Patent wars shadow research future

By Karen Charman

As new research in agricultural biotechnology proceeds and the products it yields roll onto the market, a developing legal nightmare in the United States promises to profoundly impact the industry worldwide. Most of the key components of techniques currently used in genetically engineering food crops are swamped in litigation over who owns them.

The situation has many in the industry worried because liabilities in the form of royalties are beginning to reach levels that many companies and research organisations, especially smaller ones, would not be able to afford. Once ownership is sorted out, companies or research institutions may find themselves either having to pay what the patent holder demands, forego the work they have done that included the patent holder's property, or figure out a way to pass the cost onto farmers and/or consumers.

Dr David Evans, executive vice-president of business development at DNA Plant Technology Corp (DNAP) in California, says the process of contending with newly granted ownership can be extremely irritating. His company produces Endless Summer™ tomatoes, which have been genetically modified to delay ripening and give them a longer shelf life. DNAP has been working on Endless Summer™ for several years and hopes to have the tomato widely distributed in American supermarkets by the middle of next year.

Around the end of 1994, the company hit a snag. The United States Patent and Trademark Office granted Monsanto a patent on a promoter gene DNAP used to engineer its tomatoes, a gene Evans describes as "one of the basic pieces of the genetic toolbox". Once the patent was issued, he says it was huge hassle to start over and try to re-engineer the plants. "It's not a matter of just going back into the lab and re-introducing DNA into a plant cell and 'Presto!' you have a new plant you can sell at the supermarket," he said.

Nevertheless, DNAP, a small independent ag biotech start-up at the time, shifted gears and tried to re-engineer its tomato. In September of 1996, the company was bought by Impresas La Moderna, a large, cash-rich Mexican agricultural conglomerate. Evans says in the end it was faster to negotiate a license with Monsanto than to come out with another version of Endless Summer™, though, he adds, if DNAP had remained independent, the company never would have been able to afford the license.

The best option is to try to obtain one's own patent. But, Evans points out, that process is also uncertain, difficult and expensive. "It can be very frustrating. You could be two-and-a-half years into the process of going back and forth with the Patent Office. When it finally looks like you have overcome all the arguments and you are going to get something issued, you then find out, lo and behold, somebody else has a similar patent pending." At that point the Patent Office declares what is known as an "interference", which means it has to go back and try to figure out which company came up with the invention in question first. Unlike most other countries, US patents are granted on the basis of who invented first rather than who filed first. Some as-yet unresolved ag biotech patents have been pending for nearly 15 years.

Patent owners tend to be more lenient about letting research scientists use their products as long as there are no plans to commercialise anything that comes from the research. At that point, the parties negotiate licence agreements, which means the patent holder gets a cut of any sales of the new product or process.

Scientists at the Center for Agricultural Molecular Biology at Rutgers University in New Jersey have made a transgenic herbicide-resistant creeping bent grass, using the biolistics gene gun, whose patent is held by Sanford Scientific in New York, and a pat gene claimed by the large agricultural multinational corporation, AgrEvo. Creeping bent grass is a common golf course turf, and center director Dr Peter Day says an herbicide-resistant variety would be very useful to golf courses for controlling heavy infestations of weeds. Despite having spent several hundred thousand U.S. dollars on the research, he says their grass may not get onto the market because AgrEvo may not sell them a licence to use the pat gene. They also have to strike a deal with Sanford over the use of the gene gun.

"Whatever you do, you have to do deals," Day laments, adding that that task is often distasteful and difficult for academic scientists who are frequently more interested in doing work relevant to the needs of society.

"Dealing with patents is like being tangled up in steel cable. You sort of get trapped in its coils and it's difficult to struggle free at times," he said.

Although the battles are taking place mainly in US courts, New Zealand biotechnologists, aware of the implications of the newly emerging global economy, are very concerned. Graham Smellie, business manager at Crop and Food Research Ltd in Levin, says Crop and Food scientists use a lot of patented genes and techniques under dispute by American companies and universities. "Identification of what techology is patented and who owns it is now an integral stage in the development of our research programmes. Such clarity is necessary for any future commercialisation," he said.

Biotech 101

The process of genetic engineering is much more complicated than simply identifying and isolating a gene from one thing and sticking it into something else. The technology currently involves five basic steps:

1. locating the gene that carries the trait to modify the plant;

2. separating the gene from the rest of the DNA strand where it is found;

A patent must be granted if the invention meets the three criteria laid down in the law: it must be novel, useful and non-obvious to professionals in the field.

3. inserting the gene into a plasmid vector that will carry the gene into the target plant;

4. inserting the plasmid vector with the new gene into the target plant; and

5 testing the target plant to see whether the new gene was successfully introduced.

Patents are held or are being challenged in most of these areas.

One of the most important steps in the process is transformation, the method of getting the new gene into the target plant. Currently two techniques work best in plants: the biolistics gene gun and agrobacterium. A third, less frequently used method, electroporation, inserts DNA into the cells of any species utilizing electrical shock.

Biolistics, also known as microprojectile bombardment or ballistics, works by taking a small, powder-like metal particle, coating it with a DNA solution containing the new gene and literally shooting it into the target tissue at high speed. If the target plant incorporates the new DNA and begins to develop cells containing that DNA, the transformation is successful.

This technique can be used on any plant but works particularly well with grasses. Several companies have products transformed with the gene gun on the market now. Monsanto, Mycogen and Ciba-Geigy (Novartis) have used it to engineer insect-resistant corn with Bt (Bacillus thurengiensis) genes.

Monsanto also used the gene gun on its soybeans that are resistant to its herbicide Roundup. DuPont owns the rights to the gene gun for use on everything except ornamental plants and grasses, which were retained by John Sanford, the inventor.

Agrobacterium is the preferred method for broadleaf plants such as soybeans, cotton and tomatoes. This technique employs *Agrobacterium tumefaciens*, the bacteria that causes crown gall disease, by transferring asection of its DNA into the host as it invades the plant. Biotechnologists insert the genes they want into agrobacterium that has been modified to prevent it from causing crown gall, a tumour-forming disease that has been likened to cancer in plants. Several companies used agrobacterium in transgenic insect-resistant cotton seeds sold in the US. This technique is also widely used in New Zealand.

When biotechnologists insert a new gene into a plant, they also include another gene, a selectable marker, that enables them to easily tell if their new gene was incorporated into the plant without having to grow the plant out to maturity. Herbicide or antibiotic resistance is typically used for selectable markers because they can be quickly tested by exposing the target plant to herbicides or antibiotics. Successfully transformed cells survive the exposure.

Patent wars

Four battles dominate the ag biotech patent wars: a multi-party brawl over agrobacterium; another multi-party pile-up over Bt; a two-way fight over transformation of transgenic corn; and a feud between two companies about the ownership of bar/pat genes that confer resistance to the herbicide, glufosinate.

Sano Shimoda, president of BioScience Securities, Inc., a California-based investment firm specialising in agricultural biotechnology, calls the agrobacterium dispute "the mother of all interferences". The first patents for agrobacterium were filed back around 1983, but for some reason none have been issued by the U.S. Patent Office.

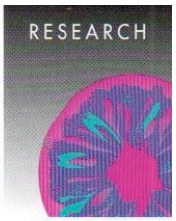
The main contenders in the fight are Monsanto and the German-based company Max Planck, though a variety of other companies and universities have also filed claims. Industry observers expect the dispute to be sorted out in the foreseeable future but say it is not clear whether one party or several will end up with a dominant position.

Mycogen, Monsanto, DeKalb Genetics, Pioneer Hi-Bred, Novartis and Plant Genetic Systems all have claims pending over Bt, with the biggest fight between Mycogen, a diversified ag biotech company majority-owned by Dow Elanco, and Monsanto. So far, the only Bt genes in products on the market are for controlling the European corn borer in corn and the budworm and bollworm in cotton. Mycogen is thought to have the largest library of Bt genes with more than 30 patents issued or pending. The company also has a process patent that covers methods of modifying synthetic Bt genes to make them more plant-like so they are more easily incorporated.

Monsanto, meanwhile, disputes Mycogen's ownership of the Bt genes and has gone on to commercialize Bt corn and cotton in deals involving DeKalb, the second largest American corn seed company, and Delta Pine and Land, a major US cotton producer. Mycogen sued the three companies for patent infringement and is still waiting for a decision.

Sano Shimoda says the logjam may be broken soon due to an expected court ruling that may be decided by the time this article is published. The California State Supreme Court has already ruled that Monsanto owes Mycogen access to some of its Bt and herbicide-resistant genes because of a deal dating back to 1989 involving a predecessor of Mycogen's. If the ruling strongly favours Mycogen, he believes it will force the various parties to begin serious negotiations to iron out the dispute. "People have been trying to figure out how much negotiating power they have before they go into the negotiating room, because the potential damages are getting too big, should someone lose — and someone will lose," he said. If Mycogen prevails over Monsanto, another industry analyst says the liability for Bt cotton alone could be US$260 million.

Another high-stakes skirmish involves DeKalb and Pioneer Hi-Bred, the world's largest seed corn company, over transformation technology for transgenic corn. DeKalb, under a cross-licensing agreement with DuPont, is claiming the rights to any kind of transformation involving corn, while other seed industry participants maintain DeKalb's rights are limited to transformation of regenerable corn cells with the gene gun. Meanwhile, Pioneer is claiming it



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was the first to invent corn transformation and therefore is entitled to all the royalties. Pioneer has not been issued a patent, however, because the Patent Office is checking for competing claims.

Industry observers estimate this dispute to be worth billions of US dollars because the outcome will likely affect all transgenic corn sold. One analyst estimates the domestic market potential of Bt corn planted for resistance to the European corn borer at between half and a third of the total US corn acreage — some 24 million to 40 million acres. She expects Bt corn to have an even greater market potential for controlling rootworm, because rootworm infestations cover a larger area and farmers are more likely to treat it. She could not estimate the market potential for transgenic herbicide-resistant corn, saying it was too early to guess.

The last of the major ag biotech patent fueds involve bar and pat genes, which confer resistance to the herbicide, glufosinate, manufactured by AgrEvo and sold under the trade names, Liberty, Basta, Ignite, Rely and Finale. Several companies also use bar/pat genes as selectable markers for other products, including those with Bt. In September 1996, DeKalb obtained a patent for transgenic corn that contains a bar or pat gene, so companies using it as a selectable marker may be infringing on DeKalb's patent.

AgrEvo, however, claims it has proprietary rights to technology that makes corn resistant to its herbicide.

Regardless of the outcome, this dispute is already affecting sales of glufosinate-resistant products, the first patent fight to have a direct market impact, according to Sano Shimoda. "Seed companies which had product ready to sell now have significant concern about liability issues and whether technology fees should or shouldn't be collected," he said. DeKalb is charging a US$12 per-bag technology fee, though AgrEvo is not. He expects the disruption of sales to prompt a settlement.

Bureaucracy and commercial reality

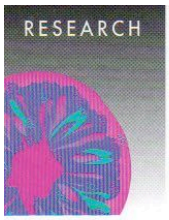
The Patent Office has come under some criticism for granting patents that are too broad and not keeping apace with technological developments in ag biotech. But Douglas Robinson, supervisory patent examiner in the Biotechnology Examining Group at the US Patent and Trademark Office, says his office is bound by the statute governing the issuance of patents, which does not leave patent examiners much flexibility.

A patent must be granted if the invention meets the three criteria laid down in the law: it must be novel, useful and non-obvious to professionals in the field. "We are bound to give [patent applicants] protection for what they have described. So we can't arbitrarily take the position that just because we think it's broader than it should be, they shouldn't get their patent," he explains. "We have to have a legitimate basis within the statute and case law provided to us to say the claim shouldn't be that large in scope." And with a new industry like agricultural biotechnology, he says case law is often scant.

So far, 836 patents have been granted by Robinson's division this year and another 1000-odd are pending on genetically engineered food and agricultural products.

When a patent application comes in, after being checked to see if it contains all the appropriate information, one of the 180 examiners in Robinson's group does a data search to see if a patent already exists for something similar. Inventors can apply for patent protection for as many uses they claim their inventions are capable of. For example, if one gene can perform 100 different functions, the applicant may make separate claims for each.

Depending on what the examiner finds, s/he will write to the applicant granting or denying the patent. If denied, the applicant must write saying why the decision is wrong and, if the applicant is denied twice, s/he can challenge the decision at the Patent



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Office's Board of Appeals. Based on the record, Robinson says the applicant has a 25-30 percent chance ofoverturning the examiner's decision.

Applicants who are not successful there can take their case to federal court and all the way up to the U.S. Supreme Court. Other than the landmark case, *Diamond vs. Chakrabarty*, in 1980 that affirmed the right of inventors to patent live, human-altered micro-organisms and thus opened the door to the biotechnology industry, no ag biotech patents have gone that far.

Douglas Robinson says the Patent Office is fairly consistent in its approach, but the courts often differ in their interpretation of the statute. In court, two parties are giving evidence, while the Patent Office considers the application in more of a vacuum. He also points out that the courts are not bound by the Patent Office's requirement to interpret the applicant's specifications as broadly as possible.

The secrecy surrounding patents demanded by the competitive nature of the marketplace only adds to the confusion, says industry analyst Sano Shimoda.

"The only ones who know [specific] patents are filed are people from the company or the Patent Office. There is no public disclosure, so nobody knows what anybody else has." But, he says, once a patent is issued, the holder of that patent demands payment for using it and that's when the litigation starts.

What does it all mean?

Shimoda expects the various companies to come to their senses and work out settlements before the disputes stall further developments in the industry.

After all, he says, ag biotech is in only the first of many waves yet to follow in an industry that looks likely to completely transform the food supply and possibly the world economy.

When he gazes into the future, he sees half a dozen or fewer leading groups that dominate food production worldwide, with smaller companies and other entities in various alliances with them. Shimoda says success for these companies will depend on their ability to master two things: the product cycle, incorporating planned obsolescence into their products, and cycle time, getting a product to market fast and first.

The current patent wars are an attempt to cement the competitive position of each of those players. "Patents create value. In technologies like agriculture, which is in the hands of a small number of players, the only way companies can maintain value is to control the value through intellectual property," he said.

The accelerating pace of mergers and acquisitions between seed and chemical companies, mainly in the past two years, add weight to Shimoda's prediction. During that time, DowElanco, a huge chemical and pharmaceutical conglomerate, has teamed up with the diversified ag biotech concern, Mycogen, to create one significant camp.

The US$9 billion a year American agricultural, chemical and pharmaceutical colossus, Monsanto Corp, has bought a number of ag biotech and seed companies to gain access to a substantial range of things: Bt patents; natural polymer technology; oil research in soybeans; soybean germplasm and distribution; cotton germplasm and market share; corn breeding material; germplasm and distribution; DeKalb's (disputed) transformation technology and Roundup resistance genes. These deals make the Monsanto empire one of the more formidable players.

DuPont, the vast chemical and energy multinational, the fourteenth largest industrial company in the US, has joined Pioneer Hi-Bred in a research alliance to develop new genetically modified corn, soy and oilseed varieties with higher oil, protein and carbohydrate content. With DuPont's rights to the gene gun and a significant portfolio of "output traits", which are meant to enhance the value of a product, and Pioneer's position as the world's top corn seed company, this union is another major force.

Novartis, the world's largest agrichemical company created last December by the merger of Ciba-Geigy and Sandoz, is the second largest seed company worldwide and has tremendous expertise in biotechnology. Though the company is being very quiet about what it is doing, Shimoda says to discount Novartis would be foolish.

Zeneca Seeds, a spin-off of British-based ICI's agrichemical, pharmaceutical and seed businesses in 1993, last year merged with the Dutch seed company, Royal VanderHave, to create Advanta, the world's fifth largest seed company. The newly formed Advanta has significant interests in corn, canola, grasses, sugar beets, sunflowers, sorghum, cereals and vegetables.

AgrEvo, the German-based global agrichemical corporation created by the merger of Hoechst and Shering, with its growing interests in seeds and ag biotech through the acquisition of Plant Genetic Systems, is another major player.

Shimoda says the future success of the various contenders will depend as much on their commercial alliances as the science and technology they produce. "The commercialization structure and the strategy — the ability to bring products to market — separate the men from the boys in this business," he said, "because technology by itself won't create value."

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life cycle analysis, for example, understanding and reducing the fossil fuel input into production systems - the energy used in tillage, planting, and harvest;

- processing, packaging ,transportation and shipping - these issues are all part of the environmental cost. The perception is that flame weed control is better than chemical weed control but this system has been shown to be a greater environmental cost because of its use of fossil fuels, $C0_2$ emissions and the health hazard of fumes affecting the operator - nothing is what it seems at first glance.