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Is Biopharming Living Up to Its Promise? Latest Trends and Implications for the Agricultural Sector

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This article examines the status of the main biopharming products and estimates the potential acreage involved with biopharming. Our review suggests that important biopharming products of high quality are about to enter the market and they have the potential to provide significant benefits to producers and consumers. Acreage estimates indicate that biopharming may not be a significant source of income for farmers. However, potential acreage requirements warrant the establishment of the right regulatory framework to reduce risks of contamination.

Key words: agricultural acreage, biopharming, consumers, regulations

Biopharming is the production of pharmaceutical therapeutic proteins using genetically engineered plants and animals. Plants are generally preferred to animals for therapeutic protein production because they are able to produce complex proteins; they are less expensive to scale up and purify; and there is less risk of pathogen contamination as there are no cross-kingdom pathogens between mammals and plants (Tremblay et al., 2010). In fact, plants are able to produce vaccines that can be used to cure important diseases such as HIV, diabetes, cholera, Alzheimer's disease, cystic fibrosis, Hepatitis B, etc. (Ahmad et al., 2012).

Biopharming efforts started more than two decades ago with the promise to develop significantly less expensive pharmaceutical products. Many studies on biopharming production methods estimate production cost reductions up to 10-fold compared to the current production methods (e.g. Mison and Curling, 2000; Kusnadi, Nikolov, and

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Howard, 1997; Hood and Woodward, 2002).[1] Biopharming products are also expected to provide cost-effective methods to generate products to prevent prevalent diseases in developing countries such as malaria and HIV (Ma et al., 2005). Farmers also hope that biopharming will provide an alternative source of income and increase their profits (Gianoli, 2004).

The first biopharming products are already in the market or in different stages of the approval process. Biotech firms and pharmaceutical companies continue to invest in generating products and implementing the necessary steps of the drug approval process in order to gain market approval from the Food and Drug Administration (FDA). Most studies on biopharming products have focused on the technical aspects of production for specific products or, more generally, on the types of products being developed (e.g. Obembe et al., 2011; Tremblay et al., 2010; Ahmad et al., 2012). There are no studies that focus on potential acreage requirements of biopharming and less attention has been paid to the potential use and benefits of biopharming products. This paper provides a synopsis of the current state of biopharming and insights on the potential acreage involved in major biopharming applications. We also provide information on the number of people that can potentially use biopharming products as well as a discussion on potential benefits and concerns related to the use of agricultural land for biopharming.

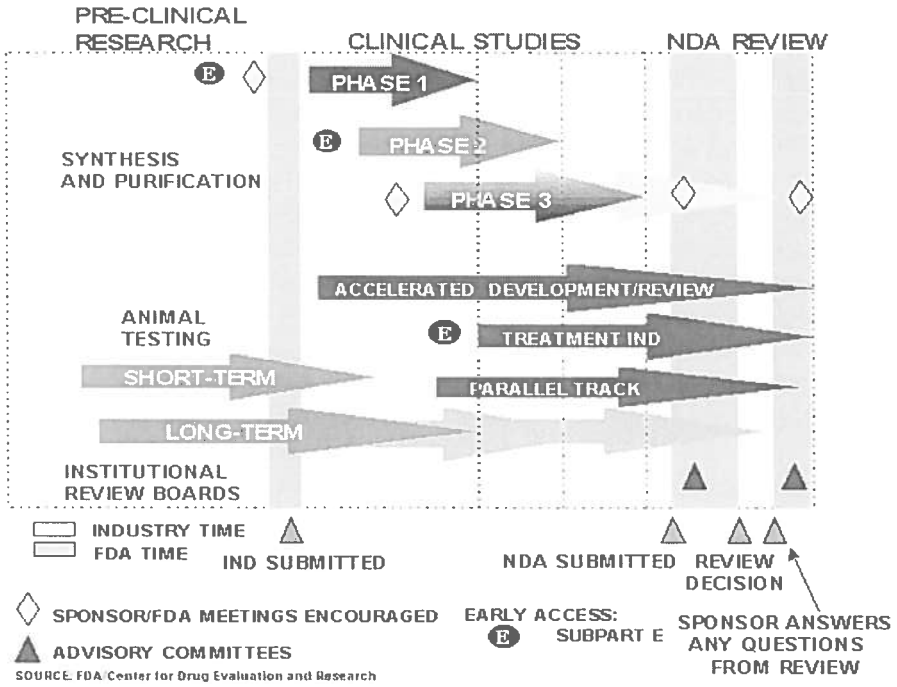
The rest of the paper provides a short description of the FDA drug approval process followed by an overview of the main biopharming products that are either in the market or in advanced stages of development. Then estimates of potential agricultural planted area involved with major biopharming products are provided, along with a short discussion on the potential benefits to consumers and producers and risks associated with biopharming. Conclusions are provided in the last section.

Biopharming and the FDA Approval Process

Biopharming products go through the same rules and procedures that main stream pharmaceuticals follow to gain approval from the Food and Drug Administration (FDA) and make it in the U.S. market. This is an extensive process which takes about twelve years to complete. Once a product is created in a laboratory, the product undergoes numerous testing before it is even submitted to the FDA for human testing. Human testing consists of three different phases. Phase I determining side effects by testing the

[1] The current most common production method of therapeutic proteins is by using bioreactors (big steel containers with controlled temperature, humidity, etc.) where suspension cells with the desired proteins are grown. This is 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 desired protein. This is called the downstream process. Biopharming eliminates bioreactors in the upstream process and provides significant overall cost reductions in the production of therapeutic proteins.

product on 20 to 80 healthy volunteers. If there is no revelation of intolerable toxicity during phase I, the product moves on to phase II of human trials (MedicineNet, 2011). Phase II determines the drug's effectiveness on 100 to 300 patients. As soon as a general effectiveness has been determined, the product moves to phase III which involves testing on between 1,000 and 3,000 patients (MedicineNet, 2011). At the end of the three phases, the producer must submit a roughly 100,000-page application to the FDA for approval. Generally, the drugs spend 3.5 years in preclinical testing, 1 year in phase I, 2 years in phase II, 3 years in phase III, and 2.5 years to get the New Drug Application (NDA) approval from the FDA (MedicineNet, 2011). Figure 1 illustrates the different stages that a company needs to go through in order to gain market approval in the United States.



Source: Food and Drug Administration (2010)

Figure 1. FDA Drug Approval Process

Table 1. Plant-derived Pharmaceuticals in Clinical Stages of Development or in the Market .

Product	Disease/Medical use	Plant	Clinical trial status	Company	Source: URL/academic
Vaccines					
Hepatitis B antigen	Hepatitis B	Lettuce	Phase I	Thomas Jefferson University	Streatfield, 2006
CTB	Cholera	Tobacco	Animal pre-clinical		Jani et al. 2004
Fusion proteins, including epitopes from rabies	Rabies	Spinach	Phase I completed	Thomas Jefferson University	www.labome.org/expert/usa/.../ hilary-koprowski-233492.html
Vibrio cholerae	Cholera	Potato	Phase I	Arizona State University	Tacket, 2005
Heat-labile toxin B subunit	Diarrhea	Maize	Phase I	ProdiGeneb, USA	Tacket, 2005
Capsid protein Norwalk virus	Diarrhea	Potato	Phase I	Arizona State University	Khalsa et al., 2004
H5N1 vaccine candidate	H5N1 pandemic influenza	Tobacco	Phase I	Medicago, USA	www.medicago.com
Antibodies					
Anti-PA mAb	Anthrax	Tobacco		Planet Biotechnology, USA	Wycoff et al. 2012
CaroRx™	Dental caries	Tobacco	Approved in EU	Planet Biotechnology, USA	www.planetbiotechnology.com/
DoxoRX	Side-effects of cancer therapy	Tobacco	Phase I completed	Planet Biotechnology, USA	www.planetbiotechnology.com/
RhinoRX	Common cold	Tobacco	Phase I completed	Planet Biotechnology, USA	www.planetbiotechnology.com/
Fv antibodies	Non-Hodgkin's lymphoma	Tobacco	Phase I	Large Scale Biology, USA	http://www.lsbc.com
IgG (ICAM1)	Common cold	Tobacco	Phase I	Planet Biotechnology, USA	www.planetbiotechnology.com/
Antibody for hepatitis B	Vaccine purification	Tobacco	On market	CIGB, Cuba	Kaiser, 2008
Therapeutic proteins					
Gastric lipase, Merispase	Cystic fibrosis	Maize	On market	Meristem Therapeutics,France	http://www.meristem-therapeutic:
2F5 mAb	HIV	Tobacco	In vitro	RWTH Aachen University, Aachen, Germany	Sack et al. 2007
b-Galactosidase	Fabry disease	Tobacco	Phase I	Planet Biotechnology, USA	www.planetbiotechnology.com/
Lactoferon.	Hepatitis B and C	Duckweed	Phase II	Biolex, USA	http://www.biolex.com/
Fibrinolytic drug	Blood clot	Duckweed	Phase I	Biolex, USA	http://www.biolex.com/
Human glucocerebrosidase	Gaucher 's disease	Carrot	Awaiting USDA's approval	Protalix Biotherapeutics, Israel	http://www.protalix.com/
Insulin	Diabetes	Safflower	Phase III	SemBioSys, Canada	http://www.sembiosys.com/
Nentraceuticals					
ISOkine , DERMOkine	Human growth factor	Barley	On market	ORF Genetics	http://www.orfgenetics.com/
Human lactoferrin	Anti-infection, anti-inflammatory	Rice	Advanced, on market as fine chemical	Ventria, USA	http://www.ventriabio.com/
Human lysozyme	Anti-infection, anti-inflammatory	Rice	Advanced, on market as fine chemical	Ventria, USA	http://www.ventria.com/
Trypsin	Research and Diagnosis	Corn	On market	Merck Chemicals	www.merck-chemicals.com
Aprotinin	Research and Diagnosis	Tobacco	On market	Bayer Bioscience	Spok and Karner, 2008

Sources: Obembe et al. 2011, Tremblay et al. 2010 and authors' research.

Current Status of Biopharming Products

To date, there are no FDA approved drugs from biopharming in the U.S. market for human use. Table 1 illustrates the major biopharming products and their status in the drug approval process. Clearly, biopharming has had some major breakthroughs; some products are in later stages of clinical trials and some (e.g. glucocerebrosidase enzyme) are close to getting FDA approval for human use.

The first true plant-made vaccine for animal use by Dow AgroSciences was approved in 2006 in the United States and it is being used successfully by the poultry industry. Other products are commercially available such as TrypZean™, and AproliZean™, by Prodigene. Another biopharming product in the market is CaroRx™, an inhibitor against dental caries produced from tobacco which is already approved in Europe (Planet Biotechnology, 2011). Some plant-made products such as trypsin (from corn), aprotinin (from tobacco), and β-Glucuronidase (from corn) are already commercially available as fine chemicals in research, diagnostics and manufacturing (Spok and Karner, 2008).

Table 2 presents the total number of patients in the United States and world that can potentially use some of these biopharming products. The underlying assumption is that biopharming products will be cheaper and they will be of the same quality and texture as the current cures for these diseases. The numbers on the potential number of patients in Table 2 suggest that hundreds of millions of people may potentially benefit from biopharming products in the pipeline.

Table 2. Number of Patients Who Can Potentially Use Biopharming Products .

Disease	Number of U.S. Patients	Source	Number of World Patients	Source
Hepatitis B	12,000,000	www.hepb.org/patients/general_information.htm	2,000,000,000	www.hepb.org/patients/general_information.htm
Cholera	61	www.cdc.gov/safewater/publications_pages/2001/steinberg_2001.pdf	4,000,000	www.bettermedicine.com/article/cholera-1
Diarrhea	73,000	www.cdc.gov/ncidod/eid/vol11no04/04-0739.htm	200,000,000	http://rehydrate.org/diarrhoea/
H5N1	17	www.cdc.gov/flu/avian/gen-info/avian-flu-humans.htm	500	www.flu.gov/individualfamily/about/h5n1/index.html
Anthrax	18	www.cdc.gov/mmwr/preview/mmwrhtml/rr4915a1.htm	60,000	www.dhpe.org/infect/Anthrax.html
Dental Caries	116,000,000	www.planetbiotechnology.com/products.html#caroRx		
Non-Hodgkin's Lymphoma	65,540	www.cancer.gov/cancertopics/types/non-hodgkin	175,123	www.nhlcyberfamily.org/statistics.htm#usa
Cystic Fibrosis	30,000	www.cff.org/AboutCF/?gclid=CIqe4d296KgCFQ175QodR2G2Dw	70,000	www.cff.org/AboutCF/?gclid=CIqe4d296KgCFQ175QodR2G2Dw
HIV	1,100,000	www.cdc.gov/mmwr/preview/mmwrhtml/mm5739a2.htm	33,000,000	www.who.int/hiv/data/2009_global_summary.png
Fabry Disease	200,000	www.wrongdiagnosis.com/f/fabrys_disease/prevalence.htm		
Gaucher's Disease	5,440	www.wrongdiagnosis.com/g/gaucher_disease/stats.htm#medical_stats		
Diabetes	25,800,000	www.diabetes.org/diabetes-basics/diabetes-statistics/	220,000,000	www.who.int/mediacentre/factsheets/fs204/en/
Rabies	18,000	http://aenear.mvweb.uga.edu/rabies.htm	55,000	www.who.int/mediacentre/factsheets/fs099/en/

Several important therapeutic proteins from biopharming such as Vibrio cholera (cure for Cholera) and Hepatitis B antigen (cure for Hepatitis B) may reduce costs, increase availability and reduce the number of deaths related to certain diseases in

developing countries. For example, around 2 million children die from diarrhea each year worldwide and 1 million people die each year from Hepatitis B. We also need to note that edible vaccines may become important products of biopharming as they can be consumed directly after harvesting and there is no need for downstream processing. For example fruits (banana) and vegetables (carrot, lettuce) can be modified to express the vaccine, which can be taken directly through plant consumption (Mason et al., 2002). In addition, some studies suggest that edible vaccines may be produced in less developed countries because of lower production costs (Paul and Ma, 2010; Biemelt and Sonnewald, 2005).

Biopharming Impacts on Farmers, Consumers, and Producers

Estimates of the potential agricultural acreage involved with the production of biopharming products are presented in Table 3. The results are based on authors' calculations and take under consideration the expression level of proteins, purification level, dosage level and the number of patients reported in Table 2.[2] For example, the acreage required to meet the demand for CaroRx™ is calculated as follows. As shown in Table 2, the potential demand for the cure in the United States and Europe comes from 116 million people and the dosage required to treat each person is 135 mg per person (6 treatments of 22.5 mg) (Ma et al., 1998). Thus a total of 15.66 billion mg are needed in the United States and Europe. Given that the acreage of tobacco for biopharming is 50 tons of fresh biomass per acre (Kostandini, Mills, and Norton, 2006) and the protein production level is 22.5 mg/kg of fresh weight (Ma et al., 1998), it is possible to produce about 1.13 million mg of the desired protein per acre. Thus a total of 13,920 acres are required to produce enough protein to treat all the patients in the United States and Europe.[3] All estimates in Table 3 represent an upper boundary as the underlying assumption is that all patients for each disease will be treated with the biopharming product. In addition, the estimates should be interpreted with caution as they are sensitive to expression levels and purification yield of the proteins. Both of these parameters may change as the products get closer to the market and production processes move from the laboratory scale to large scale commercial production.

[2] The calculations are available from the authors upon request. In some cases, such as recombinant human lactoferrin and trypsin, we use information on total annual sales, price and expression level of the proteins to estimate the total annual amount of protein that is sold in the market.

[3] This is found by dividing 15.66 billion mg which is the quantity sufficient to meet demand in the United States and Europe by 1.125 million mg/acres which is the production of one acre.

Table 3. Estimated Maximum Potential Acreage.

Product	Application	Plant	Supply	Total Acreage
2F5 mAb	HIV	Tobacco	World	2,437,679
Hepatitis B antigen	Hepatitis B	Lettuce	World	1,603,335
Various single-chain Fv antibody fragments	Non-Hodgkin's lymphoma	Tobacco	World	285,453
Anti-PA mAb	Anthrax	Tobacco	World	83
Capsid protein Norwalk	Diarrhea	Potato	World	1,839
CaroRx™	Caries prophylaxis	Tobacco	U.S. and Europe	13,290
Gastric lipase	Cystic fibrosis	Maize	World	240,000
Rabies glycoprotein	Rabies	Spinach	World	781
Human serum albumin	Multiple applications	Tobacco	World	10,000
Insulin	Diabetes	Safflower	World	12,000
H5N1 Vaccine Candidate	H5N1 pandemic influenza	Tobacco	World	600
Recombinant human lactoferrin	Anti-infection, anti-inflammatory	Barley	World	1
Trypsin	Research and Diagnosis	Corn	World	355,556

Source: Authors' calculations.

Estimates in Table 3 suggest that the acreage involved with biopharming products is small compared to more than 300 million acres planted annually in the United States. In addition, biopharmaceutical companies may use alternative innovative methods and plant biopharming plants in areas that are not used for agriculture. However, it may be able to provide some income for tobacco farmers. Total tobacco acreage in the United States in 2012 was 324 thousand (U.S. Department of Agriculture (USDA), 2012). The required tobacco acreage for several products (e.g. CaroRx™, Hepatitis B cure) is several times higher if approved in the U.S. under the assumption that it will gain wide usage. When you consider other crops, such as corn, biopharming acreage requirements are extremely small compared to the actual corn planted area in the United States, which is close to 100 million acres. Thus, biopharming is unlikely to be an important source of income for farmers in the near future.

There are several important ways in which biopharming can benefit biopharming companies and consumers. First, biopharming may provide significant benefits to producers who have invested in research and development and will reap the benefits

through price mark-ups protected by Intellectual Property Rights (IPRs) laws.[4] Second, these products will introduce more competition in markets where there are one or few firms, thus lowering the prices of these products. For example, the cure for non-Hodgkin's lymphoma is currently produced by one company which is a monopoly in the European market with global sales of $5 billion in 2007 (Scicasts, 2008). Two studies (Kostandini, Mills, and Norton, 2006; Kostandini and Mills, 2008) have applied imperfect competition models and have estimated millions of dollars of benefits related to the introduction of biopharming products. The latter will introduce more competition which will result in a lower price in the market. Third, consumers may benefit from the lower prices through more competition especially when the patents expire and generics enter the market.

Finally, it is important to highlight several risks associated with biopharming. The major problem is with respect to the contamination of the food and feed chains. There have been instances, such as the StarLink and ProdiGene transgenic corn cases, where a specific type of transgenic corn that was not authorized from the U.S. Environmental Protection Agency (EPA) for feed, entered the feed supply (Starlink case) and biopharma corn kernels (Prodigene case) were left on the ground which was later planted with non pharma soybeans (Hileman, 2003; EPA, 2000; Choi, 2002). Currently, regulations and permits for testing, producing, transporting and commercializing biopharming products are controlled from the USDA and FDA. Many groups favor biopharming in crops such as tobacco, which is not used in the food or feed chain and thus lowers the risk of contamination.

Conclusions

This article provides an overview of biopharming in terms of the status of its products and the number of patients that may potentially use these products. We also estimate potential acreages involved with biopharming drawing implications for the agricultural sector. Our review suggests that important biopharming products of high quality are close to getting market approval and have the potential to generate substantial benefits for consumers and producers. In addition, although in earlier development stages, edible vaccines from biopharming may be very beneficial, especially in developing countries. Potential acreage requirements suggest that biopharming may not be a significant source of income for farmers.

[4] The average patent life for pharmaceuticals is around 12 years (MedicineNet, 2011).

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