

**Sowing Secrecy: The Biotech Industry, USDA,
and America's Secret Pharm Belt**

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Executive Summary

After taking a one-year hiatus in the aftermath of the Prodigene incident, the biotechnology industry engaged in the genetic engineering of plants to produce pharmaceuticals, industrial compounds, and other novel proteins (“biopharming” or “pharma crops”) has stealthily returned to the business of planting crops and producing commercial products. In the past twelve months (May 2003 through April 2004), the United States Department of Agriculture (USDA) received sixteen applications to grow pharma crops, with half of those permit applications submitted in the last three months.

The private companies and public researchers who have submitted those permit applications have not listened to the outcry from the public and food-industry officials opposed to using food crops for biopharming. Approximately two-thirds of the 16 permit applications involved planting a food crop, with six applications (approximately 38%) involving corn. In addition, many of the applications request planting a food crop in the same state where there is significant commercial production of that same crop for human and animal consumption. For example, five of the six applications to plant pharma corn seek permission to grow it in either Nebraska, Iowa, or Texas, states that each grow millions of acres of corn. Finally, while the majority of the permit applications are seeking a permit for a research trial, at least some of the permits involve planting the pharma crop to extract and market a commercial product.

While the biopharm industry pushes forward toward commercialization, USDA has kept the public and interested stakeholders in the dark about this reemergence. USDA has already approved seven of the permit applications without providing the public any information about the applications or ever seeking the public’s comments and concerns. It is likely that USDA will approve the remaining nine applications in the next several months (it has denied only two pharma permits since January, 2000), which will result in pharma crops being grown in eleven states, including Nebraska, Iowa, Texas, California, and Hawaii.

Due to the lack of publicly available information from USDA, it is impossible to know whether the crops pose any environmental risks. USDA does not conduct an individual environmental risk assessment before it issues a permit, and none of an applicant’s data on environmental risks is provided to the public. It is also impossible to determine if there would be potential harms to humans if one of the pharma crops inadvertently entered the food supply. The Food and Drug Administration (FDA) does not conduct a food-safety risk assessment prior to or after commercialization of a pharma crop and has no authority to prevent a crop that might endanger the food supply from being planted.

Background

The use of genetically engineered plants to produce pharmaceuticals, industrial compounds, or novel proteins for non-food uses (collectively referred to as “pharma crops” or “biopharming”) has the potential to provide tremendous consumer benefits, but if misused, could harm consumers or the environment. Between 1995 and 2002, USDA authorized the planting of pharma crops at over 300 field test sites. (US PIRG “Raising Risk, June, 2003).¹ Potential products that manufacturers hope to produce commercially include insulin from safflower, human serum albumin (used as blood volume replacement during shock, serious burns, and surgery) from corn, hepatitis B vaccine from tobacco, cholera and Norwalk virus vaccines in potatoes, and lactoferrin (a human protein that protects against infections) in rice.²

Until the fall of 2002, the planting of pharma crops occurred without the knowledge of the public, food processors, or various other stakeholders who have an interest in the safe use of agricultural biotechnology. Then in November 2002, USDA disclosed to the public that Prodigene, an agricultural biotechnology company that was producing novel proteins in corn, had violated government-mandated permit conditions established to prevent corn that was producing a pig vaccine from escaping into the environment or contaminating the food supply. Prodigene’s violations involved improper containment at sites in Iowa and Nebraska and resulted in Prodigene being assessed a \$500,000 fine. The Nebraska violations also required the federal government to seize and destroy 500,000 bushels of contaminated soybeans at a cost of over \$3,000,000 (which Prodigene is currently supposed to be repaying to the government).

The Prodigene incident generated great public concern about the risks of biopharming, especially when it was conducted in food crops. Different stakeholders advocated much stricter regulation of biopharming and many called for the complete cessation of the use of food crops. The food industry was particularly terrified that a molecule of a chemical or pharmaceutical would be found in their products. For example, the National Food Processors Association (NFPA) stated in a position statement on November 20, 2002, that it “finds there is an *unacceptable risk* to the integrity of the food supply associated with use of food and feed crops as ‘factories’ for the production of pharmaceuticals or industrial chemicals.” (Emphasis added) Similarly, the Grocery Manufacturers of America (GMA) stated in a November 14, 2002, press release that the Prodigene incident “reaffirms GMA’s concerns” about biopharming with food crops and strongly recommended that the biotechnology industry focus on the use of non-food crops.

¹ “Raising Risk” can be found at <http://pirg.org/ge/GE.asp?id2=10195&id3=ge&>.

² Many different applications of biopharming were described by Dr. Julio Baez, Senior Research Fellow at FibroGen, at a April 22, 2004 symposium sponsored by the Biosafety Institute for Genetically Modified Agricultural Products (BIGMAP) at Iowa State University. Dr. Baez’s presentation can be found at <http://www.bigmap.iastate.edu/>.

Regulation of Biopharming at USDA

At the time of the Prodigene incident, USDA's regulatory system for biopharming required that companies wishing to plant a crop producing a human pharmaceutical submit a permit application and receive a permit before proceeding. Those permits required specific containment and confinement obligations to prevent the persistence of the crop in the environment after it was planted. For crops engineered to produce an industrial compound or other novel protein (such as a medical diagnostic protein), depending on the substance, some of those crops went through the same permitting procedures as crops engineered to produce a pharmaceutical. For others, however, the regulatory process allowed for an expedited permitting process called "notification," in which the company notified USDA about its planting and agreed to satisfy generic performance standards. USDA would then "acknowledge" the notification, which automatically authorized the planting.

In the aftermath of the Prodigene incident, USDA modified its regulations so that all plants engineered to produce a pharmaceutical, an industrial chemical, or other novel non-food substance, would need a permit before being planted (thus eliminating the "notification" option). USDA also increased the stringency of its containment requirements to decrease the likelihood that any plant would escape from the permitted site and have a detrimental effect on agricultural interests, the environment, or the food supply. The additional containment requirements, however, have not satisfied both critics of biopharming and other stakeholders, including members of the food industry. For example, NFPA stated that while the increased stringency was an "improvement," "NFPA members feel more rigorous conditions are required to preserve the integrity and reduce the liability of the food industry to a contamination incident." (NFPA comments to USDA dated May 12, 2003).³

Although USDA modified and strengthened its biopharming regulation, it did not address many criticisms of its biopharming regulatory system. USDA did not increase the transparency of its current regulatory system by making available to the public the application submitted by the applicant and the permit it issued. In addition, there is still no opportunity for public participation in the approval process. Also, USDA does not conduct an individual environmental risk assessment before granting a biopharming permit nor has USDA adequately

³ In addition to believing the current USDA regulation of pharming in food crops is not stringent enough, NFPA has stated that if it has been asked its viewpoint when pharming crops were first being developed, it "would not have supported the use of food crops for the production of plant made pharmaceuticals. The risk and impact of contamination to the food supply is simply too great..." NFPA also believes that "the use of food crops to produce plant made pharmaceuticals must only proceed under systems proven to absolutely prevent any contamination or adulteration of the food supply." See NFPA comments to USDA dated May 12, 2003, which can be found at <http://www.nfpa-food.org/Comments/NFPACommentsPMP.htm>.

restricted the use of food and feed crops for biopharming.⁴ Finally, the permit process still does not distinguish between crops grown as part of a field trial and crops grown to produce a commercial product.

Purpose and Methodology of CSPI Study

Due to the negative publicity from the Prodigene incident and the changing regulatory environment at USDA, the year following Prodigene was not a good time period for biopharming. Monsanto, a major researcher of biopharming, announced it was discontinuing its plant-made pharmaceutical program (Oct. 2003), and Crop Tech, one of the more active small companies conducting biopharming, declared bankruptcy (Feb. 2003). Only four applications to permit the growing of pharma crops were approved between July 1, 2002 and June 30, 2003 (which includes the growing season immediately following the Prodigene incident).⁵ By comparison, USDA issued 25 permits for biopharming between July 1, 2001, and June 30, 2002.⁶

In May 2004, CSPI sought to determine whether the biopharming industry was still hibernating from the aftermath of the Prodigene incident or whether there had been a resurgence of permit applications and planting activity in late 2003 and 2004. To do that, CSPI conducted numerous searches of the database of USDA biotechnology field trials permit applications maintained on the Information Systems for Biotechnology (ISB) website at Virginia Tech

⁴ USDA has ignored suggestions from the food industry to restrict the use of food and feed crops for biopharming. GMA sent a letter to USDA that stated that “USDA should adopt a presumption against the use of food or feed crops....To overcome this presumption, a pharmaceutical product developer who wishes to use such crops should be required to demonstrate that it has tested the suitability of non-food crops and has determined that the use of such crops is not feasible from either an economic or a technological standpoint.” (GMA comments to USDA dated May 5, 2003, found at <http://www.gmabrands.com/publicpolicy/docs/comment.cfm?DocID=1135>.) To date, no such presumption exists in the regulatory system and instead, USDA treats biopharming with food and non-food crops almost identically.

⁵ Five permit applications for biopharming were withdrawn between July 1, 2002, and June 30, 2003. There is no information available as to why they were withdrawn. Some possible explanations might be that the developers did not want to plant immediately after the Prodigene incident, the plantings no longer fit within the company’s business plan, or that USDA increased scrutiny might have resulted in the application being insufficient for USDA’s new requirements.

⁶ It should be noted that one Prodigene permit was denied by USDA during that time period.

University (www.isb.vt.edu).⁷ ISB handles the publicly available data from the USDA for all the genetically engineered crops that USDA regulates. CSPI collected and analyzed data from that website about permit applications for pharma crops engineered that were submitted to APHIS from May, 2003 through April, 2004. The data collected and analyzed was limited because in many instances either information was not provided (such as test acreage) or determined to be confidential business information.

Recent Pharma Crop Permit Applications

From May, 2003 through April, 2004, USDA received 16 permit applications to plant pharma crops, with half of those permit applications arriving at USDA within the last three months.⁸ See Table 1. Those applications came from ten different institutions from both the private (seven companies submitted 13 applications) and public sectors (three institutions submitted three applications). Prodigene had the most applications (4) while three other companies had two applications each (Ventria Bioscience, Large Scale Biology, and Chlorogen).

Despite the controversy and concern about biopharming using food crops, approximately two-thirds of the applications submitted involved the use of a food crop. See Figure 1. The single most used crop was corn, with six applications (38%). Other food crops that were to be used included barley (2 applications), rice (1 application), safflower (1 application), and Indian mustard (1 application).⁹ The remainder of the applications (5) involved tobacco, a non-food crop.¹⁰

⁷ Unless otherwise specifically stated in this report, all data about permit applications and permits issued by USDA comes from the database found on the ISB website.

⁸ CSPI used a conservative methodology to determine the number of pharma crop permits. Only permit applications where the USDA database specifically identified the phenotype as “pharmaceutical protein produced,” “value added protein for human consumption” or “industrial enzyme produced” were included. There were other instances in the database where the phenotype “novel protein produced” was provided but only in conjunction with numerous other phenotypic identifiers. Those instances, as well as instances where the phenotype of the organism was not disclosed, were not included in the analysis even though some of those permits may involve biopharming.

⁹ For one permit application from the USDA Agricultural Research Service, the ISB database did not identify the crop involved in the submission. CSPI contacted ISB and they provided the identification of the crop as “Indian mustard” after contacting the principal investigator.

¹⁰ For one tobacco application involving Large Scale Biology, the organism that is genetically engineered is the tobacco mosaic virus. That organism then infects the tobacco plant, which produces the protein to be extracted. Thus, this application has been listed as involving tobacco as the crop producing the protein.

It was impossible to identify the total acreage that was proposed to be grown under the permit applications since that information was rarely provided. However, if all the permits were granted, new biopharming would be allowed in 11 states. See Figure 2. Kentucky was identified on four permit applications while Texas was identified on three permit applications.¹¹ Missouri, South Carolina, California, and Iowa were each identified on two applications. The remaining states identified on only one application each were Hawaii, Florida, Washington, Nebraska, and Arizona. Two of the three permit applications that involved corn belt states – Iowa and Nebraska – involved the release of corn.

Biopharming Permits Issued by USDA

For the 16 permit applications submitted to USDA starting in May 2003, USDA has issued seven permits between October 2003 and May 2004 to seven different institutions (six private and one public). None of the remaining nine permit applications has been denied or withdrawn but all are still awaiting USDA action. All nine pending applications were submitted in the last four months, so USDA is still within its designated review time before making a determination.¹² It is anticipated that most, if not all, of the pending permits will be issued, since between 1987 and 2002 USDA only denied 3.5% of permit applications (US PIRG “Raising Risk) and denied only two biopharming permits since the beginning of 2000 (one from Prodigene in March 2000 and another from Prodigene in April 2002).

Of the seven issued permits, five involved a food crop, including two permits for corn and one each for rice, safflower, and Indian mustard. Two biopharming permits were issued for tobacco.

Based on the information available about the seven permits already issued, biopharming crops can now be legally grown in six different states. Those states included Arizona, California (two permits), Kentucky, Nebraska, Florida, and Hawaii.

Pharma Crops are Being Planted for Commercial Production

Based on the data made available from USDA, it is unclear whether the permit applications or permits issued involve commercial-scale production of a commercial product. The legal obligations to conduct a field trial of a pharma crop are identical to the obligations for growing a pharma crop on a commercial scale. When CSPI investigated other publicly available

¹¹ Under the USDA permitting system, one permit application can be submitted for the planting of a particular crop at numerous locations. Thus, a single permit can authorize numerous plantings in one or more states. USDA makes the states where the planting will occur public but the actual locations and the number of plantings is usually not disclosed.

¹² In fact, three permit applications have been pending less than three months and five other permit applications have been at USDA no more than six weeks.

information, however, it is likely that as many as five of the permit applications (and two of the permits approved to date) concerned growing a crop on a commercial scale.

Prodigene recently announced on its website and in a press release that it currently has available for purchase two products produced in maize – recombinant trypsin and recombinant aprotinin. See <http://www.prodigene.com/>. Thus, it is likely that the four permit applications from Prodigene involve growing corn to commercially produce either trypsin or aprotinin.¹³

The SemBioSys Genetics application to grow safflower in Arizona (approved by USDA in 2004) also could result in a product that is sold commercially. The SemBioSys application sought permission to grow 16 acres of the crop. One of the advantages touted by biopharming companies is that the markets for their products can be served by only a small amount of acreage. Thus, the large specified acreage for the SemBioSys permit strongly suggests that it could involve commercial-stage production rather than field trial research.

Risks to the Environment or Human Health – A Big Unknown

The potential environmental risks of any genetically engineered crop – such as gene flow to wild relatives, effects on biodiversity, or harm to other organisms – need to be assessed on a case-by-case basis. For all pharma crop applications received by USDA, it is unclear whether any individual environmental assessment is conducted prior to permit issuance. USDA does not publicly release a decision document explaining why it has granted a permit and why it believes planting the crop will not cause any environmental harm. In addition, USDA does not make publicly available the application, which is supposed to contain information about the introduced gene (including its potential toxicity) and its potential effects on other organisms. In most cases, due to a claim of “confidential business information,” the public is not even informed of the protein produced by the crop. Thus, it is impossible to determine what harmful environmental or human health effects, if any, might result from the planting of any of the pharma crops.

As for any specific risks to human health if a biopharming crop inadvertently entered the food supply, currently no federal agency addresses that issue. The USDA permitting process for genetically engineered crops is legally authorized to analyze and address only plant-pest, agricultural, and broad environmental risks. USDA does not have the legal authority – or the scientific expertise – to determine whether the crop will result in any food-safety risk to

¹³ According to Prodigene, the trypsin molecule has a number applications, including dermatological applications to facilitate wound healing, as a digestive aid breaking down difficult proteins, and in the manufacture of insulin and vaccines. See [www.prodigene.com/pdf/Trypzean\(tm\)%20Backgrounder.pdf](http://www.prodigene.com/pdf/Trypzean(tm)%20Backgrounder.pdf). Aprotinin also has a number of commercial applications including reducing bleeding and facilitating healing in patients undergoing cardiopulmonary bypass surgery, helping with purification of recombinant proteins and biopharmaceuticals, and diagnostic testing. See [www.prodigene.com/pdf/AproliZean\(tm\)%20Backgrounder.pdf](http://www.prodigene.com/pdf/AproliZean(tm)%20Backgrounder.pdf).

humans. The agency with the appropriate scientific expertise, the Food and Drug Administration (FDA), has not established any regulatory process that would require it or the applicant to conduct a food-safety risk assessment prior to the commercial planting of a pharma crop.¹⁴ Thus, under current law and federal regulatory practice, none of the sixteen permit applications has or will undergo a scientific food-safety risk analysis prior to planting. If any crop grown from the sixteen permit applications inadvertently makes its way into our food supply, there will be little information about whether that contamination could lead to a human health problem.

Conclusions and Recommendations

The biopharming industry seems to be back in business. Both private and public institutions are submitting applications to conduct field trials and produce commercial products. Sixteen applications have been submitted to USDA in the past year, eight of which were submitted within the last three months. Despite concerns by numerous stakeholders about using food crops to produce pharmaceuticals and industrial compounds, approximately two-thirds of the sixteen applications involve food crops, including six involving corn. In addition, the location of some of the pharma crops still corresponds closely with the commercial growing of the same crops for human and animal consumption. For example, two permits for pharma corn have been approved in states that grow significant amounts of corn (Iowa and Nebraska). On the other hand, five applications involve tobacco, a non-food crop that will result in significantly less risk to the public.

To date, USDA has granted permits for seven of the 16 submitted applications and not rejected any of them. There is no evidence to suggest that the remaining nine applications will not be approved. For the permits already issued, USDA did not alert the public to the pending application, nor did USDA allow the public to comment before the application was approved. There is no evidence that an environmental or food-safety assessment was conducted on any of the applications that were granted. Finally, for some of the permit applications, there is evidence that those plantings are not being conducted as field trial research, but to grow a product that can be sold commercially.

Due to the lack of transparency of the USDA regulatory process for biopharming, it is impossible to know whether any environmental or human health risks might result if the sixteen permit applications are approved and the crops released into the environment. It is also impossible to judge whether USDA has done an adequate job of assessing and managing potential risks of the pharma crops.

To address the issues raised by this report, CSPI recommends the following changes in

¹⁴ Although the FDA does not ensure the food-safety of pharma crops, it will review and approve the safety of the products of pharma crops that fall within its jurisdiction. Thus, if a pharma crop produces a biologic or a human or animal pharmaceutical, those drugs will need FDA approval before they can be marketed.

the current regulatory system for pharma crops:

1. For each pharma crop, USDA should make available to the public (a) the application, (b) the risk assessment, and © the permit that it issues.¹⁵
2. Before the permit is issued, the public should have an opportunity to review the application and risk assessment and provide comments to USDA.
3. No permit should be issued until USDA conducts an individual environmental risk assessment and identifies necessary risk management and mitigation strategies.
4. The issued permit should require state-of-the-art biological and physical confinement measures to ensure that the crop or chemical being produced does not persist dangerously in the environment or enter the food supply inadvertently.
5. No pharma crop that uses a food crop should be allowed to be grown to produce a product on a commercial scale until the FDA has conducted a food-safety risk assessment on that crop and determined the risks if that crop inadvertently entered the food supply.¹⁶
6. USDA should end its current regulatory policy of treating identically pharming using food and non-food crops and discourage the use of food crops for biopharming. Additional regulatory obligations should be imposed on any such crops to minimize the additional scientific risks posed by those crops.
7. The U.S. government should support independent risk assessment scientific research to (1) determine the reliability of physical and biological methods of confinement, and (2) establish tools and methods to conduct both site and product specific environmental and food-safety risk assessment.

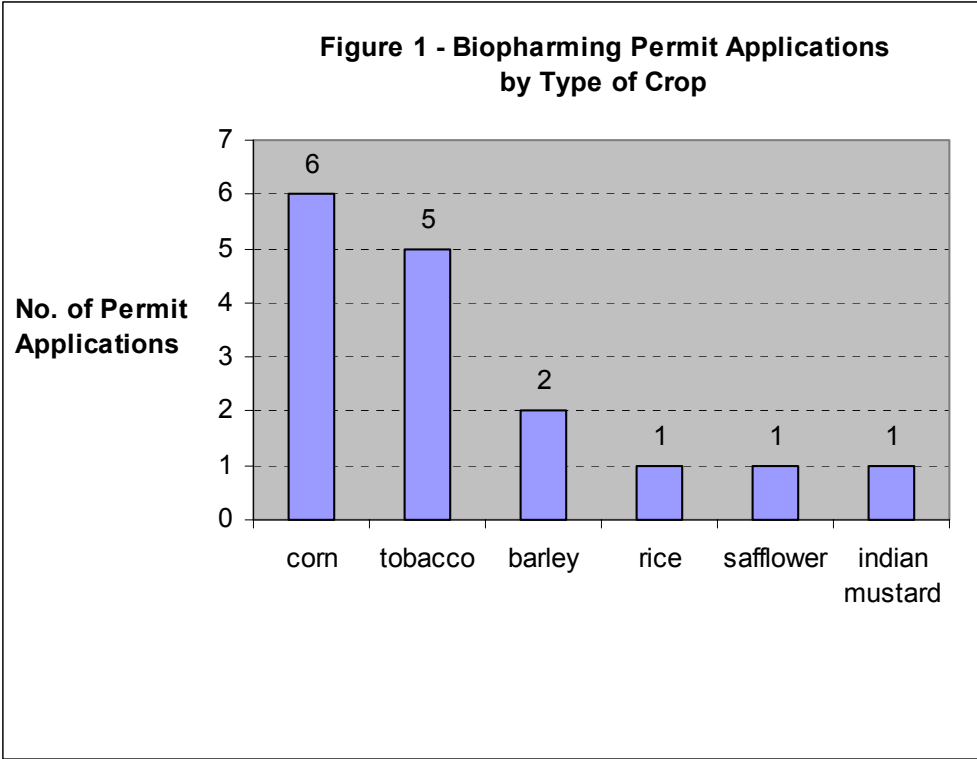
¹⁵ CSPI acknowledges that some information in the application may be confidential business information that should not be disclosed, including the exact location of the planting. However, most information contained in any environmental or food-safety risk assessment and the obligations imposed by USDA in the permit will almost never satisfy the legal tests for confidential business information.

¹⁶ Although most of the recommendations in this report could be immediately implemented by the federal government, this particular recommendation requires Congress to amend the Federal Food, Drug, and Cosmetic Act. Senator Durbin (D-IL) has introduced legislation, the Genetically Engineered Foods Act, which would require FDA to assess and approve all genetically engineered food crops, including those engineered to produce a non-food substance such as a pharmaceutical or industrial compound.

Table 1 - Biopharming Permit Applications to USDA, May 2003 - April 2004

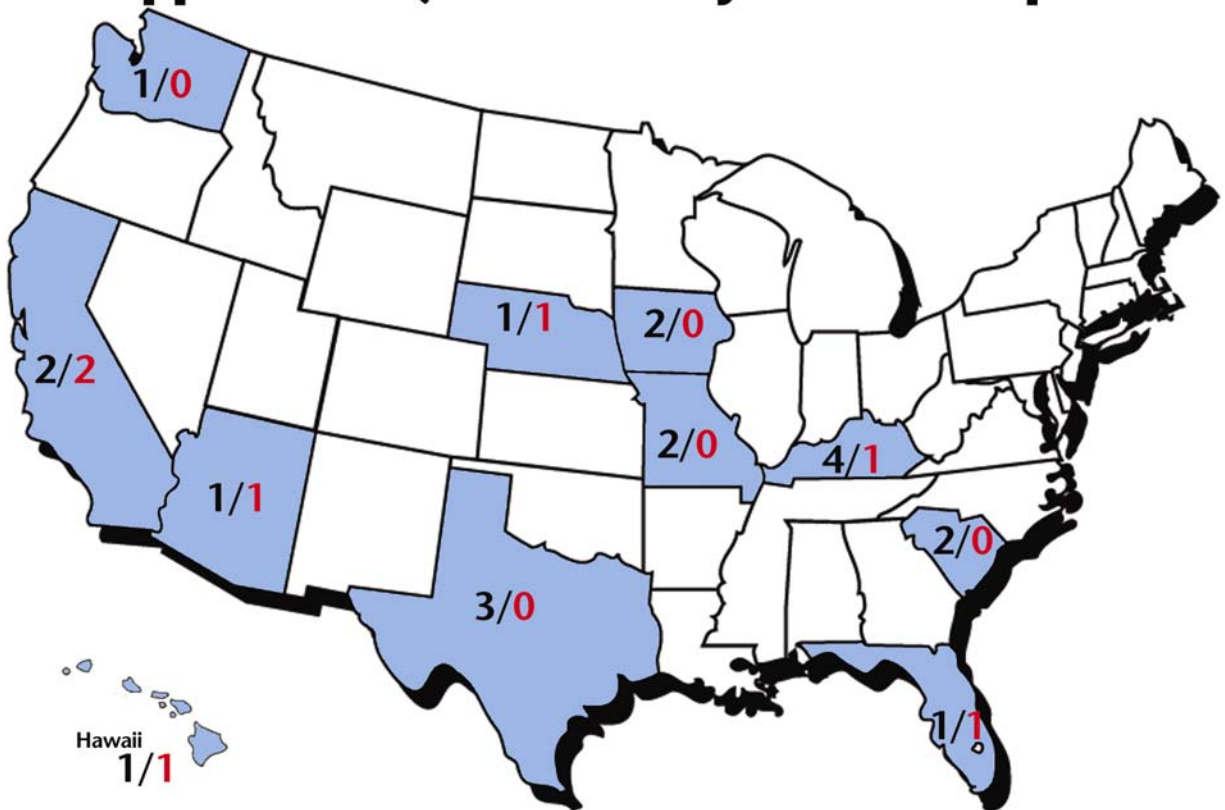
Applicant	Crop	Crop Type	Location	Submission to USDA	Permit Issuance Date
Garst	corn	pharmaceutical	HI	May-03	October-03
Large Scale Biology	tobacco	pharmaceutical	FL	May-03	December-03
SemBioSys	safflower	not provided	AZ	September-03	January-04
Ventria Bioscience	rice	value added protein	CA	December-03	May-04
ARS	indian mustard	industrial enzyme	CA	January-04	March-04
Prodigene	corn	pharmaceutical	NE	February-04	April-04
Planet Biotechnology	tobacco	pharmaceutical	KY	February-04	April-04
Large Scale Biology	tobacco	pharmaceutical	KY	February-04	pending
Washington State U.	barley	pharmaceutical	WA	March-04	pending
Iowa State U.	corn	pharmaceutical	IA	March-04	pending
Chlorogen	tobacco	pharmaceutical	KY, MO, SC	March-04	pending
Ventria Bioscience	barley	value added protein	IA	April-04	pending
Prodigene	corn	pharmaceutical	TX	April-04	pending
Prodigene	corn	pharmaceutical	TX	April-04	pending
Prodigene	corn	pharmaceutical	TX	April-04	pending
Chlorogen	tobacco	pharmaceutical	KY, MO, SC	April-04	pending

Source: ISB Website (www.nbiap.vt.edu).



Source: ISB website (www.nbiap.vt.edu).

Figure 2: States Included in Recent Biopharming Permit Applications (between May 2003 and April 2004)



Number of applications filed / Number of applications approved.

Source: ISB Website (www.nbiap.vt.edu).