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Valuing Intellectual Property Rights in an Imperfectly Competitive Market: A Biopharming Application

Genti Kostandini and Bradford F. Mills

Small research firms developing biotechnology applications often focus on establishing intellectual property rights (IPRs), which can then be sold to more established firms with existing market channels. This paper presents a method for valuing the IPRs for an innovation that lowers product production costs below those associated with the patented process of a monopolist. The application to Glucocerebrosidase enzyme from transgenic tobacco suggests an IPRs value of about $1.75 billion. Despite the innovator's market power, significant surplus gains also accrue to consumers. Further, U.S. antitrust laws that prohibit IPRs acquisition by the current monopolist increase consumer welfare by almost 50%.

Key Words: biopharmaceuticals, biopharming, economic surplus, imperfect competition, intellectual property rights

JEL Classifications: D23, M13, D43, D60

Small research firms in the biopharmaceutical industry commonly strive to establish intellectual property rights (IPRs) on innovative technologies that can then be sold to larger firms with existing market channels. For example, in 2005, the value of the top 10 acquisitions and product alliances between large pharmaceutical companies and biotech firms was $15 billion (Zimm, 2007). In 2004 the large pharmaceutical company Pfizer paid $1.3 billion for Esperion Therapeutics, a small firm with a drug that boosts levels of "good" cholesterol (Alpert, 2004). In 2003, companies paid over $5 billion for six biotech firms (Alpert, 2004). In 2001 Amgen Inc., a large biotech company bought Immunex Corp. with its very successful drug Enbrel for about $16 billion (Gillis, 2002), while in 2000, a total of $2.7 billion was paid by pharmaceutical companies for seven biotech acquisitions.

Usually small biotech firms generate biopharming applications to produce lower cost drugs for markets that are currently served by just a few (or only one) firms with substantial market power. At the same time, the U.S. antitrust laws prohibit mergers and acquisitions if they substantially lessen competition or tend to create a monopoly (Clayton Act 1914).[1] The

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[1] Patent acquisition by an incumbent with market power would not need to be reported in the Federal Trade Commission under the Hart-Scott-Rodino Act of 1978, but still would be a violation of Section 7 of the Clayton Act if the patent were the major asset of the innovator and its acquisition reduced future competition.

acquisitions of Astra by Zeneca (1999) and of Marion Merrell Dow by Hoechst (1995) are examples of proposed mergers that potentially inhibited new competition and were blocked by the U.S. Federal Trade Commission (FTC) (Balto and Mongoven, 1999). Thus, FTC regulations requiring that buyers of small biotech firms be nonparticipants in the intended market suggest the acquiring firm will enter as an oligopolist.

In this paper we assume an innovator enters the market and competes in quantity using either a Cournot or Stackelberg strategy to estimate the potential ex-ante value of IPRs for a small biotech firm. While a vast literature exists on the emergence of Cournot and Stackelberg strategies in oligopoly markets (e.g., Allen, 1992; Hamilton and Slutsky, 1990; Kreps and Scheinkman, 1983; Qin and Stuart, 1997; Robson, 1990; Saloner, 1987; Tasnádi, 2006), to our knowledge, these strategies have not been employed in ex-ante evaluations of process innovations, especially in the presence of antitrust laws. This study also contributes to the literature on innovative and competitive marketing strategies of biotech firms (e.g., Begemann, 1997; Renkoski, 1997) as well as IPRs evaluation under different market situations (e.g., Oehmke and Wolf, 2004) by examining a specific emerging biopharming innovation. In this case, the value of IPRs is estimated for an innovating firm that obtains a patent on the production of Glucocerebrosidase enzyme (Gaucher's disease treatment) from transgenic tobacco. The current market for Gaucher's disease treatment is served by one firm, Genzyme, which has the most efficient preinnovation process of production. Genzyme might potentially offer the 'highest' price for the innovator's IPRs, but acquisition by the incumbent is likely a violation of the Clayton Act and would be considered illegal by the FTC.[2] Therefore, Cournot and Stackelberg duopolist strategies are simulated to determine the value of IPRs to the innovator based on the expected profit stream from competition with the current monopolist. Both production process patent life and the emergence of fringe competition after patent expiration are considered in estimating the potential profit stream.[3] In addition, consumer welfare effects are calculated and the results are contrasted with the scenario where the innovator's production process is acquired by the current sole market participant, Genzyme.

The rest of the paper is organized as follows. Section two provides background information on biopharming, Gaucher's disease, and the Cerezyme market. The model used to determine the value of the IPRs and welfare changes is presented in the third section. The therapeutic protein production process, unit cost reductions, and other data used in the model are presented in section four and ex-ante benefits are provided in section five. Section six concludes.

Background on Biopharming, Gaucher's Disease, and the Cerezyme Market

Biopharming and Transgenic Tobacco

Genetic engineering of plants and animals holds the promise to produce therapeutic protein drugs at significantly lower costs than current pharmaceutical production methods.[4] For example, empirical studies of biopharming show 10–100 times lower production costs when compared with cell culture systems (Kusnadi, Nikolov, and Howard, 1997; Misson and Curling, 2000).[5] Further, transgenic plants are generally preferred to transgenic animals

[2] Genzyme has the strongest incentives to obtain the innovator's IPRs, since it can retain the monopoly position and reduce some of the losses incurred if the innovator or a firm acquiring the innovator's IPRs enters the market.

[3] Generic competition leads to prominent revenue losses for drug companies whose patents expire. For example, Pfizer may lose almost half of its $51 billion in 2005 sales, as a result of emerging competition from generic-drug makers, of products with expiring patents (Zimm, 2007). Similarly, Merck, the fourth-largest U.S. drugmaker, may lose $3 billion in sales this year from its top-selling Zocor cholesterol pill because of generic competition (Zimm, 2007).

[4] Protein drugs are the fastest growing area in the pharmaceutical industry.

[5] Cell culture systems are the current method of protein production in the pharmaceutical industry where the targeted protein is produced by genetically engineering mammalian or bacterial cells.

for biopharming since they are safer (by not hosting mammalian pathogens) and structurally more fit to produce complex proteins (Cramer et al., 1996).[6] Plant-produced proteins research is being conducted on a variety of agricultural crops such as corn, tobacco, potato, alfalfa, rice, and canola. Some biotech companies such as Large Scale Biology Corp. and Planet Biotechnology Inc. have targeted tobacco as a prospective production engine. Tobacco is considered to be safer than other potential candidates because of reduced risk of contaminating the food supply or other non-genetically modified tobacco.[7]

Research on tobacco has already achieved remarkable results and therapeutic proteins from transgenic tobacco are expected to be among the first marketed plant-produced medicines. Many biotech firms are now conducting clinical trials with proteins of plant origin, indicating that commercialization is not far. CaroRX, for example, is a treatment of dental caries which is already approved for sale in Europe and it is undergoing stage II U.S. clinical trials.

Gaucher's Disease

Gaucher's disease is part of some 30 family-genetic (inherited) diseases that are identified as lysosomal storage disorders (Rader, 2003). Persons that suffer from the disease lack the lysosomal enzyme Glucocerebrosidase, which is necessary for breaking down lipids. Lipids build up in the liver and spleen and result in lung, bone, kidney problems, and anemia (Goozner, 2002). Gaucher's disease is also very rare, affecting only about 20,000 people worldwide.[8]

The genetic defect causing Gaucher's disease was discovered in 1964, and the purified Glucocerebrosidase enzyme was first produced in 1974 (Goozner, 2002). The enzyme was initially purified from human placentas by Genzyme as the drug Ceredase and the process, approved by the Food and Drug Administration (FDA) in 1991, was very expensive. Genzyme continued to produce Ceredase from human placentas until 1995 when it licensed a recombinant version of the enzyme (Cerezyme) produced in Chinese Hamster Ovaries (CHO) (Goozner, 2002).[9] Cerezyme was found to be a more effective treatment than Ceredase because of a slight genetic modification on the recombinant enzyme (Rader). Cerezyme is still the most effective treatment of Gaucher's disease and can be produced in larger quantities because it does not depend on the availability of human placentas. However, production is still very costly. A patient must take between 0.25 and 3 grams of Cerezyme every year at an average annual cost of $175,000 (Rader, 2003). Studies suggest that the profit margin of Genzyme in the case of Cerezyme is more than 90% (e.g., *The New York Times*, 2008; *Wall Street Journal,* 2005).

Cerezyme Market

Genzyme is currently the only provider of a treatment of Gaucher's disease in the United States. There is another product that is approved in Europe, Zavesca by Oxford Glycosciences Plc., but it is only used for patients with mild to moderate disease conditions (Rader, 2003). Genzyme's patent on Cerezyme expired in 2001 but its current manufacturing method is patented until 2011 and its composition until 2013 (Genzyme Corporation, 2005). The market for Gaucher's disease treatment has always been a lucrative market and other companies have tried to develop more cost effective treatments, so far without success.[10] Thus, Genzyme maintains substantial market power. In the United States, the price of Cerezyme has not changed during

[6] Transgenic plants refer to genetically modified plants.

[7] Tobacco does not enter the food or feed supply and is either harvested before reaching maturity or tops are cut so that it does not flower and gene flow is almost entirely eliminated.

[8] This figure includes people that are taking treatment of Gaucher's disease and people that have not started the treatment yet (because the disease is in its initial stage) but are positively diagnosed.

[9] Recombinant proteins are proteins produced in the cells of genetically modified organisms.

[10] Vevesca, an alternative Gaucher's disease treatment by Oxford Glycosciences, went through all clinical trials and showed promising results but failed to gain approval in the United States and Europe because 11% of the patients developed nervous system complications.

the last 10 years and this is an additional indication of Genzyme's substantial market power.

The Model

An ex-ante analysis of potential benefits is conducted since the production of Glucocerebrosidase enzyme from transgenic tobacco is not currently being undertaken. The expected value of IPRs depends on the strategies of the innovating biotech firm (or of the firm that acquires the innovator's IPRs) and the incumbent. In this case Genzyme is assumed to be a perfect monopoly in the current market for Cerezyme. Further, the transgenic tobacco product is assumed to be of the same quality as Cerezyme. The successful developer of the patented transgenic production process may follow several potential strategies to compete with the existing monopoly, with no clearly preferred strategy identified in the literature. Some studies support the emergence of equilibria where firms choose between Bertrand (price-setting) and Cournot (quantity-setting) strategies (Allen, 1992; Qin and Stuart, 1997). Other studies support the emergence of a unique Cournot equilibrium (Kreps and Scheinkman, 1983; Tasnádi, 2006), and the emergence of a unique Stackelberg equilibrium (Hamilton and Slutsky, 1990; Robson, 1990; Saloner, 1987). Font and Kanavos (2007) examine the U.S. pharmaceutical industry and find that competitive effects in the U.S. pharmaceutical markets follow a Cournot model. The present study explores Cournot and Stackelberg strategies.[11] A number of authors (e.g., Rausser, Scotchmer, and Simon, 1999; Teece, 1987) note that IPRs alone do not ensure the appropriation of profits by innovators. Rather, IPRs have to be combined with a range of complementary assets such as marketing and distribution networks. In the case of Cerezyme, insurance companies can be thought of as complementary assets in distribution, as they are willing to support the high market price (CNN, 2005). However, with the emergence of competition and the drop in prices it is not in the interest of insurance companies to stay 'loyal' to Genzyme and these 'complementary assets' will be available to the innovator and the generic competition as well.

Exact specifications of demand and marginal cost curve are needed in order to calculate the profit stream to the innovator, the change in incumbent's profits, and the consumer surplus generated from the biopharming application under each strategy. For simplicity, the Cerezyme market is characterized by linear marginal cost and demand functions derived from information on prices, quantities, and elasticities.[12]

Under these assumptions the demand for Cerezyme in price dependent form is:

$$(1) \qquad P = \mu - \lambda Q_d,$$

where P is the price of one unit of Cerezyme, Q_d is the quantity demanded and μ and λ are the intercept and slope terms, respectively. Thus the marginal revenue curve is:

$$(2) \qquad MR = \mu - 2\lambda Q.$$

Similarly, a linear marginal cost curve of Cerezyme (in price dependent form) can be specified as:

$$(3) \qquad P = \psi + \eta Q,$$

where Q_S is the quantity of Cerezyme produced and ψ and η are the intercept and slope terms, respectively.

In the absence of information on the specific nature of the marginal cost shift associated with the innovation, a parallel shift is usually employed, with a pivotal shift providing a distinct contrast in sensitivity analysis.[13]

[11] The Bertrand strategy is relatively trivial with the innovator charging a markup slightly less than the marginal cost advantage over the incumbent, and serving the whole market. The Bertrand strategy is also less profitable for both the innovator and the incumbent. Therefore, we focus on Cournot and Stackelberg strategies.

[12] These can be thought of as first-order approximations of the true underlying marginal cost and demand functions.

[13] Several studies including Alston, Norton, and Pardey (1996) have found that generally, functional forms and elasticities are relatively unimportant in determining the size of total benefits compared with the nature of the supply shift. On the other hand, when determining the distribution of benefits, functional forms are relatively unimportant compared with the sizes of elasticities and the nature of the supply shift.

The parallel outward marginal cost curve shift is represented as:

$$(4) \qquad P = (\psi - k) + \eta Q_S,$$

where k is the size of the unit cost reduction expressed as cost savings for each gram of Glucocerebrosidase enzyme produced from transgenic tobacco compared with cell culture systems.

For comparison a pivotal marginal cost shift for the same unit cost reduction is represented as:

$$(5) \qquad P = \psi + \eta_1 Q_S,$$

where $\eta_1 = \frac{{}^cP^0 - k - \psi}{{}^cQ^0}$ and ${}^cP^0$ and ${}^cQ^0$ are equilibrium price and quantity under perfect competition.

The incumbent as a monopolist charges a price mark-up above the marginal cost curve of:

$$(6) \qquad \frac{P - MC}{P} = \frac{1}{PED}.$$

The price markup depends on the price elasticity of demand (PED) and the marginal cost curve of the monopolist. The point where the marginal cost curve and the marginal revenue curve meet is derived from Equation (6) and it is used to obtain the slope and intercept parameters of the marginal cost curves in Equations (4) and (5).

Cournot Model

Under the Cournot model both incumbent and entrant choose the quantities produced in response to the quantity of the other firm. In equilibrium, both firms maximize profits based on consistent beliefs about the other's output. Denote the incumbent's output level as q_1, the innovator's output level as q_2, and the aggregate output as $Q = q_1 + q_2$. Firm 1 has a cost function given by $c_1(q_1)$ and firm 2 has a cost function given by $c_2(q_2)$. The maximization problem of firm 1 is:

$$(7) \qquad \max_{q1} \Pi_1(q_1, q_2) = p(q_1 + q_2)q_1 - c_1(q_1).$$

Similarly, the maximization problem of firm 2 is:

$$(8) \qquad \max_{q2} \Pi_2(q_1, q_2) = p(q_1 + q_2)q_2 - c_2(q_2).$$

With consistent conjectures the solutions to the simultaneous equations from the first order conditions are:

$$(9) \qquad q_1^* = \frac{\lambda(\mu - 2\psi_1 + \psi_2) + \eta_2(\mu - \psi_1)}{\lambda(3\lambda + 2\eta_2 + 2\eta_1) + \eta_1\eta_2},$$

and

$$(10) \qquad q_2^* = \frac{\lambda(\mu - 2\psi_2 + \psi_1) + \eta_1(\mu - \psi_2)}{\lambda(3\lambda + 2\eta_2 + 2\eta_1) + \eta_1\eta_2}.$$

Based on equilibrium quantities, profits for each firm, the equilibrium market price, and the change in consumer surplus generated from the entrance of firm 2 can also be calculated.

Stackelberg Model

In the Stackelberg model one firm moves first, and then the other firm follows after observing the first firm's output. Again, the optimal output for the leader depends on consistent beliefs on how the follower responds. In the present study the incumbent is the follower and the innovating firm is the leader due to its entrance at a lower marginal cost.[14] To solve for equilibrium outputs we start from stage two and maximize the incumbent's profit as:

$$(11) \qquad \max_{q1} \Pi_1(q_1, q_2) = p(q_1 + q_2)q_1 - c_1(q_1).$$

Equation (11) is similar to the Cournot condition derived above. Moving from the second stage to the first, the innovator now wants to choose its optimal level of output based on the incumbent's response. The profit maximization of the innovator in this case is:

$$(12) \qquad \max_{q2} \Pi_2(q_1, q_2) = p(f_1(q_2) + q_2)q_2 - c_2(q_2).$$

From the first order conditions of Equations (11) and (12) the optimal output of the innovator and the incumbent are, respectively:

$$(13) \qquad q_2^* = \frac{\lambda(\mu + \psi_1 - 2\psi_2) + \eta_1(\mu - \psi_2)}{\lambda(2\lambda + 2\eta_1 + 2\eta_2) + \eta_1\eta_2},$$

and

$$(14) \qquad q_1^* = \frac{\mu - \lambda q_2^* - \psi_1}{2\lambda + \eta_1}.$$

[14] Harsanyi and Selten (1998) and Van Damme and Hurkens (1998) have shown that in a two-stage game the lowest cost firm emerges as the endogenous Stackelberg leader.

Profits for each firm and changes in consumer surplus are again calculated based on the equilibrium quantities of the incumbent and innovator.

The Value of IPRs

If the market is served by only one firm, acquisition of the innovator's IPRs by the incumbent allows it to obtain a patent on a more efficient manufacturing method and to retain a monopoly position in the market. As mentioned, such an acquisition likely violates Section 7 of the Clayton Act. The innovator's patent can, however, be purchased by another pharmaceutical firm not currently in the market and that is the case we consider. The effective patent life in the pharmaceutical industry is 12 years and that's the innovator's patent life assumed here.[15] The innovator may attempt to prolong the process patent life through an 'evergreening' strategy of minor process innovation (in which case the IPRs will be higher) but since there is no information on any such strategies, for the purpose of this study we assume a12-year patent life. Thus if the incumbent has operated for t-years in the market, the remaining patent life for the incumbent is 12 minus t-years. The value of the innovator's IPRs is calculated as the present value (PV) of the expected stream of profits during the effective patent life when it enters the market and competes with the incumbent. In this particular application, based on current patents, it is assumed that the incumbent's manufacturing method is patent protected for 6 more years and after that period it faces generic competition in the market.[16] Thus the present value of the expected stream of innovator's profits is the sum of profits during the first 6 years as a Cournot or Stackelberg competitor plus the profits from the 6th to the 12th year when facing a competitive fringe after the incumbent's patent expires.[17] After the 12th year incumbent's profits are driven to zero because generics are produced using the incumbent's production method.[18] Evidence from the entry of generics in pharmaceutical markets suggests that the price of existing products falls dramatically (Food and Drug Administration, 2006). To simplify the analysis, it is assumed that when facing a competitive fringe in years 6–12 the innovator can drive out the competition in the market through limit pricing.[19]

During the limit price period, the expected PV of the innovator's profits is:

$$\Pi_g = \sum_{t=6}^{12} \frac{(k^{*c}\, Q^0)}{(1+r)^t}, \tag{15}$$

where k denotes the size of unit cost reduction, ${}^cQ^0$ denotes the quantity that would result if the market was competitive with the incumbent's technology evaluated over the time generics may enter the market, $t = 6$, until the innovator's patent expires, $t = 12$, and r is the discount rate.

The value of innovator's IPRs at time 0 is:

$$P_B = \sum_{t=0}^{6} \frac{\Pi_t}{(1+r)^t} + \Pi_g, \tag{16}$$

where P_B is the price of innovator's IPRs, Π_t is the potential annual profit of the innovator

[15] Studies have found the effective patent life for pharmaceuticals to be 11–12 years on average (Grabowski and Vernon, 1994; Shulman, DiMasi, and Kaitin, 1999).

[16] Given the R&D situation in the glucocerebrosidase market, it is unlikely that competitors with further process innovations will emerge during the "effective" life of the patent. However, the framework can be adjusted to accommodate a variety of cases including the emergence of other competitors with new products or processes in the market under an oligopoly setting.

[17] The innovator enters the market with a different production process and, to the best of our knowledge, does not need to use any of the incumbent's patented process or technologies patented by a third party. But if patented processes from the incumbent or a third party are used, then the innovator would pay royalties and the value of IPRs would be lower.

[18] It is assumed that at this point generics are perfect substitutes for the original product.

[19] At the limit price the innovator faces an elastic demand because it gains the whole market with a small price decrease. However the equilibrium price may not drop to the incumbent's marginal cost if they continue to play Cournot or Stackelberg with the incumbent or with the incumbent and a limited set of entrants. In this case the innovator's profits are underestimated under the limit pricing assumption.

under Cournot or Stackelberg in year *t,* and Π_g is the expected value of profits during the limit price period.

The PV of changes in consumer surplus under a duopoly at time 0 until the time incumbent's patent expires in year six is:

$$(17) \qquad \Delta CS_d = \sum_{t=0}^{6} \frac{\{0.5[(\mu - {}^{m}P^{0})^{m}Q^{0} - (\mu - {}^{m}P_i^{1})^{m}Q_i^{1}]\}}{(1+r)^{t}},$$

where ${}^{m}Q^{0}$ and ${}^{m}P^{0}$ are the monopoly price and quantity with the incumbent's technology prior to innovator's entry, ${}^{m}P_{\mathrm{i}}^{1}$ and ${}^{m}\mathrm{Q}_{\mathrm{i}}^{1}$ are the resulting equilibrium price and quantity after the innovator enters the market following a Cournot or Stackelberg strategy (i = Cournot, Stackelberg), *t* denotes each year from the time of the buyout until the incumbent's patent expires.

The PV of changes in consumer surplus, ΔCS_g from the time when generics may enter the market, $t = 6$, until the innovator's patent expires, $t = 12$, is:

$$(18) \qquad \Delta CS_g = \sum_{t=6}^{12} \frac{\{[0.5(\mu - {}^{c}P^{0})^{c}Q^{1} - 0.5(\mu - {}^{m}P^{1})^{m}Q^{1}]\}}{(1+r)^{t}},$$

where μ is the intercept of the demand curve, ${}^{c}P^{0}$ is the competitive price in the market with the incumbent's technology, ${}^{m}P^{1}$ is the monopoly price with the innovator's technology, ${}^{m}Q^{1}$ is the quantity supplied at that price.[20]

It is important to note that the innovator and potential buyers are assumed to have the same information regarding market demand, firm marginal cost, and the time when generics may potentially enter the market. Otherwise, the price that potential buyers offer is different from the anticipated value of IPRs to the innovator. In order to highlight the role of the antitrust laws in augmenting consumer welfare we also calculate profits and welfare changes if the incumbent was allowed to acquire the innovator's technology. Under this scenario, the PV of changes in consumer surplus at time 0 (when the incumbent acquires the innovator's IPRs) until the time incumbent's patent expires, $t = 6$, is now:

$$(19) \qquad \Delta CS = \sum_{t=0}^{6} \frac{\{0.5[(\mu - {}^{m}P^{0})^{m}Q^{0} - (\mu - {}^{m}P^{1})^{m}Q^{1}]\}}{(1+r)^{t}},$$

where ${}^{m}P^{1}$ and ${}^{m}Q^{1}$ are the resulting monopoly price and quantity if the incumbent uses the innovator's technology, ${}^{m}Q^{0}$ and ${}^{m}P^{0}$ are the monopoly price and quantity with the incumbent's technology.

If the innovator accepts the offer, the PV at time 0 of nominal changes in incumbent's profits from using the transgenic production process is:

$$(20) \qquad \Delta\Pi_{\mathrm{I}} = \sum_{t=0}^{6} \frac{\{({}^{m}P^{0} - {}^{m}P^{1})[{}^{m}Q^{0} + 0.5({}^{m}Q^{1} - {}^{m}Q^{0})]\}_t}{(1+r)^{t}}.$$

The real change in profits to the incumbent in this case is found by adding to its current expected profits (with the incumbent's technology) the change in monopoly profits using the innovator's technology (during the first 6 years), the profits during the limit price period from $t = 6$ to $t = 12$ in Equation (15), and subtracting the price paid for IPRs to the innovator.

Protein Production Process, Unit Cost Reductions, and Other Model Data

Cell Culture Systems versus Transgenic Plants

A comparison of the unit cost of Glucocerebrosidase enzyme from CHO and the unit cost reduction from transgenic tobacco provides an example of the relative costs of cell culture and transgenic plants as systems for therapeutic protein production. Production of proteins from transgenic plants is similar to the production of proteins from the more established method of bioreactors using cell cultures. In both systems protein production can be divided into upstream and downstream processing. During upstream processing the proteins are produced in genetically engineered cells that express the desired proteins. Downstream processing then isolates and purifies the proteins.

[20] The assumption here is that generic competition will have the same costs as the monopoly. Given the highly technical nature of the production process of glucocerebrosidase enzyme in culture cells, followed by purification to extract the enzyme, it is unlikely that production outside the United States will result in lower costs for generic producers.

Transgenic plants aim to replace cell cultures produced in bioreactors in the upstream process and also provide further cost savings in the downstream process.[21] The economic advantages that transgenic plants can offer from the expression of proteins in their cells are lower capital requirements compared with bioreactors, lower manufacturing costs, and flexibility in supply. Increasing production capacity with cell culture systems requires a considerable fixed investment (more than $50 million for a bioreactor plant) and construction time (at least 5 years). Using transgenic plants for protein production is less expensive and production capacity can be extended by simply planting more acres. Glucocerebrosidase enzyme was successfully produced in transgenic tobacco by CropTech (Blacksburg, VA). Crop Tech's estimates indicate that 1 mg of crude Glucocerebrosidase enzyme can be produced from 1g of fresh weight of tobacco leaf tissue (Cramer et al., 1996).[22] Assuming a 40% recovery in order to achieve a pure product, and 40 metric tons of tobacco per acre (based on multiple cuttings), less than one acre of transgenic tobacco will be sufficient to meet Genzyme's current level of Glucocerebrosidase enzyme production.[23] This low acreage suggests that the innovation will have little to no impact on existing U.S. tobacco markets.

Unit Cost Reductions

Economic analysis of the production of therapeutic proteins from transgenic plants has been limited to date, largely because there is no drug of transgenic plant origin currently on the market. Consequently, there is no commercial scale processing of transgenic plants to generate accurate data on the economic benefits of biopharming. Nevertheless, estimates do exist on the production costs of proteins from transgenic plants (Evangelista et al., 1998; Farid, 2007; Kusnadi, Nikolov, and Howard, 1997; Misson and Curling, 2000; Nikolov and Woodard, 2004). Several important results can be synthesized from these studies. First, the cost savings with transgenic plant systems are realized during the upstream process and the downstream process (Glacken, 2002; Nikolov and Woodard, 2004; Watler, 2002). Downstream processing includes filtration and purification using chromatography that account for 30% of the production costs (Millan et al., 2003). Second, the unit cost reduction in the upstream process is primarily due to capital cost savings. In transgenic plants, capital costs can be more than 95% lower than those in cell culture systems. Capital costs for cell culture systems can constitute 20–30% or more of protein production costs, but they depend on the size of the operation. However, a significant share of incumbent's capital costs, especially in bioreactor infrastructure, is fixed in the short to medium term.

There have been several studies on the cost of therapeutic proteins. For example, Myleski, Oishi, and Williams (2004) review reports on the cost comparison between transgenic plants and cell culture systems in bioreactors and point out that the cost of therapeutic protein production from transgenic plants may be from 10% up to an order of magnitude lower than cell culture systems. Farid (2007) provides an extensive literature review on the economics of protein production using bioreactors and transgenic plants. He notes that besides significant capital savings, transgenic plants also offer manufacturing costs (excluding capital investments and R&D costs) as low as one sixth of the costs of pharmaceutical proteins when compared with bioreactors. For example, manufacturing costs are in the order of $50 per gram of pharmaceutical protein produced in transgenic corn, whereas they vary from $300–3000 per gram for a 100 kg/year facility (including bioreactor and downstream production). The author concludes that transgenic

[21] Bioreactors are large containers made of stainless steel, glass, or plastic, which serve as a growth medium for the genetically engineered mammalian or bacterial cells in cell culture systems.

[22] It is expected that the innovator's product will have a distinct composition that allows it to be IPR-protected and marketed.

[23] There is very little risk and uncertainty associated with agricultural production in this case. The small tobacco acreage required to meet the demand for glucocerebrosidase enzyme can be met through greenhouse production in several geographical locations.

plants can offer at least a one to two order of magnitude reduction in the manufacturing costs of goods per gram compared with CHO culture systems at the 100 kg/year scale. Wilke and Katzek's (2003) study on the same topic supports these estimates. Other studies on output levels of 50 kg/year estimate unit cost reductions of 25–28% (Glacken, 2002) and 20–40% (Watler, 2002). Annual production of Glucocerebrosidase enzyme is less than 50 kg per year commercially. Thus, there is uncertainty about the exact unit cost reduction, but they can reasonably be assumed to range from a minimum of 10% up to a maximum of 40%, with a most likely value of 25% of the original production cost.

Market Data

Estimates of the elasticity of supply of Cerezyme or similar products are not available in the literature. Nevertheless, considering that Genzyme is currently the only provider of a treatment of Gaucher's disease, information on prices and quantities over time may help to shed some light on the nature of the supply curve.[24] Cerezyme prices, quantities, and changes in quantity for five recent years are shown in Table 1. The direct price that Genzyme charges for Cerezyme has not changed from 1994 to 2004 and the initial price (${}^{m}P^{0}$) of Cerezyme in the analysis is \$740 per 200 unit vial.[25] Because the quantity has been constantly increasing, taking an average for recent years would likely underestimate the ex-ante benefits of the transgenic product.[26] Therefore, the initial quantity (${}^{m}Q^{0}$) is set equal to the quantity in 2003. The upward trend in the quantity of Cerezyme produced also suggests that Genzyme currently has some excess capacity and that the supply of Cerezyme is elastic. For the study, the elasticity of supply is considered to be 2.0.

Demand, on the other hand, appears 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 of patients that are already diagnosed can successfully control and reverse severe conditions from the disease (spleen and liver enlargement, bone disease, anemia). However, microeconomic theory suggests that a monopolist maximizing its profits will never operate in the inelastic portion of the demand curve. Consequently, the elasticity of demand is considered to be -1.25.

Results

The estimated value of IPRs along with the changes in incumbent's profits ($\Delta\Pi$) and consumer surplus changes (ΔCS) are presented in Table 2 for a minimum unit cost reduction of 10%, a most likely reduction of 25%, and a maximum reduction of 40% under both parallel and pivotal marginal cost shifts. An elasticity of demand of -1.25 and an elasticity of supply of 2.0 are used in these estimates. With linear marginal cost and demand specifications, and initial equilibrium prices and quantities, the changes in incumbent's profits, innovator's profits, and consumer surplus are calculated simply by using the area changes in consumer and producer welfare based on supply and demand curves and price changes. All results are reported as present values over a 12 year period using a 5% discount rate.

The estimated value of IPRs with the most likely unit cost reduction is \$1.72 billion if the innovator follows a Cournot strategy and \$1.77 billion if it follows a Stackelberg strategy.[27] For a pivotal shift, the most likely unit cost reduction generates IPRs valued at \$1.72 and \$1.81 billion under Cournot and Stackelberg strategies,

[24] We use the elasticity of supply to derive the slope of the marginal cost curve.

[25] Genzyme is the decision maker when it comes to the price of Cerezyme. The high price of Cerezyme is justified by the company as it "... allows the company to continue to develop other medications and fund programs that provide small amounts of treatments at no cost" (*Wall Street Journal*, 2005).

[26] Analysis over 12 year period may still underestimate the value of IPRs by assuming constant number of cases of Gaucher's Disease.

[27] If the innovator follows a Bertrand strategy, the incumbent exits the market and the estimated value of IPRs is \$614 million. Thus, it is in the incumbent's and innovator's interest to follow either Cournot or Stackelberg strategies.

Table 1. Cerezyme Price and Quantity Sold, 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)
1999	479	647,297	—	740
2000	537	725,676	12	740
2001	570	770,270	6	740
2002	620	837,838	9	740
2003	734	991,892	18	740

Notes: 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.
Source: Marketing Research Bureau (2004).

respectively. Consumers gain the most from the introduction of Glucocerebrosidase enzyme from transgenic tobacco in the market regardless of the entry strategy of the innovator. A 25% unit cost reduction with a parallel shift generates increases of $4.2 and $4.8 billion in consumer surplus under Cournot and Stackelberg strategies, respectively. Changes in consumer surplus are also slightly larger under a pivotal shift compared with a parallel shift for both strategies. As expected, the incumbent's profits decrease with the innovator's entry. Further, the innovator's IPRs value increases and incumbent's profits decrease with larger unit cost reductions under both parallel and pivotal marginal cost shifts.[28] In addition, the value of IPRs and the decrease in incumbent's profits are slightly larger under a pivotal shift compared with a parallel shift in marginal costs.

The impact of antitrust laws is also illustrated by reporting results in Table 3 for the case when the incumbent is allowed to acquire the innovator's IPRs. Contrasting the results with those in Table 2, two observations are worth noting. First, in both scenarios consumers are the main beneficiaries from the innovation. But the consumers gain significantly less if the incumbent acquires the innovator's IPRs. A $2.9 billion increase in consumer surplus is generated if the incumbent buys the innovator's IPRs, compared with the previously mentioned gains in consumer surplus of $4.2 and $4.8 billion if the incumbent competes with the innovator using Cournot and Stackelberg strategies, respectively.

Second, as expected, the incumbent's profits decrease by less when it buys the innovator's IPRs than when it faces an entrant and competes as a duopoly. If the incumbent acquires the innovators IPRs, with a 25% unit cost reduction and a parallel shift in the marginal cost curve, the reduction of the incumbent's profits is about $1.3 billion when the IPRs of the innovator are priced based on potential profit streams from either Cournot or Stackelberg strategies. Incumbent's profit reductions are also lower as the unit cost reduction increases, as larger unit cost reductions translate into greater profits. These reductions compare favorably with the $1.6 and $2.1 billion reductions in profits associated with competing under Cournot and Stackelberg strategies, respectively. The choice between a parallel and a pivotal shift does not significantly impact reductions in incumbent's profits. Thus, the incumbent's best strategy would be to acquire the innovator's technology, since incumbent's profits decrease less and it can effectively extend the life of patented IPRs. However, as noted, Federal antitrust regulations are likely to block this strategy.

The sensitivity of the results to demand and supply elasticity parameter estimates are also considered by examining alternative demand elasticities between -1.001 and -1.5 and alternative supply elasticities between 1.5 and 2.5. The results are found to be generally

[28] The incumbent still makes profits but these profits are less than the profits when it was a monopoly in the Cerezyme market. Base monopoly profit for the incumbent is $2.98 billion.

Table 2. Estimated Surplus Changes from Minimum, Most Likely, and Maximum Expected Unit Cost Reduction under Cournot and Stackelberg (PV, in thousand U.S. dollars)

		Parallel Shift		
Unit Cost Reduction		10	25	40
Cournot	Π Innovator	1,513,986	1,718,357	1,923,490
	ΔΠ Incumbent	(1,616,664)	(1,638,083)	(1,659,335)
	ΔCS	4,137,922	4,162,372	4,186,923
Stackelberg	Π Innovator	1,561,840	1,767,800	1,974,556
	ΔΠ Incumbent	(2,085,977)	(2,110,153)	(2,133,999)
	ΔCS	4,757,355	4,795,163	4,833,185
			Pivotal Shift	
Cournot	Π Innovator	1,515,601	1,723,946	1,935,078
	ΔΠ Incumbent	(1,617,410)	(1,640,606)	(1,664,431)
	ΔCS	4,138,770	4,165,265	4,192,856
Stackelberg	Π Innovator	1,577,164	1,809,959	2,048,682
	ΔΠ Incumbent	(2,093,708)	(2,130,623)	(2,168,600)
	ΔCS	4,769,364	4,827,759	4,889,713

Note: Results in parenthesis indicate negative changes in profits.

robust to these ranges of supply and demand elasticities. However, the results do appear to be more sensitive to the precision of the supply elasticity estimates than the demand elasticity estimates. Holding the supply elasticity constant, incumbent's losses, profits to the innovator, and changes in consumer surplus increase (decrease) as demand becomes less (more) elastic under both Cournot and Stackelberg strategies and for both types of marginal cost shifts. With the elasticity of demand held constant, changes in the supply elasticity do not yield as uniform a set of trends across the various scenarios. Incumbent's losses increase (decrease) as supply becomes more (less) elastic, for both types of marginal cost shifts and under both entry strategies. However, the innovator's profits increase (decrease) with an increase (decrease) in supply elasticity under a parallel shift and decrease under a pivotal shift under Cournot strategy. Under Stackelberg strategy, profits to the innovator increase with increases in the supply elasticity for both types of marginal cost shifts. Consumers gain less as supply becomes more elastic when the innovator enters as a Cournot competitor under both parallel and pivotal marginal cost shift. On the other hand, when the innovator enters as a Stackelberg competitor, changes in consumer surplus increase under a parallel shift, but decrease under a pivotal shift, as supply becomes more elastic.

Table 3. Estimated Changes in Profits to Incumbent when Acquiring Innovator's IPRs (PV, in thousand U.S. dollars)

	Parallel Shift		
Unit Cost Reduction (%MC)	10	25	40
ΔΠ Incumbent – Cournot	(1,338,421)	(1,277,896)	(1,216,276)
ΔΠ Incumbent – Stackelberg	(1,386,274)	(1,327,338)	(1,267,342)
ΔCS	2,890,855	2,944,534	2,999,141
		Pivotal Shift	
ΔΠ Incumbent – Cournot	(1,356,215)	(1,322,652)	(1,288,306)
ΔΠ Incumbent – Stackelberg	(1,417,778)	(1,408,664)	(1,401,910)
ΔCS	2,882,764	2,924,950	2,968,920

Note: Results in parenthesis indicate negative changes in profits.

Concluding Remarks

The economics of innovation in an imperfectly competitive market are explored for the case of a small biotech firm successfully generating a lower cost process of production by biopharming. We estimate the value of the innovator's IPRs and the potential distribution of economic gains from entrance into a market with an incumbent monopolist. The analysis suggests the innovator's IPRs have a value of about $1.75 billion. Thus, potential profits are very large and capable of spurring significant investments in innovations for biopharming for therapeutic protein production. However, it is worth noting that entry costs and the costs associated with FDA registration and approval are not disclosed by Genzyme or similar pharmaceutical companies that are conducting clinical trials. These costs are considered a sunk cost along with R&D costs, and are not included in the welfare analysis. Yet, even with significant profits consumers remain the main beneficiaries from the lower cost process of producing Glucocerebrosidase enzyme from transgenic tobacco.

The FTC has established antitrust laws that prevent an incumbent from retaining market power by buying the IPRs of a potential rival. The present case demonstrates the effectiveness of such antitrust laws in increasing benefits to consumers from technical innovations. In the presence of antitrust regulations consumer surplus is almost 50% higher than when the incumbent is allowed to acquire the innovator's production process. Thus, regulations can play an important role in redistributing innovation benefits to a wider share of society, albeit while slightly blunting incentives for innovation. This particular application focused on the value of IPRs from producing an identical product using a lower cost biopharming production method. Applications to the more common set of nonidentical products, which may be broadly equivalent in terms of their same therapeutic effects, are an important area of future research.

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