Barriers to Genetically Engineered Ornamentals: An Industry Perspective

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ABSTRACT

The development and commercialization of Genetically Engineered (GE) ornamentals faces significant challenges. These include overcoming product development costs, obtaining freedom to operate, and obtaining regulatory approval. This chapter examines each of these challenges in detail and points to possible solutions that may encourage further development and commercialization of this technology.

1. INTRODUCTION

Ornamental plants represent an important sector of the United States (US) agricultural market. Like other specialty crops, their production faces many challenges of scale not encountered by larger commodity crops. Despite the enormous cost savings and benefits realized by growers of GE commodity crops in the past two decades, the use of biotechnology to decrease grower production costs and develop low-maintenance high-value ornamentals for the US garden and flower industry has not yet occurred.

The US domestic floriculture and nursery industry is estimated at $8 billion wholesale (Jerado 2006; USDA 2007). Included in this total are eight major categories of plant products: cut flowers, potted flowering plants, bedding plants, shrubs and trees, ornamental grasses, palms and various vines and ground cover (**Table 1**). Excluded from this total are sod, turf and range grasses. A broad array of techniques and technologies has been applied to the development of novel ornamentals varieties. These include classical breeding through cross hybridization, mutagenesis, chromosome doubling as well as the use of a variety of tissue-culture based techniques to facilitate wide species crosses. Each of these techniques has found a niche within one or more of the product sectors. For example, cross-hybridization and the characterization of spontaneous sports accounts for most new rose varieties, whereas cross-hybridization coupled with induced mutations has proven to be particularly effective in the development of new chrysanthemum and carnation varieties. At first sight, genetic engineering is a technique well suited to the generation of new commercial varieties of ornamentals. It provides a precise and predictable method to modify color, habit, flower form shelf life and many other valuable traits. Yet, despite the technical and commercial success of genetic engineering in the development of new commodity crops, genetic engineering has not yet been broadly adopted as a tool by ornamental breeders. This review seeks to examine some of the reasons limiting the adoption of this technique.

Each of the major ornamental product categories presents significant opportunities for the development of novel ornamentals through genetic engineering (**Table 1**). Bedding plants include annuals and herbaceous perennials. In the US annuals account for $1.8 billion and herbaceous perennials account for $0.6 billion in wholesale receipts per year (Jerado 2006). The top-selling varieties of bedding plants are impatiens, petunia and pansies, each accounting for about 10% of the total bedding plant market. Changes that could be introduced by genetic engineering might include genes for novel colors (Tanaka *et al*. 2005), modifications of petal form and number (Richmann and Meyerowitz 1997) and drought tolerance (Umezawa *et al*. 2006).

Potted flowering and foliage plants accounted for more than 0.8 billion and 0.7 billion dollars respectively in 2006 (Jerado 2006). Market leaders for potted plants included chrysanthemums, poinsettias, geranium and lilies. Many of the top selling categories of potted plants are readily transformed. In addition to modifications in petal color, petal number and form, genes that reduce internode extension and replace the need for chemical growth regulators in the production of potted plants would be a valuable improvement

Table 1 Eight major categories of ornamental plants sold in the US. Based on 2003 USDA wholesale data. Total market size is approximately $8 billion. Ornamental grasses include landscape grasses other than sod and turf.

Category	Wholesale Value Billions $
Annuals	1.8
Perennials	0.6
Potted Flowering	0.8
Potted Foliage	0.6
Trees and Shrubs	2.6
Cut Flowers (domestic and imported)	2.0
Other woodies and vines	0.27
Ornamental Grasses	0.61
Palms	0.13
	8.615

for potted plants such as chrysanthemum, carnations and miniature potted roses (Peng *et al*. 1999).

The tree and shrub sector includes all deciduous and evergreen trees and shrubs such as garden roses, hydrangeas, rhododendrons, and azaleas. It accounts for just over $2.9 billion in wholesale sales (USDA 2007). With wholesale prices in the range of $5 to $10 per plant, and production being largely confined to the continental US, this sector represents a high value, high margin product that is probably one of the better target categories for genetic engineering. Simple changes in flower or foliage color, petal number or habit are eagerly picked up by growers and consumers.

Since most trees, shrubs, hybrid perennials and many annuals are clonally propagated, by tissue culture or regular cutting technique, a new variety developed by transformation of an existing traditionally bred hybrid can be commercialized without the need for backcrossing. Regulatory and patent issues aside, the evaluation and field trialing of a GE variety in which a single trait is modified is potentially more straightforward than trialing of a new hybrid, in which most or all of the properties of the new variety are unknown. Modern perennials and shrubs are generally selected to tolerate growth in a broad range of climatic zones. For example, many modern shrub roses can tolerate United Stated Department of Agriculture (USDA) zones 3-9 (Cathey 1990). As a result, novel patented varieties of perennials and shrubs are often extensively and openly cross-licensed throughout the US and global ornamental industry. Consequently, a single new shrub variety can often sell in excess of a million units per year over a multi-year period. Only a fraction of total unit sales are made by the original developer or introducer of the new variety. After seeking patent protection on a new variety, a breeder will often out-license production to regional growers throughout the country. The USDA reports that there are close to 10,000 floriculture and nursery growers. To access the entire market, a developer of a novel GE ornamental crop would need to openly out-license a transgenic variety to a large number of growers throughout the US. An exclusive closed channel marketing method restricted to a few growers would be unlikely to succeed. This may present additional costs related to product stewardship and compliance with USDA and Environmental Protection Agency (EPA) regulations.

The US cut flower market accounts for more than one billion dollars at wholesale (Jerado 2006). Two thirds of this total ($750 million) is imported from countries such as Columbia, Ecuador and Holland. The remaining $385 million is produced primarily in the Western US. Combining both imported and domestically grown cut flowers, the top selling categories are roses ($1035 million), lillies ($99 million), chrysanthemums ($65 million), *Alstroemeria* ($50 million), carnations ($42 million), tulips ($37 million) and gerbera ($31 million). Due to limited phytosanitary restrictions, compared to rooted whole plants, and the fact that the end product is not further grown or propagated by the consumers, cut flowers lend themselves well to international trade. The development of novel colors, improved fragrance, and improved shelf life are important traits for the cut flower market. To date, Florigene is the only company that has succeeded in marketing and distributing GE cut flowers modified for flower color (Tanaka *et al*. 2005). The fact that the cut flower industry deals with a product that is grown in greenhouses under controlled and contained conditions and is marketed as a product that cannot grow or readily be propagated has probably eased the regulatory burden and regulatory costs of marketing such products.

From a marketing standpoint, the commercial life of new varieties in each market sector differs significantly. The market lives of novel hybrid trees and shrubs tend to be significantly longer than that of annuals and potted flowering plants. Sales of popular varieties of garden roses and other shrubs can sometimes exceed a million units per year long after the expiration date of their plant patents, whereas commercial varieties of potted chrysanthemum are replaced by newer varieties on a yearly basis. Additional advantages of the tree and shrub sectors include a short distribution chain and high product prices per plant, compared to bedding plants or cut flowers.

Despite the above market opportunities for GE ornamentals, several breeding, production and market properties significantly limit the opportunities for the development of GE ornamentals. Thus many annuals are developed as families of related varieties, such that a novel trait would need to be transformed or backcrossed into all members of the family. Furthermore, since most bedding and potted plants are now produced as un-rooted cuttings in Central or South America and then shipped to the US for production and distribution, regulatory clearance in both countries would be needed.

A more serious consideration to developers of GE ornamentals is the highly fragmented nature of the market and the resulting relatively small market share per variety. Some of the more popular genera, such as roses, chrysanthemums and carnations are extremely diverse. The US patent databases lists more than 2000 patented varieties of roses, more than 300 varieties of patented carnations and more than 1600 varieties of chrysanthemums. Although approximately only 10-20% of these varieties are truly active in the market, these data mean that any new variety can only hope to capture a very small percentage of the overall market for that genus, and even a smaller fraction of the value of the general product category. Such fragmentation, potentially limits the market penetration of any new introduced variety.

2. TRAITS FOR ORNAMENTAL PLANTS

Traits can be categorized according to their value within the market chain. For example, some traits are of more value to the grower than to the consumer. These include traits related to ease of production and shipping (e.g., disease resistance and shelf life). Other traits have more value to the consumer. These include novel colors, shapes and sizes. A third category represents breeder traits such as traits that affect seed production or traits that facilitate out-crossing (such as male sterility).

There have been more than 65 published examples of traits used to genetically modify ornamental plant species covering more than 20 species (Chandler and Lu 2005). These include color modification via the suppression of anthocyanin biosynthesis in petunia, gerbera, chrysanthemum, rose, carnation, lisianthus, torenia, blue gentia and cyclamen; the manipulation of pigment biosynthesis for bluish/violet flowers in petunia, lobelia and carnation; the increase of vase life in carnation; the modification of plant height in petunia and carnation, and increases in disease resistance in rose and carnation (Tanaka *et al*. 2005). Other traits that are under development or that have potential in the ornamental market include those for manipulating fragrance biosynthesis (Pichersky and Dudareva 2007) as well as novel forms of disease resistance (Gurr and Rushton 2005), insect resistance (Christou *et al*. 2006) and drought tolerance (Umezawa *et al*. 2006).

An analysis of the USDA import and movement permit data revealed that thirteen companies and thirteen university and government labs have, over the past two decades, attempted to develop GE ornamentals from more than ten genera of bedding, foliage and shrub plants (**Tables 2, 3; Fig. 1**) (USDA-APHIS-BRS 2007). These data do not indicate the technical success or feasibility of the project, but are a valuable tool in

Table 2 Comparison of movement and introduction permits issued for corporate and university entities for non-turf ornamental crops. 1985-2006. Two unidentified CBI permits are not included in this table.

Corporate		University and Government	
Entity	**Permits**	**Entity**	**Permits**
Large		Arizona	5
Ball	6	Boston Museum Sci.	1
BASF	3	Uni of California	2
Monsanto	39	Colorado State Uni.	3
Pan American	7	Connecticut Uni.	8
Rogers	2	Cornell Uni.	2
Scotts	36	Florida Uni.	5
Upjohn	1	Uni. Of Hawaii	11
Jackson & Perkins	4	Mass Hort. Soc.	1
Yoder	3	Uni of Minnesota	1
	101	Ohio State Uni	1
Small		USDA-ARS	10
DNAP	1	Washington State Uni	1
NovaFlora	2	**Total University**	**51**
Ogelvee	1		
Sanford	6		
Total Small	**10**		
Total Corporate	**111**		

Table 3 Total permits for movement and introduction of non-grass ornamental crops 1985-2007. Note that three of the marigold permits were likely for testing of secondary metabolite production and not for ornamental purposes.

Genus	Permit Applications
Potted and Foliage	
Anthurium	5
Chrysanthemum	5
Dendrobium	11
Phalaenopsis	1
Orchid	1
Poinsettia	2
Bedding	
Begonia	3
Gladiolus	8
Marigold	14
Pelargonium	23
Petunia	80
Shrub	
Rose	8
Rhododendron	8
Total	164

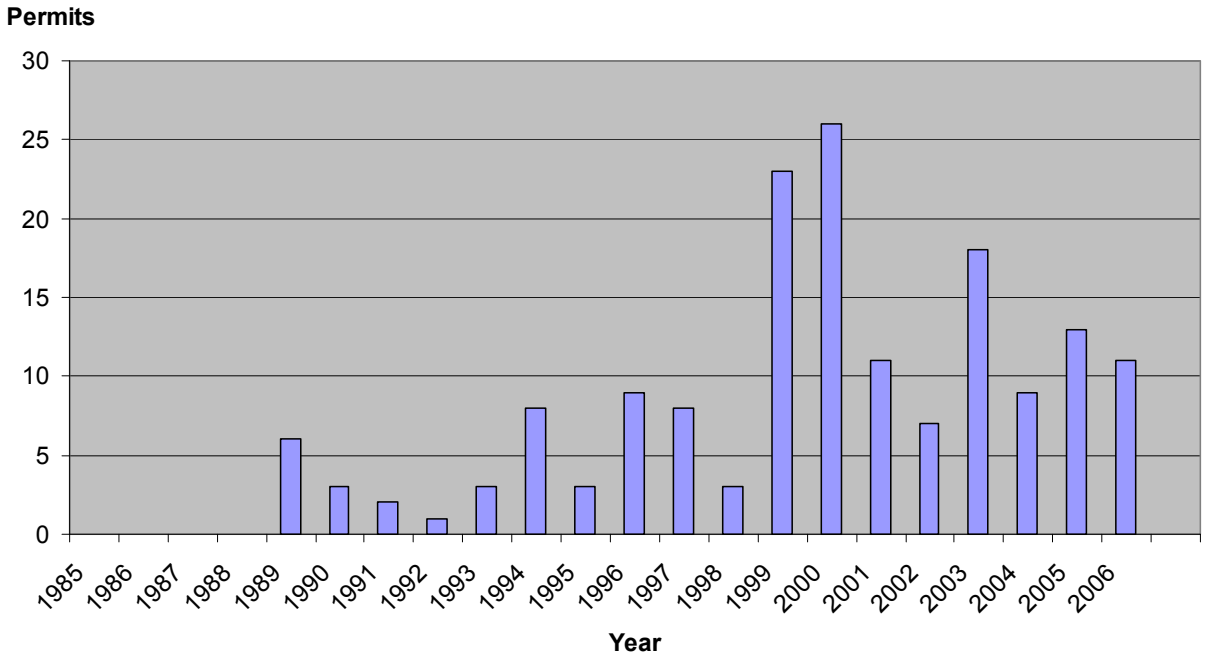

Fig. 1 Movement and release permits for ornamental crops 1985 to 2006. Data from http://www.aphis.usda.gov/biotechnology/status.shtml.

indicating the level of activity and industry interest in GE ornamentals. In total, 91 movement permits and 73 release (field trials) permits were issued over the past two decades. Traits tested included those for viral, bacterial and fungal resistance as well as herbicide tolerance and flower color. Of these permits, 112 were from corporations and 52 were from government and universities (**Table 2**).

In addition to permits issued for floricultural and nursery crops cited above, a great deal of work has been expended on the development of transgenic turf grass. More than 350 permits have been issued, about 200 to six private companies, and 150 to twelve universities, non profits and government institutions. The majority of these (more than 150) have been issued to Scotts. Commonly tested traits include herbicide resistance, sterility and growth retardation.

Despite the large number of published examples and issued permits for GE ornamentals, GE violet carnations, represents the only example of a commercial product (Tanaka 2005). Part of the reason for the failure to commercialize a broader selection of GE ornamentals may be a lack of technical success. However, there are most likely several non-technical factors underlying the delay in commercializing GE ornamentals. These include product development costs, intellectual property costs, regulatory costs and public perception. Some, such as product development costs, can be considered in terms of absolute costs. Others, such as public perception, are more difficult to quantify.

3. PRODUCT DEVELOPMENT COSTS

Discovery and characterization of a novel trait gene is a cost- and labor intensive pursuit lasting several years. In most cases developers make use of trait genes and expression cassettes that have been developed and partially characterized in model plants by a university or corporate researcher. In such cases the true research and development costs are reflected in the costs of acquiring such a previously characterized trait gene. These are discussed in the section describing Intellectual Property below.

Product development costs include transformation of commercial germplasm with a previously characterized gene expression cassette as well as all related preliminary greenhouse testing. Costs can be measured in relation to labor, materials, supplies, equipment and facilities. With a defined trait gene-expression cassette, and a reliable transformation system, a novel transgenic line of petunia can be developed in six to nine months. Even some woody species, such as roses, can be transformed and regenerated in less than a year. Although the ability to regenerate and transform is very variety specific with in a given genus, these timelines compare favorably with timelines for traditional breeding, where the time from pollination to seed set through germination can vary from one to two months in petunia, to six to nine months in certain woody species. For a defined trait gene with an established transformation procedure, a well trained master's level scientist and a technician should be able to perform most of the standard transformation and molecular analysis involved in the development of a GE plant. Combined salaries and benefits in the US would probably be approximately $100,000. This is comparable to that needed for the development of new non-transgenic varieties through classical breeding. These costs could rise two- to three-fold if initial characterization of the trait gene or development of a suitable transformation protocol is required. In terms of materials and supplies, the enzymes and reagents need to develop a new GE variety using fairly standard techniques for vector construction, PCR and Southern are probably in the range of $10 to $20,000 per year for a modest program with two scientists. By comparison to non-transgenic approaches, no such costs would be encountered for a traditional breeding project, but similar costs might be encountered for a program involving marker-assisted selection. Furthermore, investment in a very basic set of equipment needed to perform simple cloning and transformation would include the purchase of incubator, water baths, growth chambers, centrifuges, PCR machines, and electrophoresis equipment could probably be accomplished for $50,000. Amortized over ten to twenty years this represents a relatively modest investment of less than $5000 per year. Again, by comparison, similar costs for the purchase of microscopes and incubators would be encountered with breeding strategies including involving wide species crosses and embryo rescue. Perhaps the biggest perceived cost to implementing a genetic engineering program is the construction of a suitable laboratory and greenhouse facility. In the US, all laboratory and greenhouse research must be conducted under National Institutes of Health (NIH) conditions of containments (NIH 2002). There is a significant but affordable cost associated with retrofitting a standard plant tissue culture laboratory. Additional costs unique to genetic engineering are encountered in design and building of suitable greenhouse required to ensure adequate containment. This can sometimes be accomplished by screening and sealing of an existing greenhouse facility for a cost of under $10,000. For entities without access to a suitable laboratory, many research incubators or universities rent lab space for $30,000 to $70,000 per year, depending on the location. In conclusion, although product development costs can represent a significant incremental increase in costs relative to classical breeding, they probably do not necessarily represent a significant cost increase when compared to other laboratory based non-transgenic techniques such as tissue culture, embryo rescue or mutagenesis.

4. THE REGULATORY PROCESS

Transgenic plant research is perhaps one of the most highly regulated areas of genetic research. At the international level, GE plants are covered by the Cartagena Protocol on Biosafety, as adopted by signatories to the Convention on Biodiversity in 2000 (SCBD 2000). In the US, oversight and coordination of the agencies involved in ensuring that novel GE plants are developed and produced in a manner safe for the environment and human health falls under a formal policy established in 1986 termed the "Coordinated Framework for regulation of Biotechnology" (Anonymous 1986) which seeks to coordinate regulatory efforts in agricultural, medical and other applications of biotechnology.

For basic research and development, regulatory requirements start in the laboratory (NIH 2002). All recombinant DNA work needs to be approved by a company or institution's National Institute of Health Biosafety Committee. Furthermore, any facility that uses a plant pest such as *Agrobacterium* needs approval from US Department of Agriculture's Animal and Plant Health Inspection Service (USDA-APHIS) prior to commencement of work. GE plants produced in the laboratory can only be moved to a USDA-APHIS approved greenhouse facility. Both approval and movement are performed in coordination with the respective state agricultural agencies.

For release and commercialization there are three agencies involved in review and approval of GE plants. The USDA-APHIS is responsible under the Plant Protection Act (USDA 2000), for reviewing the plant pest potential of a GE crop. The EPA is, under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), responsible for reviewing and registering their pesticidal properties. The Food and Drug Administration (FDA) is involved in voluntary consultation on the safety of GE foods, which generally would not apply to ornamental plants (FDA 1992). A unified website that provides a single point of information access for all three agencies has been developed (NBII 2007). This web site provides an up to date summary of registrations and reviews by each agency, as well as access on the laws and regulations enforced by each agency.

5. THE USDA REGULATORY PROCESS

The Plant Protection Act of June 2000 gives USDA-APHIS the authority to prohibit or restrict the importation, exportation, and the interstate movement of plants, plant products, certain biological control organisms, noxious weeds, and plant pests (USDA 2000). GE plants fall under these regulations, in part because most GE crops contain sequences, such as the 35S Cauliflower Mosaic promoter and *Agrobacterium* T-DNA sequences, derived from plants pests. In practice, however, USDA-APHIS considers a plant a regulated article if it has been transformed with exogenous DNA of any source or origin (i.e., genetically engineered). A developer can petition APHIS to determine that a GE plant should no longer be regulated by submitting a petition for deregulation containing experimental and theoretical data demonstrating that the GE plant is not a plant pest risk. As part of its analysis and review of the petition, APHIS prepares and publishes an Environmental Assessment report. If APHIS determines that the regulated article does not present a plant pest risk, the GE plant is de-regulated and unrestricted introduction of the crop is allowed. Within APHIS the Biotechnology Regulatory Service (BRS) implements the regulations for GE organisms that may represent plant pests.

Experimental field data is collected under a permit or notification from USDA-APHIS-BRS allowing limited and defined growth of the organism in a secured field environment. To date all ornamentals require a permit application. Notifications are limited to a select number of commodity varieties for which a great deal of field experience has already been collected.

Field tests are conducted under conditions that are intended to minimize the chance of the regulated crop and/or transgenes escaping from the test site. This includes ensuring adequate isolation distances from related crops, as well as additional confinement measures and harvesting

procedures. Data collected during field-testing include that related to phenotypic stability, gene flow and environmental consequences, such as effects on insect populations. After extensive field testing, developers may apply for deregulated status through submission of a "petition for the determination of non-regulated status". The petitioner is expected to present a combination of direct experimental evidence and scientific literature that documents that the GE variety in question is not a plant pest, and does not pose a threat to agriculture or the environment.

There are no clearly mandated requirements for the preparation of a petition for deregulation. It is handled very much on a case-by-case basis. The information and level of detail required appears to depend greatly on the intended use, species, trait gene and selectable marker gene in question. **Table 4** shows a summary of data normally presented in a USDA and petition. The exact nature of the studies performed depends on several variables. These include the method transformation, whether the crop is annual or perennial, insect or wind pollinated, whether the trait has any perceived selective advantage. In some cases developers are able to rely on published ecological and inheritance studies performed on similar varieties. By examination of petitions on the USDA-APHIS-BRS web site, developers can determine the sort of data and level of detail typically required. The following description of experiments has been assembled by the author by reviewing petitions submitted to USDA-APHIS-BRS in the past few years for horticultural crops, and does not represent any form of government approved minimum required standard.

Table 4 Categories of information required for petition to deregulate a transgenic plant by USDA-APHIS including additional data required for an EPA PIP registration (http://www.epa.gov/pesticides/biopesticides/regtools/biotech-reg-prod.htm)

Category	Details
Biology and taxonomy of host variety	Related wild species
Genotypic description of GE plant	Source of donor genes
	Donor genes
	Plant vector
	Transformation method
	Insert copy number and sequencing
Phenotypic description of the plant	Properties related to plant pest risk
	Disease and pest susceptibility
	Expression analysis of foreign gene
	Changes to plant metabolism
	Weediness of GE plant
	Outcrossing potential to related weed species
	Agricultural or cultural practices
	Effect of GE plant on other organisms
EPA PIP specific data	Protein or gene product characterization,
	Mammalian toxicity studies
	Allergenicity potential,
	Effects on non-target organisms
	Environmental fate,
Field Test Reports	Method of observation
	Data and analysis of effects on: other plants
	Non-target organisms
	The environment
EPA PIP specific field requirements	Insect Resistance Management
	Refuge requirements
	Farmer Actions and education
	Compliance Monitoring Program
	Insect Resistance Monitoring
	Remedial Action Plan for in case of resistance

In addition to data collected from field studies, a significant section of the data presented in a USDA petition concerns the molecular characterization of the foreign gene. This includes determination of copy number through Southern blot hybridization and/or PCR, expression and transcript analysis of the expressed gene in various plant organs through Western, Northern and PCR, the search for vector sequences outside the intended insert sequence, as well as sequencing of the transgene insert and junction regions to determine whether there are any major insertions or rearrangements within the insert. Since several environmental and genetic factors can potentially combine to modify the expression of a gene in field and greenhouse conditions, expression analysis is conducted over a multi-year period to determine stability of the expressed trait in different seasons, climates and locations.

More advanced characterization also includes studies on the inheritance of the insert (Scorza 2006). Such studies may be required, even if the transgenic variety is to be commercially produced by clonal propagation and may help predict the segregation and stability of the insert in future commercial breeding programs or in unintended crosses with related non-transgenic and/or transgenic varieties. These studies entail self- and cross-pollination experiments followed by phenotypic and molecular characterization of the progeny over two to three generations. Molecular characterization includes Southern and RNA analysis of parents and offspring. In addition to determining the stability of the trait in successive generations, these studies are useful in determining if a multi-copy insert behaves as a single allele. Gene flow studies are performed to document the extent of transgene flow within a test block of plants and between the test block and adjacent non-transgenic plantings of the same species. Seed from plants within the test block and from adjacent test blocks within a defined radius are assayed for the presence of the trait and or marker gene contained within the GE plant. In the design of these studies allowance is made for known sexual incompatibilities between genotypes, differences in flowering time, as well as environmental factors that affect the activity of insect pollinators or efficiency of wind pollination.

Examination of the environmental consequences involves determination of any major alterations in the insect fauna associated with plants expressing the trait and or marker gene. For many plant scientists this would probably involve enlisting the services of a trained entomologist.

In addition to the molecular and environmental studies, a petition typically includes a thorough descriptive and quantitative comparison of the parent and related species. For ornamentals, such 'equivalency' data would be very similar to that disclosed in plant patent description and includes descriptions of plant height, leaf length flower color, and petal length.

Finally, a USDA regulatory package typically contains discussions on alterations in cultivation practices, and adverse or unintended consequences of introduction of the new GE variety. This might include any expected increase in weediness of the new variety as a consequence of increased fitness.

The USDA is now considering changes to the way that it approves commercialization of GE plants (USDA 2007). This includes the possibility that the USDA may adopt a science based tiered risk approach that would reduce the regulatory burden for well characterized low risk GE plants. The USDA indicates that this might exempt the need for event-by-event regulation. Examples of gene trait combinations that might be exempted based on familiarity and/or risk include plants engineered with well tested selectable marker genes in combination with a relatively harmless trait gene, such as a gene for flower color or dwarfism. Additional 'low risk' examples might include plants engineered with genes from sexually compatible species (intrageneric transfers), especially when the recipient is a highly domesticated species for which there are no wild relatives. For trait combinations that the agency is not familiar with, the USDA is considering partial or conditional deregulation of GE crops.

Currently once a variety is deregulated it can be crossed with any other non-transgenic or deregulated transgenic variety and its progeny are not regulated. Such partial deregulation could be used to ensure that potentially undesirable combinations of stacked traits are not created by the inter breeding of two unregulated varieties. In this way, the progeny of certain crosses would be deemed regulated articles.

6. THE EPA REGULATORY PROCESS

The EPA is responsible for the use and sale of pesticides as described in FIFRA. Under FIFRA, the sale, distribution or use of a pesticide is prohibited unless it is registered or meets a specific exemption as described in EPA regulations (EPA 1996). The EPA is responsible for enacting and enforcing regulations related to FIFRA. The EPA regulations governing plant defense compounds expressed in GE plants have steadily evolved over the past ten to fifteen years. The EPA originally published proposed rules in 1994. Seven years later, and after the publication of numerous supplemental documents, the EPA published its final rulings in 2001 (EPA 2001). In their final ruling the EPA defined the term plant incorporated protectant (PIP) as covering a "pesticidal substance that is produced in a living plant and the genetic material necessary for the production of the substance, where the substance is intended for use in the living plant". PIPs derived through conventional breeding are exempt from EPA regulations. PIPs derived from closely related species, even through genetic engineering are also exempt, although reengineering of such genes to significantly modify their function or activity would apparently void such an exemption. It is unclear if this includes only modification of the coding region, or also modification of the regulatory regions. For example, would overexpression of the pesticidal gene through use of a constitutive promoter, or inadvertent over expression due to position effect void such an exemption?

Since the 2001 final ruling there have been several recent EPA publications aimed at refining and streamlining the PIP registration process. In an April 2007 publication the EPA acknowledged the differences between PIPs and traditional pesticides, in their manner of production and use, and sought public input to modify FIFRA regulations to accommodate such differences (EPA 2007). For example, over the past decade EPA PIP experimental use permits (EUPs) and commercial registrations have conformed to FIFRA requirements designed for traditional pesticides by registering laboratories where the original transformation event occurred and seed processing facilities as pesticide production facilities. Furthermore, existing FIFRA regulations require pesticide production quantities to be reported in gallons or pounds, units that are either difficult or impractical to measure for a PIP.

Exactly what classes of plant defense agents should be included and exempted from EPA regulations is also evolving. In an April 18th, 2007 publication the EPA proposed exempting viral coat proteins from regulation (EPA 2007). This would significantly reduce the regulatory burden on developers of virus resistant fruit trees and ornamentals.

Since 1995 the EPA has registered more than twenty PIPs, one for *Bacillus thuringiensis* toxin (Bt) potato, twenty for Bt corn, three for Bt cotton, and one for replicase-potato (EPA 2007). Some of these have since expired or have been voluntary cancelled. When assessing the potential risks of GE PIPS, the EPA requires extensive studies examining numerous factors, such as risks to human health, non-target organisms and the environment, potential for gene flow, and the need for insect resistance management plans.

Data for the registration of a PIP is collected under an Experimental Use Permit (EUP). In addition, to a release permit from the USDA, an EPA-EUP is required when field testing of a PIP is to be conducted on a site in excess of 10 acres. A typical registration package contains five key sections. Many of these studies are also included in a USDA-APHIS petition for deregulation. As discussed above, according to the 1986 policy for The Coordinated Framework, for the Regulation of Biotechnology the USDA and EPA are expected to consult and collaborate in such cases of regulatory overlap. **Table 4** outlines data required for USDA petitions and EPA registrations.

The section on product characterization contains a comprehensive molecular and biochemical description of the PIP. This includes a detailed description of the vector, selectable marker used to transform the plants as well as details of copy number and sequence analysis of insert junctions. Gene product data typically include characterization of the molecular properties of the gene product in floral and vegetative tissues of the GE plant through western analysis.

A section on Human Health Assessment is required for food crops. This section is probably not required for ornamental plants, and includes acute toxicity studies, allergenicity studies, including gastric stability studies aimed at looking at the rapidity of degradation of the gene product in the human gut.

The section on Environmental Assessment presents data on the effect or toxicity of the gene product on non-target organisms such as lady bugs, earthworms, honey bees and fish. In recent registrations, a tiered testing approach has been accepted by the EPA. In this approach initial laboratory experiments are conducted at high doses at five to ten times the expected field doses. This dose is termed the Maximum Hazard Dose (MHD). If negative, less than fifty percent mortality at MHD, no further field-testing is required. In total, a typical registration application contains about two-dozen separate studies on toxicity to adult and insect larvae.

Additional studies include residual bioactivity of the PIP in soil, as well as data or literature describing the possibility of the weediness potential of the GE crop, as well as the potential for transfer of the PIP by hybridization to weedy relatives.

The EPA requires an Insect Resistance Management (IRM) plan. For large acreage field crops such as corn and soybean, this deals with the use of non-transgenic refuges to minimize the risk of insect resistant a PIP. It is currently unclear what requirements would be placed on a GE ornamental crop grown in a greenhouse or sold for garden use. For example, would an aphid-resistant BT rose be subject to the same refuge requirements as BT corn? It is possible that refuges would be required for large scale commercial growers of the GE crop, but would not be required for small retail nurseries and consumers, where GE plants would be grown among non-GE plants of the same or related genus that would act as a natural refuge for the pest.

A major component of EPA's required IRM is product stewardship. This comprises grower education, annual resistance monitoring, as well as an action plan in the event of increased pest activity on GE plants. In anticipating the possibility of resistance to the PIP, registrants also commonly present sophisticated mathematical models to predict the behavior of resistance genes in insect populations.

An EPA PIP registration is normally valid for a defined term of approximately 3-5 years and carries with it many ongoing reporting and data collection responsibilities to allow the EPA to monitor IRM and insect resistance itself.

Calculating regulatory costs: A regulatory package including time taken to perform molecular analysis and collect field data can take three to five years in the simplest cases. For the purpose of this review, costs to assemble such a package are estimated by calculating the scientific and management time needed to conduct the required experiments and field trials, molecular analyses, safety and toxicity tests, as well as the time needed to write and assemble the package and communicate with the regulatory agency concerned. It should be remembered, however, that this calculation includes data and costs that would be generated in the absence of any regulatory requirement (e.g., copy number, stability and gene flow). Furthermore, since the scope of data required for scientific and safety purposes will depend on the biology of the crop and the inserted gene, the data required by each regulatory authority will vary on a case by case basis, and it is difficult to separate 'pure' regulatory costs from product development costs.

Table 5 Costs analysis for preparation of data for a US regulatory package. Overhead includes estimates for field rental and laboratory space.

Item	Time	Base Salary $ 000s	Cost $ 000s
Principal Investigator	20%	80	16
Scientist I	100%	50	50
Scientist II	100%	50	50
Administrative support	10%	50	5
Horticultural Staff	20%	50	10
Staff total			131
Scientific Supplies			20
Amortized Equipment Costs			10
			161
Overhead at 50%			81
One Year Total			**212**
USDA Three year total			635
EPA Two year total			423
USDA and EPA combined total			**1,058**

In terms of time-lines, generation of the required regulatory data closely parallel the sort of multi-year field trials performed on traditionally bred varieties of herbaceous perennials and shrubs. However, for a GE crop additional costs are clearly incurred in meeting the strict containment conditions, the cost of molecular analysis and the need to employ an individual to oversee regulatory compliance.

For a USDA petition, for a trait-crop combination with no PIP, and no obvious weed or invasive potential, such as color modification, basic field testing, molecular analysis and package assembly could probably be managed by a small team of two MS level scientists under the direction of the principal investigator. The required experiments generally include insert structure and copy analysis using Southern hybridization; sequencing of the cloned insert and genomic junctions; organ specific analysis of RNA and protein, as well as inheritance and expression analysis over a multi year period. **Table 5** shows a cost analysis for the experimental portion of a hypothetical regulatory package. The annual budget, including overhead is calculated at more than $200,000, or $600, 000 for a three-year trial. In some cases there are additional studies required in response to questions raised by the regulatory agency, or a need to characterize unexpected molecular phenomena such as gene silencing or insert deletions or rearrangements. Such experiments could easily require an additional year or two, bringing the grand total to close to a million dollars.

If the ornamental crops contains a trait designated as a PIP by the EPA then a wide range of environmental hazard and toxicity studies need to be performed. In many of the BT registrations dozens of separate studies to demonstrate the safety of the PIP are conducted on target insects, non-target insects, and mice. A conservative estimate is that these studies would take two Masters or Doctoral level scientists two years to complete. Applying the same cost basis to the above calculated USDA petition costs means that the additional EPA data would add an additional $400,000 to the cost of the regulatory package, bringing the combined total of for a USDA and APHIS non-food regulatory package to about 1.5 million dollars.

Additional post-marketing costs associated with product stewardship and resistance monitoring would probably add at least an additional $50,000 to $100,000 a year in personnel and experimental costs. In time, as more and more petitions and registrations for commonly used PIPs are submitted and approved for review, costs may decline. Currently, however, such costs represent a major barrier to the commercialization of PIPs in ornamental plants. By comparison, varieties developed through classical breeding, mutagenesis or marker assisted selection are also field or greenhouse tested for 2-5 years to determine stability of the selected phenotype, and to allow for stock build up. However, the evaluation process is less intensive, and does not require laboratory experimentation, molecular analysis, or the preparation of documents and written packages for submission to government agencies. As pointed out at the beginning of this section, not all of the costs associated with approval of a transgenic crop are pure regulatory compliance costs. A significant portion of the data included in a regulatory package is generated in the course of field-testing and other product development activities. From a business perspective, however, this distinction is somewhat immaterial. What is important is that the total regulatory and product developments costs for transgenic crops are significantly higher than those for conventional crops. Strategies for lowering these 'total' costs are discussed below.

In a university environment, some of the costs involved in preparing a USDA or EPA regulatory package can be absorbed by existing staff and incorporated into the research and educational mission of the institution. For example, many of the experiments on expression analysis or those on non-target organisms could be conducted as part of a Masters or Doctoral or thesis, and would most likely be published in peer reviewed journals, thus serving to increase the academic communities' knowledge base of the environmental impact of PIPs. However, in a corporate environment these costs are very real. Time expended on preparing a regulatory package by scientists, management and administrative staff takes away from other revenue-generating activities. Considering that most ornamental plants are bred and introduced by private breeders, it is doubtful that ornamental breeders would be prepared to make the investment currently required for an EPA and USDA package. Indeed as **Table 2** demonstrates, large multinationals such as Monsanto, Ball and Scotts have performed most of the private sector work. Most of the smaller breeders have either participated in this technology at a reduced level or not at all.

In line with the USDA's recent proposals (USDA 2007), some have suggested rationalizing the basis for the regulatory approval of GE crops. This would include exempting selected genes and classes of genetic engineering from regulation, as well as creating tiered regulatory categories in proportion to the potential risk of the genetic modification (Bradford *et al*. 2005).

An alternative or parallel solution to lowering the cost barrier is a closer and more formalized collaboration between private breeders, universities and government researchers in the characterization of GE plants. In the US, the Specialty Crops Regulatory Initiative (SCRI) was formed in 2005 to guide developers of specialty crops through the existing regulatory procedures. The SCRI grew out of recommendations of a

workshop, “Public Research and the Regulatory Review of Small-Market (Specialty) Biotechnology-Derived Crops,” held in 2004 (Goldner *et al*. 2004). It currently exists in the form of a steering committee, and plans for establishing a formal organization are, at the time of writing this review, still in the discussion phase. The SCRI steering committee plans to develop a program involving public-private partnerships between universities, government institutions, grower groups and breeders. The SCRI does not seek to change or lower the regulatory criteria, but rather aims to guide and facilitate developers of GE ornamentals, and other specialty crops, though the regulatory process. Specific responsibilities may include clarification of regulatory data requirements, collection of the required data, maintaining of databases of information for future applications, as well as liaison with regulatory agencies.

7. THE EUROPEAN REGULATORY PROCESS

In the EEC the field testing and releases of GE are governed by Directive 2001/18/C (EEC 2001). This directive includes provisions for environmental risk assessment, product stewardship, public disclosure labeling and traceability as well as identification and detection.

In the EEC, ‘notifications’ for field tests are submitted to the relevant national authority in accordance with Article 6 of directive 2001/18/C. The member state has the authority to approve such experimental field tests. A complete list of all field test applications is publicly available on the internet at http://gmoinfo.jrc.it. Although the decision to grant the permission for an experimental release lies with the national authority, other member states and the European Commission may submit information for consideration to the country concerned.

Authorization for commercial release of GE varieties requires approval by all EEC member states. The process involves a complex sequential series of decisions at which approval can authorized or denied. Initially a notification is compiled in accordance with Article 13 of directive 2001/18/EC and is submitted to the relevant state regulatory agency. In the event of a favorable assessment, the state agency informs the other member states via the European Commission. If there are no objections, the original member state may authorize the placing of the product on the market. If there are objections, there is a conciliation phase between all members and the commission. If unresolved, a final decision can be made at the European level. The Commission first asks the opinion of the European Food Safety Authority (EFSA). The Commission then presents a draft decision to the regulatory committee. Based on a majority vote by the regulatory committee, the Commission can then either approve or reject the application. If rejected by the commission the draft decision can then be further considered by the Council of Ministers. Approved products are subject to the labeling and traceability requirement for GE products according to EC regulation 1829/2003 and 1830/2003 (EEC 2003). These regulations exempt labeling requirements of trace amounts of the product.

To date the only approved ornamental products within the EU are GE carnations (‘Moonshadow’ and ‘Moondust’) from Florigene. These were approved in 1996 and 1997 under directive 90/220 based on the decision of the Dutch authority (http://www.florigene.com/sales/regulation.php). In September 2004 an application for a new variety of carnation (‘Moonlite’) was submitted to the Dutch regulatory authority. In addition to the standard molecular and expression analysis and characterization, the data submitted included acute toxicity testing on mice, as well as Ames test and a cytotoxicity test on human embryonic intestinal cells *in vitro*. In April 2005 the Dutch authority issued a favorable opinion. Objections were raised by several member states and as result the Commission sought the opinion of the EFSA. The EFSA considered the products safe, in that they were unlikely to have adverse effects on human and animal health or the environment.

8. THE JAPANESE REGULATORY PROCESS

Information on regulations and products approved in Japan can be found at the Ministry of the Environments, Japan Biosafety Clearing House web site (Anonymous 2007). In Japan the Ministry of Education, Culture, Sport, Science and Technology (MECSST) oversees recombinant DNA activities in laboratory settings. The Ministry of Agriculture, Forestry and Fisheries (MAFF) is responsible for assessing the environmental risk and the use of GE crops used as livestock feed. The Ministry of Health, Labor and Welfare (MHLW) is responsible for regulating food crops. MAFF regulates and approves the use of GE crops in accordance with a set of laws and regulations enacted in 2003 which include the “The Law governing the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms.”

Approval of a GE ornamental crop by MAFF requires submission of an application to the Plant Safety Division, Food Safety and Consumer Affairs Bureau of the Ministry of Agriculture, Forestry and Fisheries. The information submitted includes molecular and expression characterization, as well as description of any differences in cold tolerance, heat tolerance, germination rate, fertility and production of harmful substances as compared to the original parent plant. Approval time is mandated at six months, not including time taken by applicant to respond to requests for further information. Since enactment of the 2003 law, as of June 2007, 91 products had been approved in Japan, though largely due to consumer and industry resistance, none were commercially cultivated in Japan (Sato 2007). All genetically products consumed in Japan are grown abroad and imported this includes GE carnations for sale as cut flowers.

9. THE CHINESE REGULATORY PROCESS

China is the largest market for GE products produced in the US and is the fifth largest producer of GE plants by acres. More than 400 safety certificates for field tests and commercialization products have been issued (Zhang and O'Kray 2006). Regulations are defined in the State Councils regulations entitled *“Food and Agricultural Import Regulations and Standards: Agricultural Genetically Modified Organisms Safety Administration Regulations 2001”* which is largely governed and implemented by regulations defined in decrees from the Ministry of Agriculture that cover domestic approval, import approval and labeling. In addition to the MOA, other ministries such as the General Administration on Quality and Supervision (AQSIQ), Ministry of Health (MOH), the State Environmental Protection Agency (SEPA), the Ministry of Science and Technology (MOST) and the Ministry of Commerce (MOFCOM) also have some input (Cino and Latner 2005).

There are several aspects of these regulations that could result in significant delay in the introduction of GE ornamentals developed outside of China. First, imported products must initially be approved in country of origin before applying for deregulation in China. Secondly, there are only two application deadlines per year, one in March and one in September. Finally, products must be retested for the Chinese application process before being approved for a safety certificate (Cino and Latner 2005). More recently the Chinese government announced a requirement

for the renewal of Safety Certificates. No additional experimentation is required, but the application includes an update of latest research developments for that crop (Latner and Bugang 2006).

10. THE REGULATORY PROCESS IN SOUTH AND CENTRAL AMERICA

The regulatory approval process and the public climate for the approval and commercialization of transgenic crops varies from country to country in South America. Most countries are signatories of the Cartagena Biosafey Protocol, though not all have ratified it (SCBD 2000). In many cases regulatory agencies and institutions for biotechnology and biosafety exist without specific laws and/or regulations that govern their practices. The two largest exporters of cut flowers to the US are Columbia and Ecuador.

In Ecuador the Ministry of the Environment is responsible for regulating transgenic crops production, research and import in accordance with the Environmental Management Law. Under the same law, the Ministries of Agriculture, Health and Foreign trade have authority over their respective fields of interest. Despite the existence of this general law, there are no specific laws or regulations that govern biotechnology and biosafety. This situation has not, however, prevented limited production of transgenic carnations for export. To complicate things further, in 2006 Ecuador passed a law that prohibits trade, use and handling of GE products for human consumption (Alarcon 2006). This presumably would not affect the production and export of transgenic cut flowers from Ecuador. A draft text of a law that proposed technical standards and a regulatory framework was submitted to the Ecuadoran congress in 2002, but was never approved due to opposition of certain political parties.

The situation in Colombia appears to be somewhat better than in Ecuador. Extensive and increasing acreage of transgenic cotton are grown in Colombia. Florigenes' transgenic carnations have been approved for production and export since 2000, and transgenic roses are pending approval. Biotechnology is widely supported by the government and agricultural groups and there is limited public and media opposition. The government is working to establish laws and regulations in line with the Cartagena Biosafety Protocol (SCBD 2000). Three technical committees covering agriculture & fisheries, human health and the environment have been created. The hope is that these will provide a science-based foundation for the review and approval of GE crops (Uribe and Restrepo 2006).

Costa Rica and Guatamala are major production bases for unrooted cuttings of annuals and some perennials that supply foreign markets. In Costa Rica, "The Animal and Plant Health Protection Law" of 1997 gives the National Technical Biosafety Commission (NTBC) the authority to regulate the national and international trade and marketing of GE organims for agricultural use. In 2004, mounting opposition to the planting of transgenic crops in Costa Rica resulted in the inclusion on the Commission Biosecurity of two members from an environmental group and a member from the Environmental Ministry (Gonzalez 2007). Despite these developments, the acreage of transgenic crops has been growing steadily, and transgenic cotton and soybean seed production for export has been performed since 1992. Anti-biotechnology press coverage has only been moderate. Thus, it seems that based on experience with commodity crops, the production of rooted cuttings of transgenic ornamentals would be feasible.

There is currently no commercial cultivation of ornamental or commodity GE crops in Guatamala. All cultivation is for research and field trials. Import of GE material for such uses is governed by the Ministry of Agriculture. The National Committee for Biosecurity Coordination drafted the National Biosafety Framework law in 2004. It has been held up in congress since then. The framework proposes even stricter measures than the Cartagena Protocol (SCBD 2000). It is not supported by either academia or industry (Tay 2006).

11. THE REGULATORY PROCESS IN SOUTH EAST ASIA

Thailand and Malaysia are both significant exporters of cut flowers. In Thailand, a 2001 ban on field testing GE crops has essentially frozen any research and commercial prospects for cultivation of transgenic crops. However, draft guidelines for the removal of this ban are currently under consideration by the government. Anti-biotechnology groups strongly oppose transgenic crops and press coverage is largely unbalanced and negative (Preechajarn 2007). Draft biosafety guidelines are also under development in several other countries, including Malaysia (Ho 2006) and Indonesia (Rahayu 2007).

12. THE REGULATORY PROCESS IN THE MIDDLE EAST AND AFRICA

Several Middle Eastern and African countries are major exporters of cut flowers and unrooted cuttings to Europe. These include. Israel, Kenya, Zimbabwe and South Africa.

In Israel, field testing of GE crops including flowers started in 1994. However, as of 2006 there was no commercial cultivation of transgenic crops. The Governmental New Foods Committee (NCPT) of the Ministry of Health, and the National Committee for Transgenic Plants (NCPT) of the Ministry of Agriculture are responsible for the regulatory framework (Shachar 2006).

The anti-GM debate has created significant confusion and mistrust in Kenya. This has significantly slowed development and commercialization of transgenic crops. However, with a Biosafety Bill pending, and a National Biotechnology Policy in place since 2006, Kenya has taken significant strides towards successful adoption of transgenic technology. There are several research projects on transgenic commodity and specialty crops, some of which have undergone confined field trials (Onsongo 2007).

South Africa is perhaps one of the most progressive adopters of genetic engineering technology on the continent. Ninety-two percent of cotton, 44% of corn, and 59% of soybeans are GE. It has, and probably will continue to play a lead role in the adoption of biotechnology by other countries in Africa. Its policy is based on the Genetically Modified Organism Act of 1997 and modified in accordance with the Cartagena Biosafety Protocol in 2005 and 2007 (SCBD 2000). However, the National Biodiversity Act of 2004 has the potential to slow down approval of some crops (Bickford 2007). Overall, the prospect for the use of South Africa as a production base for transgenic ornamentals seems very promising.

From the above review of regulatory requirements it is clear that a company seeking to commercialize a GE ornamental variety faces major challenges in terms of time and money needed to adhere to regulations in production and destination countries. Currently, costs expended on data collection, preparation and submission of the required regulatory package significantly exceed the profit margin expected for any single

variety of major ornamental crops. For the ornamental market, annual gross revenues for individual varieties are commonly in the range of $100, 000 to $500,000. Even with a healthy net margin of 10%, a developer of a new variety of GE plant would expect to experience an overall financial loss, or barely breakeven, over the commercial life of a new GE variety. Similar cost barriers have been recognized for other small market specialty crops (Bradford *et al*. 2005). Over time, in the US it is possible, however, for a developer to dilute the costs of developing a new GE variety by using that variety to develop new varieties through breeding or mutagenesis. This is because in the US the regulatory process is event based. At least for the USDA, a new deregulated GE variety can be used to develop additional varieties via breeding without having to encounter additional regulatory costs.

13. INTELLECTUAL PROPERTY CHALLENGES

The challenge to obtain freedom to operate (FTO) among an increasingly complex web of utility patents covering traits genes, selectable markers and transformation methods has become a major barrier to the development and commercialization of GE ornamental plants and other specialty crops. The barrier can be measured in terms of costs and risks that a developer might encounter in terms of attempting to obtain FTO. These includes costs related to FTO analysis, license negotiation, license fees and royalties, as well as risks related to undisclosed and unpublished patent applications, the refusal of a patent owner to license the technology, the uncertainty of patent ownership as well as the cost and risks of legal disputes.

In addition to considering utility patents that cover the technology required for genetic engineering, the developer should be familiar with the area of intellectual property law that covers asexually and sexually propagated varieties of ornamentals. In the US, the Plant Patent Act provides protection for asexually propagated plants (USPTO 1930) and The Plant Variety Protection Act of 1970 and amended in 1994, provides patent protection for seed propagated plants (USDA 1970). Outside the US, plant varieties are protected by breeders rights in accordance with the 1991 Act of the International Convention for the Protection of New Varieties of Plants (UPOV 1991). A developer therefore needs to use either his/her own varieties, license varieties from a variety owner or work with off-patent or non-patented varieties.

14. FREEDOM-TO-OPERATE ANALYSIS

A thorough FTO analysis is generally performed in collaboration with a patent lawyer familiar with the field of agricultural biotechnology. Understanding and interpreting the breadth of a patent is not an entirely simple task. The wording and phraseology of patent claims needs to be fully understood in the context of the prior art of the patent, the history of the patent's application process before the patent office, and the existing patent law. At standard billing rates of $150 to $300 an hour, a comprehensive FTO analysis can easily cost $10,000 to $20,000. To minimize costs, preliminary database searching is often performed by the developer. In a university setting, developers are able to consult with a technology transfer office that generally employs individuals well versed in the field of patents and intellectual property. Though this lowers costs, the cost is still born by the university in the form of overhead or administrative support.

The first key step in an FTO analysis includes documenting all materials and processes that have been, or will be involved in the construction of the GE variety. This includes accurately identifying ownership of the plant variety to be transformed, to ensure plant patent or breeders rights are not infringed, as well as documenting all trait genes, selectable markers, and promoters used to construct the plant transformation vector.

Patent searching can be performed using publicly available databases for the countries in which the product will be produced or marketed. The World Intellectual Property Organization web site contains a comprehensive listing of patent databases for most of the major PCT members and regions (WIPO 2007). **Table 6** shows a list of the major national and regional databases. In searching and reviewing the patent literature it is important to remember that patents are only valid in the territory to which they are issued. Thus a developer seeking to develop, produce and sell a product in a developing country where patents for the technology have not been filed or issued is free to use, produce or sell a patented invention within that territory. However, in most cases a developer will probably import or produce the product in Europe or the US where such a patent may be active and enforced by the owner. For example, a developer who produces a new variety of GE pelargonium in a foreign country, and then exports cuttings of that variety to the US, will be subject to any patents issued in the US that cover the technology used in the novel GE pelargonium.

The United States Patent office site lists all patents issued in the US since 1790. Due to term changes implemented in 1995, calculating the term and expiration date of a US patent is fairly involved. All patents issuing from applications filed after June 8th, 1995 do not expire until 20 years from the date the application was filed. If the application is part of a family or chain, this could include the filing date of an earlier application in the chain. If the patent is filed before June 8th 1995 and was not issued prior to this date, the term of the patent is the longer of either 17 years from date of issue or 20 years from the filing date. If the patent was filed and issued prior to the 1995 date then the term is 17 years from the date of issue.

Prior to June 1995 patent applications were not published until the patent issued. This gave rise to the phenomenon of submarine patents. Submarine patents are patents whose presence is widely unknown until they issued, or 'surface'. Since 1995, all US patents for which a foreign filing is made are published after 18 months. This has significantly reduced the risk posed by unpublished patents. However, if the applicant decides not to file in any other countries outside the US, then the US patent application is not published until issued.

Table 6 Patent database resources for five key countries and regions. Links for other counties and regions can be found at the WIPO site.

Country/Region	URL
China	http://www.sipo.gov.cn/sipo_English/zljs/default.htm
Europe	http://www.espacenet.com
Japan	http://www.ipdl.ncipi.go.jp/homepg_e.ipdl
United Kingdom	http://www.patent.gov.uk/patent/dbase/index.htm
United States of America	http://www.uspto.gov/patft/index.html
WIPO-PCTS	http://www.wipo.int/pctdb/en/search.jsp

15. UNCERTAINTY OF PATENT OWNERSHIP

A set of related patents and patent applications may become embroiled in an interference proceeding. An interference proceeding is an action brought before the patent office to decide who was first to invent when two or more similar inventions are filed with the patent office by several different parties. An interference proceeding can last for many years and can result in a great deal of uncertainty as to the owner of a patented technology, and the exact claims that will eventually be granted. One of the many consequences is that to ensure FTO after resolution of the interference action, prior to the settlement of the dispute, a developer may need to hedge its bets, by negotiating with, and licensing the technology from all parties involved in the dispute. This significantly increases the cost of licensing the required technology.

Once the relevant patents have been identified, the current patent owner needs to be identified. Patent ownership can change hands after the issuance of a patent, and it is not necessarily the same as that listed as the inventor or assignee on the patent document. For a potential licensee from a small company or academia, tracking patent transfers, and establishing contacts with the relevant licensing officer in each company as the patent ownership changes hands during technology sales, mergers and acquisitions, is a time consuming activity whose cost is measured in administrative and management time.

16. LICENSING AND CONTRACT NEGOTIATIONS

It is not uncommon for licensing negotiations to start and licenses to be issued prior to the issuance of a patent. In these cases the developer needs to assess the likelihood that a patent will issue, and that if issued, the claims granted will be sufficiently broad to require a license. To help determine the validity of a patent or the prospect that a patent application will be granted, it is essential that a prospective licensee has a thorough understanding of the prior art and case history covering a patent. Once again a large corporation will be able to dedicate the necessary scientific and legal manpower to ensure a thorough analysis of the patent. For a smaller company or a University researcher, the use of outside legal counsel is normally required. This can significantly add several thousand dollars to the cost of licensing and product development.

License negotiations for all technology contained in a GE plant entails a significant investment in time and money, in which licenses for all patents covering the plant variety, the transformation method used, as well as licenses for all patented coding sequences, promoters and selectable marker used are negotiated. In some cases licenses may not be available. A patent owner may decide that it is in its best business interest not to license out the technology. The two most common reasons are competition and liability. A patent owner may have no incentive to license its technology to a competing company, unless an equally important technology can be cross-licensed from the competitor. In terms of liability, a patent owner may hesitate to license its technology to a third party for fear that its technology be part of a product that becomes involved in a product liability suit.

License fees and royalty rates vary greatly depending on the nature of the technology and the crop in which it will be used. Upfront fees and annual payments can vary from tens of thousands to millions of dollars. For the ornamental market, gross revenues for individual varieties are commonly in the range of $50,000 to $500,000 per annum. Even with a healthy net margin of 10%, it is clear that a developer of a GE ornamental plant will be limited in it's ability to afford the required technology.

17. POTENTIAL IMPACT ON COMMERCIAL AND ACADEMIC RESEARCH

Some of the above discussed FTO issues such as license costs, or refusal of a licensor to grant a license, may represent absolute barriers. Other costs, such as administrative and management time, cost of outside counsel, delay of entry to market due to not having FTO, or the risk and costs of lawsuits related to the use of unlicensed technology represents significant disincentives that significantly slow the commercialization of a new GE variety.

FTO costs and risks apply to small, medium and large corporations alike. For example American Cyanmid was delayed in its development of herbicide-tolerant maize and rice as a result of Cornell's exclusive licensing of the particle gun to Dupont. Dow decided to use and develop Whisker's technology instead of *Agrobacterium* technology due to the uncertainty of the ownership of the technology that was, at the time, in a protracted interference proceeding between three other potential owners (Pray 2005). For smaller companies, such as those involved in developing ornamentals and other specialty crops, such restrictions can ultimately lead to the company abandoning genetic engineering as a viable breeding alternative or even to the demise of the company itself.

University and government researchers may also find their work restricted by patent-related issues. Although it is commonly believed that the early research and development work performed by university researchers are exempt from patents claims under the 'experimental use defense', a 2002 case (Federal Circuit 2002) served to illustrate that universities and university researchers are not necessarily exempt from patent infringement suits. Thus a university or government researcher performing research and early development work may potentially fall subject to the same legal restrictions as a commercial entity. However, under some circumstances US government researchers (e.g., those at the USDA-ARS) are exempt under section 202 c 4 of the Bayh-Dole Act: Under this act, the US government has a non-exclusive, paid-up royalty free license to patented technology developed as a result of funding from by a federal agency (GAO 2003). This provision is distinct from 'march-in rights' described in section 203 of the Bayh-Dole Act. Such 'march-in rights' have been requested on several occasions, but have never been enforced (O'Conner 2008).

In summary, complete FTO is very difficult to obtain in most circumstances. This is in part due to the evolving nature of the patent landscape, the uncertainty of protracted interference proceedings, and sometimes the reluctance of a patent owner of a key technology to grant licenses at affordable prices, or at all.

18. FTO PRODUCT SPECIFIC CASE STUDIES

It is beyond the scope of this chapter to provide a complete freedom to operate (FTO) analysis of any single product. However, A 2000 case study of Golden Rice serves as a reliable template from which to perform an FTO analysis on any planned GE variety (Kryder *et al*. 2000).

Table 7 Patents for key US transformation technologies. Dupont own rights for the use of the gene gun in agricultural crops. Rights for ornamental plants were granted to Sanford Scientific, now majority owned by Scotts.

Inventor	Assignee	Owner	Technology	US Patent number	Issue date
Sanford	Cornell	Dupont	Biolistic method	4945050	July 31, 1990
Sanford	Cornell	Dupont	Biolistic apparatus	5371015	December 6, 1994
Tomes	Pioneer	Pioneer	Biolistic stable transformation	6570067	May 27, 2003
Barton	Washington University	Syngenta	*Agrobacterium* method for dicots	6051757	April 18, 2000
Schilperoort	Leiden University, NL	Syngenta	*Agrobacterium* Binary Vector	4940838	July 10, 1990
Schilperoort	Leiden University, NL	Syngenta	*Agrobacterium* Binary Vector	5464763	December 23, 1993
Hiei	Japan Tobacco	Japan Tobacco	*Agrobacterium* – monocot callus	7060876	June 13, 2006
Dong	Rhone-Poulenc Agro	Bayer AG	*Agrobacterium* – monocot inflorescence	6037522	March, 14 2000
Coffee	Zeneca	Syngenta	Whiskers	5302523	April 4, 1994

Golden Rice was developed by *Agrobacterium* transformation of rice, and the study contains a good preliminary analysis of the patents that cover the technology (not including the 2000 *Agrobacterium* patent granted to Syngenta (Barton *et al*. 2000)). In addition to the genes required to direct vitamin A biosynthesis, the constructs contained many of the promoter and control sequences commonly used in plant transformation. The patents identified not only covered techniques specific to plant genetic engineering, but also covered many of the vectors and techniques commonly used in recombinant DNA, such as PCR and technologies for the expression of foreign genes in eukaryotic cells.

In total, the study identified approximately 40 patents that would cover the product if produced and sold in the USA or Europe. Because many of these patents were never filed or issued in other countries, the authors concluded that many fewer patents licenses would be required if the rice were produced in Japan (21) China (11), Brazil (10), Vietnam (9) and India (5), and Thailand (0). The authors of the Golden Rice study identified 31 separate organizations from which licenses or agreements to use the patented technology would be required. The enormity of negotiating such a large number of licenses is probably beyond the scope of many developers of ornamental crops. Since publication of the Golden Rice FTO review, some patents may have expired, and new patents may have issued. As a result, the exact number of patents may have changed since this study was undertaken, but the point is still the same.

A more recent 2006 case study undertaken by the Public-Sector Intellectual Property Resource for Agriculture (PIPRA) for an *Agrobacterium* construct designed to confer disease resistance in grapes indicated that several dozen proprietary technologies were incorporated into the GE grape (PIPRA 2006).

Table 7 shows a list of the key transformation patents issued in the US. Counterparts for some of these have also issued in Europe and Japan. Understanding the breadth, validity and enforceability of each of the claims in each of the patents is a complex and important step in developing a successful FTO strategy. A full analysis of the claims and coverage of each of the patents listed is beyond the scope of this paper. For *Agrobacterum*-related methods the reader is directed to the excellent white paper by CAMBIA (Roa-Rodriguez *et al*. 2003). Although at the time of writing this review some patents such as the Schilperoot Binary Vector patents are close to expiring, the developer may find that other patents, such as the Barton patent, may cover the technology being used by the developer. An exact understanding of the breadth of the patent claims, and its applicability to the technology used by a developer should be developed in consultation with a patent lawyer familiar with the field of agricultural biotechnology. In addition, to the broad patents listed in **Table 3**, the developer will also need to be aware of genus specific patents that may cover the technology used by the developer, such as those for roses (Firoozabady and Robinson 1996; Firoozabady and Robinson 1998), carnation (Firoozabady *et al*. 1996), and chrysanthemums (Lemieux 1996).

19. OPEN SOURCE ENABLING TECHNOLOGY: BIOS

Given the broad array of patents covering *Agrobacterium* transformation, many corporate and university researchers have attempted to develop alternative transformation systems that avoid the use of *Agrobacterium*. In 2005 Richard Jefferson and his colleagues at CAMBIA, an international independent non-profit research institute based in Canberra, Australia, demonstrated that several non-*Agrobacterium* soil bacteria are capable of transferring T-DNA bearing a foreign gene into plants cells (Broothaerts *et al*. 2005). US patent applications for this technology were published in December 2005 (Jefferson 2005; Jefferson 2005). The potential validity of any patent claims arising from this work, and their distinctness from the claims in the original Monsanto and Syngenta patents are still uncertain. The technology has been given the name TransBacter and is being made available through a licensing strategy partially modeled on the open source licensing strategy used for software. According to Cambia's BioForge website (http://www.bioforge.net), users are required to sign a Plant Enabling Technology BiOS License and an associated BiOS Technology Support Agreement. In return for rights to use the TransBacter technology licensees are required to grant back rights to improvements of the Transbacter technology to CAMBIA. Such improvements can then in turn be licensed to other BiOS licensees. This open source approach is aimed at steadily increasing the sophistication of the technology whilst preventing any one licensee or user from restricting the use of the technology to others in the TransBacter technology licensee pool. The technology is offered at no cost to universities and non-profits and at a modest cost to for-profit corporations.

20. INTELLECTUAL PROPERTY CONSORTIA: PIPRA

Most of the key patented techniques in plant transformation, though originally developed in universities, are now owned by large corporations. In 2003, in an effort to reverse this situation, officials at ten US universities formed a group called the Public-Sector Intellectual Property Resource for Agriculture (PIPRA). This group aims to dissuade universities from issuing broad exclusive licenses to corporations and to retain more rights for academic researchers and for humanitarian uses. By doing this PIPRA expects to ensure access to intellectual property developed by public and non-profit institutions.

PIPRA is steadily evolving into a global organization, and has helped seed the establishment of similar IP resources in Asia and South America. As of 2006, PIPRA had grown to 41 member institutions, comprising 32 North American, 6 Asian, 2 South American, and one European

institution. In the US and elsewhere, this includes major research universities whose scientists have and continue to develop important genetic engineering technologies for the development of improved crop varieties. Among them, its members own a considerable body of intellectual property for the development of GE plants. Its members will, however, probably still need to obtain licenses, or independently develop the plant transformation technologies needed to incorporate these technologies into GE plants. Perhaps for this reason, the PIPRA Biotechnology Resources Laboratory was established at UC Davis. One of the stated goals of this laboratory is to develop vectors and a plant transformation system that "addresses legal, regulatory, and consumer considerations."

21. PUBLIC PERCEPTION

Public perception of genetic engineering, is very much dependent on the crop and the country in which the product is to be commercialized. There has traditionally been much more public and media opposition to the commercialization of GM plants in Europe and Japan than in the United States. GE corn, soybean, canola and cotton have been widely grown for the past two decades in the United States, and as result GM ornamental commercialization in the US should represent one of the easier markets to enter. GE carnations are the only example of a commercially available GE ornamental. These are now sold in more than ten countries around the world, including Japan, the United States, and several European countries. Market acceptance has been generally good, and it does not appear that wholesalers or retailers have experienced significant opposition to these products.

22. CONCLUSIONS

Although there is considerable technology available for the development of novel ornamental plants, several factors currently make the development of GE varieties unattractive from a business perspective. These include the cost of obtaining FTO for enabling and trait technology as well as the cost of government approval for commercial release of GE plants. Over the long term, patents costs may eventually decrease, as new publicly available technologies are developed, and as key transformation patents expire. The short and long term future of regulatory costs remain uncertain, however. Will costs decrease as regulations are rationalized or become more standardized and predictable, or will regulations become more stringent and expensive to navigate? In the US, there is a possibility that the USDA may move to tired-risk system that could potentially ease the regulatory burden for some categories of GE ornamentals (USDA 2007). On the other hand a US court decision, in February 2007 requiring the USDA to reevaluate their approval of a field test permit for Scotts' transgenic turfgrass, and the May 2007 decision of a US court to vacate APHIS's 2005 decision to deregulate herbicide resistant transgenic alfalfa (Charles 2007), raises the possibility that any regulatory approval process enacted by a government agency could be challenged in the courts. At the international level, how will some of they key centers of production regulate GE crops? How will international treaties evolve and impact the development and international trade of GE ornamentals? Answers to these questions are key to the commercial future of GE technology in ornamentals crops.

Unless the existing cost barriers and regulatory uncertainty are addressed, ornamental breeding strategies will continue to shift away from GE approaches. There are very few companies actively pursuing the development of GE ornamental plants. Scotts' development of transgenic turfgrass, and Suntory's development of transgenic carnations and roses are notable well-financed exceptions. Most companies have curtailed or terminated their GE approaches in favor of less costly non-transgenic approaches. Many of these companies have refocused their attention on alternative non-transgenic approaches in combination with traditional breeding and mutagenesis. Non-transgenic alternatives include the use of marker assisted breeding, gene-based screening of mutant populations as well as advanced techniques in plant tissue culture to facilitate wide species crosses for the generation of novelty and improved disease and insect resistance. However, although these techniques are well proven and cost effective, they are not likely to reproduce the success seen using novel traits such as Bt, which cannot be developed solely from genetic resources within a sexually or genomically compatible breeding pool. University and government research labs will probably continue to play a role in developing proof of concept applications for GE ornamentals, but unless the efforts of organizations such as CAMBIA, PIPRA and SCRI are successful, few will have the IP, regulatory and financial resources to commercialize such varieties.

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