastic supply and demand and greater the more elastic supply and demand.

A parallel shift of the supply curve results in the following surplus changes[12]:

ΔTS = rectangle ${}^{c}P^{0}CML = ({}^{c}P^{0} - L)\,{}^{c}Q^{0}$

$\Delta CS = 0$

$\Delta PS = 0$

Profits = rectangle ${}^{c}P^{0}CML = ({}^{c}P^{0} - L)\,{}^{c}Q^{0}$

DWL = triangle $CMP = 0.5\,({}^{c}P^{0} - L)\,({}^{c}Q^{1} - {}^{c}Q^{0})$

With a pivotal supply shift of the same unit cost reduction, consumer surplus does not change and profits are the same as those of a parallel shift. However, changes in total surplus, change in producer surplus, and deadweight loss are different.

ΔTS = triangle $CMF = 0.5\,({}^{c}P^{0} - L)\,{}^{c}Q^{0}$

ΔPS = triangle ${}^{c}P^{0}CF$ – triangle $LMF = 0.5\,({}^{c}P^{0} - F)\,{}^{c}Q^{0} - 0.5\,(L - F)\,{}^{c}Q^{0}$

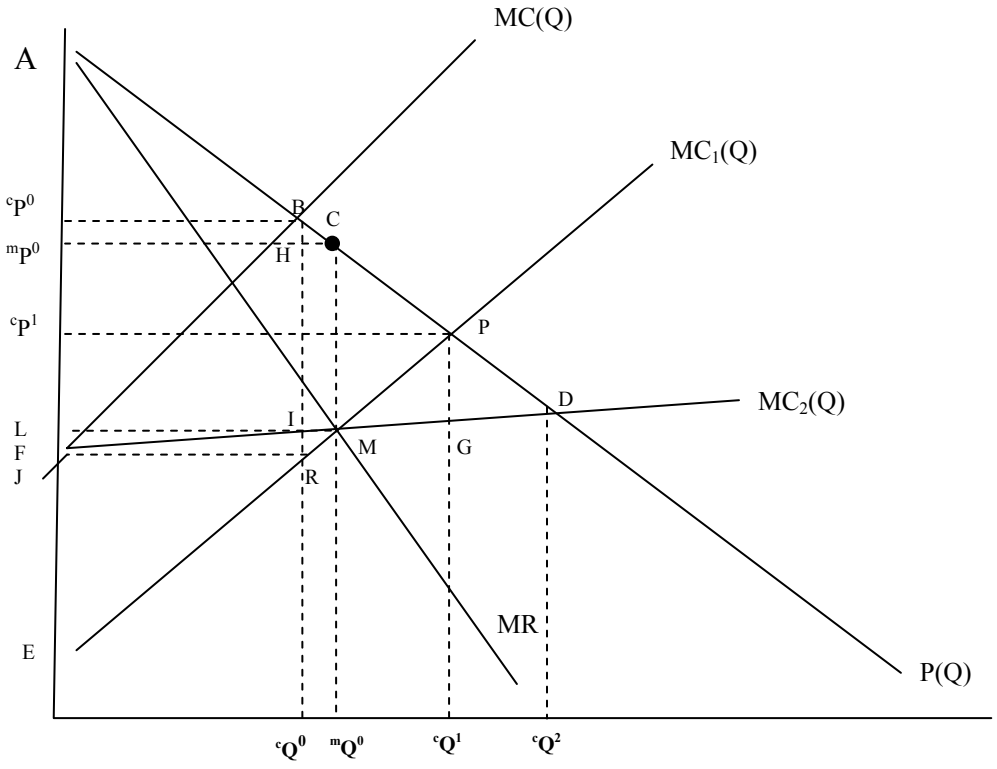
DWL = triangle $CMD = 0.5\,({}^{c}P^{0} - L)\,({}^{c}Q^{2} - {}^{c}Q^{0})$

2.4.B Model of drastic innovation

As stated above, when the innovation is drastic the firm that owns the patent of GM HSA can behave as a perfect monopoly. In figure 3 below, the profit-maximizing price of the monopoly (${}^{m}P^{0}$) is found by setting MR = MC. For some of the expected unit cost reductions scenarios, ${}^{m}P^{0}$ results to be less than the current competitive price (${}^{c}P^{0}$) of HSA, and the innovation is drastic. This outcome is important because besides generating profits for the patent holder, the innovation generates a positive change in consumer surplus.

[12] In the following formulas for surplus change calculation, point C and point K in figure 2 refer to the same point. Point K was introduced in the figure only for illustrative purposes of the limit price argument.

Figure 3. HSA market with the entry of transgenic tobacco HSA (drastic innovation)



Surplus changes for a drastic innovation with a parallel shift are:

ΔTS = rectangle ${}^{c}P^{0}BH\,{}^{m}P^{0}$ + rectangle ${}^{m}P^{0}CML$ + triangle HBC + triangle RMI + rectangle LIRJ

$\Delta TS = ({}^{c}P^{0} - {}^{m}P^{0})\,{}^{c}Q^{0} + ({}^{m}P^{0} - L)\,{}^{m}Q^{0} + 0.5\,({}^{c}P^{0} - {}^{m}P^{0})\,({}^{m}Q^{0} - {}^{c}Q^{0}) + 0.5\,({}^{m}Q^{0} - {}^{c}Q^{0})\,(L - J) + (L - J)\,{}^{c}Q^{0}$

ΔCS = rectangle ${}^{c}P^{0}BH\,{}^{m}P^{0}$ + triangle HBC = $({}^{c}P^{0} - {}^{m}P^{0})\,{}^{c}Q^{0} + 0.5\,({}^{c}P^{0} - {}^{m}P^{0})\,({}^{m}Q^{0} - {}^{c}Q^{0})$

ΔPS = triangle RMI + rectangle LIRJ = $0.5\,({}^{m}Q^{0} - {}^{c}Q^{0})\,(L - J) + (L - J)\,{}^{c}Q^{0}$

Profits = rectangle ${}^{m}P^{0}CML = ({}^{m}P^{0} - L)\,{}^{m}Q^{0}$

DWL = triangle CMP = $0.5\,({}^{m}P^{0} - L)\,({}^{c}Q^{1} - {}^{m}Q^{0})$

For a pivotal shift of the same unit cost reduction, the profits are the same as in the case of a parallel shift. Other surplus changes are:

ΔTS = triangle LMF + triangle LIB + triangle HBC + rectangle HIMC

$\Delta TS = 0.5\ (L - F)\ {}^{m}Q^{0} + 0.5\ ({}^{c}P^{0} - L)\ {}^{c}Q^{0} + 0.5\ ({}^{c}P^{0} - {}^{m}P^{0})\ ({}^{m}Q^{0} - {}^{c}Q^{0}) + ({}^{m}Q^{0} - {}^{c}Q^{0})\ ({}^{c}P^{0} - {}^{m}P^{0})$

ΔCS = rectangle ${}^{c}P^{0}BH\ {}^{m}P^{0}$ + triangle HBC = $({}^{c}P^{0} - {}^{m}P^{0})\ {}^{c}Q^{0} + 0.5\ ({}^{c}P^{0} - {}^{m}P^{0})\ ({}^{m}Q^{0} - {}^{c}Q^{0})$

ΔPS = triangle LMF - triangle ${}^{c}P^{0}BF = 0.5\ (L - F)\ {}^{c}Q^{0} - 0.5\ ({}^{c}P^{0} - F)\ {}^{c}Q^{0}$

DWL = triangle CMD = $0.5\ ({}^{c}P^{0} - L)\ ({}^{c}Q^{1} - {}^{c}Q^{0})$

2.5 Data

The elasticities, prices and unit cost reductions used to estimate surplus changes are now specified. Price elasticities of supply and demand are crucial for the surplus analysis. Information on the elasticity of supply for HSA is not available in the literature. Based on the complex nature of the fractionation industry and occasional presence of supply shortages, the supply elasticity of HSA is considered to be inelastic and is assumed to have a value of 0.5. On the demand side, consumers and hospitals seem to be sensitive to the price and availability of HSA. As mentioned, hospitals often use HSA substitutes, because they are cheaper and offer a more steady supply. Published guidelines place albumin as an alternative choice when less expensive volume expanders are available (Colgan, Moody and White, 2000). A study of the Office of Technology Assessment (OTA) in the US Congress states that HSA market is sensitive to price changes, with consumers paying attention to price and source of service rather than the manufacturing source (OTA, 1985). Alexander, Flynn and Linkins (1994) estimated price demand elasticity for prescription drugs in the US to have a demand elasticity of -2.8. Ellison et al. (1997) estimated the own price elasticity of four generic drugs that need a doctor's prescription for consumption. The drugs in their study are part of the anti-infective category and are generally prescribed when common antibiotics are not effective in curing certain diseases. The elasticities ranged from –

1.07 to –2.97. For the purpose of the study three demand elasticities in the elastic range will be taken in consideration: min. –1.07, avg. –2.02 and max. -2.97.

Price and quantity of HSA in the US market for the period from 1994-2003 in the US are shown in table 1 below (Marketing Research Bureau, 2004). The price of HSA has fluctuated extensively during that period. Norton, Alston and Pardey (1995) suggest the average price and quantity of the last three years be used for this type of analysis. Since the data for 2003 are estimates the average price and quantity from 2000 to 2002 are used.

Table 1. The Albumin Market in the US (1994-2000)

Year	Grams (000)	Price per gram
1994	106,500	$ 3.30
1995	110,875	$ 3.33
1996	109,188	$ 3.37
1997	100,625	$ 3.44
1998	99,250	$ 4.01
1999	82,188	$ 3.30
2000	74,225	$ 2.93
2001	85,438	$ 2.72
2002	87,375	$ 2.25
2003 *	88,000	$ 2.00

* Estimate

Source: Marketing Research Bureau (2004)

The magnitude of unit cost reduction (k) reflects the difference between the current HSA price and GM HSA production cost per unit and is a crucial parameter in the analysis. The value of the unit cost reduction in commercial scale based on experimental results from biotech companies is expected to be between $0.3 and $0.6 per gram. Because GM HSA is still at the laboratory level and the exact cost savings may still vary, the analysis includes a range of $0.1 up to $1.0 in order to capture a wider variety of the surpluses that may be generated.

2.6 Results

Table 2 shows estimated surplus changes under parallel and pivotal supply shifts. In the table, ε is the price elasticity of demand, K is the unit cost reduction as a percentage of initial HSA price, DTSm is the change in total surplus, DPS is the change in producer's surplus, and DWL is deadweight loss due to imperfect competition

Table 2. Economic surplus generated from a $0.1 to $1.0 unit cost reduction.

Parallel Supply Shift								Pivotal Supply Shift					
				ε =1.07	ε =2.02	ε =2.97				ε =1.07	ε =2.02	ε =2.97	
k ($)	K (% of P)	Profits	DTSm	DWL	DWL	DWL	DPS	Profits	DTSm	DWL	DWL	DWL	DPS
0.1	4	8,235	8,235	53	63	67	-	8,235	4,117	4,171	4,181	4,185	(4,117)
0.15	6	12,352	12,352	120	141	151	-	12,352	6,176	6,298	6,320	6,330	(6,176)
0.2	8	16,469	16,469	213	251	268	-	16,469	8,235	8,454	8,493	8,512	(8,235)
0.25	10	20,587	20,587	333	392	419	-	20,587	10,293	10,638	10,701	10,730	(10,293)
0.3	11	24,704	24,704	480	565	603	-	24,704	12,352	12,851	12,944	12,986	(12,352)
0.35	13	28,821	28,821	654	769	821	-	28,821	14,411	15,095	15,222	15,281	(14,411)
0.4	15	32,938	32,938	854	1,004	1,072	-	32,938	16,469	17,369	17,538	17,616	(16,469)
0.45	17	37,056	37,056	1,080	1,271	1,357	-	37,056	18,528	19,675	19,892	19,992	(18,528)
0.5	19	41,173	41,173	1,334	1,569	1,675	-	41,173	20,587	22,013	22,285	22,410	(20,587)
0.55	21	45,290	45,290	1,614	1,898	2,027	-	45,290	22,645	24,383	24,717	24,871	(22,645)
0.6	23	49,408	49,408	1,920	2,259	2,412	-	49,408	24,704	26,786	27,190	27,377	(24,704)
0.65	25	53,525	53,525	2,254	2,651	2,831	-	53,525	26,762	29,224	29,705	29,928	(26,762)
0.7	27	57,642	57,642	2,614	3,074	3,283	-	57,642	28,821	31,696	32,263	32,526	(28,821)
0.75	29	61,760	61,760	3,001	3,529	3,769	-	61,760	30,880	34,204	34,865	35,172	(30,880)
0.8	30	65,877	65,877	3,414	4,016	4,288	-	65,877	32,938	36,747	37,512	37,868	(32,938)
0.85	32	69,994	69,994	3,854	4,533	4,841	-	69,994	34,997	39,328	40,205	40,615	(34,997)
0.9	34	74,111	*74,411*	4,321	5,082	5,427	*150*	74,111	*37,228*	41,947	42,946	43,414	(37,056)
0.95	36	78,229	*79,573*	4,815	5,663	6,046	*672*	78,229	*39,891*	44,605	45,736	46,266	(39,114)
1	38	82,346	*84,740*	5,335	6,274	6,700	*1,197*	82,346	*42,570*	47,302	48,576	49,175	(41,173)

-The elasticity of supply is 0.5.
-Except for k and K, results are in thousands of dollars.

The total change in surplus varies from $8 million to $82 million for a parallel shift and from $4 million to $43 million for a pivotal shift, for unit cost reductions ranging from $0.1 to $1.0. As expected, benefits increase as the size of the unit cost reduction increases and total benefits for a pivotal shift are roughly half of those for a parallel shift. The case of HSA results in no benefits to consumers for a non-drastic innovation. As a result, only the deadweight loss is

sensitive to the choice of elasticities. To see how deadweight loss varies with different values of supply elasticities, three different values are introduced in the Appendix. Tables A, B and C indicate results for supply elasticities of 0.25, 0.75 and 1.00, respectively. As expected, deadweight loss increases as supply becomes more elastic. Changes in producer surplus for a pivotal shift are negative because the patent holder receives part of the initial producer surplus as profits.

Based on the data above, the innovation is non-drastic for unit cost reductions ranging from $0.1 to $1.0 when elasticity of demand is either -1.07 and -2.02 and it is drastic for unit cost reductions greater than or equal to $0.89 when the elasticity of demand is -2.97. This outcome is important for the analysis of the distribution of surplus because when the innovation is drastic consumers can benefit as well. For a unit cost reduction of $0.9 and a demand elasticity of -2.97 consumer surplus increases by $150,307 for a parallel shift and $172,398 for a pivotal shift. For the same demand elasticity and a unit cost reduction of $0.95, consumer surplus increases by $671,770 for a parallel shift and $777,271 for a pivotal shift. Consumer surplus increases by $1,196,921 for a parallel shift and by $1,397,250 for a pivotal shift when the unit cost reduction is $1.0. Producer surplus also changes when the innovation is drastic for a parallel supply shift. These consumer and producer surplus changes for drastic innovations are included in table 2 as part of the total benefits. Results for drastic innovations in table 2 and tables A, B and C in the Appendix are shown in italics.

2.7 Summary and Conclusion

This study estimates the benefits from the use of transgenic tobacco as a source of HSA. Because the novel application will be patented by a biotech or pharmaceutical firm, an imperfect

competition model was applied to estimate the size and distribution of benefits. The results of the study suggest that the use of transgenic tobacco for HSA production may result in significant total surplus gains.

Patent holders are the major recipients of the benefits as long as the product is under patent even if the innovation is not drastic. These potential annual flows (from $8million to $82 million annually) of monopolist's benefits appear sufficient to spur large research initiatives. Consumers, on the other hand, benefit from a drastic innovation but their benefits remain very small compared to the GM HSA producers. Furthermore, it appears that production of GM HSA will not have a significant impact on tobacco farmers since the acreage involved in transgenic tobacco production is relatively small compared to the total tobacco acreage in the US. Given this small acreage and the market power of the GM HSA patent holder, farmers are likely to be contracted with to grow GM tobacco at cost. Since GM HSA is currently one of the products expected to involve the most acreage, policy makers should not rely on this innovation to maintain the welfare of tobacco farmers.

Under most scenarios the expected unit cost reduction associated with the introduction of GM HSA results in a non-drastic innovation. However, a drastic innovation is within the reach of the current research and surprisingly the associated increase in market power may actually increase benefits to consumers.

As little attention has been given to genetically-modified agricultural crops for pharmaceutical uses, further explorations are necessary to shed more light on the scope and scale of benefits of the major private sector research initiatives being conducted on bio-pharming. Areas for further research related to the introduction of GM HSA include the benefits associated

with quality shifts in the supply of GM HSA, since the product is considered to be safer than blood plasma HSA.

Chapter 3. Potential Impacts of Pharmaceutical Uses of Transgenic Tobacco: The Case of Gaucher's Disease Treatment

3.1 Introduction

Genetic engineering has become a very promising tool for the production of biopharmaceuticals. Biotechnology/pharmaceutical companies have produced recombinant[13] therapeutic proteins that are currently on the market and hundreds of them are in different stages of clinical trials. Therapeutic protein markets are growing very rapidly and they have become very attractive for research and investment opportunities. There are currently more than 1,457 biotechnology companies in the US with a combined market capitalization of more than $250 billion (Pavlou, 2003).

Commercial recombinant therapeutic proteins are currently produced in bacteria through fermentation (yeast and E. Coli) and mammalian cell culture systems (e.g. Chinese Hamster Ovary) (Cramer et al., 1999). Although genetic engineering is an excellent method for recombinant therapeutic protein production, scale up and commercialization of those products still demands considerable financial commitments. Furthermore, there are limitations on the types of proteins that can be produced using cell culture systems and also on the expression levels[14] of proteins. Complex proteins can only be expressed in mammalian cells because they require modifications, which cannot be performed by bacteria. Since the production of the first proteins in plants by Hiatt et al. (1989), plants have emerged as a potential solution to cost and expression level limitations faced by the current biotechnology firms. The advantages of plants include low start up cost requirements, ability to produce complex proteins and flexibility of

[13] Proteins produced by modifying the cell's genome to express the desired protein.
[14] Expression level is the amount of the desired protein in the cell.

supply. Plants also provide an advantage in terms of safety because plants unlike animals cannot be infected with mammalian viruses.

Many biotechnology companies are taking their plant-based products into clinical trials and the results are very promising. Focus has recently shifted from laboratory scale towards commercialization. Successful human trials have been conducted on several proteins of plant origin indicating that commercialization time is not far away. CaroRX is a treatment for dental caries which has already received approval for production in Europe and it is now on stage III of clinical trials in the US. Planet Biotechnology, the company that invented the treatment, plans to launch it on the market by 2005. It is anticipated that the use of plants for commercial production of therapeutic proteins will not only provide plant-produced proteins at lower cost than the existing proteins of cell culture origin, but also generate new products. Thus, Bio-pharming[15] is expected to provide both quantity and quality of plant-proteins, which are very crucial for approval by the regulatory agencies.

Medicinal products that are products of R & D efforts of the private sector are patent protected. The pharmaceutical/biotech industry operates under Intellectual Property Rights laws and patent holders can significantly markup their prices. Companies conducting research on plant-based proteins are aiming to produce these proteins at a lower cost and, thereby, be able to charge a price markup. For example, Gaucher's disease and Fabry's disease are two diseases that require constant treatment throughout the life of the patient. Only one company has been able to produce the proteins to treat these diseases and the average annual treatment is currently more than $175,000 per patient. Protein production on transgenic[16] plants and animals not only

[15] Using genetically engineered plants as production systems for therapeutic proteins.
[16] Genetically modified.

promises to deliver cheaper proteins but also (indirectly) will introduce some competition into those markets that are currently served by a single firm with a patented product.

Research on plant-produced proteins includes a variety of agricultural crops such as corn, tobacco, potato, alfalfa, rice, and canola. Tobacco is one of the agricultural crops under extensive research because of safety issues and prior knowledge of the plant's genome[17]. Research on tobacco has already achieved remarkable results and proteins from transgenic tobacco are expected to be among the first plant-produced medicines in the market.

The purpose of this paper is to examine the potential size and distribution of benefits from the use of transgenic tobacco as a production vehicle for proteins. Transgenic tobacco for the production of Glucocerebrosidase Enzyme, which is currently the main treatment of Gaucher's disease, is presented as a case study. The first section of the paper provides a general description of Gaucher's disease and its market. The model used to evaluate the economic surplus and its distribution among the main stakeholders is presented in the second section. Protein production process and data used in the model are presented in the third section. A general description of the results is provided in the fourth section. The fifth section summarizes results and discusses the implications of the findings.

3.2 Gaucher's Disease

Gaucher's disease is part of some thirty family genetic (inherited) diseases that are identified as lysosomal storage disorders (Rader, 2003). Persons that suffer from the disease lack the lysosomal enzyme Glucocerebrosidase. Glucocerebrosidase Enzyme is necessary for breaking down lipids and its absence results in a lipid storage disorder. Accumulation of lipids

[17] For a discussion on advantages of using tobacco for protein production see the Chapter on HSA.

makes the cells become engorged (these are called Gaucher cells) (Rader, 2003). Lipids build up in the liver and spleen and result in lung, bone, kidney problems and anemia (Goozner, 2000).

Gaucher's disease is a very rare disease which affects around 20,000[18] people worldwide. There are three types of Gaucher's disease: type I – chronic, non – neuropathic form ; type II – infantile neuropathic ; and type III – juvenile neuropathic (Rader, 2003). Type I is the most common of the three and 1,700 patients with type I Gaucher disease are currently receiving treatment in the US.

Genetic defects causing Gaucher's disease were discovered in 1964, and the purified Glucocerebrosidase Enzyme was first produced in 1974 (Goozner, 2000). The enzyme was purified from human placentas and the purification process was very expensive. After a series of clinical trials and larger scale purification, the enzyme was finally approved from FDA in 1991 and Genzyme patented it. Genzyme continued to produce the drug (Ceredase) from human placentas until 1995 when it licensed a recombinant version of the enzyme (Goozner, 2000). The recombinant version (Cerezyme), was produced in Chinese Hampster Ovaries. Cerezyme was found to be a more effective treatment than Ceredase because of a slight genetic modification on the recombinant enzyme (Rader, 2003). Cerezyme is still the most effective treatment for Gaucher's disease. Ceredase production has been constantly reduced and patients are switching to Cerezyme. The Cerezyme production process is able to produce larger quantities, because the production of the enzyme does not depend on the availability of human placentas, but it is still very costly.

Depending on the severity of the disease, patients take different dosages of Cerezyme that are injected directly into the blood stream. Cerezyme is sold in vials containing 200 units and

[18] This figure includes people that are taking treatment for Gaucher's disease and people that have not started the treatment yet (because the disease is in its very first stages) but are positively diagnosed.

400 units[19]. Dosages can range from 2.5U/kg body weight three times weekly or 14U/kg of body weight every two weeks up to 60 U/kg body weight every two weeks. Translating the units into grams, a patient can take between 0.25 and 3 grams of Cerezyme for a one-year period (Rader, 2003). Persons suffering from Gaucher disease receive the medicine throughout their life. The average cost per patient is $175,000 annually. Cerezyme sales were $479 million in 1999, $537 million in 2000, $570 million in 2001, $619 million in 2002, and $734 million in 2003 (Genzyme Corp., 2004). The average wholesale price for 200 unit vial in 2002 was $790, and for a 400 unit vial was $1,580. Almost half of the global sales of Cerezyme are in the US. Genzyme has reached 3,600 out of 5,000-10,000 patients with Gaucher's Disease (Rader, 2003).

3.2. A Cerezyme market

Genzyme is currently the only provider of a treatment for Gaucher's disease in the US. There is another product that is approved in Europe, Zavesca which is produced by Oxford Glycosciences plc., but it is used for patients with mild to moderate disease for which Cerezyme is unsuitable (Rader, 2003). The Cerezyme patent expired in 2001 but its manufacturing method is patented until 2011 and its composition until 2013 (Genzyme Corp., 2003). The market for Gaucher's disease treatment has always been a lucrative market, and other companies have tried to develop effective treatments but so far with unsuccessful results. Vevesca, an alternative Gauscher's disease treatment by Oxford Glycosciences went through all clinical trials and showed promising results but failed to gain approval in the US and Europe because 11 percent of the patients developed nervous system disease. Thus, Genzyme maintained substantial market power.

[19] An enzyme unit (U) is defined as the amount of enzyme that catalyzes the hydrolysis of 1 micromole of a specific synthetic substrate per minute at 37°C.

Genzyme's behavior in the Cerezyme market appears to be very close to a perfect monopoly. Ceredase, the other (human-derived) glucocerebrosidase product from Genzyme is being disrupted (patients switched to Cerezyme) (Rader, 2003). Furthermore, as mentioned above, Cerezyme is found to be slightly more effective in treating the disease and sales of Ceredase are very small compared to the sales of Cerezyme. The current situation suggests that the company can act as a monopoly in the Cerezyme market and charge its profit-maximizing price. The price of Cerezyme has not changed during the last ten years and that might be an indication of a monopoly pricing behavior by Genzyme.

3.3 The Model

An ex-ante analysis is applied in this study since the Glucocerebrosidase Enzyme from transgenic tobacco is not currently in the market. Studies on the benefits of technology improvements in agriculture generally assume perfect competition with the innovation being made available to all the firms in the market. Pharmaceutical industry however is usually characterized by market power where profit opportunities encourage firms to spend billions of dollars in R & D. Consequently, IPR laws protect the products and firms can charge price mark ups to recover the capital spent on R & D.

The study assumes that Genzyme behaves as a perfect monopoly and all the surplus calculations from an ensuing unit cost reduction in Glucocerebrosidase Enzyme from transgenic tobacco will be derived under this assumption. Furthermore, it is assumed the biotechnology company that will bring Glucocerebrosidase Enzyme from transgenic tobacco in the market has enough production capacity to fulfill total world demand.

Economic surplus analysis for the Cerezyme market also assumes linear supply and demand functions, which will be derived from information on prices, quantities and price elasticities of demand and supply for Cerezyme.

Under these assumptions the demand for Cerezyme in quantity dependent form may be stated as

$Q_d = \gamma - \delta P$ (1)

Supply of Cerezyme in quantity dependent form may be stated as

$Q_s = \alpha + \beta P$ (2)

Price elasticity of demand is

$$i = \left[\frac{\partial Q}{\partial P} * \frac{P}{Q}\right] \Rightarrow \delta = \frac{\varepsilon Q}{P} \quad (3)$$

Under the linear demand assumption, the slope of the demand function is found by substituting the value of *i,* ${}^{c}P^{0}$ (initial price), and ${}^{c}Q^{0}$ (initial quantity) in equation (3). The intercept of the demand function is found by substituting the slope, and initial price and quantity into equation (1).

The end result is the linear demand function which can be written in price dependent form as

$$P = \frac{\gamma}{\delta} - \frac{1}{\delta} Q \quad (4)$$

The marginal revenue curve is

$$MR = \frac{\gamma}{\delta} - \frac{2}{\delta} Q \quad (5)$$

Linear functional form of supply is found following the same procedure. Supply of Cerezyme in price dependent form is

$$P = \frac{\alpha}{\beta} + \frac{1}{\beta} Q \quad (6)$$

Several studies including Alston, Norton and Pardey (1995) have examined the errors due to assumptions on elasticities and functional forms of supply and demand for modeling the size and distribution of research benefits. They state that 'in relation to total benefits, functional forms and elasticities are relatively unimportant compared with the nature of the supply shift. On the other hand, the distribution of benefits is very sensitive to elasticity assumptions (Alston, Norton and Pardey, p.208, 1995). Concerns have also been expressed about inelastic linear supply functions, which when extrapolated back to the origin may result in a negative intercept (implying that positive quantities will be supplied at negative prices) (Alston, Norton and Pardey, 1995). Rose (1980) suggested that the negative intercept can be averted by kinking the supply curve. The economic surplus calculations after kinking the supply curve at the original quantity are the same as the surplus calculations without the kink, demonstrating that the use of an inelastic supply curve does not alter the results (Alston, Norton and Pardey, 1995). The nature of the supply shift has also been debated broadly. In the absence of information on the specific supply shift the suggestion is the use of a parallel shift (Alston, Norton and Pardey, 1995).

In this case the parallel outward supply shift is represented as

$$P = \left(\frac{\alpha}{\beta} + k\right) + \frac{1}{\beta}Q \quad (7)$$

Where k is the size of the unit cost reduction expressed as cost savings for each gram of Glucocerebrosidase Enzyme produced from CHO compared to one gram of Glucocerebrosidase Enzyme produced from transgenic tobacco.

For comparison a pivotal supply shift for the same unit is also employed and is represented as

$$P = \frac{\alpha}{\beta} + \left(\frac{1}{\beta} + k\right)Q \quad (8)$$

The Gaucher's disease case is slightly different from the HSA case, due to the existence of only one firm (Genzyme) in the current market, which acts as a perfect monopoly. The perfect monopoly assumption has an important implication that facilitates surplus calculations in the study. Being a perfect monopoly, the company charges a price mark-up above the marginal cost curve. The magnitude of the price mark-up can be found by Lerner's Rule and it is:

$$\frac{P - MC}{P} = \frac{1}{PED} \quad (9)$$

The price markup depends on the price elasticity of demand (PED) and the price charged by the monopoly. Information on the markup size is necessary to derive the linear functional forms of supply and demand curves.

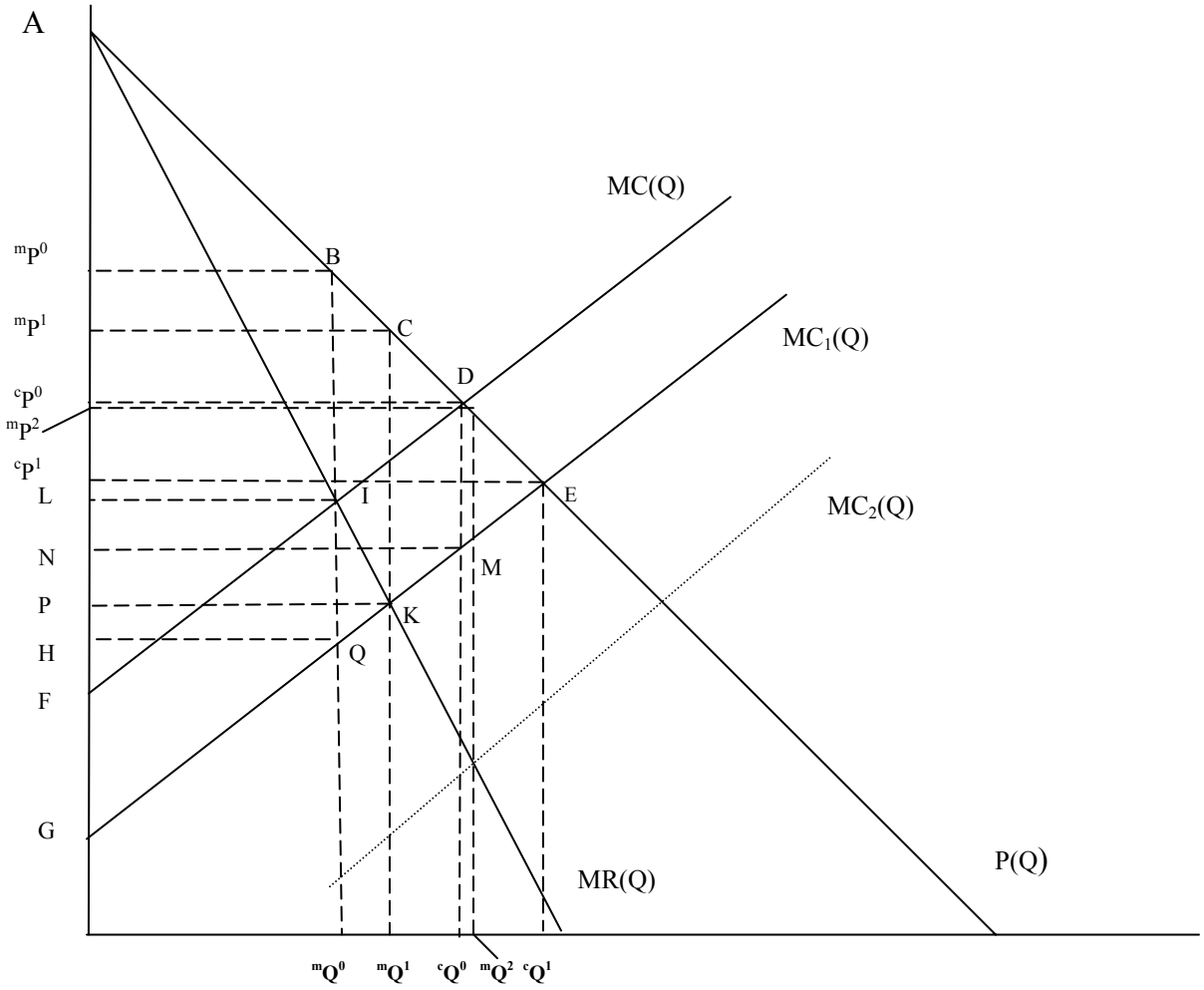
Figure 4 below illustrates Cerezyme's market. In the figure, MC(Q) represents the supply curve of Cerezyme, $MC_1(Q)$ represents the innovator's marginal cost curve as a parallel shift caused by a unit cost reduction. $MC_2(Q)$ again represents the innovator's marginal cost curve as a parallel shift caused by a larger unit cost reduction. This is done for illustrative purposes that are explained below. P(Q) is the demand for Cerezyme and MR(Q) is the marginal revenue curve. ${}^{m}P^{o}$ is the current monopoly price charged by Cerezyme and ${}^{m}Q^{o}$ is the quantity produced. ${}^{m}P^{1}$ is the monopoly price of the innovator if it decides to behave as a perfect monopoly and ${}^{m}Q^{1}$ is the quantity supplied at that price. ${}^{c}P^{o}$ and ${}^{c}Q^{0}$ represent the price and quantity of Cerezyme in a perfectly competitive market. ${}^{c}P^{1}$ and ${}^{c}Q^{1}$ represent the price and quantity after the entry of the innovator, if the market was perfectly competitive and all the firms in the market would have access to the technology used to produce Glucocerebrosidase Enzyme from transgenic tobacco.

Depending on the size of the unit cost reduction which causes the supply shift, the innovation may be non-drastic or drastic. If the innovation causes a relatively small shift in the supply curve ($MC_1(Q)$) the entrant cannot charge its profit maximizing price (${}^{m}P^{1}$) where its

$MR=MC_1$ because in that case the incumbent will reenter the market, price at ${}^{c}P^{0}$ and obtain all the market. Thus, the entrant prices slightly below ${}^{c}P^{0}$ and retains all the market as long as its price is lower than ${}^{c}P^{0}$. Therefore, the innovation will be non-drastic if the innovator cannot charge its profit maximizing price (${}^{m}P^{o}$) but charges a lower price instead. The biotechnology/pharmaceutical firm that will succeed in commercializing Glucocerebrosidase Enzyme from transgenic tobacco at a lower production cost will compete with Genzyme in the Cerezyme market. When the innovation is non-drastic, the entry of the innovator in the Cerezyme market results in a price limiting game. The innovator will price the product slightly under ${}^{m}P^{o}$ and obtain all the market. The incumbent will react by lowering the price slightly more than the innovator and obtain all the market. The price limit reactions will continue until the incumbent achieves a price equal to its marginal cost. From that point the incumbent cannot continue to lower its price because the outcome will be operating at a loss (since the innovator's marginal cost is lower than the incumbent's marginal cost). At the limit price, innovator faces an elastic demand because it gains the whole market with a small price decrease.

If the innovation causes a relatively large shift of the supply curve, the end result may be a drastic case. In figure 4, $MC_2(Q)$ represents the innovator's marginal cost curve but in this case the innovation has resulted in a larger shift. This is done for illustrative purposes to graphically indicate the case of a drastic innovation. For the Cerezyme market, the innovation will be drastic if the innovator's profit maximizing price is less than the price the incumbent would charge in a perfectly competitive market (${}^{m}P^{1} < {}^{c}P^{o}$ in figure 4). If the unit cost reduction from the innovation causes the supply curve to shift as far as $MC_2(Q)$, the innovator can charge the profit maximizing price (${}^{m}P^{2}$) where $MR=MC_2$ because ${}^{m}P^{2}$ is still lower than ${}^{c}P^{0}$ and the incumbent cannot reenter the market. At ${}^{m}P^{2}$ the quantity supplied will be ${}^{m}Q^{2}$.

Figure 4. Cerezyme market, non-drastic and drastic innovation (parallel shift)



A non-drastic innovation causing a parallel shift of the marginal cost curve results in the following surplus changes:

ΔTS = Trapezoid BDMQ + trapezoid FIQH + triangle FQG

$$\Delta TS = 0.5[(^mP^0 - H) + (^cP^0 - N)]\ (^cQ^0 - {}^mQ^0) + 0.5[(L-H) + (F-H)]\ {}^mQ^0 + 0.5(F-G)\ {}^mQ^0$$

$$\Delta CS = \text{triangle } AD^cP^0 - \text{triangle } AB^mP^0 = 0.5(A - {}^cP^0)\ {}^cQ^0 - 0.5\ (A - {}^mP^0)\ {}^mQ^0$$

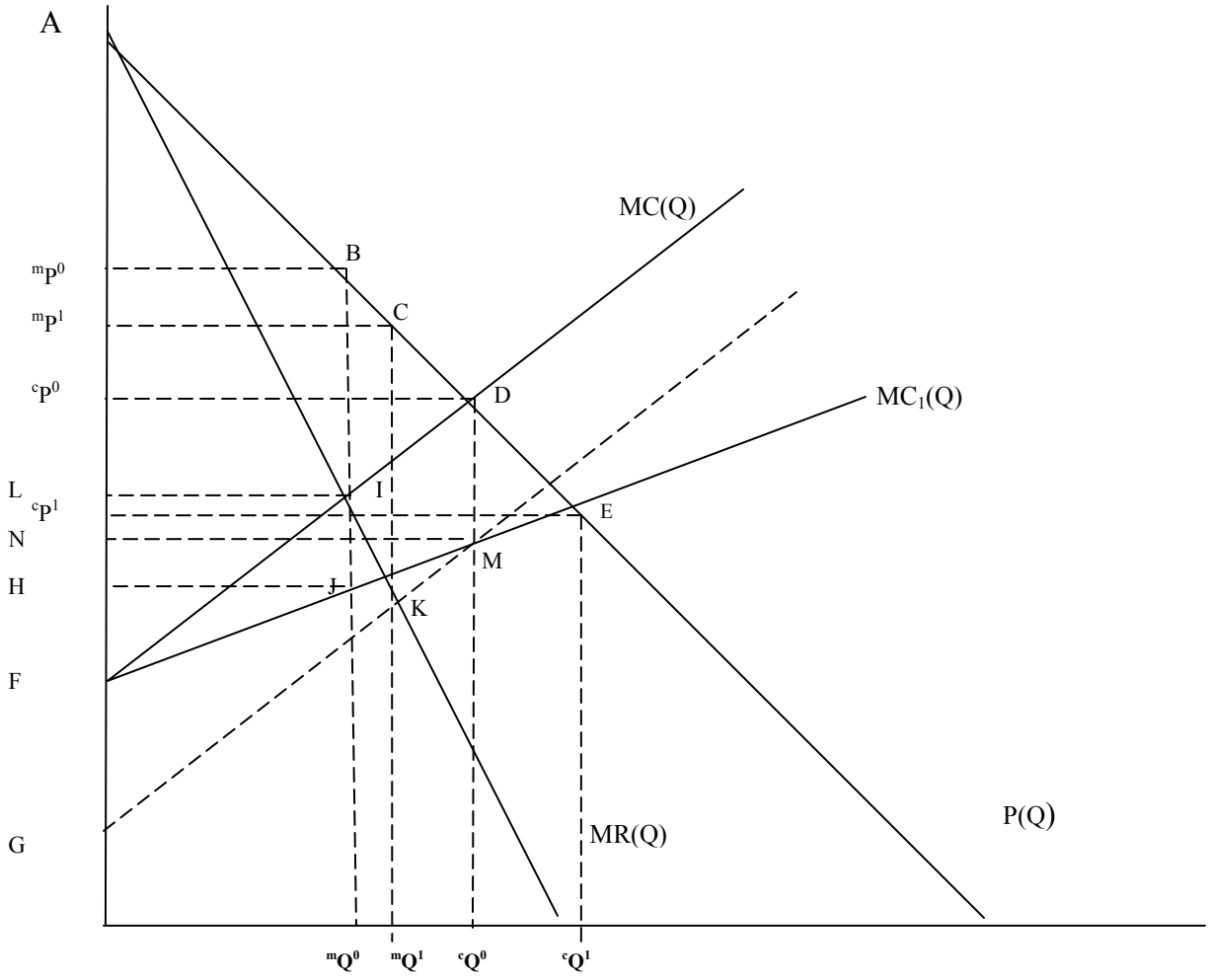
ΔPS = triangle LIF – Triangle FQG

Profits = rectangle ${}^{c}P^{0}DMN = ({}^{c}P^{0} - N)\ {}^{c}Q^{0}$

DWL = triangle DME = $0.5\ ({}^{c}P^{0} - N)\ ({}^{c}Q^{1} - {}^{c}Q^{0})$

For comparative purposes, a pivotal shift for the same unit cost reduction is illustrated in figure 5. A parallel shift is also illustrated as a dotted line to facilitate any comparison between the surplus changes for each case.

Figure 5. Cerezyme market (pivotal shift)



A pivotal shift of the marginal cost curve for a non-drastic innovation results in the following surplus changes:

ΔTS = Trapezoid BDMJ+ triangle FIJ

$\Delta TS = 0.5[(^{m}P^{0} - H) + (^{c}P^{0} - N)](\ ^{c}Q^{0} - {}^{m}Q^{0}) + 0.5(L-H)\ ^{m}Q^{0}$

ΔCS = triangle $AD^{c}P^{0}$ – triangle $AB^{m}P^{0} = 0.5(A - {}^{c}P^{0})\ ^{c}Q^{0} - 0.5\ (A - {}^{m}P^{0})\ ^{m}Q^{0}$

ΔPS = Triangle NMF - triangle LIF = $0.5(N-F)\ ^{c}Q^{0} - 0.5(L-F)\ ^{m}Q^{0}$

Profits = rectangle $^{c}P^{0}DMN = (^{c}P^{0} - N)\ ^{c}Q^{0}$

DWL = triangle DME = 0.5 ($^{c}P^{0}$ - N) ($^{c}Q^{1}$- $^{c}Q^{0}$)

Both a parallel and a pivotal supply shift in this case result in consumer surplus changes. In the case of Gaucher's disease, the innovation is non-drastic innovation and formulas for surplus changes in case of a drastic innovation are not presented in this study. However, the formulas to calculate surplus changes for a drastic innovation can be derived following the same methodology used for non-drastic innovation.

3.4 Protein Production Process and Model Data

Comparison of unit cost of Glucocerebrosidase Enzyme from CHO and Glucocerebrosidase Enzyme from transgenic tobacco provide a typical example of the relative costs of cell culture and transgenic plants as systems for protein production. Production of proteins from transgenic plants is similar to the production of proteins from bioreactors using cell cultures. The later is a well-established method of protein production in the biotechnology/pharmaceutical industry. The process of protein production from cells consists of two parts, upstream and downstream processing. During upstream processing the proteins are produced in genetically engineered cells that express the desired proteins. Downstream processing isolates and purifies the proteins.

Upstream cell culture processing methods use bioreactors and suspension cells. Bioreactors are large containers made of stainless steel, glass or plastic and suspension cells are grown in them (Wallman, 1997). These cells are genetically engineered to express the human proteins and they produce numerous copies of themselves in bioreactors. When the cells in bioreactors reproduce enough copies and reach maturity, they are removed from the bioreactors and they undergo centrifugation and/or filtration to separate the cells from the media (Wallman,

1997). Centrifugation and filtration can be considered as parts of upstream processing. So far, bacterial, animal and fungal cells are grown in bioreactors.

Transgenic plants aim to replace the upstream process by containing the desired proteins in their cells. The economic advantage that transgenic plants can offer is that the expression of proteins in their cells requires less capital than building bioreactors for cell cultures and also the supply can be very flexible. In some cases, the demand for proteins coming from bioreactors can not fulfill the demand in the market. Such is the case of Enbrel^{R} a biotech drug manufactured by Immunex. The drug was produced in bioreactors but the company did not have enough production capacity in its facilities to meet the market demand in 2002 (Biotech.org, 2004). In order to increase production of a drug using cell cultures more production capacity is needed. That requires a considerable amount of investment (more than $50 million for a bioreactor plant) and time (at least 5 years). Using transgenic plants for protein production on the other hand is less expensive and production capacity can be extended by simply planting more acres.

Downstream process includes further filtration and purification using chromatography. Depending on where exactly in the cell the protein is stored, different separation and purification methods are used and the degree of difficulty among them can vary. If the protein is stored in some storage space inside the cell such as a vesicle, granule or vacuole, then it is more difficult to isolate and purify them (Wallman, 1997). This is the case with proteins expressed in the nucleus of transgenic plants. Proteins may also be in a secreted form in the extra cellular environment and in this case it is easier to isolate and purify them (Wallman, 1997). The main step during purification is chromatography[20] and it is also the most expensive one. As Millan et al. (2003) note, traditional purification of pharmaceuticals using chromatography accounts for 30% of the production costs (Millan et al., 2003). In general, the downstream process of

[20] Several steps of physical methods to precisely separate complex mixtures (see Bungay, 1993).

purifying proteins from bioreactors and cell cultures and purifying proteins from transgenic plants will basically be the same. Minor differences in the process come as a result of the storage place of protein in the cell and also the actual form of the protein. Transgenic plant systems production costs are greatly influenced by expression levels and protein recovery.

Glucocerebrosidase Enzyme was successfully produced in transgenic tobacco by CropTech (Blacksburg, VA) and it was enzymatically active (Cramer et al., 1999). CropTech, however did not manage to continue research and enter clinical trials because it went out of business in 2003, after facing financial difficulties. Crop Tech's estimates indicated that 1 mg of crude Glucocerebrosidase Enzyme can be produced from 1 g of fresh weight of tobacco leaf tissue (Cramer et al, 1999). Assuming a 40 percent recovery in order to achieve a pure product, and 40 metric tons of tobacco per acre (based on multiple cuttings), less than an acre of transgenic tobacco will be sufficient to produce the amount of the Glucocerebrosidase Enzyme that Genzyme is producing.

3.4. A Unit Cost Reductions

To date there are a limited number of publications that have conducted economic analysis on the production of therapeutic proteins from transgenic plants largely because there is no drug of transgenic plant origin in the market yet. Second, there is not enough capacity for large scale processing of transgenic plants to generate accurate data on the economic benefits of bio-pharming. Nevertheless, sound scientific techniques have been used to estimate production costs of proteins from transgenic plants. Kusnadi, Howard, and Nikolov (1997) followed by Evangelista et al. (1998) were the first to calculate large scale production costs of proteins from transgenic plants and compared them to cell culture systems. Other studies followed, with Misson and Curling (2000) conducting a thorough examination of the production process by

breaking them down into the major different steps in the production system that had the most significant impact on production costs. Although there is a limited number of studies on large scale production costs of proteins from transgenic plants, the results have been similar and they lead to some important conclusions. It is generally accepted that when comparing cell culture systems with transgenic plants, the savings on the later are realized during the upstream process. Costs during the downstream process are similar because the same techniques are used. The unit cost reduction on the upstream process of transgenic plants is primarily due to capital cost savings. In transgenic plants, capital costs can be more than 95 percent lower than those in cell culture systems. Capital costs for cell culture systems can constitute 20 to 30 percent or more of protein production costs, but they depend on the size of the operation. For outputs of more than 10 tons of protein per year for example, production costs from transgenic plants compared to cell culture systems can be up to 10 times cheaper. For output levels of 50 kg/year unit cost reductions can range from 25 to 28 percent (Glacken, 2000) and 20 to 40 percent (Watler, 2002).

Genzyme's production of glucocerebrosidase is close to 6 kg per year. The downstream process most likely will use the same purification methods used during cell culture purification process. Since annual production of Glucocerebrosidase Enzyme is 6 kg per year, and the plant-derived product is not produced commercially, there is some uncertainty about the exact unit cost reduction. Being under the 50 kg/year range, the unit cost reductions simulated in this study will range from 5 percent up to 40 percent of the original production cost. The use of this range is based on the studies by Glacken (2000) and Watler (2002). The lower 5 percent unit cost reduction was considered because Glucocerebrosidase Enzyme from transgenic tobacco is smaller than the 50kg/year range and it accounts for any influence that this lower output level (6 kg/year versus 50 kg/year) may have on unit production costs.

3.4 B Market Data

Information on the elasticity of supply of Cerezyme or similar products could not be found in the literature. Nevertheless, considering that Genzyme is currently the only provider of a treatment for Gaucher's disease, information on prices and quantities for a period of time may help to shed some light on the nature of the supply curve. Cerezyme prices, quantities, and changes in price and quantity for the last five years are shown in table 3 below.

Table 3. Cerezyme Price and Quantity sold for the period 1999 -2003

Year	Sales of Cerezyme (millions)	Quantity of Cerezyme (number of 200 unit vials sold)	Percentage change in quantity	Price of Cerezyme ($/200 unit vial)	Percentage change in price
1999	479	647,297	-	740	0
2000	537	725,676	12	740	0
2001	570	770,270	6	740	0
2002	620	837,838	9	740	0
2003	734	991,892	18	740	0

-Prices represent the direct prices charged from the company for the 200 unit vial and sales of Cerezyme are the revenues of Genzyme for each year from charging the direct price.

As illustrated in the table, the quantity of Cerezyme produced has fluctuated extensively during this period, indicating that Genzyme has the necessary production capacity to meet demand. The direct price that Genzyme charges for Cerezyme has not changed for a period of ten years, from 1994 to 2004. This evidence suggests that the supply of Cerezyme is elastic and for the purpose of the study, the elasticity of supply will be considered to be in the range of 1.5 to 2.5.

Demand on the other hand seems to be inelastic since a very limited number of people are carriers of the Gaucher's disease and only a few persons are diagnosed each year. Regular Cerezyme treatment for patients that are already diagnosed can successfully control and reverse severe conditions from the disease (spleen and liver enlargement, bone disease, anemia). The analysis in this study assumes that Genzyme is a perfect monopoly in the Cerezyme market,

since Cerezyme provides more than half of the company's revenues and it is the backbone of every Genzyme's initiative in developing other products. Microeconomic theory suggests that a monopoly maximizing its profits will never operate in the inelastic portion of the demand curve, and if the monopoly assumption holds, then Genzyme has to operate in the elastic portion of the demand curve. The monopoly faces a linear demand curve, but with the entry of the innovator in the market, demand curve is no longer linear. The firms are going to compete in terms of prices and as described above, the innovator, having lower production costs will be able to offer a lower price slightly lower than ${}^{c}P^{0}$ in figure 4. At that point, demand actually facing the innovator is kinked and elastic at kink since the incumbent cannot follow any price decrease from that point. Consequently, elasticities of total demand between -1.001 and -1.5 will be considered in the surplus analysis, recognizing that the innovating firm actually faces a far more elastic demand at key price points.

The initial price (${}^{m}P^{0}$) of Cerezyme in the analysis was considered $740 per 200 unit vial since the price has not changed for the last decade. The initial quantity (${}^{m}Q^{0}$) was considered to be equal to the quantity for the year 2003 because the quantity has been constantly increasing and taking an average for a period of years would underestimate the ex-ante benefits of the transgenic product.

3.5 Results

Results from the analysis are shown in table 4 and table 5 below and in Appendix B. Dollar figures in these tables indicate surplus generated as a result of commercialization of Glucocerebrosidase Enzyme from transgenic tobacco during a one year period. Symbol i in the tables represents the price elasticity of demand, ε represents the price elasticity of supply, K is the unit cost reduction as a percentage of the initial Cerezyme price, DTS^{m} is the change in total

surplus, DPS is the change in producer surplus, DWL is deadweight loss due to imperfect competition and DCS is the change in consumer surplus.

The study considers a range of elasticities of supply and demand for the Gaucher's disease treatment, and table 4 and table 5 illustrate two of the scenarios, with the rest of scenarios presented in Appendix B. More specifically, table 4 contains the results when the elasticity of supply has a value of 2.0 and elasticity of demand has a value of -1.25. Table 5 indicates results for elasticity of supply of 2.0, and for elasticity of demand of -1.5. These combinations of elasticities are presented because the elasticity of supply (2.0) has the mean value of the range of elasticities chosen and also the mean (table 4) and the upper value (table 5) from the range of elasticities of demand. Hence, results in table 4 and table 5 can be thought of as the 'best' representatives from the nine scenarios that were conducted in the analysis.

Table 4. Benefits from a 5 percent to 40 percent unit cost reduction.

Results for ε = 2.0 and *i* = 1.25					
Parallel Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	69,320,911	348,649,800	753,937,738	906,136	-
10	138,641,821	399,621,058	753,937,738	3,624,545	-
15	207,962,732	487,290,044	753,937,738	8,155,226	-
20	277,492,172	575,224,335	753,937,738	14,519,994	-
25	346,614,484	662,643,730	753,937,738	22,654,704	-
30	415,935,394	750,314,293	753,937,738	32,622,462	-
35	485,256,305	837,984,857	753,937,738	44,402,492	-
40	554,577,216	925,655,421	753,937,738	57,994,795	-
Pivotal Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	69,320,911	312,909,953	753,937,738	1,050,294	59,581,762
10	138,641,821	328,141,364	753,937,738	4,332,458	24,921,307
15	207,962,732	343,372,776	753,937,738	10,062,476	(9,739,149)
20	N.A.	N.A.	N.A.	N.A.	N.A.
25	N.A.	N.A.	N.A.	N.A.	N.A.
30	N.A.	N.A.	N.A.	N.A.	N.A.
35	N.A.	N.A.	N.A.	N.A.	N.A.
40	N.A.	N.A.	N.A.	N.A.	N.A.

Table 5. Benefits from a 5 percent to 40 percent unit cost reduction.

Results for ε = 2.0 and *i* = 1.5					
Parallel Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	66,058,750	304,609,757	548,054,740	880,764	-
10	132,117,500	352,318,854	548,054,740	3,523,058	-
15	198,176,251	400,027,952	548,054,740	7,926,880	-
20	264,433,716	472,454,539	548,054,740	14,113,434	-
25	330,303,214	556,621,119	548,054,740	22,020,372	-
30	396,361,964	641,029,522	548,054,740	31,709,033	-
35	462,420,714	725,437,925	548,054,740	43,159,222	-
40	528,479,464	809,846,328	548,054,740	56,370,941	-
Pivotal Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	66,058,750	269,541,532	548,054,740	1,138,919	103,984,310
10	132,117,500	282,182,404	548,054,740	4,718,374	70,954,935
15	198,176,251	294,823,275	548,054,740	11,009,529	37,925,560
20	264,433,716	307,502,173	548,054,740	20,358,203	4,796,827
25	330,303,214	320,106,830	548,054,740	33,030,605	(28,137,922)
30	N.A.	N.A.	N.A.	N.A.	N.A.
35	N.A.	N.A.	N.A.	N.A.	N.A.
40	N.A.	N.A.	N.A.	N.A.	N.A.

- Except for K which is a percentage, results are reported in dollars.

In table 4, with ε equal to 2.0 and *i* equal to -1.25, the change in total surplus from a parallel supply shift ranges from $349 million for a unit cost reduction of 5 percent to $926 million for unit a cost reduction of 40 percent. Profits for the same range of unit cost reduction vary even more widely from $69 million to $555 million. Deadweight losses for a parallel shift vary between $906 thousand for a unit cost reduction of 5 percent and $58 million for a unit cost reduction of 40 percent. The change in consumer surplus is $754 million, and it is the same for both types of supply shifts. Consumer surplus does not change across the range of unit cost reductions employed. Profits in the tables represent the profits of the entrant. Incumbent losses are not shown but they are incorporated into the calculation of change in total surplus. A pivotal shift, for the range of elasticities of demand and supply and for the range of unit cost reductions considered in this study, in some cases results in a downward sloping supply curve. Surplus changes in those cases are reported as not available (N.A.) in the tables because a downward

sloping supply curve contradicts microeconomic theory of an upward sloping supply curve. Unit cost reductions from a pivotal shift result in smaller total surplus changes when compared to a parallel shift. For example, a 5 percent unit cost reduction generates a total change of $313 million with a pivotal shift versus $349 million for a 5 percent unit cost reduction with a parallel shift. Profits however remain unchanged in the case of a pivotal shift. Deadweight loss is slightly larger for a pivotal shift as compared to a parallel shift. For a 5 percent unit cost reduction the deadweight loss for a pivotal shift is $1 million versus $900 thousand for a parallel shift caused by a 5 percent unit cost reduction.

In table 5, ε has the same value (2.0) as in table 4, and *i* is equal to -1.5. The change in total surplus for a parallel supply shift varies between $305 million for a unit cost reduction of 5 percent to $810 million for a unit cost reduction of 40 percent. Profits range from $66 million to $528 million for unit cost reductions of 5 and 40 percent, respectively. The change in consumer surplus is $548 million and it remains constant across the range of unit cost reductions. Deadweight loss for a parallel supply shift ranges from $880 thousand for a unit cost reduction of 5 percent to $56 million for a unit cost reduction of 40 percent. Unit cost reductions of 5 percent to 40 percent for a pivotal shift result in smaller total surplus changes when compared to total surplus changes for a parallel shift. The change in total surplus for a unit cost reduction of 5 percent is $269 million for a pivotal shift versus $305 million for a parallel shift of the same unit cost reduction. Profits generated by a pivotal shift are the same as in the case of a parallel shift. Deadweight loss is slightly larger than in the case of a parallel shift. For a unit cost reduction of 5 percent, a pivotal shift produces $1million of deadweight loss, while a parallel shift results in $880 thousand of deadweight loss for a unit cost reduction of 5 percent.

As mentioned above, three values of price elasticity of supply (ε) ranging from 1.5 to 2.5 and three values of price elasticity of demand (*i)* ranging from -1.001 to -1.5 were considered to conduct a total of nine scenarios in the analysis . Results from the other seven scenarios are shown in Appendix B. The change in total surplus caused by a parallel shift for the seven scenarios ranges from $302 million to $1 billion for unit cost reductions of 5 percent and 40 percent, respectively. The change in consumer surplus for a parallel shift varies between $505 million for a unit cost reduction of 5 percent and $1 billion for a unit cost reduction of 40 percent. Profits vary from $64 million for a unit cost reduction of 5 percent million to $587 million for a unit cost reduction of 40 percent. Profits within the same table are the same for both types of supply shifts. Deadweight loss due to imperfect competition for a parallel supply shift varies from $774 thousand to $61 million for unit cost reductions of 5 and 40 percent, respectively.

The changes in total surplus for pivotal supply shifts (for those reported) vary from $266 million for a unit cost reduction of 5 percent to $358 million for a unit cost reduction of 20 percent (when $\varepsilon = 1.5$ and $i = 1.25$). Within each table, total surplus changes generated from a pivotal shift are smaller than surplus changes generated from a parallel supply shift for equivalent unit cost reductions. The positive change in producer surplus (for those reported) within each table is greater for a unit cost reduction of 5 percent and then, decreases until it becomes negative as the range of the unit cost reduction increases. A pivotal shift results in negative producer surplus as the unit cost reduction increases because the innovator receives part of the initial producer surplus in form of profits. The changes in consumer surplus and the profits caused by a pivotal supply shift are the same as those caused by a parallel shift within each table. As expected, deadweight losses for pivotal supply shifts are larger than deadweight losses caused

by parallel shifts for the same value of unit cost reductions within each table. For example, when $\varepsilon = 2.5$ and $i = 1.25$ (Appendix B), a pivotal shift caused by a unit cost reduction of 5 percent generates a deadweight loss of $1million versus a deadweight loss of $900 thousand generated by a parallel supply shift caused by a unit cost reduction of 5 percent.

Deadweight loss increases as supply and demand become more elastic[21]. The innovator's profits and the change in consumer surplus decrease as the elasticity of demand increases[22] and they increase as supply becomes more elastic[23]. Based on the data used in the study the innovation is non-drastic and the innovator cannot charge the profit-maximizing price[24].

Similar studies on the benefits of pharmaceuticals from transgenic tobacco for a one-year period have also found considerable benefits. Production of HSA from transgenic tobacco is comparable to the present study and results showed total annual surplus changes as large as $82 million. Production of Glucocerebrosidase Enzyme from transgenic tobacco generates greater surplus (from $302 million to $1 billion) but that is mainly because the market for HSA is competitive and the current Cerezyme market is very close to a perfect monopoly[25]. Another reason Glucocerebrosidase Enzyme generates greater total surplus changes is that production of GM HSA from transgenic tobacco was considered only for the US market, while the present study considers the world market for Cerezyme. The range of demand elasticities considered in the GM HSA case varies from -1.07 to -2.97 and elasticity of supply has a value of 0.5. In the present study elasticity of supply varies from 1.5 to 2.5 and elasticity of demand ranges from -

[21] Having linear supply and demand function, the area representing deadweight loss (area of triangle DME in figure 4) increases as demand and supply become flatter and decreases as demand and supply become steeper.
[22] Supply elasticity is kept constant.
[23] Demand elasticity is kept constant.
[24] The range of elasticities and unit cost reductions employed in this study do not result in any cases where the innovator's profit maximizing price ($^{m}P^{1}$ in figure 4) is greater than the price ($^{c}P^{o}$ in figure 4) that Genzyme would charge in a perfectly competitive market.
[25] The innovator will introduce some competition in the market, forcing the monopoly to reduce its profit maximizing price.

1.001 to -1.5. So, both studies employed similar demand elasticities in the elastic range. Supply on the other hand is inelastic for GM HSA and it is elastic for Cerezyme. Different combinations of demand and supply elasticity in the GM HSA case produced the same total surplus change[26]. The choice of elasticities in the GM HSA case affected slightly the value of the deadweight loss (increasing as the elasticity of demand increased). In the present study, however, total surplus changes among the nine different combinations of elasticities of supply and demand were substantial. This is mainly because the current Cerezyme market is served by one firm which acts as a monopoly. For a total of nine scenarios conducted in the analysis, total surplus generated from a 5 percent unit cost reduction and a parallel supply shift had a minimum value of $301 million (when $\varepsilon = 2.5$ and $i = 1.5$) and a maximum value of $458 million (when $\varepsilon = 2.5$ and $i = 1.001$). Total surplus generated by a parallel supply shift and a unit cost reduction of 5 percent had a minimum value of $266 million (when $\varepsilon = 2.5$ and $i = 1.5$) and a maximum value of $315 million (when $\varepsilon = 1.5$ and $i = 1.25$). Therefore, results are sensitive to the choice of supply and demand elasticities employed when the existing market is a monopoly.

Even when compared to other studies on the benefits of adopting biotechnology innovations in agriculture, production of Glucocerebrosidase Enzyme from transgenic tobacco stands to generate significant benefits. Falck-Zepeda, Traxler and Nelson (2000) measured the benefits from the introduction of Bt cotton in the United States in 1996. For the first year of Bt cotton adoption in the US the average world gains were $240 million with 59 percent of the total going to US farmers and 9 percent to the US consumers. Hareau et al., (2004) estimated ex- ante potential annual benefits from the adoption of Bt rice, drought resistance rice and herbicide resistant rice in Asia. The total annual gains of the three technologies were $ 6.97 billion. Qaim

[26] Total surplus did not change because the current blood plasma HSA market is competitive and the unit cost reductions result in the same profits and total surplus changes.

(2003) estimated ex-ante benefits of Bt cotton adoption in India which was approved for commercial cultivation in 2002. The study projected total surplus benefits of $315 million in 2005 with farmers receiving 67 percent of the total gains and the rest (33 percent) going to private companies. The present study on the benefits generated from 'total adoption' of the Glucocerebrosidase Enzyme from transgenic tobacco results in no gains to farmers since 1 acre of transgenic tobacco can provide enough Glucocerebrosidase Enzyme to fulfill the total world demand. The main beneficiaries from the use of transgenic tobacco as a vehicle for Glucocerebrosidase Enzyme production will be consumers followed by the biotech/pharmaceutical company that will introduce the patented product in the market.

3.6 Conclusions

An ex-ante imperfect competition model was employed to assess the size and distribution of benefits coming from the use transgenic plants as a source of therapeutic protein production. The case study was the production of Glucocerebrosidase Enzyme from transgenic tobacco. The results indicate that significant surplus gains can be generated compared to the current production method of Glucocerebrosidase Enzyme using cell culture systems.

Interestingly, despite concerns over the market power of biotech/pharmaceutical firms under such innovations, the main beneficiaries from the innovation are the consumers. This outcome is due to the introduction of competition in the Cerezyme market which is currently served by one firm. The innovating firm also obtains significant amount of profits. Recalling that results indicate annual profits, the size of the gains appears sufficient to spur large R & D efforts among biotech/pharmaceutical firms. The size of the total surplus gains depends on the elasiticities of demand and supply for the Gaucher's disease treatment. Although

Glucocerebrosidase Enzyme will be produced in transgenic tobacco, the acreage involved in the production of this particular protein is very small (1 acre) and will not result in any benefits to tobacco farmers[27]. Policy makers need to seek alternative ways to increase the revenues of tobacco farmers whose tobacco planted acreage has been shrinking during the last decade.

Total surplus changes for the range of unit cost reductions (from 5 to 40 percent) employed in this study, generated significant surplus gains that are comparable to the benefits of biotechnology applications that realize considerable unit cost reductions in the production of agricultural crops.

Glucocerebrosidase Enzyme is just one of the hundreds of therapeutic proteins that are being developed from the biotech companies. Studies on more products are needed in order to shed some light on the potential of bio-pharming as a source of cheaper drugs and possible benefits to farmers from this alternative use of agricultural crops. Results are crucial for the development of a cost effective process for testing, approving, and monitoring product development.

The current regulatory power on the production of pharmaceuticals from transgenic plants is divided among different governmental agencies (USDA, APHIS, and EPA) and regulations on plant-made pharmaceuticals are subject to periodic changes. Given the size and distribution of benefits policy makers should construct a more streamline regulatory process that will be more effective in materializing these potential benefits of bio-pharming.

[27] The study assumes that transgenic tobacco will be contracted at marginal cost.

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Appendix A

Table A1. Economic surplus generated from a $0.1 to $1.0 unit cost reduction.

η=0.25

Parallel Supply Shift								Pivotal Supply Shift					
				ε=1.07	ε=2.02	ε=2.97				ε=1.07	ε=2.02	ε=2.97	
k	K (% P)	Profits	DTSm	DWL	DWL	DWL	DPS	Profits	DTSm	DWL	DWL	DWL	DPS
0.1	4	8,235	8,235	32	35	36	-	8,235	4,117	4,149	4,152	4,154	(4,117)
0.15	6	12,352	12,352	71	78	81	-	12,352	6,176	6,248	6,255	6,258	(6,176)
0.2	8	16,469	16,469	127	139	144	-	16,469	8,235	8,363	8,376	8,382	(8,235)
0.25	10	20,587	20,587	198	218	226	-	20,587	10,293	10,495	10,516	10,524	(10,293)
0.3	11	24,704	24,704	286	313	325	-	24,704	12,352	12,644	12,674	12,686	(12,352)
0.35	13	28,821	28,821	389	427	442	-	28,821	14,411	14,810	14,850	14,867	(14,411)
0.4	15	32,938	32,938	508	557	578	-	32,938	16,469	16,993	17,046	17,068	(16,469)
0.45	17	37,056	37,056	642	705	731	-	37,056	18,528	19,193	19,261	19,289	(18,528)
0.5	19	41,173	41,173	793	871	902	-	41,173	20,587	21,411	21,496	21,530	(20,587)
0.55	21	45,290	45,290	960	1,054	1,092	-	45,290	22,645	23,647	23,750	23,792	(22,645)
0.6	23	49,408	49,408	1,142	1,254	1,300	-	49,408	24,704	25,901	26,025	26,076	(24,704)
0.65	25	53,525	53,525	1,340	1,471	1,525	-	53,525	26,762	28,174	28,320	28,380	(26,762)
0.7	27	57,642	57,642	1,555	1,707	1,769	-	57,642	28,821	30,464	30,635	30,706	(28,821)
0.75	29	61,760	61,760	1,785	1,959	2,031	-	61,760	30,880	32,774	32,971	33,053	(30,880)
0.8	30	65,877	65,877	2,030	2,229	2,310	-	65,877	32,938	35,102	35,329	35,423	(32,938)
0.85	32	69,994	69,994	2,292	2,516	2,608	-	69,994	34,997	37,450	37,708	37,815	(34,997)
0.9	34	74,111	*74,283*	2,570	2,821	2,924	*86*	74,111	*37,149*	39,817	40,109	40,230	(37,056)
0.95	36	78,229	*78,997*	2,863	3,143	3,258	*384*	78,229	*39,530*	42,204	42,532	42,668	(39,114)
1	38	82,346	*83,710*	3,173	3,483	3,610	*682*	82,346	*41,196*	44,610	44,978	45,130	(41,173)

η - Elasticity of supply

Table A2. Economic surplus generated from a $0.1 to $1.0 unit cost reduction.

η=0.75

Parallel Supply Shift								Pivotal Supply Shift					
				ε=1.07	ε=2.02	ε=2.97				ε=1.07	ε=2.02	ε=2.97	
k ($)	K (% P)	Profits	DTSm	DWL	DWL	DWL	DPS	Profits	DTSm	DWL	DWL	DWL	DPS
0.1	4	8,235	8,235	69	86	94	-	8,235	4,117	4,188	4,205	4,213	(4,117)
0.15	6	12,352	12,352	155	193	211	-	12,352	6,176	6,335	6,375	6,394	(6,176)
0.2	8	16,469	16,469	276	342	375	-	16,469	8,235	8,520	8,592	8,627	(8,235)
0.25	10	20,587	20,587	431	535	586	-	20,587	10,293	10,744	10,858	10,914	(10,293)
0.3	11	24,704	24,704	621	771	844	-	24,704	12,352	13,006	13,174	13,257	(12,352)
0.35	13	28,821	28,821	846	1,049	1,148	-	28,821	14,411	15,309	15,542	15,658	(14,411)
0.4	15	32,938	32,938	1,104	1,370	1,500	-	32,938	16,469	17,653	17,963	18,119	(16,469)
0.45	17	37,056	37,056	1,398	1,734	1,898	-	37,056	18,528	20,040	20,441	20,643	(18,528)
0.5	19	41,173	41,173	1,726	2,141	2,344	-	41,173	20,587	22,470	22,975	23,231	(20,587)
0.55	21	45,290	45,290	2,088	2,590	2,836	-	45,290	22,645	24,945	25,570	25,887	(22,645)
0.6	23	49,408	49,408	2,485	3,082	3,375	-	49,408	24,704	27,467	28,226	28,612	(24,704)
0.65	25	53,525	53,525	2,916	3,618	3,961	-	53,525	26,762	30,036	30,945	31,411	(26,762)
0.7	27	57,642	57,642	3,382	4,196	4,593	-	57,642	28,821	32,653	33,731	34,285	(28,821)
0.75	29	61,760	61,760	3,883	4,816	5,273	-	61,760	30,880	35,321	36,586	37,239	(30,880)
0.8	30	65,877	65,877	4,418	5,480	5,999	-	65,877	32,938	38,041	39,512	40,274	(32,938)
0.85	32	69,994	69,994	4,987	6,186	6,773	-	69,994	34,997	40,813	42,512	43,395	(34,997)
0.9	34	74,111	*74,511*	5,591	6,935	7,593	*200*	74,111	*37,298*	43,641	45,588	46,606	(37,056)
0.95	36	78,229	*80,021*	6,230	7,727	8,460	*896*	78,229	*40,209*	46,524	48,744	49,909	(39,114)
1	38	82,346	*85,544*	6,903	8,562	9,374	*1,599*	82,346	*43,151*	49,466	51,983	53,311	(41,173)

η - Elasticity of supply

Table A3. Economic surplus generated from a $0.1 to $1.0 unit cost reduction.

η=1.00

Parallel Supply Shift								Pivotal Supply Shift					
				ε=1.07	ε=2.02	ε=2.97				ε=1.07	ε=2.02	ε=2.97	
k ($)	K (% P)	Profits	DTSm	DWL	DWL	DWL	DPS	Profits	DTSm	DWL	DWL	DWL	DPS
0.1	4	8,235	8,235	81	105	117	-	8,235	4,117	4,200	4,225	4,238	(4,117)
0.15	6	12,352	12,352	182	236	264	-	12,352	6,176	6,364	6,421	6,451	(6,176)
0.2	8	16,469	16,469	324	419	468	-	16,469	8,235	8,572	8,676	8,731	(8,235)
0.25	10	20,587	20,587	506	654	732	-	20,587	10,293	10,825	10,992	11,081	(10,293)
0.3	11	24,704	24,704	728	942	1,054	-	24,704	12,352	13,126	13,372	13,504	(12,352)
0.35	13	28,821	28,821	991	1,283	1,435	-	28,821	14,411	15,475	15,819	16,004	(14,411)
0.4	15	32,938	32,938	1,295	1,675	1,874	-	32,938	16,469	17,874	18,334	18,584	(16,469)
0.45	17	37,056	37,056	1,639	2,120	2,372	-	37,056	18,528	20,326	20,922	21,248	(18,528)
0.5	19	41,173	41,173	2,023	2,618	2,928	-	41,173	20,587	22,830	23,586	24,000	(20,587)
0.55	21	45,290	45,290	2,448	3,168	3,543	-	45,290	22,645	25,390	26,328	26,845	(22,645)
0.6	23	49,408	49,408	2,913	3,770	4,216	-	49,408	24,704	28,006	29,152	29,788	(24,704)
0.65	25	53,525	53,525	3,419	4,424	4,948	-	53,525	26,762	30,682	32,063	32,833	(26,762)
0.7	27	57,642	57,642	3,965	5,131	5,739	-	57,642	28,821	33,419	35,063	35,987	(28,821)
0.75	29	61,760	61,760	4,552	5,890	6,588	-	61,760	30,880	36,219	38,158	39,254	(30,880)
0.8	30	65,877	65,877	5,179	6,702	7,496	-	65,877	32,938	39,084	41,352	42,642	(32,938)
0.85	32	69,994	69,994	5,847	7,566	8,462	-	69,994	34,997	42,016	44,649	46,157	(34,997)
0.9	34	74,111	*74,591*	6,555	8,482	9,487	*240*	74,111	*37,359*	45,019	48,055	49,807	(37,056)
0.95	36	78,229	*80,381*	7,303	9,450	10,570	*1,076*	78,229	*40,489*	48,094	51,575	53,598	(39,114)
1	38	82,346	*86,188*	8,092	10,471	11,712	*1,921*	82,346	*43,669*	51,245	55,216	57,541	(41,173)

η - Elasticity of supply

Appendix B

Table B1.

Results for ε = 1.5 and *i* = 1.001					
Parallel Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	73,374,161	457,869,439	1,098,926,047	917,157	-
10	146,748,323	549,593,254	1,098,926,047	3,668,628	-
15	220,122,484	641,317,068	1,098,926,047	8,254,414	-
20	293,717,367	733,316,803	1,098,926,047	14,696,594	-
25	366,881,318	824,777,836	1,098,926,047	22,930,241	-
30	440,255,479	916,501,650	1,098,926,047	33,019,232	-
35	513,629,641	1,008,225,464	1,098,926,047	44,942,538	-
40	587,003,802	1,099,949,278	1,098,926,047	58,700,157	-
Pivotal Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	N.A.	N.A.	N.A.	N.A.	N.A.
10	N.A.	N.A.	N.A.	N.A.	N.A.
15	N.A.	N.A.	N.A.	N.A.	N.A.
20	N.A.	N.A.	N.A.	N.A.	N.A.
25	N.A.	N.A.	N.A.	N.A.	N.A.
30	N.A.	N.A.	N.A.	N.A.	N.A.
35	N.A.	N.A.	N.A.	N.A.	N.A.
40	N.A.	N.A.	N.A.	N.A.	N.A.

Table B2.

Results for ε = 2.0 and *i* = 1.001					
Parallel Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	73,380,271	457,997,689	1,099,170,113	917,463	-
10	146,760,542	549,727,613	1,099,170,113	3,669,851	-
15	220,140,813	641,457,536	1,099,170,113	8,257,164	-
20	293,741,823	733,463,399	1,099,170,113	14,701,491	-
25	366,911,866	824,930,524	1,099,170,113	22,937,882	-
30	440,292,137	916,660,447	1,099,170,113	33,030,234	-
35	513,672,408	1,008,390,371	1,099,170,113	44,957,512	-
40	587,052,678	1,100,120,295	1,099,170,113	58,719,716	-
Pivotal Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	N.A.	N.A.	N.A.	N.A.	N.A.
10	N.A.	N.A.	N.A.	N.A.	N.A.
15	N.A.	N.A.	N.A.	N.A.	N.A.
20	N.A.	N.A.	N.A.	N.A.	N.A.
25	N.A.	N.A.	N.A.	N.A.	N.A.
30	N.A.	N.A.	N.A.	N.A.	N.A.
35	N.A.	N.A.	N.A.	N.A.	N.A.
40	N.A.	N.A.	N.A.	N.A.	N.A.

Table B3.

Results for ε = 2.5 and *i* = 1.001					
Parallel Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	73,383,937	458,074,650	1,099,316,602	917,646	-
10	146,767,875	549,808,240	1,099,316,602	3,670,585	-
15	220,151,812	641,541,830	1,099,316,602	8,258,815	-
20	293,756,501	733,551,370	1,099,316,602	14,704,430	-
25	366,930,199	825,022,151	1,099,316,602	22,942,468	-
30	440,314,137	916,755,742	1,099,316,602	33,036,838	-
35	513,698,074	1,008,489,332	1,099,316,602	44,966,501	-
40	587,082,012	1,100,222,922	1,099,316,602	58,731,455	-
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	N.A.	N.A.	N.A.	N.A.	N.A.
10	N.A.	N.A.	N.A.	N.A.	N.A.
15	N.A.	N.A.	N.A.	N.A.	N.A.
20	N.A.	N.A.	N.A.	N.A.	N.A.
25	N.A.	N.A.	N.A.	N.A.	N.A.
30	N.A.	N.A.	N.A.	N.A.	N.A.
35	N.A.	N.A.	N.A.	N.A.	N.A.
40	N.A.	N.A.	N.A.	N.A.	N.A.

Table B4.

Results for ε = 1.5 and *i* = 1.25					
Parallel Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	68,155,853	350,397,449	719,022,254	842,568	-
10	136,311,707	400,203,649	719,022,254	3,370,272	-
15	204,467,560	462,240,849	719,022,254	7,583,112	-
20	272,828,438	549,006,578	719,022,254	13,501,372	-
25	340,789,030	635,264,253	719,022,254	21,065,407	-
30	408,944,883	721,769,759	719,022,254	30,333,896	-
35	477,100,737	808,275,265	719,022,254	41,287,522	-
40	545,256,590	894,780,771	719,022,254	53,926,283	-
		Pivotal Supply Shift (Non-Drastic)			
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	68,155,853	314,908,010	719,022,254	1,012,193	85,759,116
10	136,311,707	329,224,772	719,022,254	4,172,712	51,681,189
15	204,467,560	343,541,534	719,022,254	9,685,078	17,603,262
20	272,828,438	357,901,364	719,022,254	17,807,854	(16,577,176)
25	N.A.	N.A.	N.A.	N.A.	N.A.
30	N.A.	N.A.	N.A.	N.A.	N.A.
35	N.A.	N.A.	N.A.	N.A.	N.A.
40	N.A.	N.A.	N.A.	N.A.	N.A.

Table B5.

Results for ε = 2.5 and *i* = 1.25					
Parallel Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	70,062,311	347,982,510	776,464,804	947,792	-
10	140,124,622	414,373,628	776,464,804	3,791,169	-
15	210,186,933	502,785,592	776,464,804	8,530,131	-
20	280,460,002	591,463,513	776,464,804	15,187,494	-
25	350,321,590	679,622,184	776,464,804	23,696,165	-
30	420,383,901	768,034,148	776,464,804	34,122,151	-
35	490,446,212	856,446,111	776,464,804	46,443,723	-
40	560,508,523	944,858,075	776,464,804	60,660,878	-
Pivotal Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	70,062,311	312,077,561	776,464,804	1,074,552	42,615,325
10	140,124,622	327,885,271	776,464,804	4,434,222	7,584,170
15	210,186,933	343,692,980	776,464,804	10,303,038	(27,446,986)
20	N.A.	N.A.	N.A.	N.A.	N.A.
25	N.A.	N.A.	N.A.	N.A.	N.A.
30	N.A.	N.A.	N.A.	N.A.	N.A.
35	N.A.	N.A.	N.A.	N.A.	N.A.
40	N.A.	N.A.	N.A.	N.A.	N.A.

Table B6.

Results for ε = 1.5 and *i* = 1.5					
Parallel Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	64,223,785	310,930,368	504,626,296	774,109	-
10	128,447,570	356,804,500	504,626,296	3,096,437	-
15	192,671,355	402,678,632	504,626,296	6,966,984	-
20	257,088,335	448,690,761	504,626,296	12,404,386	-
25	321,128,124	514,823,723	504,626,296	19,353,843	-
30	385,351,909	597,397,161	504,626,296	27,869,267	-
35	449,575,694	679,970,599	504,626,296	37,932,910	-
40	513,799,479	762,544,037	504,626,296	49,544,772	-
Pivotal Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	64,223,785	276,197,097	504,626,296	1,066,423	136,096,873
10	128,447,570	287,337,957	504,626,296	4,412,220	103,984,980
15	192,671,355	298,478,818	504,626,296	10,280,638	71,873,088
20	257,088,335	309,653,192	504,626,296	18,981,434	39,664,597
25	321,128,124	320,762,135	504,626,296	30,746,572	7,644,703
30	385,351,909	331,902,996	504,626,296	46,037,754	(24,467,189)
35	449,575,694	343,043,857	504,626,296	65,260,902	(56,579,082)
40	N.A.	N.A.	N.A.	N.A.	N.A.

Table B7.

Results for ε = 2.5 and *i* = 1.5					
Parallel Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	67,282,060	301,755,279	577,686,668	955,691	-
10	134,564,121	350,687,686	577,686,668	3,822,762	-
15	201,846,181	411,851,093	577,686,668	8,601,215	-
20	269,330,637	497,740,401	577,686,668	15,314,056	-
25	336,419,940	583,126,786	577,686,668	23,893,633	-
30	403,702,000	668,758,499	577,686,668	34,406,503	-
35	470,984,061	754,390,213	577,686,668	46,830,754	-
40	538,266,121	840,021,926	577,686,668	61,166,386	-
Pivotal Supply Shift (Non-Drastic)					
K (% of P)	**Profits**	**DTS^m**	**DCS**	**DWL**	**DPS**
5	67,282,060	266,446,098	577,686,668	1,187,304	81,896,303
10	134,564,121	280,069,326	577,686,668	4,922,964	48,255,273
15	201,846,181	293,692,553	577,686,668	11,497,292	14,614,243
20	269,330,637	307,356,761	577,686,668	21,280,933	(19,127,985)
25	N.A.	N.A.	N.A.	N.A.	N.A.
30	N.A.	N.A.	N.A.	N.A.	N.A.
35	N.A.	N.A.	N.A.	N.A.	N.A.
40	N.A.	N.A.	N.A.	N.A.	N.A.

VITA

Gentian Kostandini was born in Albania on June 19, 1979. His basic education was completed in Korca, Albania. In 1997 he was graduated from Preca High School. One year after high school Gentian attended Dimitris Perrotis College of Agricultural Studies in Thessaloniki, Greece and earned an Associate Degree in Agricultural Business Management.

He received a B.S. in Agricultural Business Management from the University of Arkansas in Fayetteville in 2002. Gentian joined the department of Agricultural and Applied Economics at Virginia Tech in the fall of 2002 and finished his M.S. in the fall of 2004. He stayed with the department for a Ph.D. and he is currently a Ph.D. candidate in Economics.