BIOTECHNOLOGY IN THE PIPELINE: SPARKS COMPANIES' UPDATE

J. B. Penn
Sparks Companies, Inc.
Washington, DC

Biotechnology Update - Changes in 1999

The trends in biotechnology that were emerging by late 1998 have become even more pronounced this year. The first "wave" of emerging products continues to be dominated by crops with "input traits," so-called because they affect farmers' needs for other inputs, mainly pesticides. They both reduce costs and/or improve yields.

Examples of input traits are herbicide tolerance and insect resistance. Herbicide-tolerant crops permit farmers to use potent herbicides broadly and control weeds effectively — and, they appear to be reducing herbicide use significantly.

By inserting the gene of a common soil microorganism, *Bacillus thuringiensis* (Bt), into plant tissue, scientists also have created crops that produce their own insecticide and resist attack by pests including the European corn borer, cotton bollworms and cotton budworms. In the case of the European corn borer, for example, farmers generally do not attempt to control infestations which normally reduce yields by significant amounts but not enough to pay to invoke pest control efforts. Bt crops effectively control this pest cheaply — and tend to increase overall crop yields as a result.

The first commercial, transgenic grains and oilseeds were released in the United States in 1996. The groundbreaking products were Bt corn from Ciba Seeds (now Novartis), Roundup Ready soybeans and Bollgard (Bt) cotton from Monsanto.

Biotech Crop Adoption[1]

In 1996, biotech crop area in the United States totaled just over 13 million acres. By 1998, biotech area had grown nearly fivefold to just under 75 million acres, 23% of all significant field crop area (including wheat, oats and tobacco, where biotech seed is not yet available). In 1999, biotech acreage has expanded still further, to over 90 million acres, 29% of total field crop acreage.

Still, biotech plantings are dominated by relatively few crops – soybeans, corn and cotton, and adoption rates are substantially higher for those individual crops. In 1999, for example, 45 million acres were planted to biotech soybeans, a sustained increase over the 37 million acres planted in 1998, and a dramatic increase over levels seen in 1996 and 1997 (Chart 1).

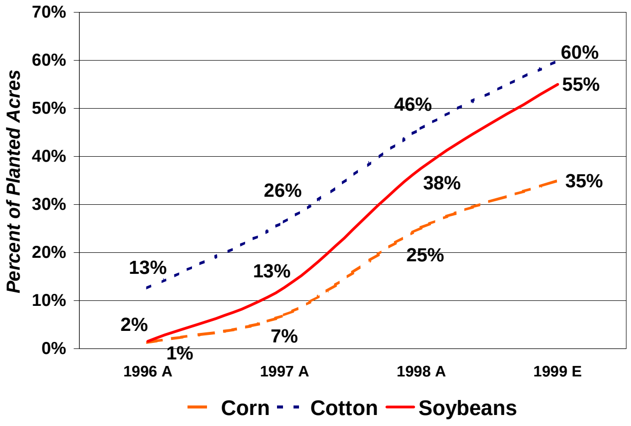

Chart 1. US Biotech Crop Acreage, 1996-99

Biotech corn area approached 40 million acres this year, up nearly 10 million acres from 1998, with most of the increases from Monsanto's YieldGard (Bt) and Roundup Ready corn. For cotton, the adoption of biotech varieties reached 60% of total land in cotton in the United States. Varieties used were mainly Monsanto's Bollgard and Roundup Ready technologies.

Other crops, such as canola and potatoes, continue to have modest amounts of biotech acreage. In 1998, 80,000 acres were planted to Monsanto's Laurate canola, which contains oil high in lauric acid that is suitable for food processing applications as well as industrial uses such as soaps and detergents. However, production of Laurate canola appears to have been halted in 1999, and Roundup Ready and Liberty Link canola together account for less than 100,000 acres. The area planted to biotech potatoes was at most 50,000 acres – all Monsanto NewLeaf potatoes – accounting for about 4% of US potato acreage.

Transgenic procedures to develop new traits are coming to dominate genetic practices in the United States, and accounted for more than 70% of the total biotech acreage in the United States in 1998 (Table 1). Soybean varieties had the largest share of the transgenic crop area with 27 million acres, while the transgenic corn area was 20 million acres. Many of the value enhanced corn varieties currently on the market have traits which were developed through conventional breeding techniques; these nontransgenic varieties accounted for 10 million acres in 1998[2]. Nontransgenic soybean varieties, mostly DuPont's STS soybeans tolerant of sulfonylurea herbicides, were planted on an additional 10 million acres.

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Table 1. Biotech Crop Acreage by Genetic Status

	Transgenic				**Nontransgenic**			
	1996 A	**1997 A**	**1998 A**	**1999 E**	**1996 A**	**1997 A**	**1998 A**	**1999 E**
				Million acres				
Canola	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0
Corn	1.0	5.6	20.2	28.8	6.0	7.4	10.1	10.7
Cotton	1.9	3.6	6.1	8.8	0.0	0.0	0.0	0.0
Potatoes	0.0	0.0	0.1	N/A	0.0	0.0	0.0	0.0
Soybeans	1.0	9.0	27.0	35.0	3.5	7.0	10.1	10.1
Total	3.9	18.3	53.5	72.7	9.5	14.4	20.2	20.8

Wheat is a notable exception to the biotech crop development profile, with no biotech product yet commercially available. This likely results both from scientists getting a late start on research and the reported greater difficulty in its genetic modification than other crops, especially oilseeds.

Herbicide Tolerant Crops

Herbicide tolerant crops were planted on 63 million acres in 1999, nearly double the combined acreage of insect-resistant and value enhanced crops. The most widely adopted biotech crop is Roundup Ready soybeans, grown on 35 million acres in 1999 (nearly one-half of all soybean acres in the United States). This acreage was up sharply from 1998 when 27 million acres (34%) were planted to Roundup Ready soybeans (Table 2). DuPont's STS soybeans have the largest area of any nontransgenic herbicide-tolerant crop, with approximately 10 million acres.

Table 2. Herbicide Tolerant Crops

Company	**Product**	**USDA Approval Date**	**Planted Area**			
			1996 A	**1997 A**	**1998 A**	**1999 E**
			Million Acres			
AgrEvo	Liberty Link canola	1/29/98	N/C	N/C	N/C	0.05
AgrEvo	Liberty Link corn	6/22/95	N/C	0.7	2.0	2.3
American Cyanamid	IMI corn*	Not Transgenic	3.4	4.5	6.6	N/A
BASF/Univ. Minnesota	Poast Protected corn	Not Transgenic	N/A	N/A	0.3	N/A
DuPont/ Pioneer	STS soybeans	Not Transgenic	3.5	7.0	10.0	10.0
Monsanto/ DEKALB	GR corn	12/19/95	N/C	0.1	0.2	N/A
Monsanto/ DEKALB	Roundup Ready corn	11/18/97	N/C	N/C	1.0	2.3
Monsanto/ DEKALB	Roundup Ready cotton	7/11/95	N/C	0.8	2.2	3.1
Monsanto/ DEKALB	Roundup Ready soybeans	5/19/94	1.0	9.0	27.0	35.0
Monsanto/ DEKALB	BXN cotton	2/15/94	0.1	0.3	0.8	1.1

*Estimate for IMI corn based on seed availability, not actual planted acres.

N/C = not commercialized; N/A = not available

Sources: Biotech/Seed Companies, US Grains Council Value Enhanced Corn Quality Report, Press Reports

Monsanto's Roundup Ready corn was available commercially last year and used on a limited number of acres, but in 1999 it likely caught up to Liberty Link corn, with about 2.3 million acres planted to each. IMI varieties have the largest acreage of any nontransgenic herbicide-tolerant corn product.

All herbicide-tolerant cotton varieties are transgenic. Roundup Ready cotton area reached 2.2 million acres in 1998 and increased to 2.9 million acres in 1999, about 20% of the US crop.   BXN cotton, sold by Monsanto's Stoneville subsidiary (in the process of being sold to the investment firm Hicks Muse), was planted on 0.8 million acres in 1998 and 1.1 million acres in 1999.

Insect Resistant Crops

All insect-resistant crops sold commercially to date contain genetic material from the *Bacillus thuringiensis* (Bt). Corn and cotton are the main Bt crops and the varieties currently available are effective against the European corn borer and the cotton bollworm and budworm. Novartis' Bt corn and Monsanto's Bollgard cotton were both introduced in 1996. Although Novartis' varieties of Bt corn were introduced first, Monsanto's YieldGard technology soon became the market leader, reaching 18 million acres in 1999, accounting for 23% of all corn acres (Table 3).

Table 3. Insect Resistant Crops

Company	**Product**	**USDA Approval Date**	**Planted Area**			
			1996 A	**1997 A**	**1998 A**	**1999 E**
			Million Acres			
Garst (AgrEvo Technology)	Star Link corn	N/A	N/A	N/A	0.4	0.4
Monsanto/ DEKALB	Bollgard cotton	6/22/95	1.8	2.5	2.5	2.2
Monsanto/ DEKALB	DEKALBt/Bt-Xtra corn	3/28/97	N/C	0.2	1.2	N/A
Monsanto/ DEKALB	NewLeaf potatoes	3/2/95	<0.1	<0.1	<0.1	<0.1
Monsanto/ DEKALB	YieldGard corn	8/22/95 & 3/15/96	N/C	2.6	11.0	18.0
Novartis	Maximizer & KnockOut corn	5/17/95 & 1/18/96	1.0	2.0	4.4	N/A

Stacked Traits

As efficacy of modifying single traits was demonstrated, it also became clear that multiple benefits could be offered in one type of seed. The first "stacked" trait variety that appeared in 1997 was Monsanto's Roundup Ready/Bollgard cotton, a variety now used more widely than standard Bollgard cotton. Stacked Roundup Ready/Bollgard cotton was used on 2.3 million acres in 1999 (Table 4). Monsanto also has sold a small amount of corn that combines Roundup herbicide tolerance and European corn borer resistance, but this product has been planted on limited acreage.

Table 4. Stacked Trait Crops

Company	Product	USDA Approval Date	Planted Area			
			1996 A	1997 A	1998 A	1999 E
			Million Acres			
Monsanto/ DEKALB	Roundup Ready & Bollgard cotton	N/A	N/C	<0.1	0.6	2.3
Monsanto/ DEKALB	BXN & Bollgard cotton	4/30/97	N/C	N/C	<0.1	0.0
Monsanto/ DEKALB	Roundup Ready & YieldGard corn	5/27/97	N/C	N/C	<0.1	N/A

Biotechnology and the Food and Feed Industries

Most current biotech products have focused on agronomic traits that add value for the producer but offer little direct benefit to the consumer. However, a few consumer-oriented products are being offered, and many more can be expected. While not every crop lends itself to such traits, those usually consumed fresh (such as fruits and vegetables) do, and several have been developed and are being used commercially. Certain grains and oilseeds tailored for specific customer uses also have been introduced, although this market is only in its infancy.

Fruits and Vegetables. Fruits and vegetables have been a focus of biotech research for more than a decade. Some modifications involve input traits intended to benefit producers, but most are clearly intended to add value downstream at the consumer end of the marketing chain (Table 5).

Table 5. Commercially Available Biotech Fruits and Vegetables

Name	Manufacturer	Description
FreshWorld Farms Tomato	DNAP/Empresas La Moderna	Developed to have improved color, taste, and texture, and a 10- to 14-day shelf life.
FreshWorld Farms Endless Summer Tomato	DNAP/Empresas La Moderna	Limited production of ethylene, the hormone that causes fruits to ripen – extends shelf life by 30 to 40 days.
Increased Pectin Tomato	Zeneca Plant Sciences	These tomatoes remain firm longer and retain pectin during processing into tomato paste.
Bt Sweet Corn	Novartis	Contains the Bt bacteria, providing protection against several pests.

Value Enhanced Grains and Oilseeds. While a few value enhanced crops are on the market, their use to date has been small. They include oilseeds with modified fatty acids (e.g., more healthful oils) and corn tailored to specific end-uses (e.g., specialized processing or inclusion in animal feed). And, nontransgenic varieties of these crops accounted for more than 95% of the 3.3 million acres of value enhanced grains and oilseeds planted in the United States in 1998 (Table 6).

The most widely used value enhanced crops are high-oil corn, waxy and high-amylose corn (with starch compositions designed for specific food and industrial uses), and "food-grade" corn (hard-endosperm), which produces large grits desired in the manufacture of extruded products (e.g., puffed breakfast cereals). High-oil corn, commercialized by DuPont/Pioneer Hi-Bred, is used mostly as an enhanced-energy animal feed.

Table 6. Value Enhanced Crops, 1996-99

Company	Product	USDA Approval Date	Planted Area			
			1996 A	1997 A	1998 A	1999 E
			Million Acres			
DuPont/ Pioneer/ Optimum	High protein soybeans	Not Transgenic	N/A	0.01	0.01	N/A
DuPont/ Pioneer/ Optimum	High sucrose soybeans	Not Transgenic	N/A	0.01	0.03	N/A
DuPont/ Pioneer/ Optimum	High oil corn	Not Transgenic	0.40	0.75	0.90	1.25
DuPont/ Pioneer/ Optimum	High oleic soybeans	5/7/97	N/C	0.01	0.03	0.03
DuPont/ Pioneer/ Optimum	High oleic sunflower	Not Transgenic	N/A	N/A	0.11	N/A
DuPont/ Pioneer Hi-Bred	Low linolenic soybeans	Not Transgenic	N/A	0.01	0.01	N/A
DuPont/ Pioneer/ Optimum	LoSatSoy (low saturates) soybeans	Not Transgenic	N/C	0.01	0.05	0.05
Monsanto/ DEKALB	Nutritionally dense corn	Not Transgenic	0.14	0.14	0.14	0.24
Monsanto/ DEKALB	Laurate canola	10/31/94	0.02	0.07	0.08	0.00
Multiple	Hard endosperm/ food-grade corn	Not Transgenic	1.00	1.00	1.00	1.00
Multiple (Main: Monsanto/ DEKALB)	High amylose corn	Not Transgenic	0.04	0.04	0.04	0.05
Multiple	White corn	Not Transgenic	0.58	0.55	0.65	0.78
Multiple (Main: Monsanto/ DEKALB)	Waxy corn	Not Transgenic	0.40	0.42	0.43	0.53

Several oilseeds are being modified to produce oils that are more healthful and/or more stable (to extend the working life of shortening used in restaurants, for example). One product designed specifically to be more healthful is soybean oil with reduced saturated fatty acids. Developed by Iowa State University and marketed by DuPont/Pioneer/Optimum, the oil has been marketed as LoSatSoy in Hy-Vee stores in the Midwest.

Also on the market are high-oleic soybeans and sunflowers, with oil that can be used in food applications with little or no hydrogenation. These changes both cut food processing costs and result in a more healthful oil.

DuPont/Pioneer/Optimum is selling other value enhanced soybean varieties with modifications in components other than oil. High-sucrose soybeans are promoted for their improved flavor and reduced incidence of undesirable side-effects (such as gas in humans) so food processors can include a higher proportion of soy in foods without incurring off-tastes or other undesirable consequences. High-protein soybeans are intended for use in soyfoods, particularly tofu and soymilk. However, these applications are, as yet, little used. Total area planted to value enhanced soybean varieties in 1998 was 120,000 acres, with area planted last year likely holding at about the same level.

Nutraceuticals

The modification of crops to produce foods that influence human health is a natural progression for biotechnology, and continues to be a widely-sought goal. This ability already has been demonstrated in the development of oilseeds with more healthful oil properties (e.g., lower saturated fats). However, biotech crops with a targeted health function, commonly called nutraceuticals, have yet to be introduced commercially.

This area continues to be actively explored, a process that could accelerate as linkages between agricultural biotechnology and the pharmaceutical industry are strengthened. Although pharmaceutical production from plants and the ability to create tailored foods for specific health needs seems futuristic, two major biotech players (Monsanto and AgrEvo) also are significant players in the pharmaceutical industry, suggesting development of “farmaceuticals” to be plausible.

Another term which is used almost interchangeably with “nutraceuticals” is “functional foods.” While there is no single definition of either term, they generally are defined as encompassing foods that provide health benefits beyond basic nutrition, either through fortification or genetic modification to contain higher levels of nutrients. The term “nutraceutical” also connotes medical properties which may be imparted to crops or foods. Based on these definitions, a soybean genetically modified to have higher levels of vitamin E could be considered a functional food, while a soybean with lower fat content would not.

Examples of functional foods currently on the market, all of which are nontransgenic, include Tropicana’s calcium-fortified orange juice, Hain Foods’ soups with added St. John’s Wort, and Benecol, a margarine which is made from ingredients derived from pine trees and which reduces blood cholesterol levels. There are no transgenic products with a specific health function that have been commercialized to date.

Biotech Crop Adoption Elsewhere

While much of the biotech crop acreage is in the United States, a number of crops have been adopted widely in Canada. The focus there also has been on input traits, specifically herbicide tolerance. Canada’s principal crops are wheat, barley and canola, but since biotech wheat and barley have not been commercialized, canola is the dominant biotech crop in use and has proven to be one of the most receptive crops to genetic manipulations, including value enhanced traits.

In 1999, three-quarters of the canola acreage in Canada was planted to biotech crops. Following a battle for market share since 1996, Monsanto’s Roundup Ready canola has become the leading biotech crop in Canada, with 5.4 million acres in 1999 (Table 7). Liberty Link and Pursuit Smart varieties also are grown on substantial area, with Liberty Link accounting for 2.8 million acres and Pursuit Smart another 2.4 million acres. Pursuit Smart crops, which are tolerant of the herbicide imidazolinone, have been developed by Pioneer Hi-Bred and are more widely grown than their counterpart IMI crops in the United States.

Table 7. Canadian Biotech Crop Area, 1996-99

Company	Brand or Common Reference	Date Approved	Planted Area			
			1996 A	**1997 A**	**1998 A**	**1999E**
			Acres			
AgrEvo	Liberty Link canola	Mar-95	370,500	2,100,000	2,030,000	2,759,000
AgrEvo	Liberty Link corn	Apr-97	N/C	N/C	59,000	114,000
DuPont/ Pioneer	Pursuit Smart (IMI tolerant) corn	Feb-96	N/A	10,000	20,000	20,000
DuPont/ Pioneer	Pursuit Smart (IMI tolerant) canola	Apr-95	N/C	1,600,000	2,000,000	2,414,000
Monsanto	Roundup Ready canola	Mar-95	50,000	450,000	3,384,000	5,400,000
Monsanto	Laurate canola	Apr-96	5,000	5,000	5,000	0
Monsanto	Roundup Ready soybeans	Apr-96	N/C	6,000	362,400	492,800
Monsanto	YieldGard corn	Feb-97	N/C	60,000	455,000	1,000,000
Monsanto	Roundup Ready & YieldGard corn	Sep-97	N/C	N/C	3,000	3,000
Monsanto	Roundup Ready corn	Sep-97	N/C	N/C	N/C	50,000
Monsanto	NewLeaf Potato	Dec-95	1,500	5,000	12,400	31,000
Univ. Saskatchewan	STS flax	May-96	440	6,000	0	0
Total			427,440	4,242,000	8,330,800	12,283,800

Sources: SCI, Canadian National Research Council/Plant Biotechnology Institute, Biotech/Seed Companies, Press Reports
N/C = Not Commercialized; N/A = Not Available

Although Canadian corn acreage is small, biotech varieties accounted for 41% of the total in 1999. The most prominent biotech varieties are Monsanto's YieldGard corn, planted on nearly 1 million acres, and AgrEvo's Liberty Link corn, on 114,000 acres.

As in the United States, considerable research on value enhanced crops is underway in Canada, but their area is quite small. However, canola varieties with higher lauric content, high oleic acid and low linolenic acid now have been approved by the government and their use can be expected to grow in the future.

Following the United States and Canada, the next-largest biotech area is in Argentina, where Roundup Ready varieties are planted on up to 70% of total soybean acreage in 1999 (an uncertain estimate because some seed purchased in Argentina may have been smuggled into Brazil and planted there illegally). Legal challenges in Brazil continue to prevent Monsanto from selling Roundup Ready soybeans there. However, trade estimates of Brazilian use of Roundup Ready soybeans run as high as 1 million acres.

Monsanto's Bollgard cotton is grown in Argentina, Australia, Mexico and China. In China alone, Bt cotton plantings are estimated to have been 200,000 acres in 1998. Bollgard cotton plantings are estimated at 250,000 acres in Australia and 62,000 acres in Mexico in 1999.

South Africa's first commercially grown, genetically modified cotton and corn crops were harvested this year. In 1996 and 1997, a cotton strain and two corn varieties were the first genetically engineered crops to be approved for commercial production by the country's official regulatory body, the South African Committee on Genetic Engineering (Sagene). Monsanto developed one of the corn varieties and Pioneer Hi-Bred developed the other. Sagene also has approved field trials – now underway– for strawberries and potatoes using locally developed technology. Upcoming field trials on eucalyptus, apples and soybeans will use imported US technology. Sagene estimates that widespread genetic crop production is likely in South Africa within four to five years.

In addition, it is likely that some Bt corn has been quietly planted in France and Spain. Although such activities tend not to be advertised, it has been reported that 4,500 acres of Bt corn were planted in France and 45,000 acres in Spain in 1998. Given the negative public opinion toward GMO crops that has surfaced over the last year in the EU, it is unknown whether any commercial plantings (i.e., beyond field tests or seed replication) were conducted in 1999.

Summary

The trends observed in 1998 have continued and accelerated this year — in spite of the fact that the biotech seed costs include fees for "genetics" and crop prices have been relatively low in both 1998 and 1999. Farmers are clearly convinced that returns from biotechnology far exceed their cost, and have moved quickly to plant these improved seeds where they were available (soybeans, cotton and corn and a few vegetable crops). In the livestock area, relatively few new developments have occurred, in spite of the excitement over the cloning of Dolly and other, later successes with similar approaches. Much of the activity concerning livestock continues to be research (rather than commercial) and is described in the following section.

Most present trends appear highly beneficial for producers, and have the potential to significantly improve the US competitive position in world markets. However, they are being challenged for a wide range of non-economic reasons in Europe and a few other markets, tactics that have led to widening confusion about their future use among US producers who are intensely conscious of the importance of world export markets.

A common conviction among US producers is that the benefits of biotechnology will become increasingly apparent as consumer-oriented products are developed and sold commercially. The following sections examine the biotechnology pipeline, and describe the flow of new products expected, based on examination of products now in the test stage that are expected to be sold commercially in the next five years.

The Pipeline: What To Expect/When

While the pace of adoption of biotech products has been spectacular, the review of products still being tested indicates that current developments are the tip of the iceberg, with many more, different products yet to emerge. And, it suggests that future developments could come even more rapidly in the next few years. This section updates the list of new products being developed for regulatory approval, and which can be expected to become commercially available in the next five years.

The US Regulatory Process

The United States Department of Agriculture (USDA), the Food and Drug Administration (FDA), and the Environmental Protection Agency (EPA) are the three agencies involved in monitoring the development and testing of genetically engineered products.

USDA/APHIS. The USDA regulates genetically engineered food plants through its Animal and Plant Health Inspection Services (APHIS) Division. APHIS administers the Federal Plant Pest Act (FPPA), which authorizes APHIS to regulate interstate movement, importation, and field testing of "organisms and products altered or produced through genetic engineering". This includes such potential products as plants with improved disease resistance and animal vaccines made with genetically-modified bacteria. APHIS also may establish specific rules under which the test must be conducted as a condition of its approval.

APHIS exercises its regulatory authority through a permit system. There are three basic types of permits that an applicant who is developing a genetically engineered plants may be required to obtain. Permit applications are handled by the Biotechnology Permits unit of Biotechnology, Biologics, and Environmental Protection (BBEP) within APHIS. An APHIS permit and approval of individual state departments of agriculture are required to move any genetically-engineered organism that is a potential plant pest into the United States or between states.

APHIS also oversees field testing or "environmental release" of genetically-engineered crops, requiring information about the plant, all new genes, their origin, the purpose of the test, the experimental design, and precautions to be taken to prevent the escape of pollen, plants, or plant parts from the field test site. Upon evaluation, APHIS prepares an environmental assessment (EA) document that analyzes any possible environmental impacts the field test could have. The EA is required by the National Environmental Policy Act, Council on Environmental Quality regulations, and USDA procedures.
Applicants also may request a courtesy permit from APHIS to move or field test a genetically-engineered plant that is not regulated by the agency. Sometimes a non-regulated plant may be similar to one that is regulated by APHIS, and an APHIS permit may make it easier to move or field test the plant.

Corn, cotton, potato, soybean, tobacco, and tomato crops are considered by APHIS using special criteria. After reviewing many permit requests, APHIS found that 85% of genetically-modified plant field tests involved varieties of these six major crops. Based on the data from these tests, APHIS determined that tests of these crops did not pose a plant pest risk. It therefore issued rules in March 1993 that allow genetically-modified varieties of these crops to undergo field tests with only a 30-day advance notification to APHIS, avoiding the permit application process.

FDA. The Food and Drug Administration has the primary responsibility for regulating food additives and new foods, except meat and poultry products (USDA's responsibility). However, the genetically-modified animal growth hormones bovine somatotropin (BST) and porcine somatotropin (PST) came under FDA's purview because it is required to determine the safety and efficacy of animal drugs. Before allowing drugs for food-producing animals to be marketed, the Food, Drug, and Cosmetic Act requires FDS to insure that these drugs are rigorously studied and that residues of the drug in meat, milk, or eggs pose no health threats.

It is FDA policy that proteins taken from commonly allergenic foods are presumed to be allergens unless demonstrated otherwise, and labeling of such foods is required. Thus, genes from foods such as fish or peanuts inserted into tomatoes or corn where people would not expect to find allergens must be labeled to alert consumers.

Labeling also could be required if the nutritional content of food is changed. Tomatoes are a major source of vitamin C, and if a tomato were developed that no longer contains vitamin C, that then would have to be disclosed. By contrast, FDA does not consider the method by which a plant is developed by a plant breeder to be material information, so there is no requirement that sweet corn be labeled "hybrid sweet corn" because it was developed through cross-hybridization. However, if the composition of corn or tomatoes is changed significantly, then it must have a different varietal name, or, in some cases, the product may no longer be called by its generic name.

EPA. The Environmental Protection Agency regulates pesticides under the authority of the Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). The former holds EPA responsible for regulating the distribution, sale, use, and testing of pesticides in order to protect humans and the environment, while the latter authorizes tolerances (or exemptions from the requirement of a tolerance) for pesticide residues in or on food crops.

Producers of biotech products are required to consult with the EPA if the pesticide meets any of the following criteria:

> The product is not derived from a known food source (e.g., *Bacillus thuringiensis* pesticides are derived from a bacteria).
>
> It is derived from a known food source and is introduced into a known food source, but the way humans are exposed to it in their diets changes.
>
> It has a different structure, function, or composition than its counterpart that already occurs in food (e.g., the structure of a protein pesticide that already occurs in food could be altered significantly).

The regulatory system described above is, in essence, a patchwork of pre-existing regulatory authorities and has been considered by some to be burdensome to the agricultural biotechnology research agenda. However, given the current consumer environment, the regulatory process is under significant scrutiny. Although regulators and US government officials contend that the US regulatory process works well, USDA and the National Academy of Sciences (NAS) are undertaking an independent, on-going, scientific review of regulatory process for biotechnology-derived plants. And, FDA is holding a series of hearings across the country through November and December to elicit comments on its process of regulating biotech food products.

Biotech Developments in the United States

Field trials for biotech crops have been underway for more than ten years in the United States. Between 1993 and October 1999, APHIS has received nearly 6,300 notifications of field trials for biotech crops. Of that total, nearly one-half have been genetically modified corn varieties (Chart 2). Potatoes and soybeans follow with 11% of the field trials while tomatoes are next with 9%. Cotton varieties account for 8% of the APHIS field trials conducted since 1993, while wheat still represents a low 1%. Other crops that have been tested (illustrating the extensive research) include alfalfa, eggplants, walnut trees, melons, barley and carrots.

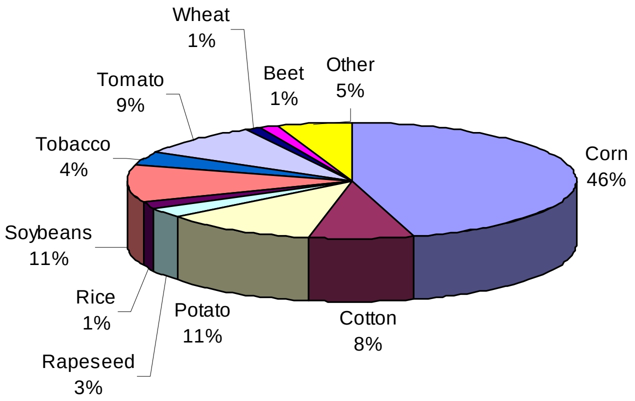

Chart 2. APHIS Field Trials by Crop – 1993 to Present

In just the past year, the nature of the genetic characteristics of crops undergoing field trials has changed. A year ago, the dominant biotech trait being tested across all crops was herbicide tolerance, followed by insect resistance and product quality (value-enhancing) characteristics. By October 1999, herbicide tolerance varieties still represented the largest segment of field trials (33%), but product quality traits (21%) surpassed insect resistance as more biotech companies and institutions rushed to demonstrate significant consumer benefits in biotech products to counter consumer concerns and opposition to biotechnology (Chart 3).

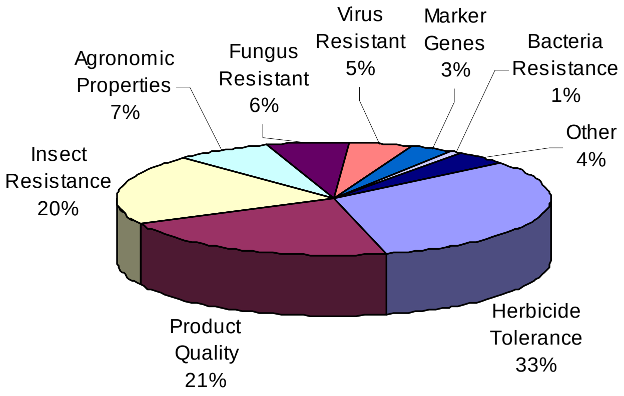

Chart 3. APHIS Field Trials by Crop Characteristic – 1993 to Present

The following subsections identify and describe the number and variety of products in the pipeline with reasonable expectation of commercial release within the next few (no more than five) years.

Crops

Herbicide Tolerance. As one of the first commercially successful biotech product traits, herbicide tolerance remains a key trait of many products in the pipeline. Companies that had significant success in the commercial application of herbicide tolerance systems plan to extend those systems into many different crops. Monsanto, for example, plans to release Roundup Ready alfalfa and sugar beets in 2000, potatoes in 2001, and rice and wheat around 2002. AgrEvo expects to extend its Liberty Link system for resistance to Liberty herbicide from corn to cotton, sugar beets, rice and wheat. A summary of the herbicide tolerant crops in the pipeline is presented in Table 8.[3]

Table 8. Herbicide Tolerant Crops -- the Pipeline

Crop	Developing Company/Institution	Specific Trait
Alfalfa	Monsanto	Glyphosate tolerant
Corn	Cargill	Glyphosate tolerant
	Limagrain	
	Pioneer	
	Monsanto/DeKalb	Glyphosate tolerant/ Phosphinothricin tolerant
	Pioneer	Imidazolinone tolerant
	Garst	Phosphinothricin tolerant
	Mycogen	
	Pioneer	
	Zeneca	Chloroacetanilide tolerant
Cotton	Chembred	2,4-D tolerant
	United Agri Products	
	AgrEvo	Glufosinate tolerant
	Boswell	Imidazolinone tolerant
Creeping Bentgrass	Rutgers University	Phosphinothricin tolerant
Lettuce	Seminis Vegetable Seeds	Glyphosate tolerant
Poplar Trees	Monsanto	Glyphosate tolerant
	Oregon State University	
	Weyerhaeuser	
Potato	University of Idaho	Bromoxynil tolerant
Rapeseed 1/	Calgene	Glyphosate tolerant
	Cargill	
	Pioneer	
	Western Ag Research	Glufosinate tolerant
Rice	Monsanto	Glyphosate tolerant
	American Cyanamid	Imidazolinone tolerant
	AgrEvo	Glufosinate tolerant
	ARS/USDA	
	Louisiana State University	
Soybean	AgrEvo	Glufosinate tolerant
	Asgrow	
	Pioneer	
	University of Illinois	
	Limagrain	Isoxazole tolerant
Sugar Beet	Monsanto	Glyphosate tolerant
	Novartis Seeds	
	American Cyanamid	Imidazolinone tolerant
	AgrEvo	Glufosinate tolerant
	Betaseed	
Sugarcane	Thermo Trilogy	Phosphinothricin tolerant
Sweetgum	Union Camp	2,4-D tolerant
Tomato	Seminis Vegetable Seeds	Glyphosate tolerant
Wheat	Monsanto	Glyphosate tolerant
	American Cyanamid	Imidazolinone tolerant

1/ The USDA/APHIS database term “rapeseed” refers to canola varieties.
Source: APHIS field trials database and biotech/seed company reports

Key observations include:

- A significant amount of research continues on developing herbicide tolerance for the high-value, high-volume crops (e.g., corn and soybeans) for which commercial products already are available. And, herbicide tolerant varieties of alfalfa, lettuce, rice, sugarcane and wheat can be expected to appear in the next five years. While herbicide tolerant varieties of wheat have trailed other crops (a result of wheat's complex genetic make-up and the lesser importance of weed problems for small grains), Monsanto appears likely to release Roundup Ready wheat by 2002. Once achieved in wheat, it likely can then be extended to other complex small grains such as barley, sorghum and oats.
- Herbicide tolerant crops are under development both by universities and private companies. The university research appears to be focused in product areas such as potatoes, rice, poplar trees, and wheat — in some cases, areas where research has been funded by multi-lateral institutions and foundations.

Insect Resistance. Most of the products available commercially today ward off lepidoptera or caterpillar-type insects – Bt corn protects against the European corn borer, for example, but in the future, resistance to other damaging of insects will emerge. Thus, a corn variety resistant to corn rootworm could be one of the next blockbuster products. Several other crop varieties are in development that will control many different insects (Table 9).

Key observations include:

- Monsanto has been working on the development of in-plant protection against corn rootworm since 1989. Commercial introduction is expected by 2001.
- Several new developments are expected in cotton over the next five years. Monsanto plans to release a second-generation Bollgard insect-protected cotton in 2001 that contains a Bt protein fatal to second generation bollworms. Monsanto also is expected to release a cotton variety resistant to the boll weevil around the same time.

- There is little likelihood of insect resistant varieties for wheat, rice or soybeans in the near future. Bacterial toxins in Bt are very specific to a few insect species, and its widespread use requires both comprehensive understanding of the crops' genetic mapping as well as the genetic coding of Bt insecticides.

Table 9. Insect Resistant Crops -- the Pipeline

Crop	Developing Company/Institution	Specific Trait
Corn	Many companies. Monsanto Pioneer	European corn borer resistant Corn rootworm resistant
	DeKalb	European corn borer/ Corn rootworm resistant
Cotton	Monsanto	Boll weevil resistant Bollworm resistant (second generation)
	Mycogen	Boll weevil resistant
Eggplant	Rutgers University	Colorado potato beetle resistant
Peanut	University of Georgia	Lesser cornstalk borer resistant
Potato	Michigan State University	Colorado potato beetle resistant
	New Mexico State University Plant Genetics	
Poplar	Oregon State University	Cottonwood leaf beetle/Phratora leaf beetle resistant
Rapeseed	University of Chicago	Lepidopteran resistant
Soybean	Monsanto University of Georgia	Lepidopteran resistant
Sugarcane	Texas A&M University	Mexican rice borer resistant
Tomato	BHN Research Monsanto	Lepidopteran resistant

Source: APHIS field trials database and biotech/seed company reports

Chemical Pesticide-Free Vegetables …

Commercial vegetable producers and home gardeners will soon have fewer problems with caterpillars eating their corn, broccoli, cauliflower and other vegetables and less exposure to chemical pesticides, too — thanks to new genes that command plant cells to produce a worm-killing protein. USDA and Mississippi State University (MSU) scientists were the first to find and isolate the protein in insect-resistant corn. They believe the protein helps keep tiny fall armyworm larvae from developing into full-grown caterpillars that eat corn and other crops.

Seminis, the world's largest vegetable seed company, has signed an agreement to investigate the potential use of the gene for controlling a variety of caterpillars in commercially grown broccoli, cauliflower and other vegetables. The researchers also have already collaborated with DeKalb Genetics Corp. in evaluating corn hybrids that possess both natural and bioengineered sources of resistance to fall armyworms.

As has been the case with the Bt technology, the protein can significantly lower the cost of pesticide inputs. The fall armyworm is a serious pest for corn, especially late-planted corn in the South. Drought stricken Texas was particularly hit with high populations of this pest last year, and losses in some years have exceeded $200 million. And, if commercial growers and home gardeners have access to these varieties, the overall reduction in pesticide use also will yield environmental benefits.

Disease Resistance Developments. Plant diseases, caused by infectious viruses, bacteria, phytoplasmas, fungi, and nematodes, result in enormous losses across agriculture, through reduced yields, lower product quality or shelf-life, decreased aesthetic or nutritional value, and, sometimes, food and feed contaminated with toxic compounds. Growers currently spend large sums to achieve partial control of pathogens that attack crops and other plants. Even so, crop and commodity losses from disease cost billions of dollars each year.

Reducing disease losses is a high priority objective for agriculture and for researchers working to control these problems through new biotechnology methods. Besides the obvious benefits for producers and processors, plant health protection is an important mechanism for increasing food supplies without increasing the land under cultivation. Very substantial amounts of research are devoted to techniques to control the deadly diseases that damage or ruin crops each year. Most of the focus is on viruses, but attention also is being given to fungi and bacteria (Table 10).

Transgenic Soybeans Shrug off White Mould

Agriculture and Agri-Food Canada scientists are field-testing a transgenic soybean which is highly resistant to white mould. Test plots were planted last year to test resistance, and have been expanded to additional locations so that yields can be compared to other commercial varieties.

White mould is a $6 million annual problem for Ontario soybean growers. It creates extra problems for seed growers as sclerotia drops down with the seed at harvest, contaminating the seed source. A wheat gene which controls oxidase enzyme production was transferred into the soybean plants. That gene was isolated by a University of Toronto researcher by accident while searching for wheat genes responsible for germination.

Table 10. Virus Resistant Crops -- the Pipeline

Crop	Developing Company/Institution	Specific Trait
Cucumber	Seminis Vegetable Seeds	Cucumber Mosaic Virus Papaya Ringspot Virus Watermelon Mosaic Virus Zucchini Yellow Mosaic Virus (all stacked)
Grape	GenApps	Nepovirus
Melon	Seminis Vegetable Seeds Harris Moran	Cucumber Mosaic Virus Papaya Ringspot Virus Squash Mosaic Virus Watermelon Mosaic Virus Zucchini Yellow Mosaic Virus (individual traits/ combination stacked/ all stacked)
Oat	Iowa State University	Barley Yellow Dwarf Virus
Papaya	ARS/USDA New York Experiment Station	Papaya Ringspot Virus
Pea	University of Idaho	Bean Leafroll Virus Bean Yellow Mosaic Virus Pea Enation Mosaic Virus Pea Seed-borne Mosaic Virus (individual traits/ combination stacked/ all stacked)
Peanut	University of Georgia	Tomato Spotted Wilt Virus
Pepper	Seminis Vegetable Seeds	Cucumber Mosaic Virus
Potato	ARS/USDA Monsanto Cornell University of Idaho	Potato Leafroll Virus Potato Virus Y Tobacco Rattle Virus (individual traits/ combination of traits stacked/ all stacked)
Soybean	Iowa State University	Soybean Mosaic Virus
Squash	Seminis Vegetable Seeds	Cucumber Mosaic Virus Papaya Ringspot Virus Watermelon Mosaic Virus Zucchini Yellow Mosaic Virus (all stacked)
Sugar Beet	Betaseed	Beet Necrotic Yellow Vein Virus
Tobacco	University of Kentucky North Carolina State University ARS/USDA	Potato Virus Y Tobacco Spot Virus Tobacco Yellow Mosaic Virus Tomato Spotted Wilt Virus (individual traits/ combination stacked/ all stacked)
Tomato	Agritope Calgene	Beet Curly Top Virus Cucumber Mosaic Virus Gemini Virus Potato Virus Y
	Cornell University Harris Moran Seminis Vegetable Seeds	Cucumber Mosaic Virus Gemini Virus Potato Virus Y
Watermelon	Seminis Vegetable Seeds	Watermelon Mosaic Virus Zucchini Yellow Mosaic Virus (all stacked)
Wheat	University of Idaho	Barley Yellow Dwarf Virus Wheat Streak Mosaic Virus (individualtraits/ both stacked)

Source: APHIS field trials database and biotech/seed company reports

Key observations include:

- A central focus of virus resistant crop research continues to be fruits and vegetables, more at risk from attack by aphids and other carriers. Management of viruses is especially important in maintaining the high value associated with these crops.
- Much attention is being focused on products with “stacked” virus resistant traits. For example, Seminis and Harris Moran are both testing melon varieties with resistance to Cucumber Mosaic Virus, Papaya Ringspot Virus, Squash Mosaic Virus, Watermelon Mosaic Virus, and Zucchini Yellow Mosaic Virus. Other multiple virus resistant crops in the pipeline include cucumbers, potatoes, peas, and wheat, among others.

Fungal diseases of fruits, vegetables and grains also cost farmers billions of dollars annually. New fungal resistant genes can be inserted into many of these vulnerable crops, resulting in a significant number of resistant crops to be released in the next few years (Table 11).

Table 11. Fungus Resistant Crops -- the Pipeline

Crop	Developing Company/Institution	Specific Trait
Apple	Cornell University	Apple scab resistant
Carrot	Seminis Vegetable Seeds	Alternaria daucii resistant
Corn	DeKalb	Leaf blight resistant Northern corn leaf blight resistant
	Northrup King	Northern corn leaf blight resistant
	Novartis Seeds	Helminthosporium resistant
	Pioneer	Leaf spot resistant Ear mold resistant/ Gray leaf spot resistant Fusarium ear rot resistant/ Gray leaf spot resistant Gray leaf spot resistant/ Northern corn leaf blight resistant Mycotoxin degradation Smut resistant
Cotton	Texas Tech University	Verticillium resistant
Creeping Bentgrass	Rutgers University Scotts	Dollar spot resistant Rhizoctonia solani resistant
Eggplant	Rutgers University	Phytophthora resistant/ Verticillium resistant
Grape	Cornell University Pebble Ridge Vineyards	Botrytis cinerea resistant/ Powdery mildew resistant
Kentucky Bluegrass	Scotts	Rhizoctonia solani resistant
Poplar	Oregon State University	Marssonina resistant/ Melamtsora resistant/ Septoria resistant/ Venturia resistant (all stacked)
Potato	ARS/USDA Boyce Thompson Institute Michigan State University	Phytophthora resistant
	Monsanto	Phytophthora resistant Verticillium resistant
	Washington State University	Phytophthora resistant Verticillium dahlae resistant
Rapeseed	Cargill	Cylindrosporium resistant/ Phoma resistant/ Sclerotinia resistant
Red Raspberry	ARS/USDA	Fruit rot resistant
Soybean	University of Illinois Michigan State University	Fusarium rot resistant Sclerotinia resistant
Strawberry	DNAP Holding Corporation	Verticillium dahlae resistant
Sunflower	Pioneer	Sclerotinia resistant
Tobacco	University of Kentucky	Black shank resistant
Tomato	Calgene Seminis Vegetable Seeds	Fusarium wilt resistant/ Verticillium dahlae resistant Fusarium wilt resistant Powdery mildew resistant
Wheat	Monsanto Novartis Seeds	Fusarium head blight resistant Septoria resistant

Source: APHIS field trials database and biotech/seed company reports

Key observations include:

- Several varieties of major crops are in the pipeline for fungus-resistance. Corn varieties likely to be released will be resistant to ear mold, gray leaf spot, northern corn leaf blight and smut, among others. Resistance to fusarium rot and wilt diseases, caused by the fusarium oxysporum fungus also is being built into corn, soybeans, tomatoes, and wheat.

Many insect pests, such as whiteflies, aphids and leafhoppers, not only transmit viruses but also bacteria that can cause devastating plant diseases while also causing billions of dollars worth of direct damage to crops by feeding on them. Several varieties with resistance to these bacteria are in the product pipeline (Table 12).

Table 12. Bacteria Resistant Crops -- the Pipeline

Crop	Developing Company/Institution	Specific Trait
Apple	Cornell University	Fire blight resistant
Poplar	Iowa State University	Crown gall resistant
Potato	ARS/USDA	Erwinia carotovora resistant
Rice	University of California-Davis	Bacterial leaf blight resistant
Sugarcane	Texas A&M University United States Sugar Corp.	Clavibacter resistant
Tomato	Ohio State University Purdue University	Bacterial speck resistant
Walnut	University of California-Davis	Bacterial leaf blight resistant

Source: APHIS field trials database and biotech/seed company reports

Key observations include:

- Virtually all research on bacteria resistant crops is being done in the public sector (ARS or universities), except that one sugarcane variety resistant to clavibacter is under development by the United States Sugar Corporation.
- The research effort on bacteria-resistance is focused mostly in minor crops and trees (poplar and walnut).

Yield Effects – Agronomic Properties. World grain production since 1950 has increased at an astonishing rate, due to the combination of improved crop varieties, irrigation, fertilizers, better management techniques and chemical pest control. During that time, world population has more than doubled, and even today, nearly 90 million new people are added each year. Biotechnology holds the promise of better access to higher quality foods, while avoiding adverse environmental consequences from increasingly intense cultivation of limited arable land resources.

Genetic engineering now can be used to modify crop production through each of its stages, from speeding up early growth of food plants to increase yields to slowing ripening or wilting. Since the form and function of a plant depends heavily on its genetic composition, the ultimate goal is to engineer plants optimal for every growing condition and market niche.

Changing crops' agronomic properties not only affects yields but also the production process itself, as crops can be tailored for specific climates and soil types. Some specific alterations in development include increased stalk strength (standability), yield increases, altered growth rate, drought tolerance, and stress tolerance and others (Table 13).

Table 13. Crops with Altered Agronomic Properties – the Pipeline

Crop	Developing Company/Institution	Specific Trait
Apple	University of California	Flowering time altered
Corn	Cargill	Male sterile
	DeKalb	Carbohydrate level increased Carbohydrate metabolism altered Stress tolerant
	ICI Garst	Modified growth characteristics
	Iowa State University	Male sterile
	Limagrain	Lipase expressed in seeds
	Monsanto	Development altered Photosynthesis enhanced
	New York State University-Albany	Male sterile
	Pioneer	Fertility altered Growth rate increased Increased stalk strength Altered maturing Yield increased
	University of Arizona	Anthocyanin produced in seed
	University of Minnesota	Vivipary increased
Cotton	Monsanto	Altered maturing Ethylene metabolism altered
	Texas Tech University	Carbohydrate metabolism altered Oxidative stress tolerant
Creeping Bentgrass	Rutgers University	Aluminum tolerant Drought tolerant Salt tolerance increased
Poplar	Michigan Technological University	Altered lignin biosynthesis
Rapeseed	Calgene	Yield increased
Rice	Monsanto	Yield increased
Soybean	Monsanto	Altered plant development
Tobacco	Southern Illinois University	Ammonium assimilation increased
	University of Hawaii-Manoa	Growth rate altered
	University of Kentucky	Senescence altered
	University of Wisconsin-Madison	Senescence altered
Walnut	University of California-Davis	Cutting rootability increased Flowering altered
Wheat	Monsanto	Carbohydrate metabolism altered Nitrogen metabolism altered
	Montana State University	Photosynthesis enhanced Yield increased Drought tolerant

Source: APHIS field trials database and biotech/seed company reports

Key observations include:

- Many of the trait modifications listed for some crops are vague or non-descriptive. This likely is for proprietary reasons, but may well suggest significant yield impacts for crops.[4]
- Many of these traits including drought tolerance, stress tolerance, and enhanced photosynthesis would have direct impacts on yields for marginal production areas. However, it is notable that many groups are working to develop “increased yield” varieties of primary crops including corn, rice, soybeans and wheat.
- The work being done in this area covers a wide range of primary and secondary crops (including such crops as apples, grasses, trees and tobacco). However, there does not appear to be large amounts of work underway on many of traditional developing country crops – a potentially huge market.
- Monsanto continues research on agronomic properties in crops in which it has already altered traits. Additional work also is underway by several universities since development of these traits likely requires more “basic” research and understanding of the crops’ genomics.

Fruits and Vegetables. Among the many products in the fruit and vegetable pipeline are insect resistant and virus resistant produce, improved-texture peppers, enhanced-taste vegetables, and ripening-altered fruits with longer shelf life (Table 14). There also are fruits and vegetables with "stacked" (multiple) traits, combining agronomic and consumer-oriented traits. Major players in this industry include DNAP (formerly known as DNA Plant Technologies), Calgene, and Agritope, as well as Monsanto and Zeneca.

Table 14. Biotech Fruit and Vegetable Crops -- the Pipeline

Trait	Product	Description
Insect/Disease Resistance	Insect Protected Tomatoes – Calgene	Plants require less insecticide to achieve higher yields.
	Virus Resistant Tomatoes – Calgene	Resistant to certain plant viruses.
Improved Texture	Firmer Peppers – DNAP	Remains firmer after harvest.
Improved Taste	High Sweetness Tomato – Calgene	Enhanced flavor.
	Sweeter Peppers – DNAP	Made sweeter by overexpressing a gene for sweetness.
	Fresh Market Tomato – Zeneca	Enhanced flavor, color, and increased antioxidant vitamin content.
Ripening Altered	Ripening-Controlled Tomatoes – Agritope	Extended shelf life
	Ripening-Controlled Cantaloupe – Agritope	Extended shelf life
	Ripening-Controlled Cherry Tomatoes – DNAP	Longer market life, improved flavor, and better harvest traits through ripening control.
	Ripening-Controlled Bananas and Pineapples – DNAP	Extended shelf life
Improved Processing	High Solids Potato – Monsanto	Contains less water, so less oil is absorbed during cooking, reducing cooking time and costs.
	Quantum Tubers Seed Potatoes – American Ag-tec Intl.	Seed-potato-producing plants have higher yields, a more rapid growing cycle, and are pathogen-free.
Multiple Traits	Transwitch Strawberries – DNAP	Modified to keep fruit firmer after harvest and to resist disease.
	NewLeaf Insect and Y Virus-Protected Potatoes – Monsanto	Better protected against the Colorado potato beetle and the potato virus Y.
	Corn w/Monoclonal Antibodies in its Leaves – Monsanto	Resistant to several plant diseases.
	Fungus Resistant Banana – Zeneca	Resistant to Black Sigatoka, and will have modified ripening characteristics.

Source: Biotechnology Industry Organization

Edible Oils. Oil crops in the product development pipeline include traits described above, as well as new ones that could add value in processing (Table 15). Monsanto is attempting to develop both low-stearate canola and soybeans, whose oil would require no hydrogenation. Not to be outdone by the introduction of LoSatSoy (the reduced saturated fatty acid oil already marketed by Optimum Quality Grains), canola varieties with even lower levels of saturated fat are being developed by Calgene and Cargill.

Table 15. Oilseed/Edible Oil Crops -- the Pipeline

Trait	Product	Description
Less Hydrogenation	High-Stearate Canola Oil – Calgene	Does not require hydrogenation, thus reducing processing costs.
	High-Stearate Soybean Oil – Monsanto	Requires no hydrogenation.
Less Saturated Fat	Very Low Saturated Fatty Acids Canola – Calgene	Lower in fat and healthier.
	Very Low Saturated Fatty Acids Canola – Cargill	In development for its more healthy, lower-fat vegetable oil.
High Monounsaturated Fat	High Monoun-Saturated Fatty Acids Canola – Cargill	Will have various food applications.
Making Industrial Oils Edible	Edible Flax Oil – DuPont	Will have a wide range of applications in deep-fat frying, candy, and margarine.
Processing Improvements	Enhanced Medium Chain Fatty Acids and Triglycerides Canola Oil – Calgene	Less-expensive sources of raw materials for nutritional formulas and high-energy foods.
	Low Stachyose Soybeans – Optimum Quality Grains	Useful in the production of meat extenders, and could be used in pet food applications to create foods that generate less methane gas.
Multiple Traits	Altered Fatty Acid Composition Canola – Optimum Quality Grains	Lower saturated fats, higher monounsaturated fats, and lower polyunsaturated fats, thus requiring little or no hydrogenation.
	High Oil and High Oleic Corn – Optimum Quality Grains	Produce an oil that is lower in monounsaturated fats, giving it better oxidative and heat stability.

Source: Biotechnology Industry Organization

Key observations include:

- The major players in oilseed development thus far have been Monsanto (or its subsidiary, Calgene), DuPont and Optimum Quality Grains.
- Most of the development to date has centered on the two major oilseeds in North America – soybeans and canola.
- The new traits in development are broadly-based, although the two most widely-developed traits are lower-fat oils and reduced-hydrogenation oils.

Value Enhanced Crops. While the initial focus in biotechnology has been on cost reducing and yield enhancing characteristics, value enhanced traits in field crops hold significant potential in the next few years and beyond. This class of innovations includes, for example, corn with higher amino acid content or methionine levels, cotton with increased fiber quality, rapeseed and soybeans with altered oil profiles, and potatoes, tomatoes and vegetables with improved shipping qualities and ripening attributes. These new traits create value for animal feeders (reduced feed costs due to increased energy value and amino acid content in grain), for food companies (healthier oils and tailor-made components for food ingredients), and personal care companies (oils for soaps and gels). These are but the first of what promises to be a series of value enhanced products for crops (Table 16).

Table 16. Product Quality -- the Pipeline

Crop	Developing Company/Institution	Specific Trait
Alfalfa	W-L Research	Altered lignin biosynthesis
Barley	Coors Brewing	Disulfides reduced in endosperm
	Washington State University	Heat stable glucanase produced
Corn	DeKalb	Altered amino acid composition Lysine level increased Methionine level increased Tryptophan level increased
	DuPont	Carbohydrate metabolism altered Increased phosphorus Protein quality altered Oil profile altered and lysine and methionine levels increased
	Monsanto	Carbohydrate metabolism altered Nitrogen metabolism altered
	Pioneer	Carbohydrate metabolism altered Increased phosphorus Lysine level increased Methionine level increased Mycotoxin production inhibited Protein lysine level increased
Corn	University of Arizona	Nutritional quality altered Anthocyanin produced in seed
	University of Minnesota	Oil profile altered Lysine level increased
	Rutgers University	Methionine level increased
Cotton	Agracetus	Fiber strength altered
	Calgene	Melanin produced in cotton fibers
	Monsanto	Fiber strength altered Natural pigments altered
	Texas Tech University	Fiber quality altered
Melon	Agritope Harris Moran	Fruit ripening altered
Pepper	DNAP Holding Corp.	Prolonged shelf life
Potato	ARS/USDA	Blackspot bruise resistant Nutritional quality altered Steroidal glycoalkaloids reduced
Potato	Frito Lay	Carbohydrate metabolism altered
	Monsanto	Bruising reduced/Carbohydrate metabolism altered Carbohydrate metabolism altered Solids increased
	North Dakota State University	Carbohydrate metabolism altered
	Rutgers University	Bruising reduced
Rapeseed	Cargill	Amino acid composition altered Fatty acid metabolism altered
	Limagrain	Nutritional quality altered
Red Raspberry	Agritope	Fruit ripening altered
Soybean	DeKalb	Protein quality altered Lysine level increased
	DuPont	Protein quality altered Carbohydrate metabolism altered Lysine level increased Oil profile altered/Seed composition altered Lysine and methionine levels increased
	Monsanto	Protein altered Seed composition altered Nitrogen metabolism altered
	Pioneer	Methionine level increased Seed methionine storage increased
	University of Illinois	Protein altered
Strawberry	Agritope DNAP Holding Corp.	Fruit ripening altered
Tomato	ARS/USDA	Polyamine metabolism altered
	Agritope	Fruit ripening altered
	BHN Research	Solids increased Fruit sugar profile altered
	Calgene	Yield increased Carbohydrate metabolism altered
	Campbell Soup Company	Fruit sugar profile altered Improved fruit quality
	DNAP Holding Corp.	Fruit ripening altered
	Gargiulo	Solids increased
	Harris Moran	Carbohydrate metabolism altered
	Hunt-Wesson	Pectin esterase level reduced
	Lipton	Antioxidant enzyme increased
	Monsanto	Fruit ripening altered
	Purdue University	Pectin esterase level reduced
	Seminis Vegetable Seeds	Pigment metabolism altered

Table 16. Product Quality -- the Pipeline continued

Crop	Developing Company/Institution	Specific Trait
Tomato	Sunseeds	Fruit sugar profile altered
	University of Florida	Fruit ripening altered
	University of Georgia	Fruit solids increased/Seed set reduced
	University of Wisconsin-Madison	Carbohydrate metabolism altered
	Zeneca	Carotenoid content altered Dry matter content increased/Yield increased Ethylene metabolism altered Fruit solids increased Solids soluble increased
Wheat	ARS/USDA	Storage protein altered

Source: APHIS field trials database and biotech/seed company reports

Key observations include:

- An enormous amount of research is underway to develop valuable food properties – high starch corn, high solids potatoes and tomatoes, and “flavor genes” for strawberries and other fruits and vegetables.
- Research in this area is being conducted by food processing companies, such as Frito Lay, Hunt-Wesson and Campbell as well as by universities and biotechnology/seed companies.
- Product development is a focus of both universities and private companies.
- The major and minor crop focus is very broad, with work on corn, potatoes, soybeans and tomatoes prominent. ARS/USDA is developing a wheat variety with an altered protein composition – apparently the only value enhanced wheat variety currently in testing.
- Many companies are working to develop crop varieties with increased lysine and other amino acid concentrations. Since lysine is one of the amino acids in low concentration in corn, animal feeders (especially poultry) often add lysine supplements to their feed mix to increase its competitive value.

A Well-Lit Christmas Tree …

British genetic engineers want to improve on the traditional Christmas tree — no lights needed. Consumers no longer would need artificial lights, scientists are working on a tree that glows. Genes that give fireflies their fire and jellyfish their glow would be inserted into the tree's DNA. The hoped-for result: a tree that fluoresces all night long.

Bright, Green Potatoes ….

A genetically-modified potato that glows when it needs watering has been created by Edinburgh scientists. The plant glows in response to internal signals normally used to deal with water shortages, and potentially will prevent overwatering and increase water use efficiency — a boon to strained water resources. The fluorescence is produced by a jellyfish protein.

The development of such a product certainly could fuel consumer concerns already present regarding biotech foods, but these potatoes would never enter the food chain. They would serve as “sentinels” - just eight plants per hectare would allow a farmer to monitor the entire field, and the watchdog plants could be planted and harvested separately from the rest of the crop.

Furthermore, humans cannot see their glow unaided. Their light is produced by absorbing a narrow wavelength of blue light, which is re-emitted as yellow. Small, special detectors can spots the yellow light and trigger a "water me" signal, so the system potentially could reduce farmers’ costs by cutting water and fertilizer use and ending run-off associated with over-watering.

Experiments so far have been confined to greenhouses, and it could be five years before glowing potatoes are sold. Future plans are to include slightly different fluorescent proteins that will report on the plants' nitrate, phosphate, and sucrose status.

Stacked Traits. With the resources to actually “stack” traits in plants, possibilities for designing new characteristics become nearly endless, especially since the “stacking” is not limited to similar traits (i.e., all traits must be herbicide tolerant). Products being tested today have five or more different traits – insect resistance, herbicide tolerance, multiple virus resistance and increased proteins or amino acids, thus combining the cost reducing/yield enhancing traits and value enhanced traits (Table 17). The ability to “stack” these traits has obvious potential for greatly enhancing the value of what once was merely commodities.

Table 17. Stacked Trait Crops -- the Pipeline

Crop	Developing Company/Institution	Specific Trait
Brassicaoleracea (Kale)	American Takii	Male sterile/Phosphinothricin tolerant
Corn	AgrEvo	Male sterile/Phosphinothricin tolerant
		Phosphinothricin tolerant/Carbohydrate metabolism altered
		Alternaria resistant/Botrytis resistant/Rhizoctonia resistant/Phosphinothricin tolerant
		Aspergillus resistant/Leaf blight resistant/Leaf spot resistant/Phosphinothricin tolerant
	Asgrow	Male sterile/Phosphinothricin tolerant
	Cargill	Male sterile/Phosphinothricin tolerant
	DeKalb	Carbohydrate metabolism altered/Phosphinothricin tolerant
		Glyphosate tolerant/European corn borer resistant
		Methionine level increased/Phosphinothricin tolerant
		Phosphinothricin tolerant/Altered amino acid composition
		Phosphinothricin tolerant/Increased lysine level
		Phosphinothricin tolerant/Increased methionine level
		Phosphinothricin tolerant/Storage protein altered
		Phosphinothricin tolerant/Tryptophan level increased
		Northern corn leaf blight resistant/Southwestern corn borer resistant
	Limagrain	Glyphosate tolerant/European corn borer resistant
		Phosphinothricin tolerant/Lipase expressed in seeds
		Phosphinothricin tolerant/Starch metabolism altered
	Holdens	Anthracnose resistant/Cercospora resistant/Eyespot resistant/Helminthosporium resistant
		Anthracnose resistant/Cercospora resistant/Helminthosporium resistant/Phosphinothricin tolerant
		Leaf blight resistant/Phosphinothricin tolerant
	Monsanto	Glyphosate tolerant/European corn borer resistant
	Pioneer	Fertility altered/Phosphinothricin tolerant
	Plant Genetic Systems	Phosphinothricin tolerant/Stress tolerant
		Male sterile/Phosphinothricin tolerant
Corn	Stine Biotechnology	Growth rate increased/ Phosphinothricin tolerant/ European corn borer resistant
		Imidazolinone tolerant/ Phosphinothricin tolerant/ European corn borer resistant
		Phosphinothricin tolerant/ European corn borer resistant
	University of Illinois	Aspergillus resistant/ Phosphinothricin tolerant
	Many companies	Phosphinothricin tolerant/ European corn borer resistant
Cotton	Calgene	Bromoxynil tolerant/ Lepidopteran resistant
	Monsanto	Glyphosate tolerant/ Coleopteran resistant
Peanut	AgraTech Seeds	Visual marker/Tomato Spotted Wilt Virus resistant
Pineapple	University of Hawaii	Flower and fruit set altered/ Root-knot nematode resistant
Potato	Boyce Thompson Institute	Phytophthora resistant/ Kanamycin resistant
	Michigan State University	Phytophthora resistant/ Coleopteran resistant/ Lepidopteran resistant
	Monsanto	Glyphosate tolerant/ Bruising reduced
		Glyphosate tolerant/ Carbohydrate metabolism altered
		Glyphosate tolerant/ Colorado potato beetle resistant/ Bruising reduced/ Potato Leafroll Virus resistant
		Glyphosate tolerant/ Colorado potato beetle resistant/ Potato Leafroll Virus resistant/ Potato Virus Y resistant
		Verticillium resistant/ Colorado potato beetle resistant/ Bruising reduced/ Carbohydrate metabolism altered
		Verticillium resistant/Colorado potato beetle resistant/ Potato Leafroll Virus resistant/ Potato Virus Y resistant
		Verticillium resistant/ Glyphosate tolerant/ Colorado potato beetle resistant/ Potato Leafroll Virus Resistant
		Colorado potato beetle resistant/ Bruising reduced/ Potato Leafroll Virus resistant/ Potato Virus Y resistant
	University of Idaho	Late blight resistant/ Potato Leafroll Virus resistant/ Potato Virus Y resistant/ Tobacco Rattle Virus resistant
Rapeseed	AgrEvo	Fertility altered/ Phosphinothricin tolerant
		Male sterile/ Fertility altered
		Phosphinothricin tolerant/ Lepidopteran resistant
	Calgene	Glyphosate tolerant/ Oil profile altered
Soybean	DeKalb	Phosphinothricin tolerant/ Lysine level increased
Tobacco	Southern Illinois U	Ammonium assimilation increased/ Visual marker

Source: APHIS field trials database and biotech/seed company reports

Key observations include:

- Potato and corn varieties appear to be the focus for stacked products in the pipeline. Companies such as DeKalb, Pioneer, AgrEvo and others are working to develop corn varieties that are herbicide tolerant, insect tolerant, fungus resistant and contain increased levels of lysine, methionine and protein. Monsanto is leading in potato development, combining in a variety of ways, traits to resist the Colorado potato beetle, potato viruses Y and X, reduce bruising, tolerate glyphosate, and alter the carbohydrate profile.
- Many companies and institutions are building on traits already successful in commercial markets

and are either joining traits together or "stacking" them with others still in the pipeline.

Livestock

While few biotech livestock products are yet in the commercial arena, significant research is well underway that potentially will result in revolutionary changes in the livestock sector in the not-too-distant future. Researchers are developing genetically engineered "super animals" with enhanced characteristics for food production, novel transgenic animals to serve as "chemical factories" to produce drugs and medicines, and animals to serve as organ donors for human transplants.

This section provides an overview of several possible applications of biotechnology in the livestock sector, including:

- Animal genomes, reproduction and development;
- Animal production systems;
- Animal health and vaccines;
- Animal well-being and stress control systems;
- Pharmaceutical product, medicines and nutrient production; and
- Cloning.

Animal Genomes, Reproduction and Development. The production of foods derived from animals has a major impact on the agricultural economy. In the United States, annual cash receipts of nearly $100 billion from livestock and poultry products account for about 50% of the receipts from all agricultural products. Identification and use of livestock and poultry with appropriate genotypes will have a major impact on the quality of animal products used for food, international competitiveness, and efficiency of production.

Significant research is underway, primarily by the public sector, to develop genomic maps and associated DNA markers to improve the accuracy of selection, increase the frequency of desirable genes in populations, and to characterize valuable germplasm populations. For each livestock species, genetic maps must be developed with sufficient resolution to permit the location, definition, and use of genes affecting economically important traits. Related program components include analyses of the fine structure of candidate genes and gene families, definition of the genetic basis of quantitative trait loci to be used to implement genetic marker-assisted selection, and development of new experimental technologies for utilization of genome information.

Much of the work that comes from the identification and definition of animal genomes is focused on improving the animals' reproductive efficiency. Research is focused on improving reproductive performance of animals through genetics, nutrition, health management, and on management of environmental factors such as temperature and humidity. Research advances and new biotechnologies will be developed to reduce losses due to reproduction problems in all species, and to maximize reproductive output of animals that produce high quality products.

Industry goals for the next five years include:

- The complete identification of genes or gene markers related to at least ten production or disease traits.
- Improve sperm sexing technology by 200-400 percent, to yield sufficient sexed sperm to inseminate 100 cows and 20 sows per day; develop deep freezing methods for sexed sperm.
- Improve cryopreservation by vitrification of embryos in swine to produce live young on a routine basis.
- Increase lean and decrease fat by at least 10% in meat producing beef and swine species and by at least 5% in poultry.
- Improve in vitro embryo production technology (two to threefold) for efficient production and transfer of sexed embryos in swine and cattle.

Animal Production Systems. Livestock producers are challenged with integrating knowledge from diverse disciplines into production practices suitable for their individual operation. Research on food animal production systems assesses the interactions between nutrition, genetics, reproduction, physiology, microbiology, immunology, and molecular biology, and also related effects on animal health, productivity, and impacts to the environment. Improvements in the production efficiency of individual components are often realized in the total system, and ensure a continuing supply of economical nutrient-dense products for the consumer. Research leading to discoveries and applications in production efficiency, sustainability, animal and environmental well-being, and high quality products are imperative if animal agriculture is to be economically viable.

Animal Nutrition - Nutrition is the single most costly component in modern animal production, and poor nutrition is a significant factor in the failure that constrains both production and susceptibility to disease. Research is focused on several areas of nutrition including: 1) chemical composition and availability of nutrients in feedstuffs, 2) nutritional requirements of grazing and non-grazing animals, 3) more efficient use of nutrients, 4) special attention to improving the use of environmentally-sensitive nutrients such as phosphorus, nitrogen, copper, and potassium, and 5) increase understanding of nutrient partitioning between biological functions. (e.g., reproduction, growth, and lactation).

Industry research goals in this area include:

- Information useful in improving animal production systems.
- Improved animal production components for use in whole farm production models.
- Improved definition of dietary nutrient needs for food animals.
- Information on improved sources of nutrients and their bioavailability.

Animal Health. Animal disease is a primary threat to efficient livestock and poultry production, with annual losses approaching17% of production costs in the developed world, and more than twice that in the developing world. Global trade, increased international travel, changing climate, intensive agriculture and reduced genetic diversity in farm animals increase the risk of emergence and spread of infectious diseases. Disease resistance genes and new genetic vaccines are needed to help prevent outbreaks and the spread of animal diseases and to prevent human infection by such pathogens. Protecting the livestock industry from animal diseases by promoting animal health ensures competitiveness of United States animal agriculture in the global marketplace and promotes a sustainable and profitable production system.

Many companies are focusing on development of technology and/or product opportunities that improve animal health and production efficiency in poultry, dairy cattle, beef cattle, swine, and sheep. This includes therapeutics used in animal health and biologicals for diagnosis and prevention of disease in production animals.

Areas of focus for both private and public research include:

> Pathogen Detection – Researchers are working on new rapid sensitive molecular diagnostic tests to facilitate identification of new disease pathogens and toxins. This research is greatly enhanced by the availability of microbial genomics. Domestic and international trade will be based on diagnostic demonstration that animals are free of important livestock and poultry diseases.
>
> Microbial Genomics - Genomics research provides new insight into microbial pathogens, their evolution, required vaccines and therapeutics. A well-developed bioinformatics approach to genome sequence analysis will yield valuable information for molecular epidemiologic analysis of disease outbreaks, for identification of virulence, and for development of new diagnostic and control approaches.
>
> Host/Pathogen Interactions - A better understanding of the molecular and cellular basis of the animal's response to disease is being investigated. Understanding the immunological responses to pathogens is needed to develop strategies for improved vaccine delivery.
>
> Genetic Resistance to Disease - Rapid through-put sequencers for host gene sequencing and the evolving technology that allows for the comparison of expression sequence tags (ESTs) will be used to investigate the genetic basis for disease resistance. Animal immunological and physiological responses will be related to genes and genetic markers. Immunogenetic studies will lead to the identification of genes of pathogenic significance that will be useful in developing novel non-immunity based disease control strategies. A new generation of more efficacious vaccines and adjuvants will be developed to improve herd health. Identification of environmental factors that predisposition livestock and poultry to disease will be investigated and improved management practices will be designed.

Work underway in this area includes:

- Sequencing the genomes of priority pathogens and viruses for use in diagnostic test development, molecular epidemiology, and new approaches to vaccine development.
- A better understanding of the disease interface between wildlife, livestock and poultry will allow the rational formulation of methods to control disease in both populations.
- New knowledge of the route of infection of pathogens, method of colonization, target organs, and immunopathology will lead to new strategies for control of livestock and poultry diseases.
- Identification of genetic markers and genes associated with disease resistance will be made.
- Determining the genetic basis of resistance and formulating breeding schemes to improve animal resistance will help to decrease the economic impact of some forms of disease.
- Developing and testing new safer efficacious vaccines, immune therapies, and drugs for the prevention and treatment of disease in livestock and poultry.

Animals Getting a Boost from Edible Vaccines

There has never been an easy way to vaccinate animals, but new edible technologies could soon have animals eating their way to immunity. Researchers from the University of Guelph, in collaboration with Agriculture and Agri-Food Canada (AAFC), are joining forces to produce edible animal vaccines in crop plants. Using genetic enhancement techniques, the researchers are introducing special genes into the plants to generate novel proteins which will ward off specific diseases. The proteins can be isolated from plants, incorporated into livestock feed and used to vaccinate animals in a more humane and economical way than by the traditional "injection" method.

The first edible product, designed to promote improved gut development and function in pigs, is expected to be available to the swine industry within five years. A vaccine for transmissible gastroenteritis virus (TGEV), a disease that causes severe diarrhea in swine and high mortality in piglets, could save the Canadian swine industry more than $10 million per year. Researchers note that they are beginning their work with pigs, but there is no reason the technology could not be applied to other species.

Edible technologies are part of biotechnology research sometimes referred to as ***molecular farming***. This form of biotechnology is used to produce medicinal or industrially significant compounds in plants traditionally used in agriculture. These "super plants" include corn, soybeans, alfalfa, potatoes and tobacco that grow, look and yield like their conventional cousins, but are outfitted with certain traits that give them therapeutic properties. Crop plants are ideal"bioreactors" to produce the prized proteins because they are able to produce large amounts of the proteins in seeds and leaves, and lend themselves to easy harvesting.

The potential of technologies like molecular farming are far-reaching for livestock and humans. Production of oral vaccines against Porcine Reproductive and Respiratory Syndrome (PRRS) is being investigated by other researchers. Oral vaccines for other diseases like parvovirus are also under development. It is likely the same technology could be used to tackle bacterial infections by producing plants with antibiotic properties. Growth factor proteins also could be grown in plants and fed to livestock to bolster production and combat stress caused by weaning or disease recovery.

Animal Well-Being and Stress Control Systems. Measures of well-being are needed to give producers and consumers information to evaluate management practices and determine which techniques best assure the well-being of animals used for food production. Development of scientific measures of well-being and an enhanced ability to interpret such measures is crucial to the evaluation of current agriculture practices and development of improved alternatives. The research strategy will focus on indicators of animal well-being that can be refined and applied to the assessment of individual management conditions. Stress caused by social and environmental stressors and the interaction of social and environmental stressors need to be understood to limit negative impacts on production efficiency and well-being. Animal well-being research will benefit animals, producers, and ultimately consumers, by reducing animal health-care costs and by improving food production efficiencies. Lack of sensitivity to animal welfare issues may be used in domestic marketing and as an artificial trade barrier of animal products in world markets.

Adaptation and Adaptedness - Most food animals have been domesticated for thousands of years, but intensive management conditions have been developed only recently and oriented primarily toward production traits. Research now is determining the roles that genetics and environment play in well-being. Research information on adaptedness will serve as the basis for modifying management practices. Genetic research is evaluated to improve animal fitness and determine the basis of adaptation to environmental stressors such as heat and cold. Marker assisted selection techniques also are being explored.

Bioenergetic Criteria for Environmental Management - Adverse environmental conditions cause livestock and poultry losses and decrease production efficiency and animal well-being. Available technology needs to be adapted for proactively managing environmental stressors. Research to develop decision support tools is needed to help producers deal with environmental stressors, provide protective measures, recognize livestock and poultry in distress, and take appropriate management actions.

- New knowledge will be available on the interactive mechanism of the immune system and growth in relation to well-being and production efficiency.
- Research will be completed to genetically select for increased productive life of dairy cattle. An evaluation will be completed on whether implementation of a national genetic evaluation for productive life of dairy cattle will result in an increased longevity of cows in the herd.
- New knowledge will be developed in the area of alternative techniques to decrease animal stressors in traditional management systems.
- Alternative management practices/modifications will be demonstrated that reduce stress and increase production efficiency.

Pharmaceutical Product, Medicines and Nutrient Production. Much of the cutting edge research in livestock is focusing on pharmaceuticals. Some livestock are becoming bio-factories to produce pharmaceutical products, medicines and nutrients. Using animals to produce human pharmaceuticals has been gaining application among biotechnologists since the development of transgenic "super mice" in 1982 and the development of the human drug produced by mice, tPA (tissue plasminogen activator to treat blood clots), in 1987.

The first successful products of the genetic engineering process were protein drugs such as insulin and growth hormones. These drugs do not have to be produced by mammals to be active in mammals. An inexpensive, easy-to-grow culture of genetically engineered bacteria like the common E. coli can manufacture these protein drugs.

However, other human drugs — such as tPA, erythropoietin for anemia and blood clotting materials for hemophilia — require modification that only cells of higher organisms like mammals can provide. The higher costs of maintaining mammalian cell cultures that produce only small amounts of the drugs have been an enormous barrier to the commercial development of this type of cell culture production method.

For these reasons, biotechnology specialists say many protein-based drugs that require complex modifications, or that are needed in large supply, are produced more efficiently with transgenic, specifically cloned, animals.

This approach has several advantages over standard chemical means of production, including relatively low operating costs and unlimited ability to multiply. As an added benefit, bioengineers can ensure that the protein products expressed by added genes are deposited in the milk of mammals or the eggs of hens, making the chemicals easy to harvest and process.

In addition, milk content is being modified by genes encoding various therapeutic proteins (see box below). Female mammals regularly produce large quantities of protein in their milk, and research is underway to modify the type and amount of proteins produced. After the milk is collected, the desired proteins are isolated and purified. Human milk proteins including human lactoferrin (a source of iron for infants), human protein C (needed for proper blood coagulation), collagen (for tissue repair) and fibrinogen (a tissue adhesive) soon will be produced in the milk of transgenic animals. These proteins may subsequently be added to milk-based infant diets and other products.

A Cow's Milk Treatment for Multiple Sclerosis

A New Zealand government research agency recently announced plans to introduce a human protein gene into cattle as part of a possible treatment for multiple sclerosis (MS). AgResearch officially applied to New Zealand's Environmental Risk Management Authority (ERMA) for permission to undertake a series of experiments on transgenic cattle.

The authority is responsible for compliance with biosecurity and other environmental safety regulations. AgResearch said it hoped the introduction of a copied human myelin basic protein (MBP) gene would lead to the production of large amounts of the protein in cows' milk. Scientists believe MS, a chronic disease of the central nervous system, is caused by the patchy degeneration of the myelin sheath that coats nerves in the brain and spinal cord. Retrieving the MBP from modified milk produced in the experiments would allow the protein to be used in tests of its efficacy as a treatment for MS sufferers.

Cattle were selected to help produce this protein since they produce large quantities of milk. If the MBP from genetically modified milk prove useful, the approach could provide a major breakthrough. The modification would be done by introducing a human gene to bovine cells in a laboratory and injecting them into bovine eggs.

Two other experiments being pursued separately by the same team of dairy researchers would involve the introduction of additional cattle casein genes, and the disruption of another gene to boost dairy production. Both were hoping to establish whether there was any long-term value to the dairy industry in improving what they called "the processing characteristics and nutritive value" of milk.

AgResearch's five-year proposal involves the production of three small herds of up to 30 head of cattle each for the projects at a secure containment site. The aim is to produce transgenic animals of the three types and raise them to sexual maturity so they can be bred and brought into lactation in order to evaluate the effect of the genetic modifications on protein production.

Genetically modified mammals were first produced in 1996, when "Dolly" the sheep was cloned in a Scottish laboratory. Earlier this year, ERMA approved an application from Dolly's developers, PPL Therapeutics, to breed a flock of sheep in New Zealand with another human protein gene in a bid to fight the lung tissue disease cystic fibrosis.

Combined with other genetic engineering techniques, cloning can eliminate one of the significant barriers to the application of dairy animals' productivity to produce scarce and expensive drugs that can prevent or control diseases in humans or other animals. Transgenic technology can also be used in xenotransplantation, the modification of animal body parts to make them acceptable for human transplantation. Cloning, described in more detail below, can create multiple copies of the genetically engineered founder animal.

Designer Genes for Future Generations

A Canadian company is the first in the world to cross a huge barrier in genetic engineering — one that could allow scientists to change the genes of one human and all his or her descendants. Chromos Molecular Systems, British Colombia, invented an artificial chromosome and implanted it into a mouse embryo. So far in Chromos's experiments, only mice have passed the artificial chromosomes from one generation to the next.

However, the technology can be used in a wide variety of mammals. And that opens the door to possible gene manipulation for entire human families, as therapy for inherited diseases such as cystic fibrosis. It also raises fears of misapplication. Chromos maintains that the technology is designed to help sick people. Scientists at the three-year-old company think of the artificial chromosome as a "platform" to carry genes that might be beneficial to people.

The company hopes the technology can be used to create herds of genetically engineered cows. The animals would carry a gene in the extra chromosome that will allow them to produce milk containing proteins that can be used to attack human illnesses, including rheumatoid arthritis and hemophilia. So far, one of the challenges of producing proteins this way has been the fact that it could take a decade or more to create a herd of cows that consistently produces the therapeutic protein. Now, with modified genes inherited, a herd could be built much more quickly.

The protein-producing genes could be used two ways. First, the proteins in the milk can be purified and used in pill or injection form to treat illnesses. They also could also be introduced into the patient's body as an engine to deliver the therapeutic proteins to a sick person. But Chromos has said it would not be used to create generations of people who are free of rheumatoid arthritis, hemophilia or other illnesses - there are too many regulatory hurdles that constrain work with human models.

Chromos put a whole artificial chromosome into mice by injecting it into the cells of a mouse embryo. The artificial chromosomes are made by starting with a natural one and altering it in the lab, leaving an artificial chromosome containing only the elements it needs to survive and copy itself. When the mice carrying the extra chromosome were crossed with normal mice, it was inherited in the same way as the rodent's natural chromosomes. This differs from traditional gene therapy, in which only small bits of DNA are added to an embryo in the hope they will join an existing, natural chromosome. These DNA bits can miss their targets, or join in the wrong place. Putting in a whole artificial chromosome at once should reduce that chance.

Now the preliminary results, reported recently at a conference in Britain, are certain to arouse debate about whether inherited genes could – or should — be used to attack inherited diseases in humans. For example, the first scientists to clone a mammal (Dolly the sheep) swore never to clone humans. Inserting genes in humans has always been considered dangerous because often the insertion in lab animals misses completely, or goes off target in ways that creates an animal with serious birth defects. And all human gene therapy carries risks as well as benefits, making this technology a huge Pandora's box.

Cloning. Despite the enormous attention given to cloning over the past few years, not just from within the livestock industry but also from the general public, over the past year there has been continued research in this area. However, the public acceptance debate remains a hindrance in the near term to the widespread application of this technology.

The concept of cloning is simple: through either selective breeding or genetic engineering, a founder organism is created and then modified to produce pharmaceuticals and nutraceuticals. Through bovine cloning, scientists replicate the founder organism, significantly increasing the capacity to produce these materials while substantially lowering the cost of doing so. It is estimated that using animals for producing human pharmaceuticals is five to ten more economical in the long term and two to three times less expensive in start-up costs than cell culture production methods.

A transgenic animal for pharmaceutical production should do two things — produce the desired drug at high levels without endangering its own health, and pass its ability to produce the drug at high levels to its offspring. Presently, scientists are achieving this by coupling the DNA gene for the protein drug with a DNA signal directing production in the mammary gland. The new gene, which is present in every cell of the animal, functions only in the mammary gland so the protein drug is made only in the milk. Since the mammary gland and milk are essentially outside the main life support systems of the animal, there is virtually no danger of disease or harm to the animal in making the foreign protein drug. The protein is extracted from the milk and converted into human pharmaceuticals. High levels of milk production coupled with the ease of milk collection from dairy cows make using transgenic dairy animals particularly attractive.

While transgenic technology is revolutionizing drug development and production, it still can be inefficient and expensive. Still, it is, in some cases the only method available to produce complex proteins and cloning provides economical alternatives. Once a transgenic founder animal is created through traditional microinjection methods, researchers can rely on cloning to produce numerous copies of that animal. The end result — abundant supplies of important drugs that are typically scarce and expensive. The same transgenic and cloning technologies used for producing pharmaceuticals can be used for making nutraceuticals and organs for xenotransplantation.

Cloning techniques also would allow dairy producers to better manage cows of the same genetic structure through feeding and breeding, since all cows in such a herd respond similarly to nutrition and the environment. Milk production, uniformity in milk quality and consistency in the content of milk are all potentially improved with the advancement of cloned cows. For example, in the future, dairymen could select cows that produce milk yielding the best mozzarella cheese, then clone these animals so the herd is identified for this purpose. Or, dairymen could also select and clone cows that produce nutrient enhanced milk for babies.

In similar ways, beef producers could clone a bull with specific desirable traits, register the clones and then use multiple bulls to produce semen with the same genetic makeup. Animals with similar or the same genetic backgrounds will perform consistently in the feedlot and produce meat with desirable nutritional and eating qualities for specific markets and customer demands.

Cloning could also enable research in feed efficiency and other important economic traits. Use of cloned animals in research eliminates genetic variability and focuses the results on the factors being tested, thus decreasing the quantity of animals needed for each research project.

Overall, this cloning technology can help dairy and beef producers improve the efficiency and profitability of their operation, and consumers will benefit from a product that is more uniformly and cost effectively produced. Advanced cloning techniques offer significant potential to improve the quality and consistency of the animal. Producing multiple copies of animals with known meat characteristics (flavor, tenderness and color) is possible. New research on gene transfer that would have the capability to produce the same types of desired effects as cloning has occurred in just the last year and is described below.

Infigen — the World's Largest Herd of Cloned Cattle

Infigen, Inc., the biotech company responsible for "Gene," the world's first cloned calf, recently announced that its herd of cloned cattle has grown to nearly 40 head. The Holstein heifer calves all are from five to eight months of age and from the same cell line. The company continues to move toward establishing cloning as a commercially viable mass production process with the capacity to introduce therapies that address a vast array of human diseases.

Infigen’s work in genomics will ultimately assist pharmaceutical and related biotechnology firms in developing new human healthcare applications such as technology for skin regeneration and replacement. In agriculture, it would enable production of plants for feed that contain genes that allow animals to self vaccinate against diseases and parasites.

Infigen has also begun to apply its cloning technology with other species and has established an aggressive program for cloning transgenic pigs, capable of producing rejection-resistant human organs.

Nutraceuticals

Nutraceuticals or functional foods are considered by many food industry analysts to be the major product innovation of the next decade. Thus far, much of the product development in this area has focused more on conventional methods than on biotech, such as the use of additives and fortification. The key to biotech development of functional foods is in finding products that can be produced more cost-effectively through biotech than through conventional means. Some of the products in development likely to reach the market in the next five years include:

- A tomato with enhanced beta carotene, developed by Zeneca. USDA's Agricultural Research Service is developing (with no apparent private-sector involvement) carrots and cucumbers with added beta carotene.
- A lycopene-enhanced tomato in development by Zeneca in conjunction with the Royal Holloway Hospital. This tomato, which has attracted interest from major food companies, could be used to create lycopene-rich ketchup, pasta sauce, and other foods. (Lycopene is an antioxidant carotenoid which may reduce the risk of cancer.)
- Milk-derived products that prevent travelers' diarrhea. ImmuCell Corporation is developing these products using bovine anti-E. coli immunoglobulins.

The industry still is very much in the formative stages, with small companies forming alliances with larger partners while continuing basic research. The next five years may see only a trickle of GMO functional foods, but the long-term impacts on the food industry of such new products are enormous. Foods could be tailored to achieve specific medical benefits, targeted for people with certain medical conditions, and designed to prevent food-borne illness. In tropical areas where widespread diseases still are prevalent, foods genetically modified to contain vaccines could control preventable diseases that have plagued humans for centuries.

Human clinical trials already have demonstrated the effectiveness of transgenic plant-derived pharmaceuticals. In the past decade, intensive research has been focused on expanding the use of plants as pharmaceutical production systems through genetic engineering. It now is clear that plants can be manipulated to produce a wide variety of such compounds, from vaccine antigens and monoclonal antibodies to pharmaceutically valuable secondary metabolites.

Vaccination by Banana

Scientists in Queensland aim to be the best banana-benders in the world, involving themselves in a project to genetically engineer plants to grow a Japanese encephalitis vaccine. A team at the Queensland University of Technology aims to manipulate banana plants to produce an edible vaccine which could be grown by farmers in tropical Third World countries, and that bananas had been chosen because they were easily grown and transgenic experiments would be safe. Researchers are using sterile plants with no pollen or seed so that once the vaccine genes are in, they stay there and cannot be transferred to other surrounding bananas.

The idea of delivering vaccines via fruit or vegetables is being widely researched around the world as a low-cost alternative for developing countries where spoilage of vaccines is a major problem. A potato vaccine against cholera has already reached clinical trial stage in the United States.

Vitamin A Fortified Rice …

Vitamin A deficiency affects about 400 million people worldwide, who are at risk of infections and blindness. Additionally, iron deficiency which is common in people with rice-based diets afflicts nearly 4 billion people, more than two-thirds of the world's population. Women consuming such diets are particularly at risk, as iron deficient women are more likely to suffer from anemia as well as from complications during childbirth.

Scientists have presented a high tech, golden-colored rice genetically modified to contain both beta-carotene, the precursor to vitamin A, and a healthy dose of iron. The new rice, described in August in *Science*, "will offer improved nutrition for the billions of people in developing nations who depend on rice as a staple food."

This is the first kind of rice genetically modified to enhance its nutritive profile. If all goes well, enhanced rice could be in the fields of developing countries in two to three years. That is, if it does not run afoul of the regulatory red-tape which has brought the flow of biotech foods to a dead stop in countries like Great Britain.

As agricultural biotechnology develops, it increasingly will find applications in non-agricultural industries. Plants are efficient producers of proteins, and since biotechnology gives scientists the tools to introduce code for proteins into plant DNA, plants eventually will be transformed into a delivery mechanism for a broad variety of commercially attractive proteins. The first of the value enhanced products already offers a glimpse of what the future could bring. Monsanto already has demonstrated that specialty oils from its canola work could have application as industrial lubricants and as ingredients in soaps and other personal care products. The key to the concept of plants as factories is economics. The plant-derived product must be less costly to produce than with traditional (chemical or other) means.

Agriculture's traditional role in providing food, feed and fiber is being expanded by biotechnology into entirely new forms of production. Some farms of the future very likely will be living factories churning out industrial chemicals from genetically engineered plants. Research projects in Sweden, Australia and England, for example, have developed plants producing unusual oils used in the production of polymers, plasticizers, lubricants, and other industrial products, thus potentially providing a renewable alternative to petrochemical oil.

Acetylenic and epoxy fatty acids are critical raw materials used in production of polymers such as plastics and certain chemicals. These fatty acids, which are modified forms of those present in edible oils, are currently derived from either non-renewable petroleum or chemically processed vegetable oils. A recent *Science* paper describes the cloning and expression in transgenic plants of genes involved in the synthesis of acetylenic and epoxy fatty acids. The chemical modifications of oil are done within the plant, obviating the need for expensive industrial processing and also eliminating waste.

The possibilities include components of detergents, nylon, glue, paints, lubricants, and plastics. Researchers believe that specialty oils eventually will be produced in flax (linseed) to minimize the risk of contaminating edible oils through gene flow (it is better to target self-pollinating oil crops such as flax rather than outcrossing ones such as canola or sunflower). But it may be beyond our five year horizon before crop "mini-factories" are producing high value industrial compounds.

Biotech Developments Elsewhere

Most of the research on and production of biotech crops has occurred in North America, with the United States and Canada leading the way, followed by Argentina, China, Australia, Mexico, Japan and South Africa. Commercialization also is beginning in Europe, and, within just a few years, Brazil likely will be a major producer of biotech products as well. The following section highlights some of the research and product development that is underway in Canada.

Canada

The early focus on crops in Canada has been on input traits, especially herbicide tolerance. Attention now has expanded to output characteristics, with a wide variety of traits being pursued for human, livestock and industrial markets. However, input characteristics such as herbicide tolerance, disease and insect resistance, and stress tolerance still dominate the research agenda. Cost reducing/yield enhancing traits accounted for 87% of the field trials in 1998, with 51% of trials still targeting herbicide tolerance (Chart 4).

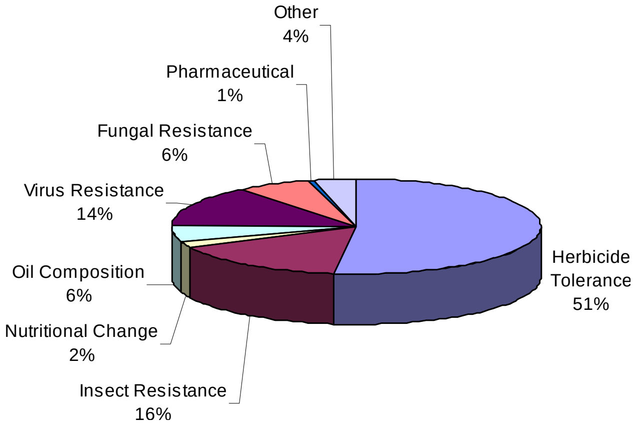

Chart 4. Canadian Field Trials by Modified Trait

Plant biotechnology research focuses heavily on the Brassica family which includes canola (Argentine and Polish varieties) and mustard. Canola has proven to be one of the most receptive crops to genetic manipulations and has been the primary focus of much research. This year, canola represented 43% of all field trials and transgenic canola varieties accounted for roughly 55% of commercial acreage in 1998 (Chart 5). Potatoes also are receiving considerable attention, with 126 field trials (24%) in 1998. Other crops of interest include alfalfa, corn, soybeans and wheat.

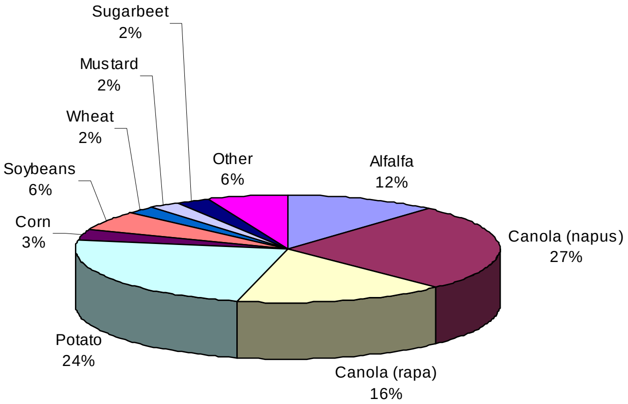

Chart 5. Canadian Field Trials by Crop Type - 1998

Some of the most significant research initiatives underway suggest commercialization of the products described in Table 18:

Table 18. Canadian Product Developments

Crop Type	**Product**	**Description**
Oilseeds	SHEAR (Super High Eurucic Acid) canola	Potential for industrial uses such as lubricants, plastics, nylon. Insertion of yeast gene resulted in 25% greater oil content.
	Low linolenic acid canola	
	High stearate canola	
	High oleic canola	
	Canola production from Juncea	Canola oil and meal characteristics introduced in juncea (mustard plant), a more drought resistant plant, allowing canola to move south in the Prairies.
	Hybrid canola	Improved hybridization, creating male sterility and herbicide tolerance traits.
	Shatter resistant varieties	
	Canola meal enhancements	Reduced levels or blocked production of “anti-nutritionals” such as glucosinolates, phytic acid and sinapine (gives meal bitter taste, acts as appetite depressant) – could make canola meal more competitive with soymeal. Yellow coated seeds to make meal more attractive, contains lower lignin levels. Reduced lignin levels.
Wheat	Waxy wheat	Modified starch composition (low amylose/high amylopectin starches). Intended for noodle markets, corn syrup replacement, and bio-fuels.
	Herbicide tolerant wheat	Commercial release expected by 2003
	High amylose wheat	Contains high levels of non-digestible starch for use in diet breads and other foods.
	High lysine wheat	Replaces synthetic lysine in livestock feeds
	Selection of large starch molecules	
	Modified protein (gluten) composition	For food applications and use as a meat replacement to provide high protein levels
	Increased starch levels	Creates plumper kernels desirable in livestock feeding
Barley	Increased disease resistance	
	Reduced protein content	Intended to boost malt yields as high protein tends to reduce yields
Alfalfa	Reduced lignin	Increases plant’s digestibility
	Enhanced chlorophyl production	Results in increased hay yields

Summary

Development of agricultural biotechnology is taking place in several other parts of the world, as well. The Consultative Group on International Agricultural Research (CGIAR) has noted the potential of biotechnology to boost agricultural production in developing countries, and may devote a portion of its resources to research in major developing-country crops such as rice and cassava.

As international trade in the ever-growing number of biotech crops expands, the plethora of regulatory approvals (normally required for each new crop in each new country) will create an increasing drag both on world agricultural trade and biotech research, possibly leading to calls for some kind of multilateral approval process.

It is clear that the proliferation of biotech crops around the world is and will continue to be rapid. However, there are many hurdles that companies must cross to get product approvals – and the approval process, its requirements and timeframe are different in every country.

Endnotes

1. In this study, a broad definition of biotechnology is used, focusing on product characteristics more than the processes used to develop the product. For example, a herbicide-tolerant crop is considered biotech whether it was developed using advanced breeding techniques or a "gene gun" to insert genetic material into the seed. Still, it is helpful to differentiate between crops that are "transgenic," with a gene inserted from another plant or organism (often referred to as "genetically modified organisms," or GMO's) and those which are "nontransgenic." In 1980, the US Supreme Court ruled that genetically engineered microorganisms were intellectual property and could be patented. See the glossary in Apendix C for additional terms and definitions.
2. For a definition of value enhanced products see the glossary in Appendix C.
3. The chemical names for the active ingredient in the herbicides are referenced. The brand names that correspond to these chemicals include:
    - Sulfonylurea – Synchrony, Merit
    - Glyphosate – Roundup
    - Glufosinate – Liberty
    - Phosphinothricin – Liberty
    - Inidazolinone – Pursuit, Odyssey, LIGHTNING (IMI)
    - Bromoxynil – BXN
4. Applications for field trials are not required to make available details of the specific trait modifications being sought to the public. A firm can claim in a permit application that some scientific data is confidential business information (CBI). APHIS can, however, use that informaiton in its safety deliberations, but may not divulge the information to the public.