

NBIAP NEWS REPORT
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GENETICALLY ENGINEERED VIRUS RESISTANT SQUASH APPROVED FOR SALE

On December 13, 1994, the Animal and Plant Health Inspection Service (APHIS) of the USDA finally deregulated the genetically engineered virus resistant yellow crookneck squash line designated ZW-20 (Federal Register, pages 64187-64189). The controversial virus resistant squash, developed by the Asgrow Seed Co., had been regulated under the Plant Pest Act in part because it contains DNA sequences derived from plant pathogens. ZW-20 squash resists infection by zucchini yellow mosaic and watermelon mosaic viruses because the coat proteins of those viruses were inserted into the line. It was field tested under 14 APHIS permits at 46 sites in 10 states.

Following submission of a petition for deregulation by Upjohn, Asgrow's parent company, APHIS sought public comment on the ZW-20 squash petition and the agency's preliminary finding of no significant environmental impact on three different occasions. Opponents of deregulation argued that the use of two viral coat proteins could lead to the creation of new plant viruses and perhaps cause the squash to become a weed, and that the virus resistance genes could move to wild squash relatives with detrimental impact on these wild plants.

Based upon an analysis of the data submitted by Upjohn, a review of scientific literature and comments received from the public, APHIS concluded that the ZW-20 squash is as safe to grow as traditionally bred virus resistant squash and therefore no longer needs to be regulated. Opponent organizations such as the Union of Concerned Scientists have expressed disappointment over APHIS' determination.

In November 1994, a U.S. Food and Drug Administration (FDA) Public Advisory Committee, after reviewing data provided by Upjohn, found that as food, ZW-20 squash appeared to be as safe as its non-engineered counterpart. This spring, Asgrow Seed will begin marketing the genetically engineered squash seeds under the name "Freedom II". The seeds will bear a label stating that they are the product of genetic engineering.

MONSANTO SEEKS DEREGULATION OF INSECT RESISTANT POTATO LINES

USDA APHIS has announced receipt of a petition from the Monsanto Company seeking a determination of nonregulated status for seven Russet Burbank potato lines that have been genetically engineered to resist the Colorado potato beetle (Federal Register, December 2, 1994, pages 61866-67). The potatoes produce an insect control protein derived from the common soil bacterium *Bacillus thuringiensis* subsp. *tenebrionis* (Bt) which is highly selective in controlling the beetle pest. The protein is expressed at a consistently effective level in potato foliage throughout the growing season.

The Monsanto potato lines were field tested and evaluated at a total of 34 locations under nine APHIS permits issued between 1991 and 1993. The lines are currently regulated under the Plant Pest Act because they contain gene sequences derived from plant pathogenic sources. During the testing period APHIS determined that the vectors and other elements were disarmed and would not present a risk of plant pest introduction or dissemination.

The genetically engineered potato lines are also subject to regulation by the Environmental Protection Agency (EPA) as a pesticide under the Federal Insecticide, Fungicide and

Rodenticide Act (FIFRA); and by the Food and Drug Administration's Federal Food Drug and Cosmetic Act (FFDCA) concerning pesticide tolerances for food; and under the FDA's 1992 Policy Statement concerning Regulation of Plants Derived from New Plant Varieties. APHIS and EPA are coordinating their reviews to avoid duplication and assure that all relevant issues are addressed.

Written comments on the petition are invited and must be received on or before January 31, 1995. To obtain a copy of the petition, contact Ms. Kay Peterson at 301-436-7601 or 301-734-7601.

PATENT OFFICE CANCELS BROAD PATENT ON TRANSGENIC COTTON

On October 27, 1993, Agracetus, Inc., a subsidiary of W.R. Grace & Co., received Patent No. 5,159,135 which covered all genetically engineered cotton varieties and gave the company monopoly control over all transgenic cotton plants and seeds until the year 2008.

Agracetus' patent claims on cotton were exceptionally broad and far-reaching in that they covered two genetic transformation techniques (the use of *Agrobacterium tumefaciens* and the company's patented "gene gun" technology), as well as all genetically engineered cotton varieties.

Since being awarded to Agracetus, the patent on genetically engineered cotton engendered a storm of protest from industry and government sources over the near monopoly control it gave to a new technology. In particular, the USDA's Agricultural Research Service, which invests heavily in cotton research, vigorously argued that other scientists had contributed important innovations to the technology.

Responding to these claims in April 1994, the Patent Office ordered a re-examination of the Agracetus patent. On December 7, 1994, the Patent Office canceled the Agracetus patent on transgenic cotton on the basis that other researchers already knew what was disclosed in the patent application as being novel and new. Under Patent Office procedures, Agracetus has two months to respond to the decision; if this fails, Agracetus can appeal the decision to the Patent Office and then to Federal Court. The patent remains valid until the company has exhausted all forms of appeal.

BROAD PATENT ON GENETICALLY ENGINEERED SOYBEANS SOUGHT

In the wake of the cancellation of Agracetus' patent on transgenic cotton, W.R. Grace & Co., Agracetus' parent company, is preparing to defend a similarly broad patent it is seeking in the U.S. and Europe for genetically engineered soybeans. The company argues that it is entitled to the patent because it was the first to perfect the techniques for genetically modifying soybeans. Once again, industry and university researchers are arguing that there are other techniques available for genetically engineering soybeans.

The issue is heating up as several American biotechnology companies are formally opposing the European patent. Monsanto Co., which has developed a herbicide tolerant soybean using an Agracetus transformation technique under license, has filed opposition papers with the European Patent Office. The status of the application for a U.S. patent on transgenic soybeans isn't clear at this time.

PROFILE OF AN AGRICULTURAL BIOTECH COMPANY

The biotechnology firm Agracetus of Middleton, Wisconsin, a subsidiary of W.R. Grace & Co. of Boca Raton, Florida, was launched in 1981 as Cetus Madison by a group of University of Wisconsin scientists. The company's focus was the development of enhanced microbial inoculants like *Rhizobium* to benefit soybean and alfalfa yields. In 1984, W.R. Grace bought 51 percent of Cetus Madison and agreed to contribute up to \$60 million for genetic R&D over five years. The company was renamed Agracetus.

Through the 1980's Agracetus and other biotechnology companies succeeded in genetically transforming *Rhizobium* to enhance its nitrogen fixing ability. However, farmers could not attribute specific yield increases to the new inoculants and the products did not do well commercially. In 1989, W.R. Grace purchased Cetus' equity position and converted Agracetus to a wholly owned subsidiary.

Sharp refocusing of R&D efforts quickly took place and development of transgenic plants was placed in the forefront. Agracetus had developed the gene gun technique for transforming plants including soybeans. The company began to market this technology as a service and also extended its transformation cotton. Profitable licenses were granted to Monsanto and Calgene to use company techniques to transform cotton. Agracetus retained in-house its techniques for genetically customizing cotton fibers.

In 1992, Agracetus was awarded a broad coverage patent for all genetically engineered cotton products. In 1994, following protests by industry, academia, and government sources, the Patent Office canceled the patents on the grounds that the cotton transformation technology wasn't new or novel. Agracetus is appealing the ruling.

In the meantime, Agracetus has reached an agreement with Bristol-Myers Squibb to develop genetically transformed corn and soybean plants to express therapeutic monoclonal antibodies.

EPA INVITES APPLICATIONS FOR GRADUATE FELLOWSHIPS

The Environmental Protection Agency (EPA) is inviting applications for graduate fellowships in academic disciplines at the forefront of environmental science and technology: the physical, biological and social sciences; mathematics and computer science and engineering. EPA expects to award approximately 100 new multi-year graduate fellowships in 1995. These fellowships are intended to help defray costs associated with enhanced environmentally-oriented study leading to a masters or doctoral degree.

Applicants must be citizens of the United States or its territories or possessions, or lawfully admitted to the U.S. for permanent residence. Women, minorities and disabled students who are pursuing graduate degrees in one of the eligible fields are especially encouraged to apply. The Graduate Fellowship Program provides up to \$34,000 per year of support for stipend, tuition and expenses.

A review panel will evaluate applicants for their potential success in graduate study, based on academic records, faculty recommendations, career goals and objectives. Students seeking a masters degree will compete against each other as will students seeking a doctoral degree. Selections of awardees will be made by EPA based on the panel evaluations, program goals, and availability of funds.

An initial application for the Graduate Fellowship Program may be requested from: Graduate Fellowships, Office of Exploratory Research (8703), Room 3102 NEM, 401 M Street, S.W., Washington, DC 20460, Attn: Virginia E. Broadway. Fax: 202-260-0211, e-mail: broadway.virginia@epamail.epa.gov

For additional details on applying see the Federal Register, Vol. 59, No. 240, Thursday, December 5, 1994. Deadline for receipt of applications is February 13, 1995. EPA will notify all applicants regarding their status by mid-April 1995.

INTERNATIONAL PLANT GENOME CONFERENCE

The third International Plant Genome Conference will take place January 15-19, 1995, at the Town and Country Hotel in San Diego, California. For registration and program information about Plant Genome III, contact Scherago International, Inc. at 212-643-1750, fax 212-643-1758, or e-mail: scherago@biotechnet.com.

EUROPEAN UNION ALLOWS BST FOR TESTING PURPOSES

European Union agricultural ministers have agreed to allow limited use of Monsanto Co.'s bovine growth hormone (Bst) in the European Union for testing purposes. At the same time, they extended a moratorium on the hormone's use and commercialization through 1999.

(The foregoing was compiled by Jay H. Blowers)

AGRICULTURAL BIOTECHNOLOGY NOTES

William O. Bullock, Jr., Institute for Biotechnology Information, Research Triangle Park, NC

BIOTECHNOLOGY IN AGRICULTURE: 1994 YEAR IN REVIEW

1994 was a turbulent year for the biotechnology industry. The industry's largest sector, biopharmaceuticals, was hit with a number of clinical trial setbacks and failures, and investors began to question the worthiness of their high risk investments in biotechnology in general (1). In fact, three of the top ten worst performing stocks for 1994 on the NASDAQ market (based on percentage change from 1993) were biotechnology stocks: Telios Pharmaceuticals; MicroProbe; and Alpha 1 Biomedicals (2). Although each of these three companies are focused on therapeutic development, agricultural biotechnology companies may have been hurt by the pharmaceutical sector and did not fare much better.

Here is a sample of some select ag-biotechnology company stocks and their percentage price change during 1994 (3):

Crop Genetics International (-82%)
AgriDyne Technologies (-71%)
Calgene (-43%)
Ecogen (-43%)
DNA Plant Technology (-36%)
Mycogen (-18%)

As was noted in our Agricultural Biotechnology Notes section from the August 1994 NBIAP News Report, the movement of agricultural biotechnology stocks closely mimics that of the biopharmaceutical sector, likely due, in addition to other factors, to large swings in individual biotechnology company stocks (usually therapeutic firms) that pull the entire biotechnology industry with them, economic conditions that impact all stocks, and a lack of sophistication and understanding of the technologies by some investors.

In addition to the poor market showing by agricultural biotechnology companies, a number of other notable developments took place in 1994 related to the agricultural biotechnology sector. Some of these include:

- Monsanto's bovine somatotropin (BST) went on the market in February 1994, creating controversy and litigation over its economic impact and product labeling provisions.
- Calgene's genetically engineered FLAVR SAVR (TM) tomato was approved by the FDA in April 1994 and went on the market in the United States. It was also issued patent protection by the European Union.
- The USDA (APHIS) approved discontinuation of regulation under the Plant Pest Act of some genetically engineered agricultural products, including BXN (TM) cotton (a herbicide-tolerant cotton), Laurate Canola, the FLAVR SAVR (TM) tomato (all developed by Calgene), and Monsanto's herbicide-tolerant soybean.
- NIH published revised guidelines for research involving recombinant DNA molecules.
- The FDA developed proposed regulations that would establish a mandatory premarket notification system for foods derived from genetically modified plants.
- The German government eased its strict biotechnology

regulations, making it easier to conduct research and development using genetic engineering. One area that this may impact is the number of field trials conducted in Germany, as only 2 field release permits had been approved there between 1986 and 1992, compared with 77 in France and 316 in the United States for that same period. The European Union also worked toward easing permit requirements for field tests of genetically engineered plants.

- The broad patent awarded to Agracetus in 1992, covering all genetically engineered cotton varieties, came under scrutiny and was considered for possible re-examination.

- The U.S. Patent Office requested comments on proposed changes in patent protection rules for biological inventions.

- The FDA found seven genetically engineered food plants safe including tomatoes from Zeneca Plant Science, DNAP Plant Technology, and Monsanto; ZW-20 squash from Asgrow; insect-resistant potato and herbicide-tolerant soybean from Monsanto, and herbicide-tolerant cotton from Calgene. Although these food crops were deemed safe by the FDA, they are also subject to approval by the USDA and/or the EPA.

In spite of the lack of confidence of investors in agricultural biotechnology companies during 1994, one end-of-the-year forecast predicts almost 30% average annual sales growth over the next ten years of agbio products, increasing from an estimated \$130 million in 1994 to almost \$1.5 billion in 2004 (4). Research discoveries continue to evolve, and this, combined with breakthroughs in ag-product commercialization and regulation as seen in 1994, continue to fuel optimism for the sector's future growth.

References:

- (1) Biotechnology in the U.S. Pharmaceutical Industry, The Institute for Biotechnology Information, January 1995, pg. 5-23.
- (2) Year-End Review of Markets and Finance, The Wall Street Journal, Tuesday, January 3, 1995, pg. R4.
- (3) The Wall Street Journal, Tuesday, January 3, 1995, pg. R25-R30.
- (4) Shamel, R.E., and M. Keough, 1994. Non-Medical Areas Expected to Show the Fastest Growth in Biotechnology. Genetic Engineering News, December 1994, pg. 11.

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