Farmers' Perceptions of Biopharming: Insights from a Tobacco Biopharming Survey

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Introduction

Genetically engineered crops have been a success for almost two decades, greatly improving productivity, enhancing nutritional value and increasing welfare (Khush, 2012). More recently, a new generation of genetically engineered crops has the prospect of becoming a cheaper and efficient alternative to producing pharmaceutical products for human use. This technology has been termed "biopharming."

Biopharming is the cultivation of crops for a pharmaceutical purpose, giving them the ability to produce desired therapeutic proteins, which are then extracted, purified and used by the pharmaceutical industry to produce large-molecule drugs based on proteins. Corn, rice, tobacco, and alfalfa are among the top candidates for being widely used in biopharming (USDA, 2012). Among others, biopharming is important for three reasons. First, studies show that biopharming can be significantly cheaper than the most common method of therapeutic protein production[1] (e.g. Hood et al. 2002; Mison and Curling, 2000; Morrow, J., 2002). Second, biopharming may be able to provide a more stable supply and increase consumers' access to much needed medicines (Ahmad et al, 2012). Third, therapeutic proteins from biopharming are believed to be purer than the ones produced by mammalian cell cultures because generally plants do not carry potentially harmful human or animal viruses (Elbehri, 2005). Finally, biopharming offers possibilities to develop new treatments that have thus far been too complex to reproduce by current production methods (Rehbinder et al., 2009). Private firms have invested hundreds of millions of dollars for production of plant-made pharmaceuticals. Some of the therapeutic proteins that have already been successfully produced in plants can be used in the treatment of

different types of cancer, HIV, diabetes, cholera, Alzheimer's disease, cystic fibrosis, hepatitis B, and malaria (Ahmad et al, 2012).

Although not many plant-made pharmaceuticals have made their way to the market, this is not because biotechnology firms are not attracted to the technology but because biopharming is a relatively new field and it usually takes about 12 years to get a product from the lab stages to the pharmaceutical market. Before this technology can be commercialized, it must overcome many regulatory challenges from the Federal Drug Administration (FDA) (same approval process that the pharmaceutical drugs go through) and from the United States Department of Agriculture (USDA), if grown in the field. Among these challenges, an important one is to eliminate the risk of biopharming crops contaminating the food supply. This is the main reason why tobacco is one of the most commonly researched crops (USDA, 2012). Tobacco has other unique advantages that address some of the other concerns regarding biopharming. First, tobacco is harvested before it reaches maturity or the tops are cut, so the tobacco plant does not flower, reducing the risk of contamination through pollen drift (Nevitt et al., 2003). Second, there is also a novel gene that delays the expression of the foreign protein in the field. The new protein would not be expressed until after the tobacco is harvested (Nevitt et al., 2003). Additionally, the nicotine found in tobacco makes the plant less desirable for animal species to feed on, which reduces the risks of contaminating the food supply and endangering local animals (Nevitt et al., 2003).

As biopharming progresses, regulatory agencies' are challenged to address public and environmental concerns, while allowing biotech firms and farmers to advance the industry. There have been several studies that evaluate the public opinions toward biopharming (e.g.Nevitt et al., 2006; Einsiedel and Medlock, 2005; Cook and Fairweather, 2007). However, thus far, there have

been no quantitative studies that evaluate farmers' perceptions of biopharming. Farmers are an important link in the prospect of commercialized biopharming and a better understanding of farmers' knowledge and how they feel about biopharming is crucial for setting up the appropriate regulatory framework for the technology However, there is limited information on farmers' perception of biopharming, whether they would be willing to be grow biopharming crops and under what conditions. Most public opinion research was conducted in the mid 2000s, and with the exception of 17 tobacco producers interviewed in a qualitative study conducted by Nevitt et al. (2003), to our knowledge, there has been no research on U.S. farmers' opinions on biopharming.

To begin to answer some of these questions, we conducted a survey on tobacco farmers Our goal is to enhance biopharming literature by contributing novel data on farmers' knowledge of biopharming, attitudes, and conditions under which they would be involved in biopharming. The findings of this study will benefit not only tobacco farmers, but also biopharming companies, as well as consumers and policy makers to better understand public knowledge of biopharming and producer attitudes.

Biopharming Progress and Approvals

Research on biopharming started more than two decades ago. However, the first commercial approval did not come until 2006 when, Dow AgroSciences received the first approval of a plant made pharmaceutical for a poultry vaccine created from tobacco cells (Katsnelson et al., 2006). Since then, many biotechnology firms have attempted to receive approval from the FDA and other countries' regulatory agencies (Obembe et al., 2011). In 2006, Planet Biotechnology received approval in Europe for CaroRX^{TM}, which is a topical treatment for the prevention of dental caries (Planet Biotechnology, 2012). However, CaroRX^{TM} was registered as a medical

device, so the product avoided the approval process as a plant made pharmaceutical (Twyman et al., 2012). The company is currently in Phase II clinicial trials in the FDA approval process in the U.S. (Planet Biotechnology, 2012). A Hepatitis B antibody made from tobacco plants was approved in Cuba, in 2006 (Twyman et al., 2012). However, the antibody is not the active ingredient in the vaccine, so it is not considered a true plant made pharmaceutical product. It is used in purification of the vaccine during the traditional production method. However, this product was subject to the same approval process as plant made pharmaceuticals that are used as active ingredients (Twyman, 2012). Additionally, as a result of more lenient regulatory policies, there have been several other approvals for plant made products used for non- pharmaceutical purposes (Spok and Karner, 2008).

In May 2012, Protalix Biotherapeutics, an Israeli company received the FDA's first approval for a plant made pharmaceutical product intended for humans. The protein is used for the treatment of Type 1 Gaucher's disease and is cultured in genetically engineered carrot cells (Maxmen, 2012; Opar, 2011; Protalix.com). It is currently being marketed by Pfizer, in the U.S. and Israel, under the product name Elelyso (Maxmen, 2012; Opar, 2011; Protalix.com). However, this protein is currently produced in carrot cells under laboratory conditions, and there are no farm based, whole plants used in the production method (Morrow, T. 2012). Nevertheless, many stakeholders in biopharming working with whole plants believe the approval of Elelyso sets a precedent for future approvals (Maxmen, 2012).

Studies (e.g. Rehbinder, 2004; Twyman 2012) indicate that the global value of the biopharmaceutical market continues to grow by billions each year. Therefore, biotechnology firms have great incentive to invest in research. However, as one biotechnology executive stated

"pharmaceutical companies don't grow tobacco; only farmers do" (Nevitt, et al., 2003). Thus, it is important to examine producers' attraction to the technology.

Prior Research on Producers' and Consumers' Attitudes on Biopharming

Nevitt, et al. (2003) conducted a broad study on the opinions of different stakeholders in tobacco biopharming. The researchers assessed agricultural sectors, private industry, academia, activist groups, and government officials. Among others, seventeen tobacco producers from Tennessee, Virginia, and North Carolina were interviewed. Most of those interviewed had some knowledge of biopharming technology, but none reported a great deal of knowledge. All of the tobacco producers expressed an interest in growing pharmaceutical tobacco, and had little concern about production so long as it was profitable. The concerns were focused on purchasing new equipment and changing current production practices. A few reported concern with maintaining a relationship with their contracted tobacco companies.

The same group of researchers administered a telephone survey about U.S. consumers' opinions on tobacco biopharming (Nevitt et al, 2006). First, respondents were asked if they held concern in the following categories; (a) companies owning the rights to genetically engineered tobacco; (b) negative effects on human health; (c) negative effects on the environment; and (d) moral/ethical considerations. Health and environmental concerns were the most frequent responses. Health and environmental concerns were the most frequent responses. They found that socioeconomic characteristics and prior knowledge did not have significant correlation with concerns about biopharming. They also found that acceptance of the technology depended on the intended pharmaceutical purpose, as well as societal benefits (Nevitt et al., 2006). Overall, this study concluded that most consumers accept biopharming technology, but there is also a

considerable share of the public that is strictly opposed to it. The next step to help advance this technology, in terms of public acceptance, is to educate people about the associated benefits and risk. People's unwillingness to support the technology would be anticipated to change thereafter.

Researchers at the University of Calgary conducted a biopharming perception study, in 2005, with focus groups in four regions of Canada (Einsiedel and Medlock, 2005). The study aimed to report public awareness, reactions to specific biopharming uses, and opinions on different containment strategies. Since most of the public is unaware of biopharming, the researchers provided background information and gave participants more time to reflect on the issues. The study reported that only 2 of the 48 participants had heard of biopharming prior to the study. The initial reactions were mixed, but the number of positive reactions was slightly higher. The most common areas of concern were contamination with food crops, regulations, long term health effects, and commercial interests overriding public safety. In terms of acceptability, when considering the end product from biopharming crops, participants had mixed views but tended slightly more toward acceptability. Also, results indicated that participants tended to be more acceptable or less acceptable, as opposed to the extremes of fully acceptable and unacceptable found by Nevitt et al. (2006).

In New Zealand, Cook and Fairweather (2007) also studied public attitudes toward biopharming. They found that only 26% would support biopharming. However, this is high compared to consumers' willingness to purchase GM food, which is only 10%. They also reported that a high percentage of support is correlated with a higher medical benefit. This study concluded that public support would likely change when apprehension about the technology was lessened. The apprehension is largely based on the same concerns from the other studies (Nevitt

et al, 2006 and Einsiedel and Medlock, 2005) and if addressed would be expected to change the public's overall opinion of biopharming.

Data

In July 2012, we conducted a telephone survey with 1,129 tobacco producer contacts and collected data on 145 tobacco farmers in Georgia, Kentucky, North Carolina, Tennessee and Virginia with a response rate of 13%. The primary data collected on the tobacco producers' consisted of: (a) concerns about unexpected effects from biopharming, (b) willingness to grow tobacco for pharmaceutical uses under certain conditions regarding production methods and net return per acre, (c) knowledge of biopharming prior to the survey and (d) characteristics such as gender, age, income, and education.

Table 1 summarizes respondents' personal characteristics and prior knowledge about biopharming. The sample of 145 was composed of 95% men and the average age was 57. Among the respondents that reported their income, 63.4% earned between $100,000 and $120,000 in 2011, 36% hold a four year degree or higher and 73.6% has been growing tobacco for 31 to 40 or more years. The respondents' level of knowledge on the subject prior to the survey shows that 68.4% know "not much" or "nothing at all".

Table 2 summarizes the respondents' acres of tobacco planted, production and average prices earned in the previous year. In 2011, 50% of the respondents planted 100 acres or less of tobacco, 51% produced 100 tons or less, and the average price received was $1.82 per pound.

Results

Concerns about Biopharming

Survey participants were told that scientists can use tobacco to create pharmaceutical medicines and some believe it can be a cost efficient alternative to meet demand for medicines. They were also told that others believe this technology could lead to unexpected effects. Then they were asked if they were concerned with (a) unexpected effects, (b) human health effects, and (c) environmental effects. These results are in Table 3. Despite reporting little familiarity with the technology, only 18.5% said they were concerned with the unexpected effects from biopharming, 4.8% concerned with health effects, and 4.4% concerned with the environmental effects.

Willingness to Grow

The tobacco growers were asked the following questions: (a) Would you be willing to grow tobacco using current equipment and production methods for a pharmaceutical company if your net return per acre was more than the net return per acre when growing conventional tobacco, (b) would you be willing to grow transgenic tobacco for medicine if they were required to change production methods and work closely with a biopharmaceutical firm, and (c) would you be willing to grow if you have to purchase additional equipment and change production methods. For each question, the tobacco grower was given a randomized net return per acre above growing conventional tobacco. The randomized percentage of net return per acre for a growing scenario was not dependent on the percentage given for the other two scenarios.

Results on willingness to grow questions are reported in Table 4. Among those that answered [2], regardless of net return per acre: (a) 81% reported they would be willing to grow tobacco using current production methods, (b) 68% reported they would be willing to grow if required to change production methods and work closely with a biopharmaceutical firm, and (c) 60% reported they would be willing to grow if they had to change production methods and

purchase additional equipment. Table 4 also reports the percentage of tobacco producers that answered yes for a given net return per acre and production scenario. Under current production methods, with a 5% increase in net return per acre, 42.9% would be willing to grow pharmaceutical tobacco. As expected, changing production and additional equipment scenarios decreased the willingness to grow under all net return per acres. Changing production methods and the requirement of additional equipment dramatically affected whether a tobacco producer answered yes with only 7.4% willing to adopt if they had to change production methods and receive a 5% increase in returns. However, the gap reduces as the net return per acre increases indicating that profitability is a very important factor for farmers.

A probit model is estimated for each of the three growing scenarios using the predictors: net return per acre, gender, age, education, income, concern about unexpected effects, level of knowledge about biopharming prior to the survey, and experience growing tobacco for 20 years or more (Table 5). The model revealed the probability of a producer willing to grow pharmaceutical tobacco is largely influenced by economic incentives. Net return per acre is statistically significant and increases the probability that a farmer is willing to grow pharmaceutical tobacco under all three growing scenarios. Additionally, male farmers with an income of more than $50 thousand dollars are more likely to adopt the technology. Interestingly, those that have a four year degree or more are less likely to adopt if they have to purchase additional equipment.

To confirm their willingness to grow pharmaceutical tobacco, producers were told about some of the current regulations, including a 1320 ft. fallow zone from other fields, a 1 year restriction to grow non-pharmaceutical crops after they have planted biopharming crops, and several annual inspections from regulatory agencies. These regulations do not seem to deter

willingness to grow, as 86.5% reported it would not prevent them from growing pharmaceutical tobacco. However, when asked what percentage of their acres they would be willing to use for pharmaceutical tobacco, only 15.4% were willing to use 31% or more of their acres. Half of the respondents answered they would be willing to experiment with 6% to 20% of their acres.

A second probit model was used to analyze the probability that regulations would prevent them from growing pharmaceutical tobacco (Table 6). The predictors used were age, income greater than $50,000 a year, gender, experience with tobacco for more than 20 years, and tobacco acres. The model revealed male producers earning more than $50,000 a year and farming a larger number of tobacco acres were more likely to report the regulations would not prevent them from growing pharmaceutical tobacco.

In the participatory assessments that Nevitt et al. (2003) conducted, they reported that some tobacco producers expressed concern with maintaining relationships with the companies they currently contract with. Our study reveals a different outcome. We find that 95.4% of the tobacco farmers would be willing to grow tobacco for a company different than the one they usually contract with.

Conclusions

Previous research on perceptions of biopharming has focused on the consumers and the challenges policy makers face in addressing the diversity in public opinion. We explore producers' perceptions as they are also important stakeholders and will be subject to biopharming regulations when more commercialization takes place.

It appears that little is known by producers on biopharming and their responses are largely driven by the information presented to them, and most importantly, by economic profits.

In addition, producers appear to have relatively less concerns about the technology compared to consumers.

As biopharming progresses and producers become more aware of the technology, more research will be needed to find how producers' willingness to grow changes and the characteristics of those that will participate. Also, this survey did not address estimates of revenues and additional costs for producers or the specifications of a contractual relationship between the biopharmaceutical firm and the producer. These could be important topics in future biopharming research.

Finally, given the low level of biopharming awareness, it is very important to provide producers with appropriate information on biopharming, its challenges and opportunities. This way they can better evaluate their costs, risks and benefits and supply important insights that will help shape current and future regulation.

Footnotes:

[1]The current most common method of therapeutic protein production is using bioreactors (big steel containers with controlled temperature, humidity, etc.) where suspension cells with the desired proteins are grown. This called the upstream process. After the cells are fully grown, they are harvested and go through several steps in order to extract and purify the desire protein. This is called the downstream process (Hood and Howard, 2007).

[2']Don't knows' were treated as refuse to answer for all summaries in this paper.

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Table 1: Personal characteristics of participants

Attribute	*% of responders*
Male	95.0%
Age >55 years	67.7%
Income $100k -$120k	63.4%
Four year degree or higher	36.0%
Growing tobacco 31-40+ years	73.6%
Prior knowledge	
A lot	5.1%
Some	26.5%
Not much	41.9%
Nothing at all	26.5%

Table 2: Production characteristics of participants

Item	*Average*	*Minimum*	*Maximum*	*St. Dev.*
Production				
Acres	143	1	750	145.45
Total Production (tons)	121	1	700	119.57
Price ($/lbs.)	1.90	1.00	11.00	1.11

Table 3: Types of concerns about biopharming

Types of Concern	*% of responders*
Unexpected Effects	18.5%
Health	4.8%
Environment	4.4%

Table 4: Willingness to grow pharmaceutical tobacco

	Willing to adopt technology		
Net Return Per Acre	Current Production Methods	Change Production Method	Additional Equipment
5%	42.9%	7.4%	4.2%
10%	51.7%	23.5%	19.0%
25%	84.8%	71.9%	44.8%
40%	84.8%	78.8%	53.1%
More than 50%	80.0%	84.2%	69.2%

Table 5: Probit model for willingness to grow

Variables	(1) Current Production Methods	(2) Change Production Methods	(3) Additional Equipment
Net return per acre	4.4452***	27.9584***	4.9949***
	(1.7189)	(6.4152)	(1.1034)
Male	0.2891	4.0548***	0.8473
	(0.5905)	(1.3973)	(0.7747)
Age 50 to 85	0.2306	-0.3039	-0.4138
	(0.3423)	(0.4287)	(0.3863)
4 year degree or higher	-0.4997	0.2453	-1.1323***
	(0.3265)	(0.4486)	(0.3742)
Income >$50K	0.6178*	0.0512	0.8564**
	(0.3274)	(0.3997)	(0.3627)
Concern about biopharming	0.3774	0.6377	-0.4544
	(0.4315)	(0.6204)	(0.3932)
Level of prior knowledge	-0.4162	-0.3145	0.4998
	(0.3488)	(0.4346)	(0.3551)
Experience more than 10 years	0.1319	-0.1943	0.4434
	(0.7836)	(0.8292)	(0.7672)
Constant	-0.4391	-6.5998***	-1.9928*
	(1.0299)	(1.9883)	(1.1336)
Observations	111	98	95
Standard errors in parentheses			
*** p<0.01, ** p<0.05, * p<0.1			

Table 6: Probit on regulations preventing willingness to grow

Variables	Regulations would prevent adopting
Age	0.0241
	(0.0194)
Income >$50K	-0.7282**
	(0.3476)
Male	-1.3542*
	(0.7259)
Experience more than 20 years	-0.6265
	(0.7087)
Acres	-0.0040**
	(0.0020)
Constant	0.1098
	(1.1227)
Observations	109
Standard errors in parentheses	
*** p<0.01, ** p<0.05, * p<0.1	