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Business Potential for Agricultural Biotechnology

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**Report of the APO Multi-country Study Mission
on the Business Potential for Agricultural
Biotechnology Products
22–28 May 2005, Republic of China**



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Business Potential for Agricultural Biotechnology Products



ASIAN PRODUCTIVITY ORGANIZATION



BUSINESS POTENTIAL FOR AGRICULTURAL BIOTECHNOLOGY PRODUCTS

2007
ASIAN PRODUCTIVITY ORGANIZATION
Tokyo

Report of the APO Multi-country Study Mission on the Business Potential for Agricultural Biotechnology Products, 22–28 May 2005, Republic of China.

This volume was edited by Dr. Paul S. Teng, Singapore.

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FOREWORD

The emergence of agricultural biotechnology as a major investment area is propelling new growth of companies worldwide. Several major players in the food and seed industries are employing biotechnology as the core of their business. Some of these companies pioneered the use of biotechnology in the development of grain and oil seeds, while others started their businesses by applying advanced biotechnology to nonfood products such as cotton and ornamental plants. Others took more traditional biotechnology approaches in the brewing and fermentation of food products and beverages. Biotechnology is providing a means to meet increasing consumer demand for more varied and higher quality products.

Despite recent advances, biotechnology still has enormous potential to create additional changes in agriculture. In many countries in the Asia and Pacific region, its application is still in the nascent stage and its benefits have not yet reached the majority of the population. In many cases, R&D outputs are still not reaching the commercialization stage, for varied reasons, and hence their full potential benefits to farmers and consumers in general remain untapped. Some consumers' and environmentalists' concerns related to food safety and the environmental ramifications of biotechnology are affecting its wider commercial applications and heightening the uncertainty surrounding its use.

The APO therefore organized a multi-country study mission on "Business Potential for Agricultural Biotechnology Products" to review the topic and identify how private companies, especially SMEs and including the government corporate sector, could capitalize on that potential in member countries to increase productivity in the agriculture sector. This volume is a compilation of the papers and proceedings of the study mission. I hope that it will serve as a useful reference on the subject in APO member countries and elsewhere.

The APO is grateful to the Government of the Republic of China for hosting the mission and to the China Productivity Center, Taiwan Agriculture Research Institute, and Council of Agriculture of the Executive Yuan for implementing the program. Special thanks are due to Dr. Paul S. Teng for editing the present volume.

Shigeo Takenaka
Secretary-General

Tokyo
February 2007

Part I

Summary of Findings

SUMMARY OF FINDINGS

INTRODUCTION

The Multi-Country Study Mission on Business Potential for Agricultural Biotechnology Products, organized by the Asian Productivity Organization (APO) and hosted by the Government of the Republic of China, was held in Taipei from 23–28 May 2005. The Taiwan Agriculture Research Institute, Taichung, hosted the meeting. Twenty-two participants from twelve member countries and seven resource persons from the U.S., Singapore, Republic of Korea, and Republic of China attended this mission.

The objectives of the study mission were to review the business potential of agriculture biotechnology products and to suggest how private companies, especially SMEs, including the government corporate sector, could actualize such potential in member countries.

The study mission consisted of presentation and discussion of resource papers as well as country papers and field visits to selected institutions and private businesses involved in agricultural biotechnology research and development and commercialization of biotechnology products. The topics covered by the resource papers were: “Why Agricultural Biotechnology?,” “Global Status and Trends of Commercialized Biotechnology in Crops,” “Frontiers and Advances in Transgenic Biotechnology of Animals and Fishes,” “Development and Application of Biofertilizers in Taiwan,” “Current Status of the Transgenic Approach for Control of *Papaya Ringspot Virus*,” “Commercial-scale Production of Valuable Plant Biomass and Secondary Metabolites Using a Bioreactor System,” and “Commercialization of Agricultural Crop Biotechnology Products.”

The following summary presents the highlights of the study mission.

HIGHLIGHTS OF THE RESOURCE PAPERS

The seven resource papers addressed different aspects of the process to commercialize agricultural biotechnology products. The rationale for agricultural biotechnology was made, and aspects of biotechnology ranging from applied microbiology to applied molecular biology to genetic engineering were discussed by authors using real-world examples. The overall performance of biotech crops was reviewed in the context of market share and market potential by geography. Issues of biosafety, food/feed safety assessment, and public acceptance were further discussed as integral components of the commercialization process.

Why Agricultural Biotechnology?

Crops improved through agricultural biotechnology have provided demonstrable economic, environmental, and social benefits globally. In the Asia-Pacific region, five countries have grown biotechnology-derived crops commercially: Australia, China, India, Indonesia, and the Philippines. Specific examples describe insect-protected cotton in China, Australia, and India, insect-protected maize in the Philippines, and herbicide-tolerant cotton in Australia. Future uses in Asia-Pacific include more widespread adoption of herbicide-tolerant crops currently grown elsewhere, including herbicide-tolerant maize. In addition, China and India are two countries within the region that have very active crop biotechnology research and development programs in a diversity of crops (including chickpea, rice, cotton, maize, mustard, and potato) and biotechnology traits (including insect, disease, and virus resistance, herbicide tolerance, stress tolerance, oil improvements, and fruit ripening). Other biotech-derived traits will improve food and feed nutrition, including vitamin and mineral enhancement, increased essential amino acids, and altered fatty acid composition. However, the successful development and commercialization of biotech-derived crops will be impacted by the costs of doing so, and the costs of regulatory ap-

provals have become an increasingly significant part of the total product development and commercialization equation. Regulators and the scientists who support them must take care to assure that data requirements are reasonable and designed to address true food, feed, and environmental risks.

Global Status and Trends of Commercialized Biotechnology in Crops

Commercial crop biotechnology products consist of different crop varieties possessing specific traits in any of four food, feed, and fiber crops, namely soybean, maize (corn), canola, and cotton. In 2004, the global area grown with biotech crops was estimated at 81 million ha, made up primarily of soybean, maize, cotton, and canola. Biotech soybean retained its position in 2004 as the biotech crop occupying the largest area, 48.4 million ha in 2004, with biotech maize in second place at 19.3 million ha, biotech cotton in third place at 9.0 million ha, and finally canola at 4.3 million ha. Between 1996 and 2003, a total of 21 countries, 11 developing and 10 industrial countries, contributed to a 40-fold increase in the global area of biotech crops, from 1.7 million ha in 1996 to 67.7 million ha in 2003. Adoption rates for biotech crops during this period have been unprecedented, and by recent agricultural industry standards they are the highest adoption rates for improved crops, reflecting farmer satisfaction with products that offer substantial benefits, including more convenient and flexible crop management, higher productivity and/or net returns per hectare, health and social benefits, and a cleaner environment through decreased use of conventional pesticides, which collectively contribute to a more sustainable agriculture. There is a growing body of consistent and compelling evidence generated by public sector institutions that clearly demonstrates the improved weed and insect pest control attainable with biotech herbicide-tolerant and insect-resistant Bt crops that also benefit from lower input and production costs. Biotech crops offer substantial economic advantages to farmers compared with corresponding conventional crops.

During the nine-year period 1996 to 2004, herbicide tolerance has consistently been the dominant trait, with insect resistance second. In 2004, herbicide tolerance, deployed in soybean, maize, canola, and cotton, occupied 72% of the 81.0 million ha. There were 15.6 million ha planted to Bt crops, equivalent to 19%, with stacked genes for herbicide tolerance and insect resistance deployed in both cotton and maize occupying 9% of the global biotech area in 2004. The increase in Bt crops reflects the significant increase in Bt maize in 2004 (2.0 million ha) and the increase of Bt cotton (1.4 million ha) in China, India, and Australia. Whereas most of the growth in Bt maize occurred in the U.S., there were also significant increases in Bt maize area in Argentina, Canada, South Africa, Spain, and the Philippines. The stacked traits of herbicide tolerance and insect resistance in both maize and cotton increased by 17% in 2004, reflecting the needs of farmers who must simultaneously address the multiple yield constraints associated with various biotic stresses. Although the substantial share (66%) of biotech crops was grown in industrial countries, the proportion of biotech crops grown in developing countries has increased consistently every year, from 14% in 1997 to 16% in 1998, 18% in 1999, 24% in 2000, 26% in 2001, 27% in 2002, 30% in 2003, and 34% in 2004. Thus, in 2004, more than one-third of the global biotech crop area of 81.0 million ha, equivalent to 27.6 million ha, was grown in developing countries. For the first time the absolute growth in the biotech crop area between 2003 and 2004 was higher in developing countries (7.2 million ha) than in industrial countries (6.1 million ha). Also, the percentage growth was almost three times as high (35%) in the developing countries of the South compared to the industrial countries of the North (13%).

Seventeen countries grew biotech crops in 2004, 11 developing countries and 6 industrial countries, including Romania from Eastern Europe. In 2004, biotech crops were grown commercially in all six continents of the world: North America, Latin America, Asia, Oceania, Europe (Eastern and Western), and Africa. The top eight countries, each growing half a million ha or more of biotech crops in 2004, are the U.S., Argentina, Canada, Brazil, China, Paraguay, India, and South Africa. These top eight biotech countries accounted for approximately 99% of the

global biotech crop area, with the balance of less than 1% growing in the other nine countries. In 2004, the number of biotech mega-countries (growing 50,000 ha or more of biotech crops) increased by 40%, from 10 in 2003 to 14 in 2004. The additional four countries that qualified as biotech mega-countries in 2004 were Paraguay, Mexico, Spain, and the Philippines. Although 17 countries were reported to have grown biotech crops in 2004, a larger number are known to have such crops in various stages of development leading up to commercial plantings. The public sector will be an important source of crop biotech products for poor farmers, as there are currently known to be more than 99 crop variety-trait modifications undergoing different stages of testing by public institutions in Asia.

The global value of total crop production from biotech crops in 2003 was estimated at USD44 billion. Net economic benefits to producers from biotech crops in the U.S. in 2003 were estimated at USD1.9 billion, while gains in Argentina for the 2001–02 season were USD1.7 billion. China has projected potential gains of USD5 billion in 2010, USD1 billion from Bt cotton and USD4 billion from Bt rice, expected to be approved in the near term. The number of farmers benefiting from biotech crops continued to grow, reaching 8.25 million in 2004, up from 7 million in 2003. Notably, 90% of these 8.25 million farmers benefiting from biotech crops in 2004 were resource-poor farmers planting Bt cotton, whose increased incomes have contributed to the alleviation of poverty. These included 7 million resource-poor farmers in all the cotton-growing provinces of China, an estimated 300,000 small farmers in India, and subsistence farmers in the Makhathini Flats in KwaZulu Natal province in South Africa and in the other nine developing countries where biotech crops were planted in 2004. In 2004, the global market value of biotech crops was estimated at USD4.70 billion, representing 15% of the USD32.5 billion global crop protection market in 2003 and 16% of the \$30 billion global commercial seed market. The market value of the global biotech crop market is based on the sale price of biotech seed plus any technology fees that apply.

The future of crop biotechnology products will depend on their proven benefits to the farming community, a regime of acceptable biosafety oversight, and public/consumer acceptance. Regulatory frameworks for biosafety are being developed by many countries that are signatories to the Cartagena Biosafety Protocol under the Convention on Biological Diversity, and the methodology for safety assessment has also increasingly been improved vis-à-vis its science and acceptance by governments.

Frontiers and Advances in Transgenic Biotechnology of Animals and Fishes

Transgenic animals are produced by introduction of foreign DNA into embryos using various transgenic technologies, such as microinjection, embryonic stem cells, pronuclear microinjection, and nuclear transfer. The foreign DNA is inserted into the genome and may be expressed in specific tissues for particular purposes. Some useful peptides relevant to animals could be used to increase yield and decrease production cost through transgenic technologies. The techniques provide a powerful approach for improving the quality of bioproducts to advance the quality of life. Potential applications of transgenics in animal production include enhanced prolificacy and reproductive performance, increased feed utilization and growth rate, increased disease resistance, and improved milk production. Furthermore, an important application of transgenics is the production of therapeutic proteins for human clinical use in so-called bioreactors. The recombinant proteins in animal milk can provide an economic and safe system for production of valuable proteins, such as pharmaceutical proteins for treatment or prevention of human disease or biomaterials for medical use. Through genetic engineering, commercial application in producing therapeutic proteins for human clinical use creates high economic value. A gene transfer system also allows the production of many transgenic varieties having special genetic traits, especially for aquacultural finfish and shellfish. Transgenic fish provide great potential benefits for enhancement of aquatic species for aquaculture by improving production efficiencies, enhancing food quality and growth rate, increasing disease resistance, and increasing

overall production to meet an ever-increasing demand for seafood products. On the other hand, commercial production of transgenic fish will depend on the assessment of risk to wild aquatic species. The concern includes ecological impacts, which may be a cause of extinction of the wild type. Therefore, genetically modified fish, for safety, should be sterile, and the infertile technology now has been developed for ornamental fish. In foundation research, mice and rats were commonly used as animal models for studying human diseases; however, recently fish was developed for use as an animal model because the vertebrate has many advantages that permit gene transfers to be more easily manipulated. In the foreseeable future, there will be a number of new and developing technologies that will have a profound impact on the genetic improvement of animals. The technologies will be incorporated into production schemes and make possible more efficient production to meet consumer and market demands.

Development and Application of Biofertilizers in the Republic of China

The Republic of China is a subtropical island characterized by high temperatures and heavy rainfall. Intensive agriculture practices have served as a strong foundation for the Republic of China's commercial and industrial "economic miracle." In recent years, agrochemicals (pesticides and fertilizers) have been extensively applied to obtain higher yield. Intensive application of agrochemicals leads to several agricultural problems and poor cropping systems. Farmers may use more chemical fertilizers than the recommended levels for some crops. Excessive application of chemical nitrogen fertilizer not only accelerates soil acidification but also risks contaminating groundwater and the atmosphere. Organic fertilizers offer a safe option for reducing the agrochemical inputs. Biofertilizers have been developed in several laboratories in the Republic of China over the years. Microorganisms including rhizobium, phosphate-solubilizing bacteria, and arbuscular-mycorrhiza (AM) fungi are continuously being isolated from various ecosystems and their performance in laboratory and field conditions assessed. The extensive research program over the years on beneficial bacteria and fungi has resulted in the development of a wide range of biofertilizers which not only fulfill the nutrient requirements of various crop species but also increase crop yield and nutrient composition. Numerous experiments in greenhouses and in field conditions have shown that many different crops respond positively to microbial inoculations. In particular, successful rhizobial inoculants were applied to leguminous plants and AM fungi for muskmelons in order to increase yield. Multifunctional biofertilizers were developed to reduce chemical fertilizer application by about one-third to one-half. Enhancement and maintenance of soil fertility through microorganisms will be an important issue in future agriculture. Long-term conservation of soil health is the key benefit of biofertilizers, equivalent to the most sustainable form of agriculture.

Current Status of the Transgenic Approach for Control of *Papaya Ringspot Virus*

Production of papaya has been limited in many areas of the world by *Papaya ringspot virus* (PRSV). PRSV causes severe mosaic and distortion on leaves, ringspots on fruits, and water-soaked oily streaks on upper stems and petioles. It stunts the plant and drastically reduces the size and the quality of the fruit. PRSV is a member of the genus *Potyvirus* and is transmitted nonpersistently by aphids and is also sap-transmissible in nature. PRSV was first reported in Hawaii in the 1940s and then became prevalent in Florida, the Caribbean countries, South America, Africa, India, the Far East, and Australia. Although tolerant selections of papaya have been described, resistance to PRSV does not exist in the species of *C. papaya*, which makes conventional breeding difficult.

A CP gene of a native Taiwan strain, PRSV YK, was used to transform Taiwan papaya cultivars by *Agrobacterium*-mediated transformation. The transgenic lines showed various levels of resistance, ranging from delay of symptom development to complete immunity. Several lines highly resistant to the homologous strain (PRSV YK) provided wide-spectrum resistance to three different geographic strains from Hawaii, Thailand, and Mexico. During four repeats of

field trials from 1996 to 1999, the transgenic papaya exhibited high degrees of protection against PRSV in the Republic of China. Unfortunately, 18 months after planting in the fourth field trial, unexpected symptoms of severe distortion on fully expanded leaves, stunning on apex, water-soaking on petioles and stem, and yellow ringspot on fruit were noticed on PRSV CP-transgenic papaya plants. The causal agent was distinguished from PRSV by host reactions and serological properties and later identified as *Papaya leaf distortion mosaic virus* (PLDMV), a potyvirus which originated from Okinawa, Japan, in 1954. All PRSV CP-transgenic papaya lines were susceptible to PLDMV infection when evaluated under greenhouse conditions. Therefore, in the Republic of China PLDMV will be considered a serious threat to papaya production once PRSV CP-transgenic papaya is widely used for the control of PRSV.

In order to control two or more viruses, transgenic plants with multiple resistances have been generated by combining the entire CP gene of more than one virus, with each gene driven by a promoter and a terminator. Transgenic lines expressing these chimeric CP constructs were resistant to the corresponding viruses and protected from mixed infection such as *Cucumber mosaic virus*, *Watermelon mosaic virus*, and *Zucchini yellow mosaic virus*. Furthermore, transgenic plants with resistance to a potyvirus and a tospovirus can be obtained through the PTGS mechanism by fusing a segment of tospoviral N gene to a segment of potyviral CP gene. This strategy was used to develop double resistance to both PRSV and PLDMV. An untranslatable chimeric construct that contained the truncated PRSV CP and PLDMV CP genes was then transferred to papaya. Through the PTGS mechanism, transgenic papaya plants carrying this chimeric transgene indeed conferred resistance against both PRSV and PLDMV under greenhouse conditions. These transgenic papaya plants with double resistance are considered to have great potential for the control of PRSV and PLDMV in Taiwan. In four-year field trials, a super PRSV strain 5-19 which infected transgenic papaya lines was found. The breakdown of the transgenic resistance by a strong gene-silencing suppressor of a super strain has a strong impact on the application of transgenic crops for virus control. A chimeric construct targeting at multiple viral genes, including the gene determining viral virulence and gene silencing suppression, such as the HC-Pro gene of a potyvirus, may minimize the chance of emergence of a super virus for overcoming the transgenic resistance.

Commercial-scale Production of Valuable Plant Biomass and Secondary Metabolites Using a Bioreactor System

Plants are a de facto biological factory that produces an immense array of fine chemical compounds highly valued in pharmaceutical, food, and bioenergy industries. Thus it is of huge business interest to grow plant cells, tissues, and even entire organisms at commercial scales. Having proven its medicinal superiority in traditional medicine, Korean Mountain Ginseng (KMG) has a high market value among Korean people that has stimulated much interest in producing its biomass for commercialization. However, there have been only a few success stories of plant cultures at the commercial scale. Recently, a group at VitroSys Inc. successfully implemented an industrial-scale bioreactor system for the commercial production of Korean Mountain Ginseng (*Panax ginseng* C. A. Meyer). The bioreactor system holds a promising future for applications, such as the large-scale production of diverse secondary metabolites from plant tissues.

Commercialization of Agricultural Crop Biotechnology Products

High-quality seed of crop cultivars with the desirable genetic background still form the foundation for farming. Biotechnology offers the best opportunity to meet the challenge of improving on the potential in seeds and also of providing the enabling knowledge to express that potential. Crops developed through biotechnology are produced by the stable insertion of one or a few well-defined genes into the genome of a plant. The gene(s) produce one or a few proteins that confer the trait of interest (e.g., insect resistance). Of the thousands of individual plants that

are produced, only one is selected, based on stringent performance standards, as the source for all the varieties eventually sold commercially. Before any food crop produced using modern biotechnology can be marketed, the food product must undergo multiple years of rigorous safety assessment. Steps in taking a proof of concept from the laboratory to the market include those in the R&D phase—desired traits identified, genes tagged and mapped, transformation process under biosafety purview, phenotype evaluation in contained environment, open field tests under supervision of biosafety regulators—and the commercialization phase—deregulation approval based on scientific review of data and public hearings, incorporation into commercial variety, multilocation performance trials, seed certification boards’ approval for multiplication use, and food/feed use approval for consumption. National and international regulatory authorities require that food produced through biotechnology must meet the same safety standards as food grown conventionally, that is, there must be “reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption.” The food safety standard for biotech food therefore is that these foods must be “as safe as” food produced by conventional methods. The comprehensive safety testing described above provides a thorough assessment of potential risks relevant to food safety, all in a comparative assessment with foods derived from conventional crop varieties. It is through this holistic approach that regulatory agencies around the world have repeatedly concluded that foods derived from biotech crops are as safe and nutritious as foods developed through other technologies. Above and beyond regulatory requirements, producers of GM crops assure the biosafety and food safety of their products through product stewardship by providing the subsequent after-sales support to ensure that the product is properly used, including, among other things, resistance management schemes especially for the insect-protected products (Bt corn, Bt cotton), and detection techniques. There have been about 25,000 field trials in 45 countries on 60 crop species without a single ecological accident—an impeccable record of government-supervised field trials.

Successful commercialization of crop biotech requires not just sound technology relevant to farmers’ needs, but also a supporting environment. Public knowledge, attitudes, and perception of GM products are very important factors that ultimately determine whether GM crops will make an important contribution to the world’s food supply. It is important that public concerns be recognized and properly addressed. Some of these have to do with the environment—regulation of field releases, outcrossing, and effects on nontarget organisms—and food safety—the safety assessment process, regulation, the presence of allergens or toxins, nutritional value, and the presence of antibiotic resistance markers. Being aware of the issues helps the scientist understand and generate data to address them. Science currently addresses these concerns very well. There are elements of risk, but these are far outweighed by the benefits.

HIGHLIGHTS OF THE COUNTRY PAPERS

Marching Towards the Market: The Business Potential of Agricultural Biotechnology in the Republic of China

Due to its high application potential, and in order to accelerate its development, biotechnology was included by the government in 1982 among the eight key areas of research. Many related education and training programs were also initiated at this time. The Development Center for Biotechnology (DCB), the first autonomous and nonprofit organization specifically for biotechnological research, was established in 1984. After nearly a decade of effort, the research gradually proceeded to more practical and important activities, including the development of transgenic plants and animals, DNA-based genotyping for breeding, and the development of biopesticides, biofertilizer, and animal vaccines. From the late 1980s to the middle 1990s, important regulations and guidelines concerning biotechnology and biosafety were established by the government. The Experimental Rule of Recombinant DNA was issued by the National Science Council (NSC) and the Guidelines for Risk Assessment in GM Plants and GM Animals by the

Council of Agriculture (COA). The Plant Variety and Seed Act, the most important law in agriculture, was enacted by COA in 2003; by taking biotechnology into account, it opened the door to a new era. Creation of some animal- and fish-related regulations and laws in this field has also been ongoing. Today a fundamental framework has been constructed for the management of biotechnology and biosafety in this country. In 2005, total investment in biotechnology has reached TWD150 billion. 11.3% of companies related to the agricultural biotechnology business existed before 1980. Sixteen percent were established during 1980–95. More than two-thirds (66.9%) were created after 1996. This indicates that in Taiwan, the industry entered the era of agricultural biotechnology only about a decade ago. Most companies (63.2%) are small in scale, with a staff of less than 25.

Plant tissue culture is now not only a matured technology but has grown into a flourishing industry. The orchid nursery in particular has become very reliant on tissue culture for the mass production of healthy young plants. Commercial orchid varieties consisted of plant tissue culture products in percentages as high as 51% and 85% in 1998 and 2002, respectively. The main categories of orchids produced by tissue culture include *Phalaenopsis*, *Oncidium*, *Cymbidium*, *Dendrobium*, and *Paphiopedilum*. In 2003, the total export value of tissue culture products reached TWD272 million, 27% more than in 2002. About 95% of the export value came from orchids, especially *Phalaenopsis*. In export, the major trading partners came from the U.S. (30.1%), Japan (28.8%), South Korea (13.4%), the Netherlands (7.4%), and China (4.0%). The number of nursery companies engaged in tissue culture has ranged between 100 and 120 during the past decade.

In applied microbiology, biopesticide and biofertilizer are the two hot items in agriculture. Several major companies, such as Yuen-Foongyu Paper Co., Tai-En Co., and Biontech Inc., have begun to produce and merchandise these products under their own brands. Although at present the total value of this new industry is only about 0.5%–1% of the total traditional pesticide market, it is growing at the rate of 10%–15% annually. Recently, a brand called Biowork (*Bacillus subtilis*) has opened a new market in Japan, and some products of *Streptomyces* have created an annual value of TWD10–20 million in the domestic market. Several fungi and bacteria have been studied for their potential as biofertilizer, including the genera *Pseudomonas*, *Bacillus*, *Thiobacillus*, *Penicillium*, and *Aspergillus*. There have been some good products marketed by different companies that have been quite well accepted by farmers. Other products of agricultural biotechnology with high market potential will likely result from genetic engineering, including genetically modified organisms (GMOs) for producing specific bioproducts, detection kits derived from recombinant DNA techniques, transgenic plants, and transgenic animals. There has been a great effort to promote developments in this field of research, and much research is ongoing. One of the important achievements is the transgenic papaya resistant to *papaya ringspot virus* developed by Chung-Hsin University about 10 years ago, which passed environmental risk assessment in 2000. It must still undergo food safety assessment before being marketed. There are several transgenic crops, including rice, broccoli, potato, and tomato, now in the process of environmental risk assessment at the Taiwan Agricultural Research Institute and the Asian Vegetable Research and Development Center but not yet subject to food safety assessment.

The Business Potential and Development Strategy for Agricultural Biotechnology Products in the Republic of China

Taiwan is a subtropical mountainous island with a diverse climate ranging from tropical to subfrigid. This diverse environment creates a large amount of biodiversity, which is a key factor in the development of the country's agricultural biotechnology industry. The analysis of the overall development vision, objectives, and current status of the industry, agricultural resources, and global competition with respect to agricultural biotechnology indicates that the development of the Republic of China's biotechnology industry should focus on subtropical agriculture. In the

initial stage, the Republic of China should develop an industry in plant sprouts, aquaculture farming, animal vaccines, functional food polypeptides, biofertilizer, and biopesticides. The goal is two-fold: to accelerate the pace of transforming traditional farming and to accumulate technical know-how and talent in the field of new applications.

The Republic of China should also invest in infrastructure establishment, including creating an agricultural biotechnology information and certification management system, amending current regulations and administrative operations, and strengthening product design and sales. In addition, the Republic of China should establish agricultural biotechnology parks to concentrate resources in order to become an agricultural high-tech center that can fulfill the multiple purposes of research and development, production and marketing, processing and transportation to market. This strategy will create a healthy industrial development environment and gradually build a new agricultural biotechnology industry in the Republic of China.

The Republic of China has amended the Plant Variety and Seedling Act to make the law more comprehensive and allow new plant variety rights. This has included passing regulations for conducting isolated field observation trials of genetically modified organisms (GMOs) as well as the harvesting and direct processing of products of GM species. Currently, the country's existing laws on biotechnology are in accordance with the TRIPs 27.3 Law of the World Trade Organization, indicating that the country is protecting both inherited resources and traditional knowledge. The Republic of China has drafted the Field Trial and Biosafety Evaluation Regulations for Transgenic Breeding Flock, the Guidelines for Field Trials of Transgenic Plants, and the Management Regulations for the Field Experimentation of Transgenic Aquatic Organisms to establish a management system for GMO field trials. The country is also planning the establishment of isolated field trial stations for transgenic animals and plants (including aquatic organisms).

The Republic of China is planning to establish a series of agricultural biotechnology parks. Currently, the Republic of China has already established the Agricultural Biotechnology Park in Pingtung, the National Flower Park in Changhua, the Taiwan Orchid Plantation in Tainan, the Medicinal and Spice Herb Biotechnology Park in Chiayi, and the Marine Biotechnology Park in Ilan, combining private capitalization and governmental research and development capacity to create a high-value-added industry in agriculture. The Agricultural Biotechnology Park Establishment and Management Act was enacted in April 2004; the law primarily provides full access to factory facilities and clarifying the amenities and benefits offered to agricultural biotechnology companies.

In addition to focusing efforts on building infrastructure to attract various sectors of society to become involved in agricultural biotechnology, the Republic of China will focus on the influence and effect biotech has on traditional agriculture and farming villages, making a thorough evaluation and suggesting countermeasures. The Republic of China will also take one step further, combining agricultural biotechnology with other domestic industries, such as medicine, food processing, and information technology, thus opening up new fields of application and creating industries that promote public health and welfare.

Research and Development Priorities for Biopesticide and Biofertilizer Products for Sustainable Agriculture in India

Indian agriculture has undergone dynamic change since the "Green Revolution," which provided self-sufficiency and ushered in an era of rural prosperity. While the production of food grains increased fourfold, soil and environment health have been affected adversely by the application of 250 times more chemical fertilizers and 400 times higher applications of pesticides than needed. This has prompted a search for biological alternatives such as biopesticides and biofertilizers. Estimates indicate that biopesticides have about a 2.5% share in the Indian pesticide market and may reach 12%–15% by 2006. Similarly, the use of biopesticides and biofertilizers at present is estimated to be USD1.5 billion, and the market is anticipated to grow sub-

stantially with greater demands for quality produce free from pesticides and other toxic residues amidst growing public concern about sustainability. Excessive and indiscriminate use of agrochemicals resulting deteriorating soil health has led to reduced profitability from agriculture in spite of the development of high-yielding varieties and superior agrotechnologies. The gaps between expected and actual yields from best agropractices continue to widen, forcing farmers towards urbanization. The major causes are deterioration in soil structure and texture, deficiency in soil micro-flora and -fauna, and nutritional imbalances. Emphasis is now being placed on overcoming this situation by managing nutritional and biological stresses through organic, cultural, and biological means. Here biofertilizers and biopesticides may play a significant role.

The area under organic cultivation has increased substantially and is presently estimated to be more than 100,000 hectares (certified); it is expected to expand at a faster rate in the coming years. This will require biological sources as nutritional and pesticide input supplements, and thus there will be a significant demand for biofertilizer and biopesticide products. In 1983, 100 metric tons of biofertilizer was produced in India; by 2002–03 production had increased almost 100-fold, to 90,000 metric tons. Currently there are 126 biofertilizer units engaged in biofertilizer production, and the government has extended financial assistance to 73 biofertilizer units for commercial production. The use of biopesticides and biocontrol agents in India is on the increase, but not to the desired level of growth, although presently a decrease in chemical pesticide consumption is indicated. Many small entrepreneurs are developing biopesticides and biocontrol agent products, but many of them have little quality consciousness. Success stories of biopesticides in India include control of diamondback moths by *Bacillus thuringiensis*, control of mango hopppers, mealy bugs, and coffee pod borers by *Beauveria*, control of *Helicoverpa* on cotton, pigeon-pea, and tomato by *Bacillus thuringiensis*, control of white fly on cotton by neem products, control of sugarcane borers by *Trichogramma*, and control of rots and wilts in various crops by *Trichoderma*-based products.

There is a large market potential for biofertilizer and biopesticide products that can only be tapped through a better understanding of rural markets and product/marketing constraints. To achieve these objectives, an extensive research and development effort in areas pertaining to production, quality assurance, field application, and knowledge transmission of biocontrol products is of great importance.

Potential for Agribiotechnology Products in India

The estimated size of the Indian biotech industry is over INR2,305 billion. Specific advantages include low operational costs, low-cost technologies, a skilled human resource base, a large network of research labs, and an abundance of raw materials in the form of plant, animal, and human genetic diversity. Biotechnology as a business segment for India has the potential of generating USD5 billion in revenues and creating one million jobs through products and services by 2010. Biopharmaceuticals alone have the potential to be a USD2 billion market opportunity, largely driven by vaccines and biogenerics. Clinical development services can generate in excess of USD1.5 billion, while bioservices or outsourced research services can garner a market of USD1 billion over this time period. The balance of USD500 million is attributable to agricultural and industrial biotechnology.

India has a strong pool of scientists and engineers, vast institutional networks, and cost-effective manufacturing. There are over a hundred national research laboratories employing thousands of scientists. There are more than 300 college-level educational and training institutes across the country offering degrees and diplomas in biotechnology, bioinformatics, and the biological sciences, producing nearly 500,000 students on an annual basis. About 300,000 post-graduates and 1,500 Ph.D.s qualify in biosciences and engineering each year.

The National Science and Technology Policy and the Vision Statement on Biotechnology issued by the Department of Biotechnology have mandated significant interventions in the public and private sectors to foster life sciences and biotechnology. There has been substantial

progress over the past decade in terms of support for R&D, human resource generation, and infrastructure development. Key recommendations include human resource development, infrastructure development and manufacture, promotion of industry and trade, public investment for commercialization, establishment of biotechnology parks and incubators, a regulatory mechanism for monitoring, and public communication and participation. The biotechnology sector in India has approximately 200 industries that have grown rapidly. Current estimates indicate that the industry grew by 39% annually to reach a value of USD705 million in 2003–04. Total investment also increased by 26% in that time period, to reach USD137 million. Exports presently account for 56% of revenue. The biopharma sector occupies the largest market share, 76%, followed by bioagri 8.42%, bioservices 7.70%, industrial products 5.50%, and bioinformatics 2.45%. The bioservice sector registered the highest growth—100%—in 2003–04, with bioagri at 63.64% and biopharma at 38.55%. The current policy review envisages an annual turnover of USD5 billion by 2010.

A task force headed by Dr. M.S. Swaminthan under the Ministry of Agriculture (2004) has prepared a detailed framework on the application of biotechnology in agriculture that rightly emphasizes the judicious use of biotechnologies for the economic well-being of farm families, the food security of the nation, the health security of the consumer, protection of the environment, and the security of national and international trade in farm commodities. It is proposed to do away with large-scale field testing of released transgenic events and make it compliant with agronomic test requirements.

Agricultural Biotechnology Development in Indonesia

In 1985, the Indonesian government declared biotechnology a priority area for national development. Agricultural biotechnology is considered to have the most potential for investment, but some industries are reluctant to invest in it because of the economic crisis in Indonesia. Some applications of biotechnology in the agribusiness sector with great potential are:

- Cell breeding and plant tissue culture involving the development of new clones, disease-free plants, and hybrid plants using embryo breeding and cell fusion. The potential plants for investment are for food (hybrid corn, rice, soybean, and potato), plantation (oil palm, cacao, coffee, pepper, rubber, golden teak wood, etc.), horticulture (mango, banana, durian, leafy vegetables, cut flowers, etc.), and forestry, especially plant species used for pulp and paper production.
- Embryo transfer techniques and super-ovulation, embryo fusion (twinning), and low-temperature preservation for animal husbandry. The animals selected are cattle, sheep, buffaloes, and pigs.
- Diagnostic techniques, using monoclonal antibodies, for early detection of plant and animal diseases caused by virus, bacteria, or fungi that are difficult to detect by conventional methods. Areas of potential importance are in the aquaculture (shrimp, tilapia, carp, seabass, ornamental fish, etc.), poultry, and cattle and sheep businesses.
- Vaccine production for the livestock and aquaculture businesses.
- Development of bio-industries for the production of food (organic acids, conventional foods, liquid sugars, fermented foods, etc.), feed (poultry and livestock), and enzymes (papain, bromelain, and microbial enzymes from agro-industrial waste materials).
- Development of biotechnology for degrading biological waste or byproducts, such as composting, ensilage, etc.

One of Indonesia's potential biotechnological domestic resources is microbial. Research in this area relates primarily to the application of the best selected native microbial isolates to facilitate better growth performance of plants and/or animals. In food crops, the use of vesicular-arbuscular mycorrhizae, rhizobium, bradyrhizobium, and azospirillum has been proven beneficial in promoting nutrient efficiency and yield of rainfed rice, soybean, and peanut on acid soils.

Bioconversion of cellulose material, i.e., rice straw, has been found to be accelerated by the use of cytophaga and trichoderma as activators. Several native strains of *Bacillus thuringiensis* have been identified as effective in controlling army worm, Asian corn borer, rice stem borer, cotton bollworm, and sugarcane borer. Development of biofertilizers consisting of effective nonsymbiotic N-fixing, phosphate-solubilizing, and aggregate-stabilizing microbes, of bioinsecticides composed of entomophogenic fungus, *Beuvvaria bassiana*, of biopulping activators using white rot fungi, and of microbially induced flavoring agents are major activities in the application of microbial technology in the estate crops area. Antagonistic fungal isolates have also been recognized as effective in controlling the white-rot disease of rubber and the pod-rot disease of cacao. Some biotechnological products have been launched and commercialized and treated as biofertilizers and biopesticides.

There are many biotechnology products based on applied microbiology in Indonesia, all of which together constitute a small but growing industry. The production and marketing experience gained from this aspect of biotechnology can provide a basis for the expansion of more modern biotechnology applications.

Agricultural Biotechnology Status in the Islamic Republic of Iran: Progress, Products, Limitations, and Future

Although there has been some biotechnological research in the Islamic Republic of Iran during the past 20 years, effective research in the field of agricultural biotechnology began only after the establishment in 1998 of the Agricultural Biotechnology Research Institute of Iran (ABRII), the most advanced agricultural biotechnology research center in the country. Nowadays molecular research in agriculture is growing very fast, not only in ABRII, but also in other research centers in the country. Despite the short time, the products are satisfactory. Bt-transgenic rice, biofertilizers, biopesticides, *in vitro*-derived pistachio seedlings, and virus-free potato are the most important products and are produced on a commercial scale.

Status of Agricultural Biotechnology in the Islamic Republic of Iran

Iran started using modern biotechnology one or two decades after the developed countries, that is, from the mid-1990s, but only in the past five years has this technology been seriously considered. The government's investments in agricultural biotechnology together with the efforts of researchers and experts led to the production of transgenic rice and cotton, biofertilizers for paddy, biopesticides to kill agricultural pests, virus-free potato seed, and date and pistachio seedlings, as well as the use of tissue culture methods for mass production of seedlings. It is likely that in the upcoming years a considerable increase in agricultural products will be witnessed.

Despite the efforts of researchers, Iran still has no share of the increasing trade of biotechnological products and is only an importer of some of these products. Without exact statistical reports, the amount of imported products cannot be determined. In keeping with the capabilities and facilities for biotechnology and the needs of the country, agricultural biotechnology plans are being prepared. Long-term plans for agricultural biotechnology include:

- Cultivation of transgenic plants amounting to 0.5% of the global area of biotech plants by the end of the long-term plan period.
- Production of forage and supplements of livestock amounting to 10% of the needs of the country.
- Production of biofertilizers and biopesticides amounting to 10% of the needs of the country, replacing chemical fertilizers and pesticides.
- Production of at least five kinds of new vaccines for livestock diseases and the export of 30% of total products.

- Production of biological products usable in the food industry amounting to 15% of the need of the country.

Benefiting from biotechnology is considered a way to decrease overuse of basic resources and contribute to their sustainability.

Trends in Korean Animal Biotechnology and Production of Transgenic Livestock Harboring Recombinant Human Proteins in Milk and Urine

The Republic of Korea has a large number of government institutes which undertake research on GMOs. Although the issue of GM food safety has not been settled, several GM crops are currently being imported as food ingredients as well as for industrial purposes. On the other hand, many researchers as well as biocompanies are in favor of GMOs that produce useful materials, since the organisms are accepted more easily by the general public when compared with GM food itself. The field of animal biotechnology has produced the most promising results in Korea, with special emphasis on the production of therapeutic proteins from transgenic animals, which is a highly cost-effective process. Although manufacture of pharmaceutical human proteins from transgenic animals is considered feasible using cost-effective bioreactor systems, only a few existing businesses seem successful in producing such animals. Only a single product has completed clinical trials and reached the market, after decades of research, but researchers and the pharmaceutical industry have continued pursuing the technology in the hope of achieving this goal within the next few years.

There are two major targets for the production of foreign protein from the transgenic animal: milk and urine. In Korea, the National Livestock Research Institute (NLRI), Suwon, has been a leader in Korean livestock research since 1906. The Institute has a well-organized research system covering almost every aspect of farm animal research. Although the Animal Biotechnology Division is relatively new, it has focused on current technologies, including the field of livestock cloning and transgenic animals. Using mouse whey acidic protein promoter as an expression controller, NLRI scientists designed a human erythropoietin (EPO) transgenic expression vector and introduced it into pig embryos via microinjection. The founder male was born in 1998. After the identification and analysis of hEPO proteins in its milk, NLRI has been producing TG progeny. NLRI researchers have also microinjected cloned transgene constructs into a one-celled embryo, which was then transferred to a surrogate sow. The resulting piglets were identified by PCR using genomic DNA from each piglet's tail. In 1998, a transgenic founder was identified out of 47 candidate piglets using PCR and Southern blot analysis. The founder was later named "Saerome," meaning "novel one" in Korean. Since 1999, a transgenic pig herd has been propagated. The milk from the transgenic female has about 880 units of human EPO in one milliliter of pig's milk. After removal of glycosylation, this EPO showed the same molecular weight as commercial EPO that is identical to natural EPO without glycosylation. Amino acid sequence analysis showed that the EPO is indeed human EPO, not porcine EPO. Since Saerome, NLRI has produced a number of transgenic pig lines harboring human genes encoding therapeutic proteins such as human blood coagulation factor VIII or tissue plasminogen activator (t-PA) under regulatory control of mammary-gland-specific promoters (whey acidic protein or beta-casein promoter) or urinary-bladder-specific uroplakin II (UPII) promoter. NLRI has already shortened the timelines for the production of transgenic pigs.

The Korea Research Institute of Bioscience and Biotechnology (KRIBB) announced that a transgenic cow, "Boram," that can express human lactoferrin (hLF) in its milk, was generated utilizing microinjection. hLF is a pivotal protein, abundant in mother's milk, that confers anti-bacterial functions on babies and elevates their immune responses. The complete gene encoding the hLF was isolated from a cosmid library and its structure was characterized. The expression level of hLF protein in a transgenic animal ranged from 0.1 to 34µg per ml.

The pharmaceutical company Hanmi has produced the transgenic goat, “Meddy” (in collaboration with KAIST, KRIBB, and ChungNam National University), which produced human granulocyte colony-stimulating factor (hG-CSF), one of the hematopoietic factors that control the differentiation of pluripotent stem cells into many kinds of blood cells during hematopoiesis. It also plays a key role in the stimulation of proliferation and differentiation for other types of blood cells, in addition to granulocytes and macrophages. This is a promising drug for many kinds of disorders related to reduction of neutrophil and other blood cell levels. If the materials derived from the goat’s milk are effective, the price of G-CSF will be decreased. Humans produce on the average only small amounts of G-CSF, which has made the protein extremely expensive for white-cell-deficient cancer patients. The cost of producing G-CSF from genetically altered animals is one-tenth of the cost of obtaining it from mammalian cells, the method commonly used in advanced countries.

Transgenic animal research has received firm support from the Korean government since the late 1990s and will be given a major stimulus in 2005 with the launching of the national grants program. Although the technology has yet to produce a final product, there have been several successfully created transgenic farm animals. It is expected that the first successful product that can undergo clinical trials will be produced within the next few years.

Business Potential for Agricultural Biotechnology Products in Malaysia

The biotechnology industry is relatively new in Malaysia, especially in the agricultural sector. Under a new strategy, the development of biotechnology will be spread out using the concept of a bionexus network, in which the development of biotechnology will be divided into three main fields: pharmaceutical and nutraceutical, agrobiotechnology, and genomic and molecular biology. The value proposition of the bionexus network is that it will leverage on the facilities, infrastructure, and capabilities of existing universities and research institutes. For example, a Pharmaceutical and Nutraceutical Institute will be established at the present biovalley site at Dengkil. The Institute of Agrobiotechnology is situated at MARDI, Serdang, and the Genomic and Molecular Biology Institute is situated at existing facilities in the National University Malaysia in Bangi. Bionexus will link these institutes with industries throughout the country. The government recognizes that biotechnology processes such as genetic engineering have the potential to increase production and productivity in the agricultural sector. Malaysia is among the few ASEAN countries that have approved the use of GM food crops as human food and animal feed. It has successfully conducted field trials of GMOs and developed guidelines for their release. GM activities and products are governed by guidelines formulated by the Genetic Modification Advisory Committee (GMAC), which has published the National Guidelines for Release of Genetically Modified Organisms into the Environment. The National Guidelines have been revised and drafted into a new piece of legislation, the Malaysian Biosafety Bill, which will be considered in Parliament in December 2005. Under these guidelines, commercialization of biotech crops requires GMAC approval for all field evaluations. GMO release into the environment is currently restricted to research fields. Malaysia has also set up a National Biosafety Central Body to be responsible for monitoring biotechnology activities.

The biotechnology industry in Malaysia consists of companies specializing in biotechnology, biopharmaceuticals, bioinformatics, and agricultural biotechnology that focus on a range of products such as tissue culture, diagnostics, vaccine production, and blood bank collection. Companies involved in agricultural biotech are primarily plantation (palm oil), herbal-based, and aquaculture companies. The biotech industry is dominated by small- to medium-sized companies. Only a few larger companies are involved in biotechnology; most of them focus on plant tissue culture. Currently there are about 100 companies registered with the Malaysian Biotechnology Directorate under the Ministry of Science and Innovation. Of these, 20 are involved in the agricultural sector. However, there are about 50 companies that utilize biotechnological processes, primarily in food production, herbal products, and pharmaceuticals. There is still great potential

for SMEs and large-scale firms in this industry. The production of orchids via tissue culture is another example of activities carried out by SMEs with an eye to the potential market. Annual production of orchids via tissue culture alone was estimated at USD13 million for 2003, of which USD8.7 million was for the export market.

To spur growth and further development of the biotechnology industry, the government offers attractive investment incentives to local and foreign-owned companies. Besides those incentives, Malaysia has established the Malaysian Biotechnology Corporation, a one-stop agency that has as its primary objective developing the country's biotech industry. The government has also extended attractive tax incentives to further spearhead the modernization and commercialization of the agricultural sector. These include a 100% deduction on capital expenditure, pioneer status, or investment tax allowance. To further expand food production, companies are provided with an investment allowance or group relief, while their subsidiaries undertaking the projects are given 100% tax exemption until 2010. These incentives also apply to all foreign companies investing in Malaysia.

Business Potential for Agricultural Biotechnology Products in the Philippines: The National Agricultural Research System Experience

While the Philippines has experienced several challenges over the past two decades in embracing of modern biotechnology, it has nonetheless achieved a number of milestones necessary for the growth of the agricultural biotech industry, specifically in areas relating to capability building, regulation, IPR, and public acceptance. Core competencies have been established in developing and evaluating biotechnology products produced in the country as well as those from other countries. The National Committee on Biosafety of the Philippines was established and the commercialization guidelines for modern agricultural biotechnology products were issued. The country responded to the threat of biopiracy with Executive Order 247 and Republic Act 9147, ensuring that benefits accrue to the appropriate stakeholders. Likewise, the Plant Variety Protection Law was enacted to protect the intellectual properties of technology generators. Public acceptance was clearly attained last year when the Philippines joined for the first time the mega-country group producing agricultural biotech products. The Agriculture and Fisheries Modernization Act passed in 1997 provides for the allocation of specific funds for the development of modern biotechnology, more open and transparent dialogue among key stakeholders, including government, the private sector, academia, NGOs, and farmers. Recently the President approved the formation of a biotechnology industry cluster.

Most agri-biotech products that have reached the market are conventional biotechnologies. These include biofertilizers, biopesticides, tissue cultured planting materials, enzyme products, vaccines, and diagnostic and detection kits. Most of these products were developed by the University of the Philippines at Los Baños-National Institute of Biotechnology and Molecular Biology (UPLB-BIOTECH), funded by the government. Commercialization was carried out primarily by UPLB-BIOTECH, with limited private sector participation. Currently, among genetically modified products, only Bt corn has been commercialized. Major challenges impacting the commercialization of these products include a lack of awareness by the general public on product benefits and safety, the absence of market orientation from research to enterprise, and limited policy support on price, transport, microfinancing, and technical assistance. Initiatives being undertaken to address these challenges include the education of local government units on biotechnology, the formation of bio-industry clusters and e-networks, policy advocacy on important enabling mechanisms to support industry, and intensive retooling for developing global entrepreneurial scientists and corporate public servants.

Status of Public Rice Biotechnology Research and Development and Commercialization in the Philippines

The Philippine government has signed international treaties concerning agricultural biotechnology. Among these are the Convention on Biological Diversity, signed on June 12, 1992, and ratified on October 8, 1993 (recently the Philippine Congress passed into law the Wildlife Conservation Act, which, in effect, puts into law the provisions of the Convention), and the Cartagena Protocol on Biosafety, signed in May 2000 (not ratified to date). In anticipation of the advent of modern biotechnology, the government issued Executive Order No. 430 creating the National Committee on Biosafety, tasking it with evaluating applications for testing biotechnology products. In December 1994, the Philippines ratified the General Agreements on Tariffs and Trade (GATT), including the provision on Trade-Related Aspects of Intellectual Property Rights (TRIPS). The Congress also ratified the country's World Trade Organization (WTO) membership. Subsequently, the Congress enacted the Intellectual Property Code of the Philippines pursuant to the TRIPS Agreement. The code took effect on January 1, 1998.

To demonstrate the government's resolve to modernize agriculture utilizing biotechnology, the Agriculture and Fisheries Modernization Act was enacted in 1997 mandating the use of biotechnology as a tool in modernizing agriculture and increasing productivity. Administrative Order No. 8 of the Department of Agriculture was issued in 2002, setting up the rules on laboratory testing up to commercialization and even importation of products of modern agricultural biotechnology (<http://www.da.gov.ph>). In the same year, Congress enacted the Plant Variety Protection Act, which provides protection to newly developed transgenic plant varieties. These and other laws, legislation, and rules provide the legal and institutional framework for commercialization of agricultural biotechnology in the Philippines.

Few public or private research institutions conduct modern agricultural biotechnology research. Most modern agricultural biotechnology R&D is conducted by the public sector. The private sector, mostly multinational companies, imports agricultural biotechnologies. The major public institutions engaged in modern agricultural biotechnology R&D are the Institute of Plant Breeding (IPB) and the National Institute of Microbiology and Molecular Biology (BIOTECH) at the University of the Philippines Los Baños (UPLB), the National Institute of Molecular Biology (NIMB) of UP-Diliman, the Philippine Coconut Authority (PCA), and the Philippine Rice Research Institute (PhilRice). The Bureau of Agricultural Research (BAR) of the Department of Agriculture and the Philippine Council for Agriculture, Forestry and Fishery Research and Development (PCARRD) of the Department of Science and Technology (DOST) coordinate and fund R&D in modern agricultural biotechnology conducted by these and other institutions. The private sector, however, also dynamically takes part in the promotion of biotechnology. The International Service for the Acquisition of Agri-biotech Applications (ISAAA), which has its Southeast Asia Center based in the country, is a nonprofit international organization that works for the delivery of biotechnology benefits to developing countries through the promotion of technology transfer. One of the leading private companies conducting field trials and commercializing agricultural biotechnology is Monsanto Philippines, through its Bt corn.

Rice biotechnology research is undertaken in the genetics and tissue culture laboratories of PhilRice. Equipment in these two laboratories has been provided through an initial JICA grant, JICA Technical Assistance, ARBN, RF, and funds from the Philippine government. The present biotechnology facilities include laboratory areas for transgenic work, anther culture, and molecular marker analyses. Specifically, the biotechnology R&D currently being pursued includes utilization of molecular marker technology for assessing the diversity of germplasm resources, for fingerprinting or establishing genetic identity of specific genotypes, for identification of appropriate parental materials for breeding purposes, for tagging agronomically important genes, and for pyramiding different bacterial blight resistance genes; *in vitro* culture to facilitate line purification, production of stable lines adapted to adverse environments, and induction of useful mutants/variants; genetic transformation for introducing genes such as *Xa21* for bacterial blight

resistance, *protease inhibitor2* for stemborer resistance, *Hva1* for drought and salinity tolerance, and *chitinase/glucanase* for fungal disease resistance; and DNA marker tagging and cloning of genes involved in aroma, tungro resistance, fertility restoration, and salinity tolerance.

Business Potential for Agricultural Biotechnology in Singapore

The agriculture biotechnology or agri-biotechnology industry in Singapore is focused on both food (leafy vegetables, rice, marine foodfish) and nonfood-based products (diagnostic kits, vaccines, ornamental fish, and plants). Several products have been commercialized to date, such as nonfood ornamental fish (trademarked GloFish), while many potential products are in the pipeline awaiting approval from the relevant authority.

The government has adopted an active approach in coordinating biotechnology strategies and funding programs and establishing supporting infrastructures to kick-start agri-biotech R&D and commercialization. The Temasek Life Sciences Laboratory (TLL) has 15 research groups working in the areas of cell biology, developmental biology, pathogenesis, and bioinformatics. Since 2003, the AVA has been working closely with TLL, NUS, and other tertiary research institutes on agri-biotechnology to develop key applied upstream farming technology in specific areas of food crop research, plant biotechnology, animal and fish health research, fish biotechnology, and aquaculture in the following agri-food areas:

- Vegetable: identification of genes for abiotic and biotic stress resistance in Asian leaf vegetables, downstream field testing, molecular diagnostics for leafy vegetable diseases, and GMO testing for food crops.
- Rice biotechnology: disease resistance.
- Aquaculture biotechnology: molecular selective breeding of fish, molecular diagnostics and vaccines for food fish and shrimps, genetic transformation of indigenous foodfish for improved traits.
- Animal biotechnology: molecular diagnostics and vaccines against zoonotic diseases or those of food safety concern.

The Science Park, established in 1981, together with incubators designed by the government, provides the high-quality infrastructure essential for industrial R&D, as well as an environment conducive to interaction between industry, academia, and research groups. The Technopreneur Assistance Center established within the park provides a range of technical, business, training, and shared facilities. Other support for early-stage companies includes financing for innovators, venture capital, and a patent application fund, as well as state agencies providing productivity, quality, and design services. Today, the Science Park houses some 180 local and MNC tenants within the 270,000 sq m gross floor space and an Innovation Center of 2,000 sq m with 29 start-up companies from the different industrial sectors, i.e., information technology, electronics, chemicals, materials, and biotechnology. AVA and EDB have also developed the Agri-Bio Park (APB) located next to the Lim Chu Kang Agrotechnology Park in northwest Singapore. In addition, Agri-food and Technologies Pte. Ltd. (ATP), a private arm of AVA, was incorporated in October 2000 to further support regional developing agribusiness, including the agri-biotechnology business. In support of a large-scale financial commitment to the life sciences and biotechnology sector, the government has created a number of mechanisms—PharmBio Growth Fund, Singapore Bio-Innovations and Life Sciences Investments—to provide funds to the private sector to upgrade technologies and form joint ventures with leading international biotechnology and pharmaceutical companies. It has channeled more than SGD1.7 billion into biotech funds and has allocated SGD1.5 billion for biotech R&D and SGD2 billion to attract local and foreign investment in biotech start-ups. This risk-sharing environment also includes numerous investment and start-up assistance schemes—SEEDS, Patent Application Fund PLUS, Enterprise Investment (Technopreneur) Scheme, Venture Capital—and programs—Growth Financing Program—for innovation, R&D, and intellectual property managed by EDB. The Patents Act of

Singapore contains no restriction to the patentability of plants and animals or other biotechnological inventions such as DNA or living tissues as long as the bio-intervention does not contradict public morality. Even though it is in compliance with international treaties, the current Singapore IP regime was further strengthened when Singapore acceded in 2004 to the UPOV convention (for the protection of new plant varieties) under the requirements of the U.S.-Singapore Free Trade Agreement. This IP regime will give agri-biotechnological interventions exclusive protection in Singapore should they be developed and patented there.

Singapore established the national Genetic Modification Advisory Committee (GMAC) in 1999 to oversee and advise in this matter. The key initiatives of GMAC lie in establishing bio-safety regulations and guidelines for the conduct of GMO research and the commercial release of GMO-derived products and in facilitating public education and creating awareness on GM issues. Two guidelines, one covering release of GMOs (Singapore Guidelines on the Release of Agriculture-Related GMOs, August 1999) and the other covering research on GMOs (Singapore Biosafety Guidelines for Research on GMOs), have been released. As an advisory committee, GMAC leverages on the regulatory powers of various national agencies, including AVA, MOH, and the National Environment Agency (NEA), to oversee safe movement, transfer, and containment of GMOs, relevant, respectively, to food/feed, human health, and environment. The AVA is the approving authority for the import and release of agriculture-related GMOs and GM foods in Singapore. Under AVA's Animals and Birds Act and Control of Plant Act, importers are required to seek approval from AVA before importing agriculture-related GMOs into Singapore. GMAC will evaluate the applications to import or release GMOs through expert panels to ensure that food safety and environmental issues have been assessed and found to be satisfactory. AVA will take into consideration GMAC's evaluation before permitting the import or release of the GMOs. Thus far, GMAC and AVA have allowed the sale of GM corn, soybean, and canola oil.

Business Potential for Agricultural Biotechnology Products in Thailand

The National Biotechnology Policy Committee, chaired by the Prime Minister, approved Thailand's National Biotechnology Policy Framework (2004–11) in December 2003. Biotechnology is expected to play a vital role in the country's development by the year 2011, in keeping with the government's policy and the national agenda encompassing sustainable competitiveness, health care for all, income distribution, and a self-sufficient economy. Emphasis will be placed on applying core technology to accelerate development in areas such as agriculture and food, medical care, and protection of the environment, new knowledge creation for the development of higher-value-added products as well as helping to promote high-value biotechnology business and creating new types of services where modern technology is required. There are six goals for biotechnology development in Thailand; those related to agricultural business are primarily the first and second: emergence and development of new biobusiness and biotechnology promoting Thailand as the kitchen of the world.

Traditionally, research and development of agricultural biotechnology was done primarily by the public sector through government organizations, including the Ministry of Agriculture and Agriculture Cooperatives, the Ministry of University Affairs, the Thailand Research Fund, the National Research Council, and the National Science and Technology Development Agency. Thailand's agricultural biotechnology research is focused on curing diseases and dealing with insect infestation and environmental stress using genetic modification, DNA markers, breeding, and biocontrol. Local crop varieties such as papaya, tomato, and pineapple have been genetically engineered with gene/DNA from local strains of pathogens or other genes with desired characteristics in order to produce crops with disease resistance. Other research programs include determination of molecular markers in rice, tomato, cucumbers, and orchids, development of insect-, drought-, and disease-resistant rice within one variety via pyramiding of the necessary genes, and production of monoclonal and polyclonal antibodies against plant viruses. In animal-related biotechnology, there are programs for the development of disease diagnostic products

and animal production techniques. Although technologies such as embryo transfer, *in vitro* fertilization, and embryo sexing are known to some scientists, there are still technological and economical limitations to their use.

The agrobiotechnology business is still in its initial phase. It is divided into three main areas: disease diagnosis, biocontrol, and tissue culture. Diagnostic kits have been developed for several important plant and animal diseases; the Avian influenza virus test kit, widely used in both the public and the private sectors, was developed in 2004 with the cooperation of the National Science and Technology Agency and INNOVA Biotechnology. The Shrimp Biotechnology Business Unit (SBBU) was established in 1999 under the National Center for Genetic Engineering and Biotechnology (BIOTEC) to assist the shrimp industry. SBBU has commercialized diagnostic kits (EZEE Gene) for important viral diseases in shrimp, including White Spot Syndrome Virus, Infectious Hypodermal and Hematopoietic Necrosis Virus, Monodon Baculovirus, Taura Syndrome Virus, and Yellow Head Virus/Gill Associated Virus. Most of the test kits are stripped kits, simple and portable. Others are PCR-based. The income is returned to the investor, BIOTEC, and royalties go to the inventor, Mahidol University. Recently, the technology was transferred to a private company, Farming IntelliGene Technology Corp. For plant diseases, monoclonal antibodies for detection of Tomato Yellow Leaf Curl Virus (TYLCV) were developed, commercialized, and proven to be useful to several seed companies in viral detection.

The use of commercial microbial insecticides such as *Bacillus thuringiensis* (Bt) is common in many countries. In Thailand, similar practices started in 1996 when the Department of Agriculture approved the use of *Trichoderma harzianum* as the first registered biofungicide under the trade name of UNIGREEN UN-1 (Uniseed Co. Ltd.). There are currently two companies producing *Trichoderma* and *Ketomium* (for *Phytophthora* control) commercially. Cut flowers, particularly orchids, have become an important source of revenue for Thailand. Micro-propagation is widely used in the cut flower industry for commercialization of many cut flowers including orchids, gerberas, carnations, chrysanthemums, anthuriums, cucumas, red ginger, torch ginger, lilies, and calla lilies.

It is clear that development of agricultural biotechnology products is still in the initial phase and that strategic improvement is needed. The major issues, such as the weak link between the private and public sectors, lack of a proactive plan for upgrading local technical capability, and high levels of technology transfer, urgently require solutions. There are several good signs for the future, including the establishment of new companies using local technologies and agricultural biotechnology projects initiated by the private sector.

Part II

Resource Papers

1. WHY AGRICULTURAL BIOTECHNOLOGY?

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INTRODUCTION

Crops improved through biotechnology were first grown commercially on a large scale in 1996. Since that time, adoption has increased rapidly. In 2004, 8.25 million farmers in 17 countries grew biotech crops covering 81M ha (James, 2004). While the first commercial production was in the developed world, by 2004 34% of the hectares were in the developing world, and for the first time the absolute annual growth in biotech crop area was higher for the developing countries (7.2M ha) than for developed countries (6.1M ha). Herbicide tolerance and insect protection are the major traits being utilized currently, occupying 72% and 19%, respectively, of the hectares in 2004 (James, 2004).

Biotechnology is a valuable tool to complement other agricultural production tools. In the U.S., the impacts of biotechnology on agriculture have been extensively studied (Table 1). One of the most comprehensive treatments of this topic was done by the National Center for Food and Agricultural Policy (NCFAP) (Gianessi et al., 2002).

Table 1. Impact of Biotechnology on U.S. Agriculture

	Net economic impact	Pesticide reduction (pounds)
Current products	USD1.5 billion	46 million
Potential products	USD1.0 billion	117 million
Total	USD2.5 billion	163 million

Source: Adapted from Gianessi et al., 2002

For 2001, it has been estimated that the net economic impact of the eight products currently on the market was USD1.5 billion, and these benefits are expected to increase substantially as additional potential traits are developed (Gianessi et al., 2002). From an environmental standpoint, significant reductions in pesticide usage in the U.S. were also observed, calculated in this study to be 46 million pounds of active ingredient in 2001 (Gianessi et al., 2002). The study also examined the impact of individual traits. The authors found that herbicide-tolerant maize has reduced costs to the farmer by an average of USD10 per acre and herbicide usage by an average of 1 lb per acre (Gianessi et al., 2002), while herbicide-tolerant cotton delivered a net value of USD133M and reduced herbicide usage by 6 million pounds of active ingredient per year (Gianessi et al., 2002). Other U.S.-based studies have examined an additional environmental benefit: that herbicide-tolerant crops allow for much greater adoption of conservation tillage practices, allowing farmers to make fewer tillage passes and thus improving soil and water quality (Cotton Council, 2002; Fawcett and Towery, 2002). The increases in agricultural productivity, coupled with the environmental benefits of reduced pesticide usage and increased use of conservation tillage, have overall benefits for consumers globally. Other studies, some of which are described in the following sections, show that similar benefits are being experienced by farmers worldwide.

WHY AGRICULTURAL BIOTECHNOLOGY FOR THE ASIA–PACIFIC REGION?

Adoption in Asia–Pacific

In the Asia–Pacific region, five countries have grown biotechnology crops commercially (Table 2).

Table 2. Biotechnology Traits and Crops That Have Been Commercially Grown in the Asia–Pacific Region

Trait and crop	Nations with commercial growings
Insect-protected cotton	India, China, Australia, Indonesia
Herbicide-tolerant cotton	Australia
Insect-protected maize	Philippines

Importation of Biotechnology Crops

In addition to crops being grown within Asia, a significant amount of crops grown in the Americas are exported to Asia, especially to the Pacific Rim countries, for feed and food use. USDA data shows that in 2003, approximately 19 million metric tons of maize were exported from the U.S. to Japan, Taiwan, and Korea and approximately 17 million metric tons of soybeans were exported to China, Japan, Korea, and Taiwan (USDA–FAS, 2004). Given that large amounts of herbicide-tolerant soybean (85% of total soybean) and herbicide-tolerant and insect-protected maize (45% of total maize) are grown in the U.S. (James, 2003), these major grain-importing countries, as well as other Asia–Pacific countries, including Australia, New Zealand, and the Philippines, have established science-based regulatory approval systems for import of biotechnology crops.

Uses and Benefits to Date

Insect-protected Cotton

China was an early adopter of insect-protected (Bt) cotton and now has the highest number of hectares in the region. In 2004, insect-protected cotton was grown by seven million farmers in China on 3.7M ha (James, 2004). A number of studies have documented the economic, environmental, and social benefits from this technology (Table 3). The improved economics and reduced use of pesticides seen with the adoption of insect-protected cotton have also yielded social benefits for the individual and for society as a whole in China (Huang et al., 2002).

Table 3. Impact of Insect-protected Cotton, China

Year	Net revenue (USD per hectare)		Pesticide usage (Kg per hectare)	
	Insect-protected	Conventional	Insect-protected	Conventional
1999	277	-225	11.8	60.7
2000	367	-183	20.5	48.5
2001	351	-6	32.9	87.5

Source: Adapted from Pray et al., 2002; Huang et al., 2002

India has seen a rapid expansion in the number of acres on which insect-protected cotton is being grown. The product was first introduced in 2002. In 2004, India had highest percentage annual growth of biotech acres of the eight leading biotech crop countries, with 0.5M ha planted, providing a 400% increase over the hectares planted in 2003 (James, 2004). Studies are now being published documenting the impact of the product. For example, the performance of insect-

protected cotton under Integrated Pest Management (IPM) regimes was recently assessed in field trials in India (Table 4). Insect-protected cotton reduced damage due to bollworms with a reduction in pesticide usage when compared to conventional cotton and delivered higher net returns (Bambawale et al., 2004). Significant yield increases, combined with reductions in insecticide sprays, were also found in a previous analysis of insect-protected cotton field trial data (Qaim and Zilberman, 2003).

Table 4. Net Returns from Different Cotton Systems, India

System	Net returns (INR per ha)
Insect-protected cotton under IPM	16,231
Conventional under IPM	10,507
Conventional (non-IPM)	9440

Source: Adapted from Bambawale et al., 2004

In Australia, insect-protected cotton has been grown commercially since 1996, with 0.20M ha projected in 2004–05, much of which will have a combined herbicide tolerance trait (James, 2004). Field studies have demonstrated that insect-protected cotton provided economic and environmental benefits in the 2001–02 season. From an economic perspective, the average yield was increased by 0.44 bales per ha (9.21 vs. 8.77), and 78% of paired plot comparisons showed an economic benefit of growing insect-protected cotton (Doyle et al., 2002). In the same study, insecticide sprays were reduced 64% when comparing insect-protected cotton with conventional cotton (Doyle et al., 2002). Another study found only small differences in net economic returns compared to conventional varieties (Fitt, 2003), but environmental benefits were more dramatic. In the four years studied, pesticide spray applications targeting the major insect pest, *Helicoverpa* species, were consistently reduced, ranging from 43% (1998/1999) to 57% (1996–97), with a total reduction of 1.75 million liters of insecticide (Fitt, 2003). The environmental benefits of insect-protected cotton are particularly profound since the products have been used successfully in “environmentally sensitive areas near watercourses or townships where continued use of conventional varieties may have entailed unacceptable community risks” (Fitt, 2003). Australia is now looking forward to taking advantage of second-generation insect-protected cotton. The country has recently approved the commercial production of varieties that express two different genes to control Lepidopteran insects, which should provide value from both an efficacy as well as an insect resistance management perspective (U.S. EPA, 2002).

Insect-protected Maize

Insect-protected maize is grown commercially in North and South America, Europe, Africa, and Asia. In 2002, the Philippines was the first Asian country to adopt insect-protected (Bt) maize, with 52,000 ha planted in 2004 (James, 2004). The impact of the technology is being assessed, and one such study was an *ex ante* analysis on the impacts of insect-protected maize. The study was conducted based on field trial sites over two seasons (one wet and one dry). Calculated production costs were lower and profitability higher using insect-protected maize (Gonzales, 2002). The analysis also determined that yields with insect-protected maize increased 40% and 25% over those with non-insect-protected maize in both wet and dry seasons, respectively (Gonzalez, 2002).

Herbicide-tolerant Crops

Herbicide-tolerant crops have had a major positive impact on agricultural practices. Worldwide, 72% of the total hectares planted to biotechnology crops were herbicide tolerant, and an additional 9% of the hectares were herbicide tolerant combined with insect protection (James,

2004). Growers of soybean, cotton, maize, and canola in much of the world enjoy the benefits brought by herbicide-tolerant traits. So far, adoption of herbicide-tolerant traits in the Asia-Pacific region lags behind adoption in other areas of the world. Herbicide-tolerant cotton in Australia is the only such crop being grown commercially in the region. This product has been swiftly adopted since its introduction in Australia in 2000, and it exceeded 40% of the total cotton area in the 2003–04 growing season (Crossan and Kennedy, 2004), with 0.18M ha projected plantings in 2004–05, much of which will be combined with one or two insect-protected traits (James, 2004). Economic benefits result from increases in yield and reductions in costs associated with the system and explain why the adoption rate is so high (Crossan and Kennedy, 2004; Taylor, 2003). Environmental benefits of the system come from the favorable environmental characteristics of glyphosate (the active ingredient in the Roundup® family of herbicides, used in Roundup Ready® cotton), fewer applications of residual herbicides, and the ability to use reduced tillage practices (Crossan and Kennedy, 2004). Recently, the Philippines has approved the production of Roundup Ready® maize, and commercial plantings are expected in 2005. Other countries in the region also are assessing herbicide-tolerant cotton and herbicide-tolerant maize.

WHY AGRICULTURAL BIOTECHNOLOGY FOR THE FUTURE?

Current agricultural biotechnology products are focused on improving agronomic properties and production systems at the grower level. In the future, traits will be developed to continue improvements in these areas but also to extend the impact into the food and feed sectors. Future agronomic traits that are being actively pursued include providing stress tolerances as a means of preserving yield under diverse environmental conditions (Cheikh et al., 2000; Kasuga et al., 1999) such as cold (Gilmour, 2000; Thomashow, 2001), heat (Alia et al., 1998), or salinity (Xu et al., 1996; Zhang et al., 2001). In the future, biotechnology will produce crops with improved feed or food quality or nutritional enhancements. A number of such products are currently in development (IFT, 2004; Cockburn, 2004; Falk et al., 2002; Fuchs, 2002; Mackey, 2002). Vitamin and mineral enhancement are two areas of particular importance to the developing world. One well-publicized effort is the initiative to produce rice with increased levels of beta-carotene to address Vitamin A deficiency (Ye et al., 2000; Potrykus, 2001). Improvement of rice by enhancing levels of minerals is also in development (Lucca, 2002; Grusak, 2002). Proteins (and their constituent amino acids) are critical components of mammalian diets, so improvement of crop plants to generate food and feed that meet the amino acid dietary requirements of humans and animals is another area of active interest. Lysine and methionine levels are two such essential amino acids whose levels have been increased using biotechnology (Day, 1996; Falco et al., 1995; O'Quinn et al., 2000). Modification of oils is another area of active research in the public and private sector. Plant biotechnology has successfully altered fatty acid compositions of major oilseed crops to produce oils with improved processing characteristics or oils with enhanced nutritional characteristics (Budziszewski et al., 1996; Kinney and Knowlton, 1998; Liu et al., 2002).

A number of traits of potential relevance to agriculture and the food and feed sector in Asia and Oceania are in development. From a research and development perspective, China and India have been among the most active in the region. In China, for example, 16 different crop plants with biotechnology traits had been approved for commercialization or were in trials in 1999 (Huang et al., 2002), and in 2005 China intends to invest USD500 million in crop biotechnology, making China the second-largest global investor in crop biotechnology after the U.S (James, 2004). India also has very active research efforts in plant biotechnology in both the public and the private sectors. Multiple crops (e.g., chickpea, rice, cotton, mustard, and potato) and biotechnology traits (e.g., insect, disease and virus resistance, herbicide tolerance, stress tolerance, and

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fruit ripening) are being pursued (Sharma et al., 2003). The hope is that the efforts in these countries will provide a number of products of value for these nations and the region.

The future role of biotechnology in the developing world has been examined. A recent FAO report (FAO, 2004) reinforced the potential value of agricultural biotechnology in helping the poor. Since the technology is scale-neutral, even small farmers in developing countries can gain economic, environmental, and social benefits from the adoption of crops improved by biotechnology.

CHALLENGES FACING AGRICULTURAL BIOTECHNOLOGY

As described in the previous sections, biotechnology-derived crops have provided significant value to growers, the environment, and the public and have the potential to provide even greater value with the traits currently in the developmental pipeline. However, there are some challenges that will impact the introduction of these products. One of these is the significant costs and time associated with obtaining regulatory approvals.

Impacts of Regulatory Requirements and Processes

The regulatory requirements for products produced by recombinant DNA techniques are considerably greater than those required by techniques that are considered to be part of conventional breeding, even though conventional breeding may utilize techniques that are comparably sophisticated and “modern” (e.g., mutagenesis by gamma irradiation and plant tissue culture and regeneration) and can have comparable results. Crops that have been developed with tolerance to imidazolinone- and sulfonylurea-based herbicides (e.g., IMI maize¹ and Clearfield® wheat) are examples. These herbicide-tolerant crops have required considerably less regulatory review than the herbicide-tolerant crops containing a gene from a glyphosate-tolerant strain of *Agrobacterium* (e.g., the various Roundup Ready² crops).

The additional regulatory requirements for biotechnology-derived crops have increased the costs (both pre- and post-commercial) and time to market compared to conventionally developed crops and have reduced the number and types of products being developed. Although there are no studies known that have specifically examined this issue in detail, this is a widely-held view among many academic and industry scientists³ (Damodaran, 2004; De Greef, 2004; Kalaitzandonakes, 2004) and is credited with the current delays in the development of golden rice (Potrykus, 2004).

Current Status of Regulatory Requirements for Biotech Traits Combined by Conventional Breeding

Regulations proposed to cover biotechnology-derived traits that have been combined by conventional breeding (termed “combined-trait products” or “stacks”) are a more recent example of the expansion of regulatory requirements for biotechnology-derived crops. The combination of separately selected traits is routinely used in seed variety development by conventional breeders. For example, in maize a number of mutants have been identified that affect carbohydrate metabolism.⁴ The genes carrying these mutations have been combined by conventional breeding to produce sweet corn and field corn varieties with multiple and different food and feed uses

¹ IMI corn (maize) was developed by American Cyanamid and first marketed by Pioneer in 1991 (Ritchie, 1998).

® Clearfield is a registered trademark of BASF Corporation. Clearfield wheat was developed through mutagenesis (Lyon, 2003).

² Commercial Roundup Ready crops include maize, soy, canola, and cotton.

³ Nicholas Kalaitzandonakes, professor of agribusiness and director of the Agribusiness Center at the University of Missouri at Columbia, is planning such a study and has communicated that this view is consistent with his interactions with scientists to date.

⁴ e.g., *shrunk2*, *sugary1*, *sugary enhancer1*, *brittle2*, *amylose extender1*, *dull1* and *waxy1*.

(Boyer and Shannon, 2003; Carey et al., 1982; Marshall and Tracey, 2003; Sprague and Dudley, 1988). Conventional plant breeding is also being used to combine two or more separately developed biotechnology-derived traits. Biotechnology-derived combined-trait products were first introduced in 1997 and were grown on 6.8M ha globally in 2004 (James, 2004). Examples of crops that are being grown or developed through the combination of biotechnology-derived traits by conventional breeding include varieties of maize that combine the Roundup Ready, YieldGard® Corn Borer, and YieldGard Rootworm traits and varieties of cotton that combine the Roundup Ready trait with either Bollgard® or Bollgard II® traits.

Any new regulatory requirements for combined-trait crops should be carefully considered to determine whether they address risks that are any greater than those in crops developed by conventional methods. Australia, Canada, and the U.S. do not generally require submission of additional safety data on combined-trait products developed by conventional breeding if the single-trait products have completed the regulatory process and the two traits are unrelated. The U.S. EPA regulates products that contain two insect-control traits, requiring the identification of any synergistic effects and confirmation that the insect resistance management (IRM) plan for the combined-trait product is appropriate. Canada and Australia require that developers notify them of their intent to commercialize combined-trait products. Canada also reserves the right to request data demonstrating that combined-trait products are substantially equivalent to the parents, although this has not been done to date for the currently commercial combined-trait products.

Japanese regulatory authorities recently issued guidelines for combined-trait products, based on a classification system. Category 1 includes traits that do not alter a metabolic pathway of host plants, for example, agronomic traits such as insect protection or herbicide resistance. Category 2 includes traits that alter a metabolic pathway of host plants, resulting in the enhancement of nutritional content. Category 3 includes traits that introduce new metabolites that have previously not been present in the host plant. Based on this classification scheme, there is no need for a separate review for combined-trait products developed by conventional breeding of Category 1 traits, as long as the individual traits have been previously reviewed. A separate food safety review is required for combined-trait products comprised of Category 2 or Category 3 traits. Whether the individual traits are related or interact metabolically will be key to determining if additional safety data are required for combined-trait products that contain Category 2 or 3 traits.

In Korea, a notification system is in place where the applicant files a justification for exemption from further safety assessment of the combined-trait product, based on three criteria: no change in the stacked-trait progeny produced from conventional crossing of the single traits (other than the additional trait), no crossing between different species, and no change anticipated in the resulting human consumption levels, edible plant portions, or purpose of usage. If the product is not exempted, a separate safety assessment must take place, with data requirements to be specified.

In the Philippines, developers submit a notification for evaluation of combined-trait products for which the individual traits have prior approval and where the combined-trait products are used directly for food, feed, or processing. A risk assessment is conducted on possible or expected interactions between genes or gene products, where the potential for genetic interaction to form new allergen or toxins, affect protein compartmentalization, or change phenotypic characteristics and the impact on mode of action and protein levels for single- and combined-trait products are assessed.

The Republic of China has a voluntary notification process for traits combined by conventional breeding and where the individual traits have received prior approval. In some other Asia–

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Pacific countries, including China and India, the regulation of traits combined by conventional breeding is under consideration.

In contrast, the European Union and Argentina consider combined-trait products to be novel or unique and therefore require a new submission or the inclusion of the foreseen combined-trait products in the submission of one of the parents. Extensive bridging regulatory data on the combined-trait products needs to be generated. No combined-trait products produced through conventional breeding have been approved to date in either the EU or Argentina.

A reasonable regulatory approach for combined-trait products is set forth in a document prepared by scientists and regulatory specialists from member companies of CropLife International (CropLife International, 2005). Separate safety assessments should not be required if the individual traits are unrelated and the individual traits were previously approved. However, to confirm the presence of the individual traits in the combined-trait product, regulatory agencies might request greenhouse or field bioefficacy data or gene expression levels. Data from any one of these sources would be appropriate to demonstrate that the individual traits are present and functioning as intended in the combined-trait product. Additional safety data are scientifically justified only when the traits target the same metabolic pathway or they are otherwise expected to have interactions. On a case-by-case basis, studies may be required to determine whether there are any interactions, either synergistic or antagonistic, between the traits, or to assess the products of the metabolic pathway.

Reasonable rules for the review of crops with biotechnology-derived traits combined by conventional breeding will preserve the significant benefits of these technologies. For example, combining traits by conventional breeding would allow the combination of traits that have region- or country-specific uses but may not justify the expense of separate development through plant transformation. Additionally, reasonable regulations that are consistent between trading countries and regions will facilitate the movement of commodities containing these traits.

CONCLUSION

As described herein, crops developed through agricultural biotechnology have provided demonstrable economic, environmental, and social benefits globally. Within the Asia-Pacific region, five countries have grown biotechnology-derived crops commercially: Australia, China, India, Indonesia, and the Philippines. Specific examples described insect-protected cotton in China, Australia, and India, insect-protected maize in the Philippines, and herbicide-tolerant cotton in Australia. Future uses in the Asia-Pacific region include more widespread adoption of herbicide-tolerant crops currently grown elsewhere, including herbicide-tolerant maize. In addition, China and India have very active crop biotechnology research and development programs in a diversity of crops (including chickpea, rice, cotton, maize, mustard, and potato) and biotechnology traits (including insect, disease, and virus resistance, herbicide tolerance, stress tolerance, oil improvements, and fruit ripening). Other biotech-derived traits will improve food and feed nutrition, including vitamin and mineral enhancement, increased essential amino acids and altered fatty acid composition. However, the successful development and commercialization of biotech-derived crops will be impacted by the costs of doing so, and the costs of regulatory approvals have become an increasingly significant part of the total product development and commercialization equation. Regulators and the scientists who support them must make take care to assure that data requirements are reasonable and designed to address true food, feed, and environmental risks.

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2. GLOBAL STATUS AND TRENDS OF COMMERCIALIZED BIOTECHNOLOGY IN CROPS

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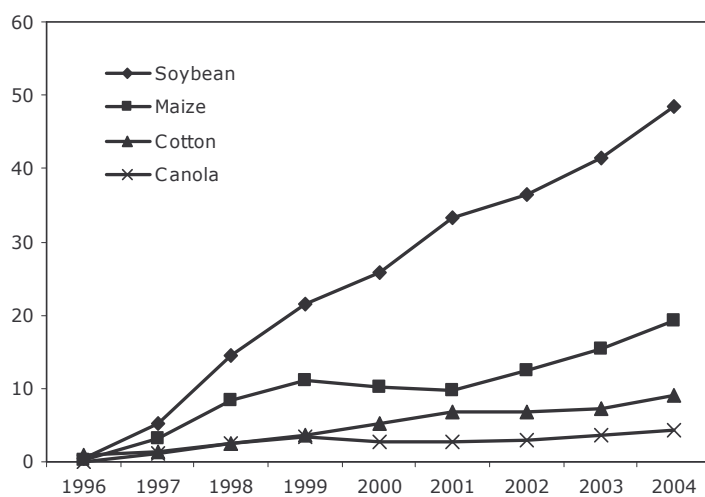
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INTRODUCTION

Commercial crop biotechnology products consist of different crop varieties possessing specific traits in any of four food, feed, and fiber crops, namely, soybean, maize (corn), canola, and cotton. Admittedly, there are many other plant species which have been genetically modified for various traits, but these are all still in the research and development phase or are undergoing government regulatory approval prior to commercialization. In 2004, the global area grown with biotech crops was estimated at 81 million ha, made up primarily of four crops: soybean, maize, cotton, and canola (James, 2004). These four crops have increased markedly in area since their introduction (Figure 1), and the data clearly show the continuing dominance of biotech soybean, which occupied 60% of the global area of biotech crops in 2004 (Table 1). Biotech soybean retained its position in 2004 as the biotech crop occupying the largest area. Globally, biotech soybean occupied 48.4 million ha in 2004, with biotech maize in second place at 19.3 million ha, biotech cotton in third place at 9.0 million ha, and finally canola at 4.3 million ha (Table 2). This paper will discuss only biotech crops and not other crop biotech products such as pathogen diagnostic kits or molecular marker selected varieties (Teng, 1999).



Source: Clive James, 2004

Figure 1. Global Area of Biotech Crops, 1996–2004
by Crop (million ha)

Table 1. Global Area of Biotech Crops in 2003 and 2004 by Crop (million ha)

Crop	2003	%	2004	%	+/-	%
Soybean	41.4	61	48.4	60	+7.0	+17
Maize	15.5	23	19.3	23	+3.8	+25
Cotton	7.2	11	9.0	11	+1.8	+25
Canola	3.6	5	4.3	6	+0.7	+19
Squash	<0.1	<1	<0.1	<1	–	–
Papaya	<0.1	<1	<0.1	<1	–	–
Total	67.7	100	81.0	100	+13.3	+20

Source: Clive James, 2004

Table 2. Biotech Crop Area as % of Global Area of Principal Crops, 2004 (million ha)

Crop	Global area	Biotech crop area	Biotech area as % of global area
Soybean	86	48.4	56%
Cotton	32	9.0	28%
Canola	23	4.3	19%
Maize	143	19.3	14%
Total	284	81.0	29%

Source: Clive James, 2004

ANALYSIS OF THE GLOBAL AND REGIONAL DISTRIBUTION OF COMMERCIALIZED CROP BIOTECHNOLOGY PRODUCTS

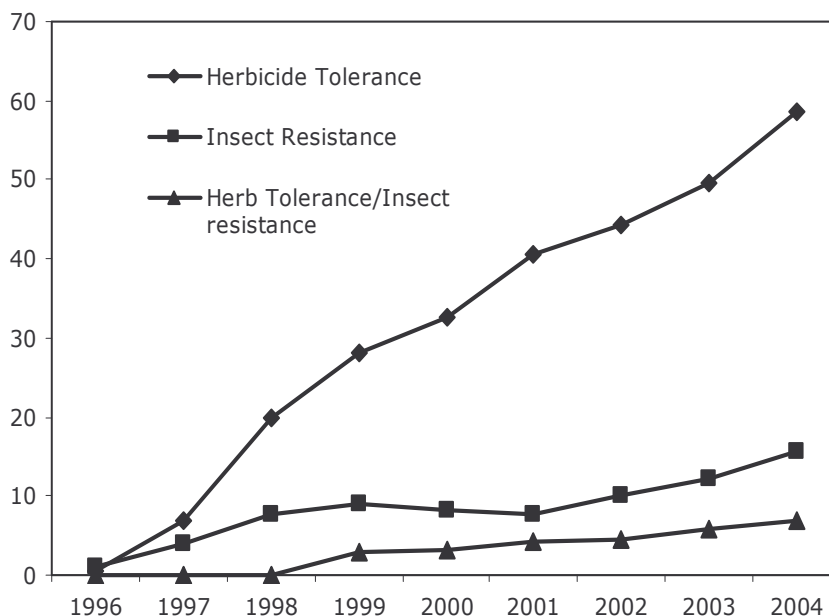
Global Status

The experience of the first eight years, 1996 to 2003, during which a cumulative total of 300 million ha (approximately 750 million acres) of biotech crops were planted globally in 21 countries, has confirmed that the early promise of crop biotechnology has been fulfilled. Biotech crops have delivered substantial agronomic, environmental, economic, health, and social benefits to farmers and, increasingly, to society at large. The rapid adoption of biotech crops during the initial eight-year period reflects the substantial multiple benefits realized by both large and small farmers in industrial and developing countries that have grown biotech crops commercially. Between 1996 and 2003, a total of 21 countries, 11 developing and 10 industrial countries, contributed to a 40-fold increase in the global area of biotech crops, from 1.7 million ha in 1996 to 67.7 million ha in 2003. Adoption rates for biotech crops during this period have been unprecedented, and by recent agricultural industry standards they are the highest for improved crops, for example, up to twice as high as the adoption of hybrid corn in the U.S. Midwest. High adoption rates reflect farmer satisfaction with products that offer substantial benefits, including more convenient and flexible crop management, higher productivity and/or net returns per hectare, health and social benefits, and a cleaner environment through decreased use of conventional pesticides, which collectively contribute to a more sustainable agriculture. There is a growing body of consistent and compelling evidence generated by public sector institutions that clearly demonstrates the improved weed and insect pest control attainable with biotech herbicide-tolerant and insect-resistant Bt crops that also benefit from lower input and production

costs. Biotech crops offer substantial economic advantages to farmers compared with corresponding conventional crops. The severity of weed and insect pests varies from year to year and hence will directly impact pest control costs and the economic advantages of biotech crops in any given time or place.

Distribution of Biotech Crops, by Trait

During the nine-year period 1996 to 2004, herbicide tolerance has consistently been the dominant trait, with insect resistance second (Figure 2). In 2004, herbicide tolerance, deployed in soybean, maize, canola, and cotton, occupied 72% of the 81.0 million ha (Table 3). There were 15.6 million ha planted to Bt crops, equivalent to 19%, with stacked genes for herbicide tolerance and insect resistance deployed in both cotton and maize occupying 9% of the global biotech area in 2004. It is noteworthy that whereas the area of herbicide-tolerant crops increased by a significant 18% (8.9 million ha) between 2003 and 2004, Bt crops increased at a higher level of 28% (3.4 million ha). This increase in Bt crops reflects the significant increase in Bt maize in 2004 (2.0 million ha) and the increase of Bt cotton (1.4 million ha) in China, India, and Australia. Whereas most of the growth in Bt maize occurred in the U.S., there were also significant increases in Bt maize area in Argentina, Canada, South Africa, Spain, and the Philippines. The stacked traits of herbicide tolerance and insect resistance in both maize and cotton increased by 17% in 2004, reflecting the needs of farmers who must simultaneously address the multiple yield constraints associated with various biotic stresses. This trend will continue and intensify as more traits become available to farmers, and it is an important feature of the technology.



Source: Clive James, 2004

Figure 2. Global Area of Biotech Crops, 1996–2004
by Trait (million ha)

Table 3. Global Area of Biotech Crops in 2003 and 2004 by Trait (million ha)

Trait	2003	%	2004	%	+/-	%
Herbicide tolerance	49.7	73	58.6	72	+8.9	+18
Insect resistance (Bt)	12.2	18	15.6	19	+3.4	+28
Bt/herbicide tolerance	5.8	9	6.8	9	1.0	+17
Virus resistance/other	<0.1	<1	<0.1	<1	<0.1	–
Global totals	67.7	100	81.0	100	+13.3	+20

Source: Clive James, 2004

Distribution of Biotech Crops in Industrial and Developing Countries

Figure 3 shows the relative area of biotech crops in industrial and developing countries during the period 1996 to 2004. It clearly illustrates that although the substantial share (66%) of biotech crops was grown in industrial countries, the proportion of biotech crops grown in developing countries has increased consistently every year, from 14% in 1997 to 16% in 1998, 18% in 1999, 24% in 2000, 26% in 2001, 27% in 2002, 30% in 2003, and 34% in 2004. Thus, in 2004, more than one-third of the global biotech crop area of 81.0 million ha, equivalent to 27.6 million ha, was grown in developing countries, where growth continued to be very strong between 2003 and 2004 (Table 4). Continued strong growth was reported by China, India, and the Philippines in Asia as well as by the three large economies of Latin America: Argentina, Brazil, and Mexico, plus Uruguay and Paraguay and South Africa on the African continent. It is noteworthy that for the first time the absolute growth in the biotech crop area between 2003 and 2004 was higher in developing countries (7.2 million ha) than in industrial countries (6.1 million ha). Equally important to note is that the percentage growth was almost three times as high (35%) in the developing countries of the South compared to the industrial countries of the North (13%).

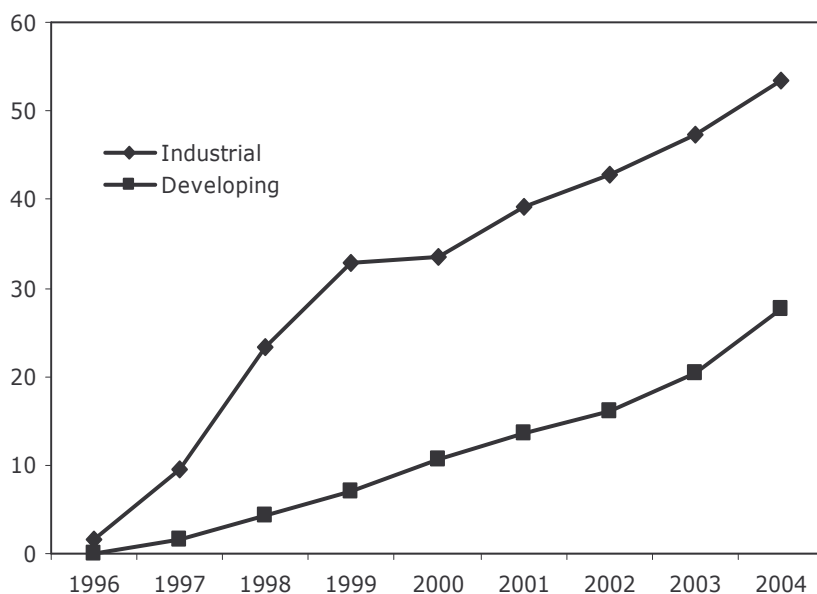
Table 4. Global Area of Biotech Crops, 1996–2003, Industrial and Developing Countries (million ha)

	2003	%	2004	%	+/-	%
Industrial countries	47.3	70	53.4	66	6.1	+13
Developing countries	20.4	30	27.6	34	7.2	+35
Total	67.7	100	81.0	100	13.3	+20

Source: Clive James, 2004

It is particularly noteworthy that the number of mega-countries (countries which grow 50,000 ha or more of biotech crops) increased from 10 in 2003 to 14 in 2004, with Paraguay, Spain, Mexico, and the Philippines joining the mega-country group in 2004. This is a very important development which reflects a broadening, deepening, and stabilizing of the group of more progressive countries adopting biotech crops. The principal countries that grew biotech crops in 2004 included the U.S., which grew 47.6 million ha of biotech crops (59% of the global total), followed by Argentina with 16.2 million ha (20%), Canada with 5.4 million ha (6%), Brazil with 5 million ha (6%), China with 3.7 million ha (5%), Paraguay with 1.2 million ha (2%), and India and South Africa at 0.5 million ha each (1%) (Table 3, Figure 3). It should be noted that of these top eight countries growing half a million ha or more of biotech crops, the majority (six) are developing countries: Argentina, Brazil, China, Paraguay, India, and South Africa, compared with a minority of two industrial countries: the U.S. and Canada. Of the top

six biotech developing countries, Brazil enacted a Presidential decree in October 2004 to sanction the continued growing of biotech crops officially for the second year, whilst the other five countries all reported continued significant growth of biotech crops between 2003 and 2004. The projected 5 million ha of herbicide-tolerant soybean in Brazil represents a conservative 22% of the projected plantings of around 23 million ha of the national soybean area in 2004–05. Notably, Paraguay registered four varieties of herbicide-tolerant soybean for the first time in 2004, with an estimated area of biotech soybean of 1.2 million ha; this represents approximately 60% of the national area of 2 million ha of soybean in Paraguay in 2004.



Source: Clive James, 2004

Figure 3. Global Area of Biotech Crops, 1996–2003, Industrial and Developing Countries (million ha)

Based on annual percentage growth in area, of the eight leading biotech crop countries, India had the highest percentage of year-on-year growth in 2004 with an increase of 400% in Bt cotton area over 2003, followed by Uruguay (200%), Australia (100%), Brazil (66%), China (32%), South Africa (25%), Canada (23%), Argentina (17%), and the U.S. at 11%. In 2004, India increased its area of approved Bt cotton, introduced only two years before, from approximately 100,000 ha in 2003 to 500,000 ha in 2004. Whereas growth in Uruguay in 2004 was accentuated by a conservative 2003 adoption rate, biotech soybean now occupies more than 99% of the total soybean area. There was also a significant increase in biotech maize in Uruguay in 2004, bringing the total biotech area to more than 300,000 ha. After suffering severe drought for the last two years, Australia increased its total cotton plantings in 2004 to about 310,000 ha, of which 80%, equivalent to 250,000 ha, were planted with biotech cotton⁴. Brazil increased its biotech soybean area by two-thirds, from 3 million ha in 2003 to a projected 5 million ha in 2004, with another significant increase likely in 2005. China increased its Bt cotton area for the seventh consecutive year, an increase of one-third, from 2.8 million ha in 2003 to 3.7 million ha in 2004, equivalent to 66% of the total cotton area of 5.6 million ha in 2004, the largest national cotton area planted in China since the introduction of Bt cotton in 1997. South Africa reported a 25% increase in its combined area of biotech maize, soybean, and cotton to 0.5 million ha in

2004, with continued growth in both white maize, used for food, and yellow maize, used for feed, as well as strong growth in biotech soybean, up from 35% adoption in 2003 to 50% in 2004, while Bt cotton has stabilized at about 85% adoption. Canada increased its combined area of biotech canola, maize, and soybean by 23%, to a total of 5.4 million ha, with 77% of its canola area planted to biotech varieties. The adoption of herbicide-tolerant soybeans in Argentina, which was close to 100% in 2003, continued to climb in 2004 as total plantings of soybean increased, which along with biotech maize and cotton reached an all-time high of 16.2 million ha of biotech crops. In the U.S., there was an estimated net gain of 11% of biotech crops in 2004 as a result of significant increases in the area of biotech maize, followed by biotech soybean, with modest growth in biotech cotton, which started to peak in the U.S. in 2004 as adoption approached 80%.

Table 5. Global Area of Biotech Crops in 2003–04 by Country (million ha)

	2003	%	2004	%	+/-	%
U.S.*	42.8	63	47.6	59	+4.8	+11
Argentina*	13.9	21	16.2	20	+2.3	+17
Canada*	4.4	6	5.4	6	+1.0	+23
Brazil*	3.0	4	5.0	6	+2.0	+66
China*	2.8	4	3.7	5	+0.9	+32
Paraguay*	—	—	1.2	2	+1.2	—
India*	0.1	<1	0.5	1	+0.4	+400
South Africa*	0.4	1	0.5	1	+0.1	+25
Uruguay*	0.1	<1	0.3	<1	+0.2	+200
Australia*	0.1	<1	0.2	<1	+0.1	+100
Romania*	<0.1	<1	0.1	<1	<1	—
Mexico*	<0.1	<1	0.1	<1	<1	—
Spain*	<0.1	<1	0.1	<1	<1	—
Philippines*	<0.1	<1	0.1	<1	<1	—
Colombia	<0.1	<1	<0.1	<1	<1	—
Honduras	<0.1	<1	<0.1	<1	<1	—
Germany	<0.1	<1	<0.1	<1	<1	—
Total	67.7	100	81.0	100	+13.3	+20
*Biotech mega-countries which grew more than 50,000 ha or more of biotech crops in 2004						

Source: Clive James, 2004

The 17 countries that grew biotech crops in 2004 are listed in descending order of their biotech crop areas in Table 5. There were 11 developing countries and 6 industrial countries, including Romania from Eastern Europe. In 2004, biotech crops were grown commercially in all six continents of the world: North America, Latin America, Asia, Oceania, Europe (Eastern and Western), and Africa. The top eight countries, each growing half a million ha or more of biotech crops in 2004, are listed in order of crop biotech area in Table 3: the U.S., Argentina, Canada, Brazil, China, Paraguay, India, and South Africa. These countries accounted for approximately 99% of the global biotech crop area, with the balance of less than 1% growing in the other nine countries. In 2004, the number of biotech mega-countries growing 50,000 ha or more of biotech crops increased by 40%, from 10 in 2003 to 14 in 2004. The additional four countries that qualified as biotech mega-countries in 2004, listed in order of biotech crop area, were Paraguay, Mexico, Spain, and the Philippines. See Table 5 for the complete list of the 14 biotech crop mega-countries (identified by an *asterisk) that grew 50,000 or more ha of biotech crops in 2004.

The following paragraphs provide a more detailed analysis of the biotech crop situation in selected countries.

In the U.S., there was an estimated net gain of 11% in biotech crops in 2004 as a result of significant increases in the area of biotech maize, followed by biotech soybean. There was modest growth in biotech cotton, which started to peak in the U.S. in 2004 as adoption approached 80% of the total area planted to upland cotton crop of approximately 5.5 million ha. In contrast, there was growth in the national area of maize and soybean, which were more profitable than biotech cotton or canola, and this stimulated an increase in biotech maize and soybean. A small decrease of the area of biotech canola was reported as farmers replaced canola with the more profitable soybean and maize crops.

After growing biotech soybean unofficially for several years, Brazil officially approved biotech soybeans in 2003 and 2004 by two successive Presidential decrees granting temporary approval pending the passage of a biotech bill that will provide a permanent framework for evaluating and approving biotech crops. The new broad-ranging biotech bill, which includes medical applications, is expected to become law in 2005 and will for the first time provide a regulated legal system that should greatly facilitate the evaluation and approval of biotech crops other than soybean, including biotech maize and cotton (already commercialized in nine other countries), papaya and beans (being developed as a public good product by EMBRAPA in Brazil), and rice, a relatively important crop in Brazil, which has by far the largest rice area in Latin America (3 million ha).

Developments in the Asian Region

Four countries in Asia now report the commercial planting of biotech crops: China, India, the Philippines, and Australia.

The area planted to Bt cotton in China increased by a significant 0.9 million ha, equivalent to over 32% growth, increasing from 2.8 million ha in 2003 to 3.7 million ha in 2004. An estimated 7 million small farmers grew Bt cotton in China in 2004, up from 6 million in 2003. This brings the total number of biotech crop farmers globally in 2004 to approximately 8.25 million, 90% of whom are resource-poor farmers from developing countries, particularly in China, India, and South Africa and the other eight developing countries in Asia, Africa, and Latin America benefiting from biotech crops in 2004.

India, which grew approximately 50,000 ha of officially approved hybrid Bt cotton for the first time in 2002, doubled its Bt cotton area to approximately 100,000 ha in 2003, and this increased by 400% in 2004 to reach over half a million ha. It is estimated that approximately 300,000 small farmers, growing an average of less than 2 ha of Bt cotton, benefited from growing approved hybrid Bt cotton in India in 2004. The adoption of approved Bt cotton hybrids is expected to continue to increase significantly in 2005.

The Philippines, which grew Bt maize for the first time in 2003, is projected to increase its total area in the wet and dry season (now being planted) in 2004 to just over 50,000 ha; this will make the Philippines the first biotech country to achieve the mega-country status with a major feed/food crop, Bt maize, in Asia, which grows 30% of the global 140 million ha maize, with China growing 25 million ha, plus significant production in India, Indonesia, Thailand, and Vietnam.

Australia is expected to plant slightly over 300,000 ha of cotton (approximately 90% irrigated) in 2004–05, with 80% of the national cotton area planted to biotech varieties. It is projected that about 40% of the biotech cotton varieties in Australia will feature the stacked genes for herbicide tolerance and insect resistance (the dual Bt gene Bollgard II), 25% with the dual Bt gene on its own, 15% with a single gene for herbicide tolerance, and the remaining 20% in conventional cotton.

Developments in Other Geographic Regions

In 2004, Paraguay reported for the first time that 1.2 million ha of biotech soybean had been planted, equivalent to 60% of its total national area of 2 million ha of soybean. Spain, the only EU country to grow a significant area of a commercial biotech crop, increased its Bt maize area by over 80%, from 32,000 ha in 2003 to 58,000 ha in 2004, equivalent to 12% of the national maize crop. In Eastern Europe, Romania, a biotech mega-country growing more than 50,000 ha of biotech soybean, also reported significant growth. Two countries, Mexico and the Philippines, which attained the status of biotech mega-countries for the first time in 2004, reported 75,000 ha and 52,000 ha of biotech crops, respectively, for 2004. Other countries that have only recently introduced biotech crops for the first time, such as Colombia and Honduras, reported modest growth, while Germany planted a token area of Bt maize.

In Argentina in 2004 the year-to-year increase compared with 2003 was 2.3 million ha. Of the 16.2 million ha of biotech crops projected for Argentina in 2004–05, 14.5 million ha are biotech soybean, an increase of 1.7 million ha in soybean area over 2003, all of which is biotech soybeans. There was continued growth in Argentina of Bt maize, which now represents 55% of the national maize area and is expected to reach almost 3 million ha in 2004, with continued growth in area in 2005 and beyond as domestic and export demand grows for both processing and feed maize.

For Canada, a net gain of 1.0 million ha was reported, equivalent to a total of 5.4 million ha in 2004; this compares with an increase of 0.9 million ha in 2003, from 3.5 million ha in 2002 to 4.4 million ha in 2003. The continued high growth rate in Canada reflects higher total plantings of canola in 2004 and consistent increased adoption rates in all three biotech crops: canola, soybean, and maize.

Brazil, the second-largest producer of soybeans in the world after the U.S., enacted a second Presidential decree in mid-October 2004 to approve the planting of biotech soybean farmer-saved seed for the 2004–05 season. At the time when this Brief went to press in early December 2004, more than 50% of the soybean crop had been planted in Brazil; it is projected that biotech soybean will occupy approximately 22% of the 23 million ha crop in the 2004–05 season.

Paraguay is the world's fourth-largest exporter of soybeans and has grown biotech soybean unofficially for several years. It approved four herbicide-tolerant soybean varieties on 20 October 2004, thus becoming the ninth country in the world to officially approve and adopt herbicide-tolerant biotech soybean. The four varieties of soybean tolerant to the herbicide Roundup® were approved and placed on the approved registered seed list, thus allowing farmers to plant these biotech seeds officially in the 2004–05 season. The four registered varieties were AW 7110, AW5581, M-Soy 7878, and M-Soy 8080. Thus Paraguay officially grew biotech soybean for the first time in 2004, and it joins the following eight countries, listed in order of biotech soybean area, which have successfully grown biotech soybeans for several years: the U.S., Argentina, Brazil, Canada, Uruguay, Romania, South Africa, and Mexico. In 2004, Paraguay is expected to plant approximately 60% of its total area of 2 million ha of soybean to biotech varieties, equivalent to 1.2 million ha of biotech soybean in 2004.

A significant increase in biotech crop area was also reported for South Africa, where the combined area of biotech maize, cotton, and soybean is expected to be almost half a million ha in 2004–05.

Spain increased its area of Bt maize by 80% in 2004 to 58,000 ha from 32,000 ha in 2003, thus becoming the first EU country to achieve the status of a biotech mega-country (a country growing 50,000 ha or more). Elsewhere in Europe, Romania continued to increase its area of biotech soybean, and Germany continued to grow a token area of Bt maize. Bulgaria did not report the cultivation of herbicide-tolerant maize in 2004, which it has done successfully for several years, because government-issued special permits expired and the new bill intended to regulate evaluation and approval of biotech crops is not yet in place. Mexico doubled its area of

biotech cotton and soybean to over 75,000 ha and became a biotech mega-country for the first time, with most of the increase in Bt cotton as well as the stacked product for insect resistance and herbicide tolerance. Uruguay, which introduced biotech soybean in 2000, increased its biotech crop area significantly to reach approximately 325,000 ha in 2004, with most of the gain coming from a substantial increase in the area of herbicide-tolerant soybean that is now virtually 100% of the 300,000 ha of national soybean area. The cultivation of Bt maize, first approved in 2003, continued to grow and occupied approximately 30% of the 90,000 ha of maize planted in 2004. Colombia doubled its area of Bt cotton in 2004, to approximately 10,000 ha. Honduras continued with modest small Bt maize plantings, after becoming the first country in Central America to grow a biotech crop in 2002, when it grew a precommercial introductory area of approximately 500 ha of Bt maize.

THE R&D PIPELINE

Although 17 countries are reported to have grown biotech crops in 2004, a larger number are known to have such crops in various stages of development leading up to commercial plantings. Of these 17, 11 are developing countries. Indeed, Cohen has suggested that the public sector will be an important source of crop biotech products for poor farmers, as there are currently known to be more than 99 crop variety-trait modifications undergoing different stages of testing by public institutions in Asia (Cohen, 2005; ADB, 2001).

The countries that will exert leadership and have a significant influence on future adoption and acceptance of biotech crops globally because of their significant biotech investments and pipeline of potential products are China, India, Brazil, and South Africa.

China

China was one of the pioneers in crop biotechnology. Unlike the industrial countries with private sector investments, China's biotech investments are entirely derived from the public sector. China has over a dozen biotech crops being field tested, including the three major staples—rice, maize, and wheat—as well as cotton, potato, tomato, soybean, cabbage, peanut, melon, papaya, sweet pepper, chili, rapeseed, and tobacco.

At the beginning of this decade, China was investing just over USD100 million per year in crop biotechnology; this investment has benefited from quantum annual increases, with an intent to reach USD500 million in 2005, making China the second-largest global investor in crop biotechnology, after the U.S., where most of the investment is by the private sector (Huang and Wang, 2002). The most recent survey, conducted in 2004, reports government spending on agricultural biotechnology at USD200 million annually, equivalent to USD1 billion in terms of purchasing power parity. China has 2,000 professionals dedicated to crop biotechnology, and the scientific community is recommending even more resources for this area, which they consider to be a strategic investment.

Approximately 20% of the government's investments in crop biotechnology have been devoted to rice. This is equivalent to a current annual investment of USD24 million at official exchange rates. Three insect-resistant hybrid rice varieties, two featuring the Bt gene and the other with the CpTi trypsin gene, entered preproduction field trials in 2001, plus a rice variety carrying the Xa 21 gene that confers resistance to the important bacterial blight disease of rice. Extensive annual large-scale preproduction trials of these new biotech hybrids of rice, starting in 2001, confirmed yield increases of approximately 4% to 8%, plus a saving of 17 kg per hectare in pesticides, with positive health implications, along with a labor saving of 8 days per ha, resulting in an overall increase in net income per hectare of USD80 to USD100. It is projected that with full adoption, the new biotech rice hybrids will result in a national benefit to China of USD4 billion in 2010. Insect borers, which can be controlled by Bt, are prevalent on up to 75% of approximately 30 million ha of rice in China. It is likely that biotech rice will be approved in

China in the near term, probably in 2005. The approval of biotech rice in China will have major implications not only for China but for the rest of the world, since rice is the major food crop of the world, and biotech rice will be the first major food crop to be approved, adopted, and commercialized globally.

India

India has also identified crop biotechnology as a strategic science investment that can coincidentally contribute to food, feed, and fiber security and to a more sustainable agriculture. India first adopted the officially approved Bt cotton hybrids in 2002, and due to their success, by 2004 approximately 300,000 farmers planted over half a million ha with a quantum five-fold increase in Bt cotton area between 2003 and 2004. With 9 million ha, India is the largest cotton-growing country in the world; almost half, 4 million ha, is hybrid cotton. The government of India, through the Department of Biotechnology (DBT) in the Ministry of Science and Technology, established six centers of plant molecular biology in 1990 and more recently established a new institute, the National Center for Plant Genome Research, to focus on genomics and strengthen plant biotechnology research in the country. The increased public sector investments in crop biotechnology are complemented by private sector investments from indigenous Indian seed companies and subsidiaries of multinationals involved in biotech crops. Crop biotech investments from both the public and private sectors, estimated at USD25 million per annum in 2001, are focused on the development of biotech food, feed, and fiber crops that can contribute to higher and more stable yields and enhanced nutrition. Much emphasis has been placed on genomics in rice and the development of improved varieties tolerant to the abiotic stresses of salinity and drought and the biotic stresses associated with pests. Reduction of post-harvest losses, particularly in fruits and vegetables, through delayed ripening genes is also a major thrust. Two international collaborative projects reflecting the emphasis on improved crop nutrition involve golden rice and mustard with enhanced levels of beta carotene and an initiative to enhance the nutritional value of potatoes with the *amal* gene.

Several public institutions and private companies in India have projects to develop improved varieties of the important drought-tolerant perennial eggplant, known locally as brinjal. The goal of these projects is to improve resistance to shoot and fruit borers, pests that require several applications of insecticide costing USD40–100 per season, with environmental and health implications, since eggplant is a food crop. The projects are geared to deliver biotech products for government evaluation and approval in the near term, representing India's first biotech food product. Bt eggplant will be an important new biotech crop and will complement the hybrid Bt cotton that has already been approved and other Bt cottons being developed by both the public and private sectors. Biotech crops in development by the public sector include banana, blackgram, brassica, cabbage, cauliflower, chickpea, coffee, cotton, eggplant, muskmelon, mustard/rapeseed, potato, rice (including basmati), tobacco, tomato, and wheat. The private sector has the following biotech crops under development: brassica, cabbage, cauliflower, cotton, maize, mustard/rapeseed, tomato, pigeonpea, and rice.

Brazil

Brazilian universities, foundations, and the national agricultural research system EMBRAPA have significant investments in biotechnology, and two EMBRAPA public-good products are well advanced, a virus-resistant papaya and bean, both of which can deliver significant economic and social benefits to resource-poor farmers and thus meet one of the government's important priority goals.

In 2004, of the projected 23 million ha of soybean, 22% or 5 million ha are likely to be planted with biotech soybean, up from 3 million ha in 2003. The long-term potential for biotech soybean in Brazil is up to 30 million ha or more, as the area sown to soybean increases to meet global demand, particularly that of China. It is notable that Brazil has more new land that can be

brought into agricultural production than any other country in the world, up to 100 million ha or more, with an ample water supply—the major global constraint to increased crop production. Brazil also has the third-largest area of maize in the world, after the U.S. and China, with significant potential for both biotech insect-resistant and herbicide-tolerant varieties. Unlike soybean, which are generally produced on larger farms, the 12 million ha of maize in Brazil is farmed mainly by small farmers to whom the social benefits of increased income would be very important and consistent with the government's top priority of alleviating poverty. Brazil also has the sixth-largest area of cotton in the world and uses the greatest quantity of cotton insecticides in Latin America. Adoption of insect-resistant biotech cotton could result in significant advantages for both the small and large farmers who grow cotton, including less exposure to insecticides and higher net incomes. Using only current proven biotech crops of soybean, maize, and cotton, already successfully commercialized in other countries, the collective value for these three crops in Brazil could probably be increased by up to USD1 billion per year, with significant added environmental, health, and social benefits that are particularly important for small, resource-poor farmers who could enhance their income and have less exposure to pesticides.

South Africa

A draft National Biotechnology Strategy was completed in 2001 that provided for three centers of excellence funded at USD64 million over three years. These centers provide a framework for a national PlantBio network, with facilities worth USD4 million at the University of Pretoria, which acts as a hub for crop biotechnology, including an informatics and gene technology center. The most advanced public-sector product is a Bt potato resistant to the tuber moth, currently being field tested. Other potential new biotech crops from both the private and the public sectors that are in advanced field tests are stacked Bt/herbicide-tolerant cotton and maize, sugarcane with modified carbohydrate, and virus-resistant potatoes undergoing tests in greenhouses. The stacked Bt/herbicide-tolerant cotton is currently under advanced field testing. Despite a shortage of biotech maize seed, which has constrained adoption rates, 240,000 ha of yellow maize (24% of the total) and 155,000 ha (10% adoption) of white maize are estimated for 2004–05, with continued strong growth projected for the future. It is notable that Bt white maize has been rapidly accepted as a food crop, increasing from 6,000 ha in 2001 to 155,000 ha in 2004. The stacked Bt/herbicide-tolerant maize is currently under advanced field testing, and expedited approval of this product is important so that South Africa can maintain its lead role in biotech crops. Biotech soybeans were introduced in 2001, and the adoption rate moved rapidly from 5% in 2001 to an estimated 50% in 2004, with continued strong growth expected for 2005 and beyond.

TRENDS AND FUTURE DEVELOPMENTS

The future of crop biotechnology products will depend, to a large extent, on their proven benefits to the farming community, a regime of acceptable biosafety oversight, and public/consumer acceptance. Regulatory frameworks for biosafety are being developed by many countries that are signatories to the Cartagena Biosafety Protocol under the Convention on Biological Diversity, and the methodology for safety assessment has also increasingly been improved vis-à-vis its science and acceptance by governments (Thomas and Fuchs, 2002).

Benefits from Biotech Crops

The experience of the first nine years, 1996 to 2004, during which a cumulative total of over 385 million ha (951 million acres, equivalent to 40% of the total land area of the U.S. or China) of biotech crops were planted globally in 22 countries, has met the expectations of millions of large and small farmers in both industrial and developing countries. Biotech crops are also delivering benefits to consumers and society at large, through more affordable food,

feed, and fiber that require less pesticide and hence maintain a more sustainable environment. The global value of total crop production from biotech crops in 2003 was estimated at USD44 billion. Net economic benefits to producers from biotech crops in the U.S. in 2003 were estimated at USD1.9 billion, while gains in Argentina for the 2001–02 season were USD1.7 billion. China has projected potential gains of USD5 billion in 2010, USD1 billion from Bt cotton and USD4 billion from Bt rice, expected to be approved in the near term. A global study by Australian economists on biotech grains, oil seeds, fruit, and vegetables projects a global potential gain of USD210 billion by 2015; the projection is based on full adoption with 10% productivity gains in high- and middle-income countries and 20% in low-income countries. The 2004 data are consistent with previous experience confirming that commercialized biotech crops continue to deliver significant economic, environmental, health, and social benefits to both small and large farmers in developing and industrial countries. The number of farmers benefiting from biotech crops continued to grow, reaching 8.25 million in 2004, up from 7 million in 2003. Notably, 90% of these 8.25 million farmers benefiting from biotech crops in 2004 were resource-poor farmers planting Bt cotton whose increased incomes have contributed to the alleviation of poverty. These included 7 million resource-poor farmers in all the cotton-growing provinces of China, an estimated 300,000 small farmers in India, and subsistence farmers in the Makhathini Flats in KwaZulu Natal province in South Africa and in the other nine developing countries where biotech crops were planted in 2004.

The Global Value of the Biotech Crop Market

In 2004, the global market value of biotech crops, forecasted by Croprosis, was USD4.70 billion, representing 15% of the USD32.5 billion global crop protection market in 2003 and 16% of the USD30 billion global commercial seed market. The market value of the global biotech crop market is based on the sale price of biotech seed plus any technology fees that apply. The accumulated global value for the nine-year period 1996 to 2004 (since biotech crops were first commercialized in 1996) is USD24 billion. The global value of the biotech crop market is projected at more than USD5 billion for 2005. These figures do not take into account any potential release of seed produced by the public sector through government sources. As the ADB (2001) has shown, there is a significant pipeline of products that are undergoing regulatory approval in many Asian countries.

CONCLUSION

The number of crop biotech products in the marketplace is strongly influenced by the number of transformation events recorded in the R&D phase in the public and private sectors. For the public sector, at least 99 out of the known 201 transformation events are from Asian countries (approximately 50%), known to be from China, India, Indonesia, Malaysia, Pakistan, the Philippines, and Thailand (Cohen, 2005). Less information is available from the private sector, but annual reports of companies such as Monsanto and Syngenta indicate that there is a smaller pipeline, but closer to commercialization, than in the public sector. In the near term, the single event that is likely to have the greatest impact is the approval and adoption of Bt rice in China, considered to be likely in 2005. The adoption of biotech rice by China involves not only the most important food crop in the world but the culture of Asia. Adoption of biotech rice will contribute to a global momentum that will herald a new chapter in the debate on the acceptance of biotech crops which will be increasingly influenced by countries in the South, where the new technology can contribute the biggest benefits and where the humanitarian needs are greatest—the alleviation of malnutrition, hunger, and poverty.

The sharing of the significant body of knowledge and experience that has been accumulated in developing countries on biotech crops since their commercialization in 1996 is an essential ingredient for a transparent and knowledge-based discussion by an informed global society

about the potential humanitarian and material benefits that biotech crops offer developing countries. The five leading biotech crop countries from the South—China, India, Argentina, Brazil, and South Africa—grew approximately one-third of global biotech crops in 2004 and can offer a unique experience from the perspective of developing countries in all three continents of the South: Asia, Latin America, and Africa.

On a global basis, there is cause for cautious optimism, with the global area and the number of farmers planting biotech crops expected to continue to grow in 2005 and beyond. In the established industrial country markets of the U.S. and Canada, growth will continue with the introduction of new traits, for example, the significant biotech area planted in 2004 in North America to MON 863 for corn rootworm control (approximately 700,000 ha of the single/stacked product) and TC 1507 for broader lepidopteran control (approximately 1.2 million ha). The global number and proportion of small farmers from developing countries growing biotech crops are expected to increase significantly to meet the food/feed crop requirements and meat demands of their burgeoning and more affluent populations. A similar trend may also apply to the poorer and more agriculturally based countries of Eastern Europe which have recently joined the EU and those expected to join in 2007 and beyond.

Finally, there were signs of progress in the European Union in 2004, with the EU Commission approving for import two events in biotech maize (Bt 11 and NK603) for food and feed use, signaling the end of the 1998 moratorium. The Commission also approved 17 maize varieties with insect resistance conferred by MON 810, making it the first biotech crop to be approved for planting in all 25 EU countries. The use of MON 810 maize, in conjunction with practical and equitable coexistence policies, opens up new opportunities for EU member countries to benefit from the commercialization of biotech maize, which Spain has successfully planted since 1998.

2004 is the penultimate year of the first decade of the commercialization of biotech crops, during which double-digit growth in the global area of biotech crops has been achieved every single year. This is an unwavering and resolute vote of confidence in the technology from 25 million farmers who are masters in risk aversion and who have consistently chosen, year after year, to plant an increasing area of biotech crops. The experience of the first nine years has met the expectations of millions of large and small farmers in both industrial and developing countries. Taking all factors into account, the outlook for 2010 points to continued growth in the global area of biotech crops, up to 150 million ha, with up to 15 million farmers growing biotech crops in up to 30 countries.

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3. FRONTIERS AND ADVANCES IN TRANSGENIC BIOTECHNOLOGY OF ANIMALS AND FISHES

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INTRODUCTION

Transgenic technology has become widely applied worldwide since the creation of transgenic mice in 1987 to produce tissue plasminogen activator (tPA). Various transgenic animals carrying segments of foreign DNA have been genetically engineered in diverse research areas, such as in providing developmental models for drug testing, xenotransplantation, and the production of pharmaceutical proteins. Furthermore, in 1997, the successful cloning of “Dolly” the sheep attracted the concern of media and society about transgenic technology, and animal cloning became a topic of intense discussion. Transgenic farm animals represent an attractive system for efficient production of large, complex, and biologically active recombinant proteins. A large number of useful proteins have been successfully expressed in sheep, goats, pigs, and cattle, and several recombinant proteins are now in clinical trials. However, because of the threat of variant Creutzfeldt-Jacob disease (CDJ) and other human and animal virus infections, fishes may provide an alternative animal system for transgenic application and research. Since the first transgenic fish were successfully produced in 1985 (Zhu et al., 1985), gene transfer studies have been conducted in over 35 important fish species for aquaculture.

According to a report published by Business Communication Company Inc. (BCC), the pharmaceutical market worldwide was over USD33 billion in 2003 and is predicted to be more than USD60 billion in 2006. This shows that the biotechnology industry has a high potential for growth. Currently, the major topics in transgenic animal and fish research include improving the quality of bioproducts, use as animal models for human disease research, use as a bioreactor for the production of pharmaceutical recombinant protein or additional nutrient food, and as a source of organs to be used in xenotransplantation. This paper will describe the current status of transgenic animals and fish, genetically modified for commercial use. In addition to a brief review of the application of transgenic animals, the content will focus on the advancement of transgenic fish.

ADVANCES IN DEVELOPING TRANSGENIC ANIMALS

Commercial production of bioproducts using natural protein factories such as the mammary glands of dairy animals has been a goal of animal scientists since the first report of a transgenic mouse (Gordon and Ruddle, 1981). This method of production is frequently referred to as bio-pharming. The conventional production of rare human therapeutic proteins from blood or tissue extracts is an inefficient, expensive, and time-consuming process. Prokaryotic expression systems are only suited for simple proteins, and post-translational modifications are often incorrect, leading to immune reactions against the protein. Therefore, farm animals such as cattle, sheep, goats, and pigs provide several advantages for production of recombinant proteins, including their potential for large-scale production, post-translational modifications, and correct structure. To date, large amounts of numerous heterologous recombinant proteins—including pharmaceutical proteins, vaccine, and various antibodies—have been produced by expression in mammary glands through mammary-gland-specific promoters (Table 1).

Table 1. Proteins Produced in the Mammary Gland of Transgenic Farm Animals

Protein	Production species	Therapeutic application
Antithrombin III	Goat	Genetic heparin resistance
Tissue plasminogen activator	Goat	Dissolving coronary clots
α -A ₁ -antitrypsin	Goat and sheep	Lung emphysema
		Cystic fibrosis
Human clotting factor	Sheep	Hemophilia A
Human serum albumin	Cattle	Blood substitute
Blood coagulating factor VIII	Pig	Haemophilia
Blood coagulating factor IX	Pig	Haemophilia
Various antibodies	Goat	

Source: Wilfried and Heiner (2004)

There are several methodologies which can be used for the production of transgenic animals. Pronuclear microinjection and nuclear transfer (cloning) have been the predominant techniques used to produce transgenic animals, and they provide benefits for organ transplantation as well. Over 250,000 people are alive because of the successful allotransplantation of an appropriate human organ. On average, 75%–90% of patients survive the first year after a transplant, and the average survival of a patient with a transplanted heart, liver, and kidney is 10–15 years (Wilfried and Heiner, 2004). This progress in organ transplantation technology has led to an acute shortage of appropriate organs. Therefore, transgenic animals can help meet the demand for organ transplantation through cloning technology.

ADVANCES IN DEVELOPING TRANSGENIC FISH

Growth Enhancement of Transgenic Fish

Enhanced growth rates of transgenic fish have the potential to increase production efficiency by improving feed conversion efficiencies and by reducing production time. The expression of growth factors such as growth hormones (GH) and insulin-like growth factors (IGFs) has further resulted in significant growth stimulation in several fish species to date (Martinez et al., 1999; Nam et al., 2001; Chen et al., 2000). A significant increase in growth rate was observed in the majority of fish with transgenic GH; for instance, salmon can reach approximately double the normal body size in half of the normal time (Pitkanen et al., 1999). The mechanism of growth improvement in transgenic fish is not clear, whether the growth acceleration is a result of better growth efficiency or a higher rate of food consumption. Some studies have shown more efficient metabolism in transgenic fish in comparison to their wild counterparts. For example, transgenic tilapia showed higher protein synthesis and growth rate concomitant with enhanced glycolysis and increased oxidation of amino acid (Martinez et al., 2000). Transgenic tilapia carrying carp β -actin gene promoter fused to a rainbow trout growth hormone (GH) or insulin-like growth factor-I (IGF-I) cDNA have been produced by electroporating the transgenes into newly fertilized tilapia eggs. These transgenic fish not only transmit the transgenes into subsequent generations but also grow substantially faster than their nontransgenic siblings. These results point to the potential of improving the growth rate of aquaculture fish by gene transfer technology involving growth hormone or IGF genes.

Disease and Freeze Resistance

One of the most important goals in the fish industry is to improve the resistance of farmed fish to pathogens and increase their tolerance to cold water. Preliminary studies show that biotechnology methods offer new approaches. One approach is to express a lysozyme that has been

considered as an antibacterial agent against some fish pathogens, including *Aeromonas salmonicida*, which causes furunculosis in rainbow trout (Siwicki et al., 1998). In fish the lysozyme cDNA have already been cloned from rainbow trout and Japanese flounder (Hikima et al., 2001). Another approach is to induce fish to express some antimicrobial peptides, for example, pleurocidin and moronecidin (Douglas et al., 2001; Lauth et al., 2002). The antimicrobial peptide monodoncin, which consists of 55 amino acid residues, was isolated from the haemocyte of black tiger shrimp (*Penaeus monodon*) and showed efficient antimicrobial ability against some aquatic pathogens such as *Aerococcus viridans*, *Fusarium pisi*, and *Fusarium oxysporum* (Chen et al., 2005; Chio et al., 2005). On the other hand, a liposome-based gene transfer platform was developed to transfer useful genes into silver sea bream (*Sparus sarba*) (Lu et al., 2002).

Many species of polar fish secrete antifreeze proteins (AFPs) into their plasma to avoid freezing. Diverse types of antifreeze proteins have been characterized and cloned from a variety of fish, including winter flounder (*Pleuronectes americanus*) and ocean pout (*Macrozoarces americanus*). These proteins have the unique property of inhibiting ice crystal growth by binding to the ice surface and lowering the freezing temperature. Therefore, introducing an AFP gene would generate a freeze-tolerant transgenic fish. The enzyme creatine kinase plays a key role in the energy metabolism of cells that have fluctuating energy requirements. Three forms of creatine kinase (CK) muscle isoenzyme cDNAs were isolated from carp (*Cyprinus carpio*). M3-CK was found to be the major regulatory enzyme of energy metabolism, and cold tolerance was improved in transgenic zebrafish. It is expected that the application of CK would decrease losses in the aquaculture industry in cold waters.

Infertile Technology for Genetically Modified Fish

Commercial production of transgenic fish will depend on the risk posed to wild species. Although useful transgenic fish strains have been developed, so far they have not been generally used in aquaculture because of concerns that genetically modified fish may threaten natural ecosystems. If these genetically modified fish escaped and bred with their wild type, the consequences of spreading the modified gene into the environment are unpredictable (Reichhardt, 2000). Therefore, genetically modified fish for human consumption should be made sterile. Experiments will have to be conducted on transgenic fish survivability and infertility, not only in the laboratory but also in natural conditions. The common practices to produce sterile fish are heat-shock or pressure-shock treatment of the freshly fertilized fish eggs, treatment of females with male sex hormones, and polyploid infertile technology, but the methods are not 100% effective (Razak et al., 1999). Gonadotropin-releasing hormone (GnRH) is a decapeptide which regulates synthesis and release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and thereby plays a primary role in the control of reproductive function in vertebrates. Therefore, an alternative method could produce induced sterility in transgenic lines by blocking the gonadotropin-releasing hormone (GnRH) with antisense RNA. A report has shown that deletion of the GAP region of the GnRH gene decreased the level of gonadotropin in mice, resulting in complete sterility (Mason et al., 1996). In fish, GnRH is thought to play an important role in sexual maturation and reproductive behavior, and two or three forms of GnRH peptide have been identified. Three forms of GnRH cDNA, seabream form (sbGnRH), chicken type II form (cGnRH-II), and salmon form (sGnRH) have been cloned from *Sparus saeba*, and the promoter regions were cloned by genome walking. Estrogen responsive element (ERE) and progesterone responsive element (PRE), which are involved in the modulation of estrogen and progesterone and the expression of vitellogenin gene, were found in these promoter regions. Depending on promoter structure and regulatory function of three forms of GnRH, the expression of gonadotropin (GTH) gene would be down-regulation in the pituitary gland to cause gonad undevelopment by using the specific and inducible promoter to drive the expression of antisense RNA or cell apoptotic gene such as the *bax* and *bok* gene. The establishment of infertile technology may lead to genetically modified fish being unable to spawn in the wild during the next generation.

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4. DEVELOPMENT AND APPLICATION OF BIOFERTILIZERS IN THE REPUBLIC OF CHINA

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INTRODUCTION

Taiwan experiences a humid, subtropical climate, with a mean temperature of around 20°C (November to April) and above 30°C (June to November). Rainfall is over 3,000 mm in the central region, 1,500–3,000 mm on the east coast, and 1,500–2,000 mm in the western region adjacent to mountains, with frequent typhoons during summer and autumn impacting agriculture. Uncontrolled application of chemical fertilizer is a common practice in most areas. The estimated consumption of chemical fertilizer is about 1,140,000 tons for 844,000 ha. However, many upland regions and lowland soils are less fertile and need greater fertilizer input to sustain yields.

Agriculture is oriented towards intensive farming practices, and every effort is being made to shorten the growth period of each crop so that more crops can be grown during the following season. Intensive multiple cropping systems have drastically reduced the use of leguminous plants as green manure, since this requires a longer growth period. Still, legumes such as soybean, peanut, mungbean, pea, etc. are planted, but only as part of an intensive multiple cropping system (Young and Chao, 1983).

It is well known that the crop root zone (rhizosphere) provides a unique microsite for the association of symbiotic and nonsymbiotic microorganisms (Young, 1994). N₂-fixing and P-solubilizing bacteria have been well characterized from various soil types and aquatic environments (Seshadri et al., 2000; Garg et al., 2001; Berman-Frank et al., 2001; Young et al., 1982; Young and Cheng, 1998; Young et al., 2003a,b&c), and many isolates have been shown successful in improving crop yield (Subba Rao, 1982; Young et al., 1988a&b; Young, 1994). Hence, several beneficial microorganisms can be used effectively as a chemical fertilizer alternative to minimize the application of inorganic fertilizers.

Biofertilizers, which can be more appropriately called microbial inoculants, can be generally defined as preparations containing live or latent cells of an efficient microbial strain capable of nitrogen-fixing, phosphate-solubilizing (bacteria, fungi, or algae), or any other beneficial activity derived from this process. Biofertilizers may be applied to either seed or soil to accelerate microbial processes in soil, thereby augmenting the availability of nutrients by making them easily assimilated by crop plants.

This paper briefly reviews the status of biofertilizers that have been developed in a few Republic of China laboratories in recent years, with a major emphasis on microorganisms, including rhizobium, P-solubilizing bacterium, and mycorrhizal fungi that were identified as suitable candidates able to meet the nutrient requirements of various crop species and known to increase yields.

SELECTION AND DEVELOPMENT OF BIOFERTILIZERS

Rhizobial Inoculants

In the Republic of China, research on the selection of efficient rhizobial strains for inoculation started in 1958. Collection, isolation, and subsequent selection of effective rhizobial strains and their uses in agriculture have yielded fruitful results. Since marked variations were observed

among rhizobial strains (Young and Chao 1983), Wu (1958) selected a number of pure rhizobial strains from lupin, alfalfa, peanut, crotalaria, and soybean and conducted a wide range of field experiments to select the effective inoculants. Yield was significantly increased when lupin, alfalfa, peanut, and soybean were inoculated with selected rhizobial strains, compared to those with non-inoculated plants.

After the 1980s, fast- and slow-growing soybean rhizobial strains were isolated and selected from Taiwan soils for inoculation (Young et al., 1982; Young and Chao, 1983), and several effective isolates were deposited in the Culture Collection and Research Center (CCRC) of the Food Industry Research and Development Institute (CCRC, 1991).

Field experiments have been conducted to determine the effects of single and mixed inoculations with rhizobium and Arbuscular-Mycorrhiza (AM) in six different tropical Taiwan soils (Young et al., 1988b). The results indicated that inoculation with rhizobial strains alone increased N_2 fixation and soybean yield in three out of six fields. Inoculations with rhizobial strains singly, or in combination with AM, without any N_2 fertilizer application, significantly increased soybean yield, from 5% to 134%, in the field experiments. The results from other experimental sites also showed that a mixed inoculum of rhizobium and AM can be an efficient biological fertilizer that maximizes soybean yields. The combined effect of the mixed inoculum was a striking finding in the field of biofertilization. The AM might have provided the essential P for the growth of soybean plants.

P-solubilizing Microbial Inoculants

P-solubilizing bacteria have been isolated from various tropical soils of Taiwan. Aliquots of soil diluted with sterile water (1:10 soil/water) were plated on calcium phosphate medium (modified from Subba Rao, 1982) for the isolation of P-solubilizing bacteria.

The basic research on P-solubilizing biofertilizers was successfully established during the 1990s (Young, 1990; Chang and Young, 1992a&b; Young et al., 1998a&b; Chang and Young, 1999, Young et al., 2000; Liou and Young, 2002; Young et al., 2003a,b&c). Crop plants such as peanut, various horticultural plants, and vegetables were successfully inoculated with PSBs to obtain higher yields. Several field experiments concluded that P-solubilizing bacteria not only improved the growth and quality of crops but also drastically reduced (one-third to one-half) the usage of chemical or organic fertilizers.

A-Mycorrhizal Inoculants

The major VAM fungi used as inoculants are *Glomus* spp. isolated from tropical soils of Taiwan (Young, 1986). Chlamydospores are borne terminally on single undifferentiated hyphae in soil. The mature spores were separated from the attached hyphae by a septum. The AM fungal inoculant was placed in pots containing sterilized mineral attapulgite $[(Mg,Al)_5Si_8O_{22}(OH)_4 \cdot 4H_2O]$ with *Zea mays* as the host plant. The VAM fungal inoculant used in pot experiments contained approx. 50 spores/g soil together with infected roots (Young et al., 1988b).

Young et al. (1986) used two species of AM in a pot experiment to observe the effects of inoculation of AM fungi on the yield and mineral P utilization in soybean. The results showed that the AM fungi inoculation increased soybean yields over the uninoculated treatments, but results depended on the soil type. Moreover, the P uptake by soybean was significantly improved in the inoculated treatments. In a similar experiment, rhizosphere soil was used to assess the difference in P uptake by soybean plants. Soybean in non-inoculated treatments took up minimum Al-P from acidic soils, less Ca-P from calcareous soil, but failed to absorb Fe-P from any soil type. Inoculation with either of the two mycorrhizal fungi improved the uptake of Al-P by soybean in acidic soils and also increased the uptake of Ca-P in calcareous soils, and a significant amount of Fe-P uptake was evidenced. These results suggested that AM can enhance uptake of fixed soil P. The efficiency rate and utilization of various forms of mineral P by mycorrhizal plants depends on the species of mycorrhizal fungi inoculated and on the soil type.

Further, Chang and Young (1992b) showed that tea cuttings (cv. TTES No. 12) inoculated with A-mycorrhiza or P-solubilizing bacteria significantly enhanced the growth of tea seedlings.

Application of Biofertilizers in the Republic of China

In order to promote sustainable agriculture, both central and local government agencies in the Republic of China are supporting extensive applications of biofertilizers. Major programs for the application of biofertilizers include production of rhizobial, P-solubilizing microbial inoculants for soybeans used as vegetables and for other crops and the production of AM-inoculants for melons and other horticultural crops. One project also aimed at improving biological nitrogen fixation in soybeans that are consumed as vegetables, in peanuts, and in red bean. Similarly, emphasis is also laid on attaining higher yields and better quality horticultural crops through three major programs: the production of inoculants, extension programs so that farmers can apply inoculants onto their farms, and demonstrations and awareness programs to show farmers the benefits of inoculated plots.

Soybeans for vegetable purposes are produced extensively in the Republic of China and exported to Japan. Constant maintenance of superior quality will be an important factor governing the export value of soybeans in the international market. Earlier, farmers were applying more chemical fertilizers than the recommended levels, leading to inferior quality in the beans. The Department of Soil and Environmental Sciences at National Chung Hsing University in the Republic of China has since 1988 been actively producing and distributing efficient inoculum (liquid and solid biofertilizers) that can maintain yield and produce superior quality soybeans which are exported and consumed presently as vegetables in several countries. Figures 1–3 show the increase in the area of inoculated crops over the past years. During the last 18 years (from 1987 to 2004), inoculants were produced to inoculate approximately 65,091 ha of farmland. In the same period, farmers' economic gains have also increased significantly after application of rhizobial inoculants (USD27 million). Moreover, a great deal of chemical fertilizer was saved, and further groundwater pollution caused by N leaching was significantly reduced.

Healthy seedlings are one of the essential factors affecting the growth and yield of crops. Over the past decade, mycorrhizal inoculants have been produced in Taiwan and applied to many crops, particularly horticultural and ornamental plants such as muskmelon, citrus, strawberry, lily, tomato, chrysanthemum, gerbera, tea, and fruit trees (Chang 1987, 1993, 1994; Chang and Young 1992a&b; Cheng and Chung 1991; Chen and Hung 1994; Young 1990).

CONCLUSIONS

An excess of nutrients, particularly P, has accumulated in Taiwan soils as a result of over-application of chemical fertilizers by farmers during intensive agricultural practices. Hence, a major research focus should be on the production of efficient and sustainable biofertilizers for crop plants so that inorganic fertilizer applications can be reduced significantly to avoid further pollution problems. With the view of overcoming this bottleneck, it will be necessary to undertake short-, medium-, and long-term research in which soil microbiologists, agronomists, plant breeders, plant pathologists, and even nutritionists and economists must work together.

The most important and strategic research initiatives should highlight the following points:

Selection of effective and competitive multifunctional biofertilizers for a variety of crops.

Quality control systems for the production of inoculants and their application in the field to explore and ensure the benefits of plant-microbe symbiosis.

Study of microbial persistence of biofertilizers in soil environments under stressful conditions.

Agronomic, soil, and economic evaluation of biofertilizers for diverse agricultural production systems.

Business Potential for Agricultural Biotechnology Products

Transfer of technological know-how for biofertilizer production at industrial level for optimal formulation.

Establishment of a Biofertilizer Act and strict user guidelines for quality control in markets and applications.

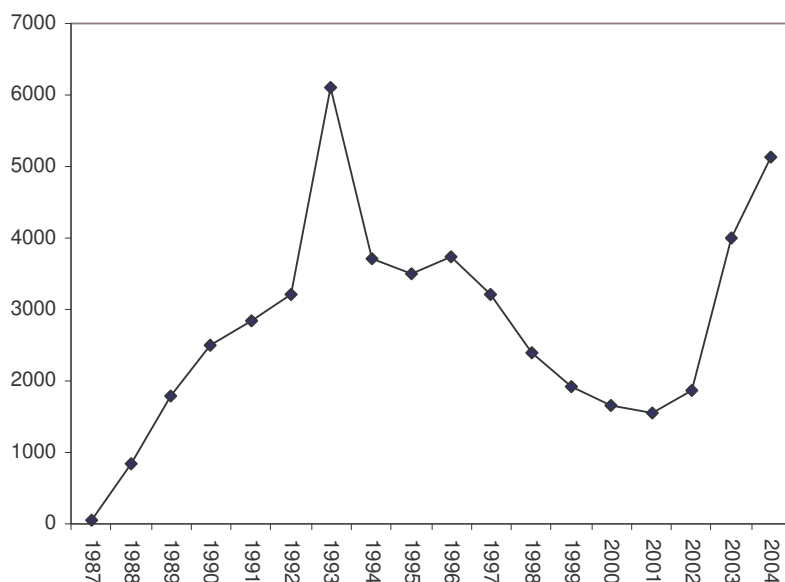


Figure 1. Total Area of Vegetable Soybean Inoculant Used in the Republic of China

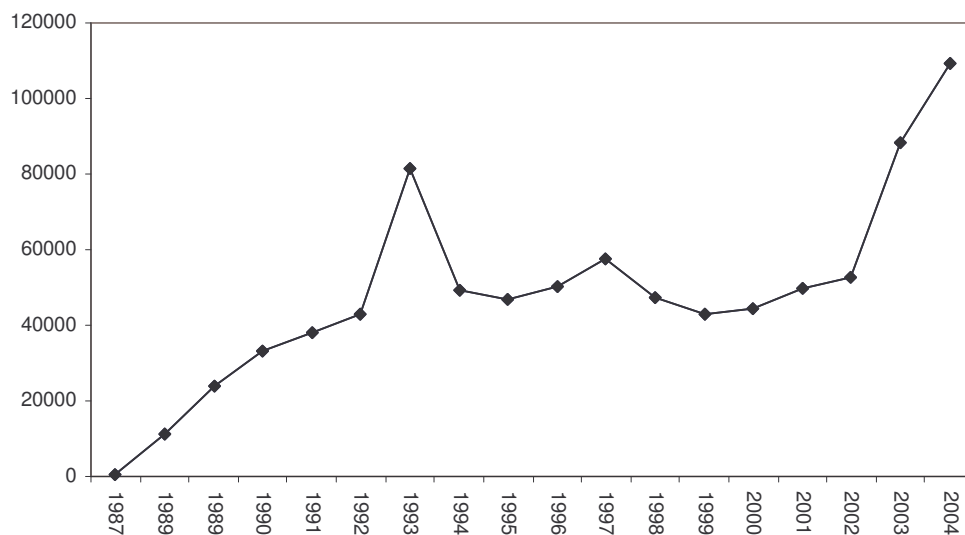


Figure 2. Total Area Covered Under Biofertilizer Application and Extension Programs Over the Years in the Republic of China

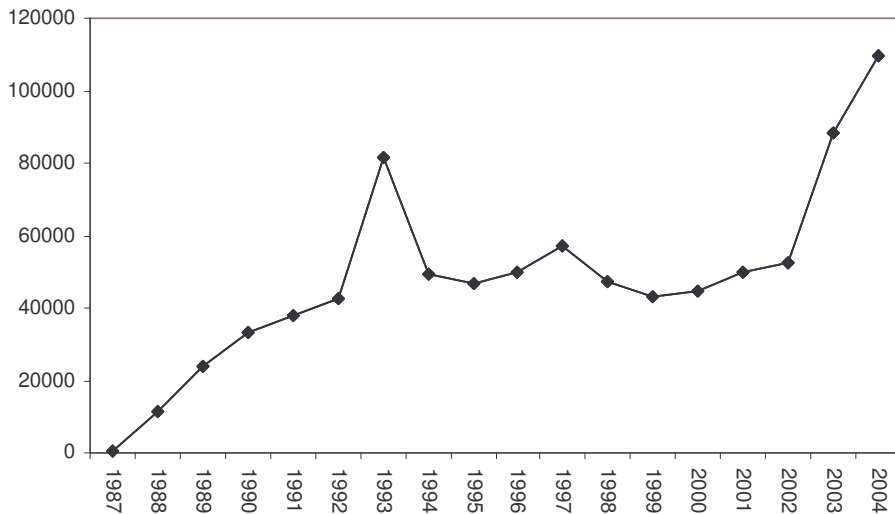


Figure 3. Total Net Benefit Achieved by the Farmer from the Biofertilizer Application and Extension Programs over the Years

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5. CURRENT STATUS OF THE TRANSGENIC APPROACH FOR CONTROL OF *PAPAYA RINGSPOT VIRUS*

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INTRODUCTION

There are many common names for papaya (*Carica papaya* L.), including papaw or paw paw (Australia), mamao (Brazil), and tree melon (China). The species is believed to be native in southern Mexico and neighboring Central America and was brought to Caribbean countries and Southeast Asia during the Spanish exploration in the sixteenth century (Storey, 1969). It then spread rapidly to India and Africa, and today it is widely distributed throughout the tropical and subtropical areas of the world.

A papaya plant has a single erect and tree-like herbaceous stem, with a crown of large palmately and deeply-lobed leaves. The main stem is cylindrical, hollow, with prominent leaf scars and spongy-fibrous tissue. Leaves are arranged spirally, with petioles extending horizontally up to 1 m long. Trees contain white latex in all parts. Flowers are male, female, or hermaphrodite, found on separate trees, and are borne in the axils of the leaves. The modified cymose inflorescences structure allows the flowers to be easily pollinated by wind and insects. The type of flowers produced may change on the same tree, depending on age and environmental factors such as drought and broad temperature fluctuations. Hermaphroditic trees consistently produce male flowers, but only with few female flowers that produce fruits during warmer or cooler seasons, whereas female trees are more stable and always produce pistillate flowers under these conditions.

Papaya fruits are fleshy berries and superficially resemble melons. Fruits from female trees are spherical, whereas those from hermaphroditic trees are pyriform, oval, or cylindrical with grooved surfaces. Since the female fruits contain thinner flesh and more seeds in the central cavity, the hermaphrodite fruits are more in demand by consumers. The fruit is a good source of vitamins A and C (Manshardt 1992). Ripe fruits are largely used as fresh dessert fruits, and green fruits are often used as salad and pickled or cooked as vegetable. Papain, a proteolytic enzyme present in the latex, collected mainly from green fruits, has various usages in the beverage, food, and pharmaceutical industries, e.g., chill-proofing beer, tenderizing meat, and drug preparations for digestive ailments (Chan and Tang, 1978). It is also used in bathing hides, softening wool, and as soap for washing cloth.

Papaya grows relatively easily and quickly from seeds. It can grow up to 10 or 12 feet in height. Fruits are ready to be harvested 9–12 months after planting, and a tree can continue producing fruits for about 2–3 years, up to when plant height is too tall for efficient harvesting. Since plant sex cannot be distinguished before flowering, 3–5 seedlings are normally planted together and only the most vigorous hermaphrodite ones during flowering are selected and cultivated. In 2004, the FAO estimated that about 3.7 hundred thousand harvested hectares and about 6.5 million metric tons of fruit were harvested (Table 1). Brazil, Mexico, Nigeria, India, and Indonesia yield more than 70% of the total world production. The extensive adaptation of this plant and wide acceptance of the fruit offer considerable promise for papaya as a commercial crop for local and export purposes. Like banana, pineapple, and mango, papaya is one of the important cash crops in the tropics and subtropics. However, the production of this economically important fruit crop is limited by the destructive disease caused by *Papaya ringspot virus*

(PRSV), and the fragile and perishable fruit traits are unfavorable for large-scale export. As a result, papaya lags far behind banana and pineapple in world markets.

Table 1. World Papaya Production in 2004

Country	Hectares (×1,000)	Metric tons (×1,000)
Brazil	36.0	1,600
Mexico	26.3	956
Nigeria	91.0	755
India	80.0	700
Indonesia	10.0	650
Ethiopia	11.0	230
Congo	12.5	211
Venezuela	11.0	170
Peru	13.0	170
China	6.2	165
Cuba	7.0	125
Thailand	10.5	125
Colombia	4.0	102
Philippines	6.6	79
Malaysia	6.5	65
Other	34.2	401
Total	365.8	6,504

Source: Food and Agriculture Organization (FAO), Statistical Division, 2004 (<http://faostat.fao.org/faostat/>)

THE WORLDWIDE THREAT OF PRSV INFECTION

Production of papaya has been limited in many areas of the world due to the disease caused by *Papaya ringspot virus* (PRSV) (Purcifull et al., 1984). Papaya ringspot disease is the major obstacle to large-scale commercial production of papaya (Yeh and Gonsalves, 1984). PRSV was first reported in Hawaii in the 1940s (Jensen, 1949a) and then became prevalent in Florida (Conover, 1964), Caribbean countries (Adsuar, 1946; Jensen, 1949b), South America (Herold and Weibel, 1962), Africa (Lana 1980), India (Capoor and Varma, 1948; Singh, 1969), the Far East (Wang et al., 1978), and Australia (Thomas and Dodman, 1993). To date, most of the major papaya plantation areas of the world suffer from the devastation of this noxious virus.

Characteristics of PRSV

PRSV, a member of the genus *Potyvirus* (Purcifull et al., 1984; Murphy et al., 1995), is transmitted nonpersistently by aphids and is also sap-transmissible in nature. The PRSV genome contains a single-stranded positive-sense RNA of about 40 S (De La Rosa and Lastra, 1983; Yeh and Gonsalves, 1985). Strains of PRSV from Hawaii (Yeh et al., 1992) and Taiwan (Wang and Yeh, 1997) have been completely sequenced; both contain 10,326 nucleotides in length. The viral RNA encodes a polypeptide that is proteolytically cleaved to generate 8–9 final proteins, including the coat protein for encapsidation of viral genome (Yeh et al., 1992). The virus has a single type of coat protein (CP) of 36 kDa (Purcifull and Hiebert, 1979; Gonsalves and Ishii, 1980). It induces cylindrical inclusion (CI) (Purcifull and Edwardson, 1967) and amorphous inclusion (AI) (Martelli and Russo, 1976) in the cytoplasm of host cells. The former consists of a protein of 70 kDa (cylindrical inclusion protein CIP; Yeh and Gonsalves, 1984), and the latter

consists of a protein 51 kDa (amorphous inclusion protein, AIP; De Mejia et al., 1985a, 1985b). On papaya plants, PRSV causes severe mosaic and distortion on leaves, ringspots on fruits, and water-soaked oily streaks on upper stems and petioles. It stunts the plant and drastically reduces the size and the quality of the fruit.

No Effective Control Measures

Although tolerant selections of papaya have been described (Cook and Zettler, 1970; Conover, 1976; Conover et al., 1986), resistance to PRSV does not exist in the species of *C. papaya*, which makes conventional breeding difficult (Cook and Zettler, 1970; Wang et al., 1978). Tolerance to PRSV has been found in some papaya lines and introduced into the commercial varieties, but their horticultural properties are still not commercially desirable (Mekako and Nakasone, 1975; Conover and Litz, 1978). Other control methods for PRSV include agricultural practices such as rouging, quarantine, intercropping with corn as a barrier crop, and protecting transplanted seedlings with plastic bags. All provide only temporary or partial solutions to the problem (Wang et al., 1987; Yeh and Gonsalves, 1994).

PRSV HA 5-1, a cross-protecting mild mutant strain of PRSV that was selected following nitrous acid treatment of a severe strain (HA) from Hawaii (Yeh and Gonsalves, 1984), was tested extensively in the field and has been used commercially in Taiwan and Hawaii since 1985 to permit an economic return from papaya production (Wang et al., 1987; Yeh et al., 1988; Yeh and Gonsalves, 1994). However, the approach of deliberate infection of a crop with a mild virus strain to prevent economic damage by more virulent strains has several drawbacks, including the requirement for a large-scale inoculation program. There may also be reduction in crop yield and losses of cross-protected plants due to superinfection by virulent strains (Stubbs, 1964; Gonsalves and Garnsey, 1989; Yeh and Gonsalves, 1994).

CONTROL OF PRSV BY THE TRANSGENIC APPROACH

The concept of “pathogen-derived resistance” (Sanford and Johnston, 1985) proposes that transforming plants with a pathogen’s gene would generate resistance to the infection of the corresponding pathogen. By this concept, Powell-Abel et al. (1986) first demonstrated that transgenic tobacco plants expressing the coat protein (CP) gene of *Tobacco mosaic virus* (TMV) conferred resistance to TMV infection. The CP gene-mediated transgenic resistance has been proven effective for protecting tobacco, tomato, potato, and other crops from infection by many different viruses (Beachy, 1990; Lomonosoff, 1995; Goldbach et al., 2003). Thus, the transgenic approach has become the most effective method of protecting crops from virus infection.

In order to solve the problems caused by PRSV, the Gonsalves group at Cornell University and Hawaii started a research project in the late 1980s to develop transgenic papaya. Ling et al. (1991) first demonstrated that the expression of the PRSV HA 5-1 CP gene in tobacco afforded a broad spectrum of protection against different potyviruses. However, effective gene transfer systems require reliable and efficient procedures for plant regeneration from cells. Fitch and Manshardt (1990) reported that somatic embryogenesis from immature zygotic embryos of papaya can be integrated into a useful gene transfer technology. In the same year, Fitch et al. (1990) successfully incorporated the CP gene of HA 5-1 into papaya via microprojectile bombardment and obtained plants resistant to infection by the severe Hawaii HA strain. Among their transgenic papaya lines, line 55-1 was virtually immune to infection by HA.

A Successful Application of Transgenic Papaya in Hawaii

The plants of transgenic papaya line 55-1 are highly resistant to Hawaiian PRSV isolates under greenhouse and field conditions (Fitch et al., 1992; Lius et al., 1997). The resistance is triggered by the post transcriptional gene silencing (PTGS), an RNA-mediated specific degradation process of the innate nature of plants against pathogens (Baulcombe, 1996; Baulcombe,

1999; Hamilton and Baulcombe, 1999; Gonsalves, 2002). However, the resistance is affected by the sequence identity between the CP transgene and the CP coding region of the challenge virus (Tennant et al., 1994). For example, Rainbow (a CP-hemizygous line derived from SunUp crossed with nontransgenic Kapoho) is susceptible to PRSV isolates outside Hawaii, and SunUp (a CP-homozygous line of 55-1) is resistant to a wider range of isolates from Jamaica and Brazil but susceptible to isolates from Thailand and Taiwan (Gonsalves, 1998; Tennant et al., 2001; Gonsalves, 2002). This characteristic of sequence homology-dependent resistance limits the application of CP-transgenic papaya for controlling PRSV in geographic regions other than Hawaii (Gonsalves, 2002).

The field trial of the homozygous line Sunup and hemizygous line Rainbow indicates that both offer a good solution to the PRSV problem in Hawaii (Ferreira et al., 2002). By May 1998, Rainbow and SunUp had been deregulated by the U.S. Animal and Plant Health Inspection Service and the Environmental Protection Agency and granted approval from the Food and Drug Administration for commercial application (Gonsalves, 2002). This is the first successful case of a transgenic fruit tree being commercialized.

Transgenic Papaya Generated in Taiwan

Other than Hawaii, a CP gene of a native Taiwan strain PRSV YK was used to transform Taiwan papaya cultivars by *Agrobacterium*-mediated transformation (Cheng et al., 1996). The transgenic lines obtained showed various levels of resistance, ranging from delay of symptom development to complete immunity (Bau et al., 2003). Several lines highly resistant to the homologous strain (PRSV YK) provided wide-spectrum resistance to three different geographic strains from Hawaii, Thailand, and Mexico (Bau et al., 2003). During four repeats of field trials from 1996 to 1999, the transgenic papaya exhibited high degrees of protection against PRSV in Taiwan (Bau et al., 2004). Unfortunately, 18 months after planting in the fourth field trial, unexpected symptoms of severe distortion on fully expanded leaves, stunning on apex, water-soaking on petioles and stem, and yellow ringspot on fruit were noticed on PRSV CP-transgenic papaya plants. The causal agent was distinguished from PRSV by host reactions and serological properties (Bau, 2000) and later identified as *Papaya leaf distortion mosaic virus* (PLDMV), a potyvirus which originated from Okinawa, Japan, in 1954 (Maoka et al., 1996). All of PRSV CP-transgenic papaya lines were susceptible to PLDMV infection when evaluated under greenhouse conditions. Therefore, in Taiwan PLDMV will be considered a serious threat to papaya production once PRSV CP-transgenic papaya is widely used for the control of PRSV.

MULTIPLE AND DURABLE RESISTANCE AGAINST DIFFERENT VIRUSES

In order to control two or more viruses, transgenic plants with multiple resistances have been generated by combining the entire CP gene of more than one virus, with each gene driven by a promoter and a terminator (Fuchs and Gonsalves, 1995). Transgenic lines expressing these chimeric CP constructs were resistant to the corresponding viruses and protected from mixed infection such as *Cucumber mosaic virus*, *Watermelon mosaic virus*, and *Zucchini yellow mosaic virus* (Fuchs and Gonsalves, 1995; Tricoli et al., 1995; Fuchs et al., 1998). Furthermore, the novel approach proposed by Jan et al. (2000) showed that transgenic plants with resistance to a potyvirus and a tospovirus can be obtained through the PTGS mechanism by fusing a segment of tospoviral N gene to a segment of potyviral CP gene. The same strategy was used to develop double resistance to both PRSV and PLDMV. An untranslatable chimeric construct that contained the truncated PRSV CP and PLDMV CP genes was then transferred to papaya. Through the PTGS mechanism, transgenic papaya plants carrying this chimeric transgene indeed conferred resistance against both PRSV and PLDMV under greenhouse conditions (S.D. Yeh, unpublished results). These transgenic papaya plants with double resistance are considered to have great potential for the control of PRSV and PLDMV in the Republic of China.

In four-year field trials, a super PRSV strain 5-19 which infected transgenic papaya lines was found (Tripathi et al., 2004). The nucleotide identity between the transcript of the CP transgene and PRSV 5-19 RNA was less divergent than that between the CP transgene and other PRSV geographic strains that are not able to overcome the transgenic resistance (Tripathi et al., 2004), indicating that the breakdown of the transgenic resistance was not correlated to the sequence divergence between the infecting virus and the transgene. In order to analyze the role of the gene-silencing suppressor HC-Pro of this super strain, the virus recombinant was constructed by replacing a HC-Pro region of PRSV YK with that of 5-19, and the resistance against the recombinant was evaluated on transgenic papaya. The results showed that the heterologous HC-Pro region of 5-19 alone provides the ability to break down the transgenic resistance in a transgene sequence-homology independent manner, even though the sequences of the transgene transcript shares 100% identity with the genome of the infecting virus (S.D. Yeh, unpublished results). The breakdown of the transgenic resistance by a strong gene-silencing suppressor of a super strain has strong impacts on the application of transgenic crops for virus control. It is suggested that a chimeric construct targeting at multiple viral genes, including the gene determining viral virulence and gene silencing suppression, such as the HC-Pro gene of a potyvirus, may minimize the chance of emergence of a supervirus for overcoming the transgenic resistance.

TRANSGENIC PAPAYA GENERATED IN OTHER GEOGRAPHIC AREAS

Because of the apparent homology dependence of PRSV CP transgene-associated resistance, the utilization of a CP gene of a local prevalent strain is a prerequisite to obtain effective PRSV resistance in transgenic papaya lines for a particular geographic region, as long as genetic variation among virus strains in that region is not a limiting factor (Gonsalves, 2002). Using the CP genes of local PRSV isolates to transform local papaya cultivars has been successfully reported in different countries. Lines et al. (2002) used an untranslatable PRSV CP coding region as a transgene to develop two Australian transgenic papaya cultivars which showed immunity to the local PRSV isolate in the greenhouse and field tests. Fermin et al. (2004) constructed PRSV-resistant plants by transforming independently with the CP genes of PRSV isolates from two different areas of Venezuela. All the transgenic lines, including R_0 and inter-crossed or self-crossed progenies, revealed different levels of resistance to homologous and heterologous isolates from Hawaii and Thailand. In Florida, transgenic papaya lines carrying the CP gene of the local strain were generated, and the transgenic resistances were introduced to elite papaya cultivars by conventional breeding (Davis and Ying, 2004). In addition to the CP gene, the truncated replicase (RP) gene of PRSV was used as a transgene to generate transgenic papaya through *Agrobacterium*-mediated transformation (Chen et al., 2001). PRSV inoculation tests showed that the RP gene conferred resistance to PRSV in transgenic papaya.

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6. COMMERCIAL-SCALE PRODUCTION OF VALUABLE PLANT BIOMASS AND SECONDARY METABOLITES USING A BIOREACTOR SYSTEM

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INTRODUCTION

Plants produce an array of secondary metabolites that are potential sources of highly valuable fine chemicals, including pharmaceuticals, agrichemicals, flavors, and fragrances (Hadacek, 2002; Rao and Ravishankar, 2002). It is therefore of economic importance to cultivate plant resources for commercial production of secondary metabolites. Unfortunately, however, many secondary metabolites are synthesized at a very low level in field-grown plants. As an alternative to field cultivation, plant tissue culture technology has been developed to allow *in vitro* rapid propagation of plant masses and to produce the secondary metabolites under controlled culture conditions (Mulabagal and Tsay, 2004).

KOREAN MOUNTAIN GINSENG— OUR CHOICE OF MEDICINAL PLANT FOR TISSUE CULTURE

Ginseng, one of the most widely used medicinal herbs in the world, is obtained from the roots of several species of the plant family *Araliaceae* and the genus *Panax*. Popular commercial species include Korean (*Panax ginseng* C.A. Meyer) (Figure 1), American (*Panax quinquefolius* L.), Japanese (*Panax japonicus* C.A. Meyer), and the non-*Panax* species Siberian (*Eleutherococcus senticosus*) ginseng (Kiefer and Pantuso, 2003). Currently, ginseng's therapeutic uses, already recorded around 2,000 years ago, are as diverse and potent as its genus name *Panax* (Greek "cure-all") implies. In Germany, ginseng is one of the few economically important herbal drugs listed separately in the Foreign Trade Statistics and is officially approved for use as a tonic for invigoration and fortification in cases of fatigue.

Korean ginseng is considered the best in quality because of its superb pharmaceutical efficacy, due largely to the specific climate and soil conditions of Korea and also the cultivation technology developed by Korean people through many generations.



Figure 1. A Typical Root Harvested from Korean Mountain Ginseng (*Panax ginseng* C.A. Meyer)

TISSUE CULTURE FOR GINSENG ROOT PROLIFERATION

Although hairy root (transformed root) cultures are a promising method known to be superior for ginseng cell culture, this has also been known to produce opine-like chemicals which are lethal to humans. To avoid this problem, the adventitious roots (Figure 2) induced from ginseng callus were chosen for cultivation instead of the hairy roots (Son et al., 1999; Seon et al., 1999; Choi et al., 2000; Paek et al., 2001).

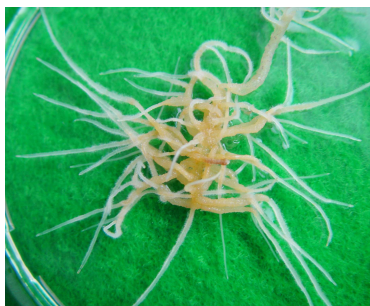


Figure 2. Adventitious Roots Induced from Explants of Korean Mountain Ginseng Root

INDUCTION OF MULTIPLE ADVENTITIOUS ROOTS

Donor ginseng plants were washed and surface-sterilized before being subjected to aseptic dissection into small pieces of explants. The explants were then cultured on MS solid media supplied with various combinations of plant growth regulators (PGRs). After four weeks of cultivation, rapidly growing cells produced on the surface of explants were isolated and subcultured onto the same media for further growth of callus. The subcultures were repeated six times before the effect of PGRs on the induction of adventitious roots from these calli was tested. It was found that the levels and types of auxin in the growth medium played an essential role in determining the number of induced roots (Son et al., 1999). IBA in particular induced significantly more roots per segment than the other auxins. The roots induced by the IAA and 2,4-D treatments displayed a slower growth rate and a vitrified morphology. However, the roots induced by IBA and NAA showed a normal morphology.

BIOREACTOR CULTURE

For small-scale culture (5L and 20L) in the laboratory, a balloon-type bubble bioreactor (BTBB) system made of glass, as shown in Figure 3A, was established. The root suspension cultures grown in 1L Erlenmeyer flasks were harvested and cut using a motor-driven blade at 60 rpm to prepare a seed culture of 2-mm-sized root segments. The inoculum for each BTBB was adjusted to 1% (w/v) of fresh weight. Culture growth in 5L and 20L bioreactors followed a sigmoidal curve and produced the maximum biomass of 500g and 2.2 kg in fresh weight after 42 days of cultivation. Root cutting during the culture increased the root mass yield but did not affect the saponin content per gram dry weight. Among the different growth media, SH media gave the highest mean number of multiple roots.

For commercial-scale cultures, an airlift drum-type bubble bioreactor (DTBB) of 20 kL volume capacity (Figure 3B) was employed. The DTBB was constructed of stainless steel with a sliding-type front door. Importantly, an air sparger was positioned at the bottom of the DTBB for the generation of air bubbles smaller than 0.5 μm in diameter. Sterilization of the DTBB was performed by using filtrated pressure steam. The same media composition for DTBB as the BTBB was used. The seed culture for DTBB was prepared by cutting the cultivated roots in the

seed bioreactor with a motor-driven blade. The growth temperature of the DTBB was controlled by circulating tempered water into the outside jacket.



Figure 3. Balloon-type Bubble Bioreactor (A) and Drum-type Bubble Bioreactor (B)

To develop a contamination-free system, a simple transfer system automatically controlled (Figure 4) for root cultures and media was deliberately designed in which the culture material was transferred from the small bioreactor to the main bioreactor by using sterilized air pressure.

The growth and saponin production patterns were almost the same regardless of the culture scale. The mean maximum biomass produced from a 20 kL DTBB was more than 500 kg in fresh weight after 56 days from inoculation. For the analysis of ginseng saponins, ginseng roots were air-dried, extracted with 70% ethanol for 3 hr, concentrated to dryness by evaporation, and redissolved in water for HPLC analysis. To improve the saponin yield in the cultures, various types of elicitors were tested.



Figure 4. Operation of the Commercial-scale Bioreactor System (left)
Is Centrally Controlled (right)

APPLICATIONS OF ROOT CULTURE

Plant secondary metabolites are usually produced in differentiated tissues (roots and shoots) at distinct developmental stages, but they are not synthesized at significant levels in undifferentiated cultures (callus and suspension cultures). In most cases, root culture provides an efficient method of secondary metabolite production, attributable to the rapid growth rate of roots in *in vitro* culture and the stable production of secondary metabolites in roots (Hadacek, 2002; Rao

and Ravishankar, 2002; Mulabagal and Tsay, 2004). Therefore, it is highly recommended that root culture be used for the cultivation of diverse medicinal plants. Root culture, however, had been considered very difficult for a long time because the roots were known to form ball-like aggregates during cultivation in bioreactors. This ball structure usually hinders the insides of the tissue mass from being properly nourished by nutrients and thus causes the browning of the inside.

In this mini-review, a system that enabled successful utilization of an industrial-scale bioreactor for the commercial production of ginseng roots was briefly described. This bioreactor system holds a promising future for many commercial applications, such as the large-scale production of diverse secondary metabolites from plant tissues.

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7. COMMERCIALIZATION OF AGRICULTURAL CROP BIOTECHNOLOGY PRODUCTS

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INTRODUCTION

One of the greatest achievements of the twentieth century has been the efforts of the global agricultural research community to achieve food security through the phenomenal increase in research-based crop and animal productivity that has fed millions and served as the basis of economic transformation in many poor countries, especially in the south Asian subcontinent (Conway, 1998; Teng, Fischer, and Hossain, 1995). This “Green Revolution” has belied the dire predictions of death and famine in Asia in the years following the Second World War. However, Nobel laureate Norman Borlaug has estimated that to meet projected food demands by 2025, average cereal yields must increase by 80% over 1990 figures (Borlaug and Doswell, 1999). This formidable task—ensuring that food production is coupled with both poverty reduction and environmental conservation—is made even more difficult because it will need to take into account policies and actions to promote agriculture and rural development, an enabling regulatory framework, fair trade, flexible and responsive institutions, increased investments in health and education, especially for women, and access to credit, roads, marketing, and extension. The development community has increasingly realized that new knowledge and products are necessary but not sufficient conditions for sustainable agricultural development, just as food production is a necessary but not sufficient condition for food security (Serageldin, 1999). Access to and ability to apply technological advances will become important preconditions for increased productivity, and in this, information technology and biotechnology will be key.

The greatest threat to sustaining food security and achieving real progress in alleviating poverty and hunger is the continuous unchecked growth of population. Although there has been notable progress in the reduction of fertility in Asia, particularly in countries which have made significant economic progress, the number of consumers is currently increasing by 1.8% per year. Population growth is the major driver in the food demand equation. Demographers now project that the world’s population will double during the first half of the next century—from 5.3 billion in 1990 to more than 10 billion by 2050 (United Nations Population Division, 1999). However, underpinning the population growth figures is a more insidious phenomenon, viz., that there will also be more people living in poverty, that most of the poor people in the world will live in Asia and Africa, and that there will be more people living in “megacities” than in rural areas (Naisbitt, 1995). The World Bank estimated that in 1990, there were 1.3 billion people living below the poverty line, of whom 65% were in Asia. Currently, most of these poor are rural, but Naisbitt’s predictions sound loud alarm bells. Concomitant with the move to freer markets worldwide, there will be fewer farmers to produce more per unit area, on less land with less water, to feed growing urban populations.

Indeed, public concern about food has resurfaced in recent years, especially in Asia, after what appeared to be a period of relative complacency following the success of the “Green Revolution.” Poverty continues to limit access to food, leaving hundreds of millions of people in developing countries undernourished. Improvement of the genetic material of crop plants and maintenance of the natural resource base which sustains their productivity are the major means of improving the welfare of poor people. In the developing world, people are not only the source

of the demand for food, jobs, and income; they are also a labor and management resource to be employed in a vast range of activities, from the production of inputs into farming to post-harvest processing and marketing.

Four sets of technologies have affected and will continue to have a significant impact on farming practices in the new millennium: biotechnology (BT), information technology (IT), physical technology (PT), and knowledge technology (KT). One or more of these will develop new approaches for farming, such as precision farming, which utilizes IT and PT to develop miniaturized systems for location-specific application of inputs and for land preparation and water management (Teng, 1999). Biotechnology offers the best opportunity to meet the challenge of improving on the potential in seeds and also of providing the enabling knowledge to express that potential. High-quality seed of crop cultivars with the desirable genetic background still form the foundation for farming. Increasing crop production under developing world conditions is strongly dependent on farmers having access to seeds with high potential yields and the inputs (fertilizer, water) necessary for this potential to be expressed. High-yielding crop cultivars are of limited benefit unless their potential high yields can be captured by farmers. In practice, both biotic and abiotic constraints operate to prevent many farmers from achieving the yield potential inherent in their seeds (Savary et al., 1997). This is tantamount to a “hidden loss.” At the same time, the potential will need to be protected during the crop’s growing period from infestations and infections which cause actual loss. Biotech crops have the capability, through new traits, to both raise yields and reduce losses.

CURRENT STATUS OF COMMERCIALIZED CROP BIOTECHNOLOGY

Nature and Value of Crop Biotech Products

A detailed review of the global status of commercialized biotech crops is presented in the accompanying paper, prepared by this author for this Mission Study (Teng, 2005), and only some points relevant to commercialization are presented here. Commercial crop biotech products consist of different crop varieties possessing specific traits. In 2004, the global area grown with biotech crops was estimated at 81 million ha, made up primarily of four crops: soybean, maize, cotton, and canola (Table 1).

Table 1. Biotech Crop Area as % of Global Area of Principal Crops, 2004 (million ha)

Crop	Global area	Biotech crop area	Biotech area as % of global area
Soybean	86	48.4	56%
Cotton	32	9.0	28%
Canola	23	4.3	19%
Maize	143	19.3	14%
Total	284	81.0	29%

Source: Clive James, 2004

During the nine-year period 1996 to 2004, herbicide tolerance has consistently been the dominant trait, with insect resistance second (James, 2004). In 2004, herbicide tolerance, deployed in soybean, maize, canola, and cotton, occupied 72% of the 81.0 million ha. There were 15.6 million ha planted to Bt crops, equivalent to 19%, with stacked genes for herbicide tolerance and insect resistance deployed in both cotton and maize occupying 9% of the global biotech area in 2004. It is noteworthy that whereas the area of herbicide-tolerant crops increased by a significant 18% (8.9 million ha) between 2003 and 2004, Bt crops increased at a higher level of 28% (3.4 million ha). This increase in Bt crops reflects the significant increase in Bt

maize in 2004 (2.0 million ha) and the increase of Bt cotton (1.4 million ha) in China, India, and Australia. Whereas most of the growth in Bt maize occurred in the U.S., significant increases in Bt maize area also occurred in Argentina, Canada, South Africa, Spain, and the Philippines. The stacked traits of herbicide tolerance and insect resistance in both maize and cotton increased by 17% in 2004, reflecting the needs of farmers who must simultaneously address the multiple yield constraints associated with various biotic stresses. This trend will continue and intensify as more traits become available to farmers and is an important feature of the technology.

Seeds conferring protection against insect pests and pathogens were among the first wave of biotechnology products; genetically modified crops possessing traits which confer tolerance to herbicides, resistance to insects using Bt endotoxins, and virus resistance are the most common traits. All these contain “transgenes.” Over the last three years, there have been dramatic and continuing increases in the area planted to transgenic crops. The adoption rates for transgenic crops are the highest for new technologies by agricultural industry standards (Table 2). The U.S. alone accounted for 74% of the area planted to transgenics. Argentina and China are the only developing countries with significant transgenic plantings. Total transgenic crop sales grew more than sixfold, from USD235 million in 1996 to USD1.2–1.5 billion in 1998. The market is projected to increase to USD3 billion or more in the year 2000, to USD6 billion in 2005, and to USD20 billion in 2010 as more crops and more traits are introduced (James, 2004).

Table 2. Global Value of the iotech Crop Market, 1996–2004

Year	Value (USD million)
1996	115
1997	842
1998	1,973
1999	2,703
2000	2,734
2001	3,235
2002	3,656
2003	4,152
2004*	4,663
Total	24,073
*Forecast	

Source: Cropnosis 2004 (personal communication) (James, 2004)

The principal transgenic crops, in descending order of area, were soybean, maize, tobacco, cotton, and rapeseed/canola (James, 2004). The dominant transgenic crops and traits in 2004 were herbicide-tolerant soybean, Bt corn, insect resistant/herbicide-tolerant cotton, herbicide-tolerant canola, and herbicide-tolerant corn (James, 2004). Overall, the largest proportion of transgenic crops are those which possess the trait of tolerance to a herbicide. Many other traits have been engineered into crop cultivars for improved resistance to pests by both the private and the public sectors. For rice, transgenic plants have been developed with resistance to stemborers (Bt gene), resistance to pathogens (sheath blight, bacterial blight, tungro viruses, ragged stunt virus), tolerance to herbicides, and tolerance to drought, salinity, and submergence (ADB, 2001; Cohen, 2005).

The product pipeline for a major company like Monsanto shows that crop protection traits like combined resistances to Colorado potato beetle and potato virus Y, tolerance to potato leaf-

roll virus, are likely to be introduced in the near term, contributing to the growth worldwide in transgenic crops engineered for improved host plant resistance (Monsanto, 1998).

Although 17 countries are reported to have grown biotech crops in 2004, a larger number are known to have such crops in various stages of development leading up to commercial plantings. Of these 17 countries, 11 are developing countries. Indeed, Cohen (2005) has suggested that the public sector will be an important source of crop biotech products for poor farmers, as there are currently known to be more than 99 crop variety-trait modifications undergoing different stages of testing by public institutions in Asia.

Estimates of Market Potential

One way to provide a global perspective of the status of biotech crops is to characterize the global adoption rates as a percentage of the respective global areas of the four principal crops—soybean, cotton, canola, and maize—in which biotech technology is utilized (Table 2). The data indicate that in 2004, 56% of the 86 million ha of soybean planted globally were biotech, up from 55% in 2003, despite an increase in the global area of soybean from 76 million ha in 2003 to 86 million ha in 2004. Of the 32 million ha of cotton, 28% or 9.0 million ha were planted to biotech cotton in 2004. The area planted to biotech canola, expressed on a percentage basis, increased from 16% in 2003 to 19% or 4.3 million ha of the 23 million ha of canola planted globally in 2004. Similarly, of the 143 million ha of maize planted in 2004, 14% was planted to biotech maize, up significantly from 11% in 2003. Thus, the global adoption rates for all four biotech crops—soybeans, maize, cotton, and canola—all increased significantly between 2003 and 2004. If the global areas (conventional and biotech) of these four crops are aggregated, the total area is 284 million ha, of which 29%, were biotech, up significantly from 25% in 2003. Two-thirds of these 284 million ha are in the developing countries, farmed mainly by millions of small, resource-poor farmers, where yields are lower, constraints are greater, and the need for improved production of food, feed, and fiber crops is the greatest.

In 2004, the global market value of biotech crops, forecasted by Cropnosis, was USD4.70 billion, representing 15% of the USD32.5 billion global crop protection market in 2003 and 16% of the USD30 billion global commercial seed market (James, 2004). The market value of the global biotech crop market is based on the sale price of biotech seed plus any technology fees that apply. The accumulated global value for the nine-year period 1996 to 2004 (biotech crops were first commercialized in 1996), is USD24 billion (Table 2). The global value of the biotech crop market is projected at more than USD5 billion for 2005. These figures do not take into account any potential release of seed produced by the public sector through government sources. As the ADB (2001) has shown, there is a significant pipeline of products undergoing regulatory approval in many Asian countries.

Taking all factors into account, the outlook for 2010 points to continued growth in the global area of biotech crops, up to 150 million ha, with up to 15 million farmers growing biotech crops in up to 30 countries.

LAB TO MARKET PROCESSES IN COMMERCIALIZATION

Product Development

It is obvious that there is much ongoing research in Asia using recombinant DNA technology to produce genetically engineered plants with improved traits (Asian Development Bank, 2001). Much of this research, unfortunately, may not lead to commercialized products or products available to farmers on a large scale, largely because the work has been “technology pushed” rather than demand driven. In commercial product development, it is important to first conduct the market analysis of demand before any initial proof of concept research is done.

There are many steps needed to commercialize a crop biotech product from product concept to market product, and the time required ranges from 10 to 13 years. The individual

steps may vary by country, depending mainly on the regulatory regime in place for biosafety and food/feed safety.

Typically, a discovery group identifies a valuable protein which helps to confer a useful trait, such as insect resistance. The Bt protein is an example. At this stage, many questions are asked about the history of the protein, especially its safe use in its conventional form. When the history of safety is satisfied, a next step commonly is for molecular biologists to develop artificial constructs of the gene which makes the protein. These steps may take up to a year. So far, there is little biosafety consideration.

The insertion of the artificial gene construct into target plant cells is next accomplished through a process commonly called transformation. The target cells are from plant varieties with desirable commercial traits as well as being useful parents in a breeding program. Several transformation techniques are in use in labs worldwide; the biolistic or particle bombardment technique and agrobacterium insertion are the most common. The success fraction of transformations is very low, hence in some laboratories facilities are developed for automation. Successfully transformed cells containing the desired gene are then grown to whole plants using tissue culture techniques. All the above is done under biosafety regulatory purview, usually by means of an institutional biosafety committee made up of representatives from research, government, and society.

Next comes testing the plantlets or whole plants to determine if the desired trait is expressed in strong enough levels to justify a useful product. For example, a plant purported to contain the Bt gene may be tested by exposing it to insect larvae from the pest which it was developed to resist. This screening process again is often done en masse under biosafety supervision in greenhouses and may take one to three years.

When a crop variety containing the desired improved trait has been obtained, enough seed is prepared for field tests, commonly starting with a single location and progressing to multiple locations and crop seasons. All this is done in compliance with the existing biosafety regulations of the country concerned. Countries typically also require public notification and hearings to enable the proponents of the technology to dialogue with communities. At the same time that this is taking place, companies or public institutions proposing commercialization or release of the biotech crops in question are also accumulating evidence on the food/feed safety of the biotech crop. After two to three years of field evaluations and food/feed safety testing, the government body empowered to make a decision to approve the product must weigh all the evidence and render its decision.

In Asia, only the Philippines and India have had significant experience with the full cycle of commercialization. An important question to be asked is whether governments will expect public institutions to be subject to the same long, expensive process of testing a biotech crop before it is approved. In North America, regulatory agencies are willing to allow data sharing between products, on a scientific basis, so that the process is less cumbersome.

Regulatory Approval (Biosafety, Food/Feed Safety)

Regulatory approval is typically required for biosafety (environmental safety) and food/feed safety before any biotech crop can be released for commercialization. The status of biosafety approvals in Asia is shown in Table 3.

Table 3. Stage of Development of Biotech Crops, Asia, May 2005

Country	Laboratory	Field experiments	Precommercial (+) or commercial cropping (++)
China	+	+	++
Australia	+	+	++
Japan	+	+	+
(continued on next page)			

Business Potential for Agricultural Biotechnology Products

India	+	+	++
Indonesia	+	+	+ (++)
Thailand	+	+	+
Philippines	+	+	++
Vietnam	+	+	–
Malaysia	+	–	–
Singapore	+	–	–
Iran	+	+	++

Biosafety

The commercialization of any biotechnology product in agriculture produced using genetic engineering (R-DNA technology) requires that policies and procedures be in place to ensure that these products are environmentally safe. Such policies and procedures have come to be known collectively as biosafety. Biosafety is now the subject of an international protocol, called the Cartagena Biosafety Protocol (CPB) under the Convention for Biological Diversity. The CPB, ratified by 119 countries, provides the international legal basis for the movement of biotech products such as genetically modified (GM) seeds used for food, feed, or processing. Trade in GM products is worth several billion USD per year, and worldwide over 85 million hectares of GM crops are grown in some 17 countries, including countries from the developing world, such as Brazil, Argentina, South Africa, China, India, and the Philippines.

The CPB requires that countries have clear and transparent national policies and procedures to deal with research and development involving modern biotechnology. It also requires that risk assessments be carried out before laboratory and field experiments are conducted using GM seeds and that frameworks be established for performing biosafety evaluations prior to the commercial release of any GM product for food or feed. Key issues revolving around biosafety are liability and redress, risk assessment/management techniques, economic considerations, public awareness, handling and packaging of GM products, and notification and labeling requirements. A science-based approach is endorsed under the CPB. A Second Meeting of Parties (MOP-2) in Montreal, 30 May–3 June 2005, will discuss procedures for implementation of the Protocol. Biosafety issues therefore need to be effectively handled if they are not to become nontariff barriers to trade.

Biosafety is assessed using a process called risk assessment (Hancock, 2003). This takes into consideration the properties of the biotech plant, the ecosystem in which it is to be grown, and societal concerns, as well as economic benefits. Some issues concerning biosafety will be discussed in a later section of this paper.

Food Safety Criteria

National and international regulatory authorities require that food produced through biotechnology must meet the same safety standards as food grown conventionally; that is, there must be “reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption.” The safety standard for biotech food, therefore, is that these foods must be “as safe as” food produced by conventional methods. This standard of “reasonable certainty of no harm” is critical, since foods in general are not absolutely safe, and many current food products would not meet an absolute safety standard. The World Health Organization and the Organization for Economic Cooperation and Development have established a safety assessment process called “substantial equivalence” to ensure that foods derived from new processes are as safe as foods produced from conventionally bred crops. This process considers two main categories of risk: the properties of the introduced trait and any effects generated by the introduction or expression of the new trait in the crop or food. This is a comparative safety assess-

ment whereby conventional foods that have a history of safe use and consumption serve as a reference point for all safety testing.

Testing for Food and Feed Safety

Before any food crop produced using modern biotechnology can be marketed, the food product must undergo multiple years of rigorous safety assessment. In meeting stringent food safety requirements and standards, biotech foods are among the most thoroughly tested foods available. No other food crops in history—including foods currently available on grocers' shelves—have been tested and regulated as thoroughly as have foods developed through biotechnology. The safety of these foods is reviewed by regulatory agencies around the world according to internationally agreed-upon safety assessment guidelines.

Data are collected systematically to assess food safety. The five main categories of testing are the safety of the new trait (most often the introduced protein), a comparison of the agronomic characteristics of the new plant to conventionally bred plants, also called "agronomic equivalence," a comparison of the nutritional and biochemical composition of the new food with conventional food, also called "compositional equivalence," the safety of the resulting food or feed established by comparative animal feeding studies, and the nutritional wholesomeness of the new food or feed established by testing in farm animals.

Safety of the new trait (introduced protein). The safety assessment of products derived through biotechnology is unique in that the DNA inserted into the plant is well defined and well characterized. Therefore, the newly produced protein(s) will be clearly identified. It is also important that the new substance produced in most biotech crops is a protein because very few proteins are harmful to humans and the specific protein(s) produced can be directly assessed for safety.

Each introduced protein is extensively characterized to understand how it functions and assess its similarity to proteins already present in foods. For example, the protein used to confer tolerance to Monsanto's Roundup® herbicide, a member of a family of proteins present in most foods, has a well-defined function and is "generally recognized as safe" due to its history of safe consumption. The amount of the introduced protein is measured in key raw agricultural commodities to evaluate consumption levels and patterns. Comparison of the amino acid sequence of the introduced protein(s) to known toxins and allergens assures that the protein is neither a toxin nor an allergen nor closely related to either.

Since proteins are a key component in food and are typically rapidly digested, the digestibility of the protein plays an important role in predicting safety. All proteins that have been introduced into biotech crops have been rapidly digested. To assess the potential to cause harm, animal toxicology studies are conducted with each new protein at high levels (thousands to hundreds of thousands of times greater than the highest predicted consumption). Not surprisingly, given the nature and digestibility of proteins used as well as the history of safe consumption, no adverse effects have been observed in these studies.

The likelihood of the protein being an allergen or becoming an allergen is commonly assessed in detail according to international standards. The proteins used in commercial crops share none of the important characteristics that are common among known allergenic protein: none of these proteins is derived from allergenic sources or related to known allergens, the proteins are rapidly digested, and they are produced at low levels in the portions of the plant that are consumed. Therefore, it has been concluded that these proteins pose no significant allergenic concerns.

Agronomic equivalence. As part of the overall safety assessment of a crop developed via biotechnology, numerous agronomic and phenotypic parameters of the crop are compared with those of its conventional counterpart to assure that there are no meaningful changes caused by the transformation process or the introduced genes or trait. The morphology, yield, and other agronomic parameters are sensitive indicators of changes in the metabolism or physiology of the

plant. Plants developed through biotechnology must meet very stringent agronomic and performance criteria. This is a survey for unintended effects which, as in conventional breeding practices, helps eliminate plants with unintended effects.

Compositional equivalence. A key focus of substantial equivalence is a comprehensive comparison of key nutrients, antinutrients, toxins, and other compounds naturally present in foods. Biotech and conventional plant varieties are grown under a variety of field conditions to assess the composition under commercially representative growing conditions. The key macronutrients (e.g., protein, oil, carbohydrate, fiber, ash, and moisture), the levels of the individual amino acids, fatty acids, vitamins, and minerals, and the levels of key toxicants, antinutrients, and allergens are assessed. The values for the biotech crop are compared with both the parental control and other commercial varieties of that crop to assess whether the range of values obtained for the biotech crop fall within the levels of the conventional varieties. Typically 60 to 90 different components are analyzed.

Whole food comparative toxicology testing. To confirm that new foods and feeds developed by biotechnology are as safe as traditional foods or feeds, subchronic comparative feeding studies are typically performed with grain from both the biotech and conventional plant varieties, a very robust and internationally recognized testing approach that assesses the safety of the intentionally introduced proteins as well as any unintended consequences due to insertion of the genes into the plant genome or other unintended consequences relative to conventional plant varieties.

Nutritional wholesomeness in farm animal testing. Many companies involved in commercializing crop biotech products have conducted animal feed performance studies using farm animals such as dairy cows, beef cattle, swine, and poultry to confirm the compositional data, which showed that the grain from these crops is nutritionally equivalent to feed from conventional crops. These studies are sensitive to unexpected long-term consequences of consumption and provide confirmation on the safety of the introduced trait (protein), the nutritional/compositional equivalence, and whole food feeding studies in rodents. Animal studies completed to date have confirmed that grain or forage from biotech crops is nutritionally equivalent to grain or forage from conventionally bred crops (Thomas and Fuchs, 2002).

Typically, developers of biotechnology products spend three to four years conducting the testing necessary for regulatory approval of food/feed safety. The safety data for each product is contained in 20–22 study volumes of data and information submitted to regulatory agencies around the world. For example, the safety data that was generated for Monsanto's Roundup Ready® soybean totaled over 4,000 pages and was more than a foot and a half thick. The safety of this product has been reviewed and this product has been approved by over 32 regulatory bodies; it has been approved for production in or import into 17 countries (Thomas and Fuchs, 2002).

Finally, international expert bodies, such as the World Health Organization, the U.S. National Research Council, the Australia/New Zealand Food Authority, the U.S. Food and Drug Administration, the American Medical Association, and other scientific organizations, have reviewed the safety information on the plant biotechnology products currently in the market and have concluded that there has not been a single confirmed adverse human health effect caused by the production or consumption of crops developed through biotechnology.

Costs Associated with Commercialization

There are few reports in the literature on the cost of commercializing a biotech crop product, since almost all products in the market today have been developed by private companies which commonly view this kind of information as confidential. Commercialization costs may be divided into R&D costs, which are variable and depend on the purchasing power parity of currencies in the particular country, product development costs, which cover the laboratory evaluations, large-scale field tests, and ecological studies on potential risks, which depend on the costs

associated with the respective country, and regulatory approvals for food and feed safety, including submitting complete dossiers of information required by regulatory agencies and conducting public hearings. Experience with commercialization in several Asian countries shows that the costs range from USD700,000 to USD4.2 million per crop event (Cohen, 2005; Teng, unpublished data).

Product Stewardship

In addition to regulatory requirements, producers of GM crops ensure the biosafety and food safety of their products through product stewardship. The public sector may not be as strong as the private sector in such follow-through, and international organizations like the FAO can play an important role here, especially in developing and strengthening public sector capability in product stewardship.

Product stewardship means providing subsequent after-sales support to ensure that the product is properly used, including, among other things, resistance management schemes, especially for the insect-protected products (Bt corn, Bt cotton), and detection techniques. There has been a great deal of research on the scientific basis for insect resistance management vis-à-vis Bt crops (Gould, 1998). In North America, resistance management strategies for Bt crops rely on deployment of non-Bt crops within specified geographic areas, a strategy commonly called refugia management (Gould, 1998). Resistance management for diseases using conventional resistances has been practiced in developed and developing countries for decades (Teng, Heong, and Moody, 1995), and it is only now that the lessons learned are being applied to the management of transgenic resistance for disease control.

Biotechnology has demonstrated its usefulness in generating products and knowledge for improving resistance to pests, for improving the application of fungicides, and for biological control. Underpinning biotechnology's role in crop protection is its appropriateness in integrated pest management (IPM), generally accepted worldwide as a cornerstone concept on product stewardship of crop varieties containing major genes conferring resistance to insects or pathogens. In its broadest sense, IPM is concerned with maximizing the use of indigenous resources for keeping pest populations at non-economic levels, and it relies only when necessary on the use of external inputs such as pesticides. It is an ecological approach to pest management which relies on pest control through natural enemies and cultural practices, augmented by pesticides when cropping systems in intensifying systems do not adequately support the effectiveness of indigenous and internal means (Teng, 1994). Biotechnology does not in any way contradict the principles on which IPM is based; rather, it builds on existing genetic material to enhance the effectiveness of host plant resistance, which remains the main technique available to the majority of resource-poor farmers in developing countries.

Obtaining Freedom to Operate

Successful commercialization of crop biotech requires not just sound technology relevant to farmers' needs but also a supporting environment that includes science-based regulatory frameworks and also a public that understands and supports mainstream government programs and science. Public awareness of biotechnology is thus an essential ingredient in the overall preparedness of a country to commercialize biotech products.

Public Awareness and Socialization

Public knowledge, attitudes, and perception of biotech products are very important factors that ultimately determine whether biotech crops will make an important contribution to the world's food supply. Balancing information and news on biotechnology and GM food has been a challenge in some parts of the world. How does one separate emotion from science? Most of the major life science companies, when they started commercializing biotech products, did not foresee the many challenges they would encounter. They believed in the value of the product and

were confident of public acceptance. Looking back, this may be viewed as a failure on the part of these companies to anticipate public sentiments about the safety of the food supply.

Many surveys have shown that people want to know how food safety is assured. It is interesting to note that most common food products currently consumed are not subjected to the same rigorous testing now required for biotech genetically modified foods. Were they subjected to the same testing, many of today's common foods would not be approved. The testing of biotech foods is a science-based process that includes actual and potential information on, among other things, risk assessment for the presence of allergens or toxins, what genes are transferred, and what proteins are produced. The question then is how the current process for assuring food safety can be improved. Surveys such as those conducted in Malaysia have shown that general awareness about biotech foods is very low: 80% to 90% of those sampled are unaware of the issues. In Singapore, Malaysia, Thailand, and the Philippines, there has been increasing recognition in the media of biotech foods as an issue, but these same surveys have not revealed increased concern about biotech food or biotechnologies on the part of the general population. In fact, surveys have showed that people are more concerned about the price of food and about health, especially cholesterol (Teng, 1999).

It is important that public concerns be recognized and properly addressed. Some of these concerns have to do with the environment—regulation of field releases, outcrossing, and effects on nontarget organisms—and food safety—the safety assessment process, regulation, the presence of allergens or toxins, nutritional value, and the presence of antibiotic resistance markers. Being aware of the issues helps scientists understand them and generate data to address them. Science currently addresses these concerns very well; scientists generally acknowledge that there are elements of risk, but the benefits far outweigh the risks. There is certainly a high level of speculative fear associated with the topic of biotech food. The more emotion is separated from science and fear from reality, the better it is for all. It is important to demystify the process of biotech crop production and the nature of biotech crop products so that the public can understand them.

ADDRESSING CONCERNS ABOUT BIOTECH CROPS

Producing more food is no longer a justification for any perceived or real negative internalities or externalities. Increasingly, questions are asked of the role that new technologies like biotechnology play in the food chain. Are there nontechnological alternatives? Who benefits? Who has access? Who owns it? Is it safe for humans and animals? Is it safe for the environment? Is it within the morals and ethics of civilized society? These questions may in turn be translated into a set of topics discussed in published papers (Teng, 1999).

Intellectual Property Protection: Ownership of Genetic Resources

Consolidations in the form of acquisitions, mergers, and alliances have been a noted feature of the biotechnology industry. Since 1996, more than 25 major acquisitions and alliances valued at USD15 billion have taken place among agrobiotech, seed, and farm chemical firms (James, 2004). While these are expected to result in increased efficiencies for the private sector, fears arise of dominance and of marginalization of the role of public sector institutions charged with helping the poorest of the poor. The challenge to both sectors is to identify common ground for action to benefit resource-poor farmers based on the common vision of ensuring food security for all, whether rural or urban.

One issue that epitomizes social and ethical concern about biotechnology is intellectual property protection. Multinational companies are increasing their ownership of biological material, which will be protected by patents, relative to the public sector. Supporters of patenting point out that if the private sector is to mobilize and invest large sums of money in biotechnology R&D for agriculture, it must protect and recoup what it has put in. This is especially so

when the returns on investment in agriculture do not compare as favorably as with pharmaceuticals. On the other side of the argument is the fear that patenting will lead to monopolization of knowledge, restricted access to germplasm, controls over the research process, selectivity in research focus, and increasing marginalization of the majority of the world's population (Serageldin, 1999).

New developments in biotechnology and information technology have forced a re-examination of the traditional roles of the public sector relative to the private sector. This has affected crops which traditionally have been only of interest to the public sector, such as rice; opportunities for the private sector started with the introduction of hybrid rice but are now extending into biotech rice. When the U.S. Supreme Court upheld a patent in 1980 for a genetically engineered bacterium, it probably triggered what is now seen as a new gold rush to own genes. The proprietary nature of future rice varieties can be seen for Bt rice with resistance to stemborers: an insect-resistant rice variety could have as many as seven patents associated with it. This new situation has caused much international discussion with regard to its impact on plant breeders' rights (PBR) and farmers' rights protected by conventions such as UPOV. Most Asian countries do not as yet have patent protection for biological material, although plant varietal protection laws exist. The direct effect of intellectual property protection on germplasm exchange is likely to be the requirement that companies or institutions using proprietary material acknowledge its use in some way. It is also likely that trade issues will become intermingled with development objectives, especially in resource-poor countries.

Concerns about private sector domination of agricultural production cannot and must not be ignored. Effective regulatory mechanisms and safeguards need to be universal so that the impact of biotechnology is both productive and benign. Intellectual property protection and private sector participation in research are key to continued technological innovations, but there is also a moral obligation to ensure that scientific research helps address the needs of the poor and safeguards the environment for future generations. It should also be noted that a small number of public institutions have taken out IP protection on their genetic resources as well. Protection of intellectual property rights encourages private sector investment, but in developing countries the needs of smallholder farmers and environmental conservation are unlikely to attract private funds. Public investment will be needed, and new and imaginative public-private collaboration can make the gene revolution beneficial to developing countries (Serageldin, 1999).

Biosafety and Biodiversity

Concerns have been expressed by environmental groups—often without supporting evidence—that the use of GM crops will reduce biological diversity and lead to as yet unspecified ecological disasters. This kind of speculative fear has found willing ears in communities which have opposed any attempt by developing countries to benefit from the technological advances of the Green Revolution. The same criticism is raised against GM crops as was brought against the high-yielding crop cultivars that so successfully fed millions during the Green Revolution, yet data from eminent breeders show that modern rice cultivars are more genetically diverse than traditional cultivars or land races (Khush, 1996). Analysis of the serious pest outbreaks or disease epidemics which have occurred in developing countries has shown that, almost without exception, these have not been due to genetic homogeneity but because of the untimely occurrence of sets of predisposing factors (Teng, Heong, and Moody, 1993; Teng, 1999). GM crops are anticipated to maintain the diverse background of the successful commercial cultivars but have genes added to confer additional, needed traits. There is also unfounded fear by some that the process of genetic modification itself produces changes in the crop genomes which are as yet undescribed.

Biosafety is a generic term used to cover any aspect of safety associated with the potential or actual effects on the biological environment (ecosystem) of genetically modified (GM) organisms produced with recombinant DNA techniques. It includes concerns about the outcrossing of

transgenes to related and unrelated species of the GM organism, negative effects on nontarget organisms, and the development of “super-pests,” and also techniques of risk assessment, the containment or amelioration of risk, and the conduct of field experiments using GM organisms. Much has been written on these topics (NRC 1989; Teng and Yang 1993). Common steps to ensure biosafety in developing countries are:

Researchers develop a proposal in accordance with the relevant biosafety guidelines of a national committee on biosafety. The proposal is reviewed by the relevant authorities. Risk assessments and other required information are provided. The proposal is submitted to an institutional biosafety committee for review, approval, and endorsement to the national committee. The proposal is reviewed by the national biosafety committee for possible revision or approval, and research starts only after notification of approval by the national committee. Biosafety regulations that govern the conduct of experiments under containment and in “open” field experiments are in place in a growing number of developing countries, including China, India, Indonesia, Malaysia, the Philippines, Thailand, Mexico, Argentina, and South Africa. These regulations commonly require that before any experiment involving recombinant DNA techniques is done, a formal application must be made, accompanied by site visits and public hearings involving nonscientists. In North America, the earliest region to approve and commercialize GM crops, it has been seen that with increased experience by regulatory agencies and greater public acceptance through more exposure to biotechnology, the process has gradually become more routine and attracted less interest from the public. The process of developing a transgenic plant with the desired trait is as long as, if not longer, than the equivalent process required to take a pesticide to market—typically about a decade. Safeguards and rigorous testing are in place throughout this process. Developing countries which have deregulated GM crops include China, Argentina, Mexico, and South Africa.

Between 1986 and 1998, more than 25,000 field trials of transgenic plants from more than 60 important agricultural crops were approved by 45 countries (James, 2004). In the U.S., several transgenic products for use in crop protection were no longer subject to regulation as of September 1997: Bt corn, herbicide-resistant cotton, Colorado Potato Beetle-resistant potato, virus-resistant squash, herbicide-resistant soybean, and virus-resistant papaya. Public perception has improved, and concern about field trials involving transgenic crops has significantly decreased in North America with the establishment of transparent regulatory processes.

Food Safety and Health Issues

Most agricultural crops that have been genetically modified end up as food or feed. Public acceptance or rejection of any GM product is therefore a strong consideration of its selection as a crop production or pest management tool. To provide assurance that biotechnology will generate food as safe as that produced by traditional breeding programs, safety assessment strategies have been developed for products of plant biotechnology which are more thorough than those used to evaluate new foods using conventional breeding techniques.

The process used by Monsanto, one of the pioneers in applying biotechnology, is illustrative of the steps taken to assure the safety of genetically-modified plants for use as food: molecular characterization of the genetic modification, agronomic characterization, nutritional assessment (key nutrients), toxicological assessment (key antinutrients, toxicants), and safety assessment of the gene expression product. The overall goal of this assessment is to determine whether the genetically modified plant is substantially equivalent to food derived from a conventional source which has a history of safe use (OECD, 1996). A substantial equivalence evaluation focuses on the product rather than the process used to develop the food or feed. If the new product is substantially equivalent to the conventional food or feed, then the biotechnology-derived product is considered as safe as the nontransgenic counterpart.

When a genetically modified food crop has been shown to be substantially equivalent to the conventional crop with the exception of the introduced trait(s), which may impart one or more

characteristics, such as pest resistance or selectivity to preferred herbicides, then the safety assessment focuses on the introduced trait and the protein expression product of the cloned gene. If the protein is an enzyme, the potential effects of the enzyme on metabolic pathways and levels of endogenous metabolites based on its mode of action and specificity are assessed. The amino acid sequence of the protein is compared to known sequences in protein to determine if the protein has sequence homology to food proteins, toxins, or allergens. The inherent digestibility of the protein is assessed in a test tube using simulated gastric and intestinal protease preparations, and the level of expression of the protein in the food is determined. This assessment is focused on the appropriate raw agricultural product or a specific processed food component (e.g., oil). Specific criteria have been developed in consultation with nutritionists and regulatory agencies to establish that the introduced protein is as safe as proteins already present in foods.

Key nutrients are those components in a particular food product which may have a substantial health impact in the overall diet. These may be major constituents—fats, proteins, carbohydrates—or minor components—essential minerals, vitamins. Critical nutrients to be assessed are determined, in part, by knowledge of the function and expression product of the inserted gene (e.g., if an inserted gene expresses an enzyme which is involved in amino acid biosynthesis, then the amino acid profile is determined). Critical toxicants and antinutrients are those compounds known to be inherently present in the crop variety whose potency could have an impact on health if the levels were increased significantly (e.g., solanine glycoalkaloids in potatoes, trypsin inhibitors in soybeans). Knowledge of the biologic function of the protein expression product of the inserted gene provides clues as to which toxicants or antinutrients are examined. The levels of key antinutrients in the genetically modified line are compared to the parental line or conventional varieties grown under comparable environmental and agronomic conditions.

CONCLUSION

Globally, the increase in area grown to biotech crops has been an amazing story in technology adoption. In China today, there are over two million smallholders farming Bt cotton in just one province. Farmers like Bt cotton because, they say, it improves income, reduces their exposure to insecticides, and assures them of getting a good harvest of cotton at the end of the season. A U.S. Department of Agriculture study done by some universities has also shown that farmers are the main beneficiaries of the products now available from GM technologies. In the U.S. alone, insecticide use on cotton was reduced by an estimated 20 million kg in 2003 due to the planting of biotech cotton with the Bt gene (www.ncfap.org).

Consumer benefits are the least even though prices are maintained. This may contribute to opposition to GM crops in some countries because with this current set of products the benefits of the technology have not been obvious to consumers. In the near future, another set of products that focuses more on nutritional traits may more clearly demonstrate the benefits of biotechnology to the general public. Many of the crop biotech products in the public sector research pipeline (see the paper by Teng and James in this Study Mission) will demonstrate more clearly the benefits to small farmers as they focus on a range of crops collectively known as “orphan crops”; the private sector has so far commercialized only soybean, corn, cotton, and canola. Another significant development will be the move towards quality traits, such as enhanced levels of vitamins and other nutrition or diet-preferred food. Countries like Malaysia are also working on the concept of plants as factories, using the oil palm tree in particular as a manufacturer of hydrocarbons with industrial applications. There is also ongoing work on using crops as carriers of medicine, such as vaccines (Cohen, 2005).

The major bottlenecks to large-scale commercialization of crop biotech products are not technological or scientific issues, but rather related to public acceptance, trade, and adequate frameworks for government oversight. In this paper, these issues have been discussed in depth. The recent meeting in Montreal to review recommendations for actioning the Cartagena Bio-

safety Protocol under the Convention on Biological Diversity is important, as it will influence national approaches. Developing countries stand to derive the most benefit from this new technology, and any excessive regulation will hinder progress and the sharing of benefits with small resource-poor farmers in Asia. Asia is unique in its natural biological diversity, which serves as a resource (and therefore justifies protection) but also as an important natural buffer to the monocultural cropping systems needed to produce food efficiently in large enough quantities to feed a growing population. It is hoped that as experience with biotech crops increases and its safety is demonstrated, misconceptions and misinformation on this technology will decrease. Promising signs are already in evidence, for example, the European Union's recent decisions in favor of selected field trials of biotech crops and the continued importation, albeit regulated, of millions of tons of biotech crop products from North and Latin America.

Many countries in developing Asia have espoused national policies to promote biotechnology in agriculture, the most recent being the National Biotechnology Policy of Malaysia (MOSTI, 2005). Most of these have been developed based on biotechnology's anticipated role in creating new value and adding value to existing agricultural businesses such as the seed business (Oliver, 2003; Sashi, 2004). Singapore government websites show that Singapore alone has invested over USD3 billion in the past few years to make biotechnology a major engine for economic growth. Its optimism is based on the anticipation that in a globalized, knowledge-based economy, creating value through biology will likely add to or even exceed the value created by digital information-communication technologies.

Ultimately, it is likely that the future of agricultural biotechnology in Asia will be decided by its relevance to feeding people and providing the food security essential for national development. The widely known economist Jeffrey Sachs (1999) has noted that most of the world's new technologies are generated and owned by a small group of countries which collectively account for only about a third of the world's population. Asia, in which more than 60% of the world's inhabitants live, is as yet not a notable contributor to new technologies, but rather has been a major user and adapter of technology. This will change. Countries which recognize the potential of biotechnology will likely benefit most from it, even in the seemingly mundane business of commercializing biotech seeds.

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Part III

Selected Country Papers

1. MARCHING TOWARDS THE MARKET: THE BUSINESS POTENTIAL OF AGRICULTURAL BIOTECHNOLOGY IN THE REPUBLIC OF CHINA

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INTRODUCTION

One of the important potential benefits of biotechnology is its application to improve agricultural production. In agriculture, the scope of biotechnology, using a broad definition, includes tissue culture, applied microbiology, and applied molecular biology. As in many other countries, the research and commercial applications of plant tissue culture and applied microbiology in the Republic of China have a longer history than molecular biology. Research on molecular biology in agriculture may be traced back to the early 1980s. In its early stage, this was confined to basic activities such as gene cloning, transformation, and genetic marker analysis in plants and animals. During this period, most of the research was funded by the government, and it was done primarily in universities and public research institutes. Due to its high application potential, and in order to accelerate its development, biotechnology was included by the government in 1982 among the eight key areas of research. Many related education or training programs were also initiated at this time. The Development Center for Biotechnology (DCB), the first autonomous and nonprofit organization specifically for biotechnological research, was established in 1984.

After nearly a decade of effort, the research gradually proceeded to more practical and important activities, including the development of transgenic plants and animals, DNA-based genotyping for breeding, and the development of biopesticides, biofertilizer, and animal vaccines. With more private companies joining in different aspects, preparations were made for marketing the products from agricultural biotechnology. From the late 1980s to the middle 1990s, important regulations and guidelines concerning biotechnology and biosafety were established by the government. The Experimental Rule of Recombinant DNA was issued by the National Science Council (NSC) and the Guidelines for Risk Assessment in GM Plants and GM Animals by the Council of Agriculture (COA). The Plant Variety and Seed Act, the most important law in agriculture, was enacted in 2003; in taking biotechnology into account, it opened the door to a new era. Creation of some animal- and fish-related regulations and laws in this field has also been ongoing. Today a fundamental framework has been constructed for managing biotechnology and biosafety. During the past five years, further effort, on the part of both government and society, has promoted the development of agricultural biotechnology, including the establishment of several biotech science parks, among which at least four are specifically set up for agricultural development. In 2005, total investment in biotechnology has reached TWD150 billion. All these efforts have laid a good groundwork for the further development and application of agricultural biotechnology in Taiwan.

CURRENT STATUS OF THE AGRICULTURAL BIOTECHNOLOGY PRODUCTS INDUSTRY

Profile of the Agricultural Biotechnology Business

In industry, there is always great interest in adopting new technology with a high potential for economic benefits. Biotechnology, a relatively new science born in the 1970s, is regarded in the world as a highly promising profitmaker. However, industry in the Republic of China seems to have responded rather late, especially in agriculture. An inquiry conducted by the Taiwan

Institute of Economic Research showed that only 11.3% of companies related to the agricultural biotechnology business existed before 1980. Sixteen percent were established during 1980–95. More than two-thirds (66.9%) were created after 1996. This indicates that in the Republic of China the industry entered the era of agricultural biotechnology only about a decade ago. Most companies (63.2%) are small in scale, with a staff of fewer than 25. Only 9.4% hire more than 100 employees. The turnover of most companies (54.7%) is below TWD50 million, and only 7.5% of them reach TWD500 million or more. In general, their income comes primarily from the manufacture and sale of products: disease and pest detection kits for plants or animals (28.8%), functional foods (23.1%), biofertilizer (14.1%), aquatic nursery and related products (12.2%), and plant tissue culture (7.7%). It would appear that many companies still do not conduct active research. About half (47.2%) of the techniques and know-how used to build up the agricultural biotechnology business were obtained from within the island, while 11.3%, 4.7%, and 9.4% of the know-how was introduced from the U.S., Europe, and Japan, respectively. This report will briefly describe some aspects of the current business situation in regard to plant tissue culture, biopesticides, and biofertilizers and then discuss some GMO issues.

Plant Tissue Culture

Plant tissue culture, an early activity in biotechnology research, is now not only a matured technology but has grown into a flourishing industry in the Republic of China. Many products have been traded domestically and internationally for more than two decades. Since tissue culture is a powerful technique for the mass production of many crops and also a useful method for producing healthy plants, it has become an important tool in the nursery industry. Worldwide, many plants are now propagated by tissue culture. In Taiwan, the orchid nursery in particular has become very reliant on tissue culture for the mass production of healthy young plants. Commercial orchid varieties consisted of plant tissue culture products in percentages as high as 51% and 85% in 1998 and 2002, respectively. This is very different from many other countries, where tissue culture is mainly used to propagate ornamental foliage plants. The main categories of orchids produced by tissue culture in Taiwan include *Phalaenopsis*, *Oncidium*, *Cymbidium*, *Dendrobium*, and *Paphiopedilum*.

The tissue culture business has been growing steadily during the past decade, and recently trading activity has been quite prosperous both in local and international markets. In 2003, the total export value reached TWD0.272 billion, 27% more than the year 2002. About 95% of the export value came from orchids, especially *Phalaenopsis*. However, a very large percent (72%) of the *Phalaenopsis* is for domestic consumption. In export, the major trading partners came from the U.S. (30.1%), Japan (28.8%), South Korea (13.4%), Netherlands (7.4%), and China (4.0%). The number of nursery companies engaged in tissue culture has ranged between 100 and 120 during the past decade. About 94% of these nurseries are located in the western part of Taiwan, with 6% located in the eastern part. In the western part, more than half (54%) are in the central region, which is also the most important agricultural area on the island. There has been a significant change in the scale of nursery companies during the past several years. In 1998, more than half (58%) were small producers, i.e., fewer than 500 thousand plantlets produced per year, and only 12% produced 5,000 thousands plantlets or more. However, in 2002, one quarter (25%) of the companies had the capacity of an annual production of up to 1,000–5,000 thousand plantlets, and 17% produced more than 5,000 thousand yearly. This indicates that many nurseries may have increased in size due to the intense competition. It was estimated that during the past several years 10%–15% of small nurseries either went out of business or consolidated with other partners, and 10%–12% expanded. Fifteen new large nurseries have also been established recently. Specialization in production has also become a new characteristic in the tissue culture industry and will likely be beneficial in increasing future competitiveness.

Biopesticide and Biofertilizer

In applied microbiology, biopesticide and biofertilizer are the two hot items in agriculture. Because of environmental safety and ecology considerations, biological control of pests has been increasingly welcomed by both farmers and consumers. Research on biopesticides began early at public institutes and universities, and some important results have been obtained. The fungi of *Trichoderma* spp. have been used to control many pathogens, including *Rhizoctonia solani*, *Sclerotium rolfsii*, *Sclerotinia sclerotiorum*, and *Pythium aphanidermatum*. They also can reduce the damage caused by *Botrytis cinerea*, *Pseuoperonospora cubensis*, *Sclerotinia sclerotinia*, and *Sphaerotheca fusca* and thus are valuable for protecting leaves. These well-studied biocontrol agents have become an ideal subject for commercialization. Other well-studied natural anti-fungal agents include *Bacillus subtilis* and *Streptomyces*. Further studies have shown how to make these natural resources easy to use in agricultural practices. The Agricultural Research Institute (ARI) has undertaken significant efforts in the commercialization and marketing of these agents. Several major companies, such as Yuen-Foongyu Paper Co., Tai-En Co., and Biontech Inc., have begun to produce and merchandise these products under their own brands. Although at present the value of this new industry is only about 0.5%–1% of the total traditional pesticide market, it is growing at the rate of 10%–15% annually. Recently, a brand called Bio-work (*Bacillus subtilis*) has opened a new market in Japan, and some products of *Streptomyces* have created an annual value of TWD10–20 million in the domestic market.

As potted plants become popular in the modern horticultural industry, the use of biofertilizers has also become more accepted by growers. A culture medium made of vermiculite, peat moss, and perlite is quite suitable for the application of biofertilizer, since it demands less fungus and gives better plant growth. Several fungi and bacteria have been studied for their potential as biofertilizer, including the genera *Pseudomonas*, *Bacillus*, *Thiobacillus*, *Penicillium*, and *Aspergillus*. There have been some good products marketed by different companies that have been quite well accepted by farmers. Based on long-term experiments, ARI has also transferred some of its know-how to different companies. Some of these bacteria are now being marketed under names such as Dr. Root (Vesicular-arbuscular mycorrhizal fungi, VAMF) by Tai-En Co., Mycovam (VAMF) by Taiwan Biological Research Co., Ai-gen-how (in Chinese) (VAMF) by Lei-ju Co., and Agroguard (*Bacillus*) by the Taiwan Biological Research Co. At present, the annual value created by the biofertilizer industry is estimated to be slightly less than that of biopesticides.

GMOs and Other Items

Other products of agricultural biotechnology with high market potential will likely result from applied molecular biology, also known as genetic engineering, including genetically modified organisms (GMOs) for producing specific bioproducts, detection kits derived from recombinant DNA techniques, transgenic plants, and transgenic animals. It is believed that applied molecular biology will create much higher value than ever before for industry and agriculture. In the Republic of China, great effort has been taken to promote developments in this field of research, and much research is ongoing. Using recombinant DNA techniques to produce highly sensitive and highly accurate detection kits for disease analysis is one of the important achievements of the Agricultural Research Institute (ARI). This kind of product was initially developed several years ago to serve the nursery industry and has now proven very helpful for quality control of tissue cultured plants. Transgenic papaya resistant to *papaya ringspot virus* was established by Chung-Hsin University about 10 years ago and passed environmental risk assessment in 2000. It must still undergo food safety assessment before being marketed. There are several transgenic crops, including rice, broccoli, potato, and tomato, now in the process of undergoing environmental risk assessment at ARI and AVRDC (Asian Vegetable Research and Development Center) but not yet subject to food safety assessment. Another important GM plant is transgenic eucalyptus, created by the Forest Research Institute, which is now under field

evaluation according to the biosafety guidelines. In the animal realm, transgenic ornamental fish containing a fluorescence gene created by a private company and duplicated goats derived from somatic cell cloning created by the Livestock Research Institute and National Taiwan University are two examples of outstanding achievements. Many of these genetic engineering products are ready for application, although so far none has been commercialized or marketed.

POTENTIAL OBSTACLES IN THE COMMERCIALIZATION OF AGRICULTURAL BIOTECHNOLOGY PRODUCTS

The Republic of China has considered the development of biotechnology to be important. Today a substantive business in plant tissue culture has been established, and commercialization of some microbiological products has also been achieved. However, the business of agricultural biotechnology is still far from maturity, as it lacks the application of molecular biology. Although some good advances in research in GMOs have been made during the past decade, no products have been marketed. The following issues may represent obstacles in the development of this industry:

A framework for the legal and regulatory systems has not been established. Although much work has been done, legislation and regulations concerning GMOs such as transgenic animals and fish have not been completed.

There is a need for a stronger connection between laboratories and factories. NSC and COA have been working for more than a decade to build a strong linkage between researchers and producers to speed up commercialization and marketing in this field, but connection needs strengthening.

As most of the companies are Small and Medium Enterprises (SME), their size may limit their competitiveness due to the relatively higher production costs of biotech products and their low R&D budgets.

There is a need for more public communication and education. Many people do not understand biotechnology and its products, which may hinder the commercialization and marketing of agricultural biotechnology products.

More traditional nursery companies need to join the GMO business. To date many companies associated with the nursery business have shown no interest in transgenic technology and GMO products, perhaps due to concern about end user response. Their experience in marketing will be very helpful and is needed in the development of GMO business.

More international cooperation in research is required. This is one of the weakest points in the Republic of China's agricultural biotechnology.

CONCLUSION

Two important factors will strongly influence the Republic of China's future development. First, the Republic of China has to become a member of the WTO. Second, the 21st century will be the century of biotechnology. To be a player, the Republic of China cannot neglect the role of biotechnology in international trade. The challenges must be confronted: increase R&D capability in both basic research and manufacturing procedures; build a complete system for managing biotechnology that will take into account all related matters, including laws and regulations, risk assessment, product monitoring, etc. Most of these issues are in the process of being dealt with, but the speed of progress must increase; create an ideal environment for SMEs so that they can become more competitive. It will be crucial to intensify cooperation in research and to establish biotech science parks as future production bases; and increase public communication and education to strengthen support from within society for research and commercialization.

2. THE BUSINESS POTENTIAL AND DEVELOPMENT STRATEGY FOR AGRICULTURAL BIOTECHNOLOGY PRODUCTS IN THE REPUBLIC OF CHINA

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INTRODUCTION

Taiwan is a subtropical mountainous island with a diverse climate ranging from tropical to subfrigid. This diverse environment creates a large amount of biodiversity, which is a key factor in the development of the country's agricultural biotechnology industry. The agricultural technology of the Republic of China is well established, and the active research community in this area has generated valuable agricultural know-how and advanced technology. Based on the unique agricultural styles, geography, climate, and biological resources, strategic planning for developing agricultural biotechnology in the Republic of China will not only transform the local agricultural industry but also create a market segment different from those of industrialized countries. Furthermore, such a strategy will help the Republic of China to become a research and development center of excellence for subtropical fruits, vegetables, flowers, livestock, and aquatic products.

DEVELOPMENT STRATEGY

An analysis of the overall development vision, objectives, and current status of the industry, agricultural resources, and global competition with respect to agricultural biotechnology indicates that the development of the Republic of China's biotechnology industry should focus on subtropical agriculture.

In the initial stage, the Republic of China should develop an industry in plant sprouts, aquaculture farming, animal vaccines, functional food polypeptides, biofertilizer, and biopesticides. The goal is two-fold: to accelerate the pace of transforming traditional farming and to accumulate technical know-how and talent in the field of new applications.

The Republic of China should also invest in infrastructure establishment, including creating an agricultural biotechnology information and certification management system, amending current regulations and administrative operations, and strengthening product design and sales. In addition, the Republic of China should establish agricultural biotechnology parks to concentrate resources in order to become an agricultural high-tech center that can fulfill the multiple purposes of research and development, production and marketing, processing, and transportation to market. This strategy will create a healthy industrial development environment and gradually build a new agricultural biotechnology industry.

MEANS OF ENHANCING INVESTMENT

Protection and Application of Intellectual Property

Because agricultural biotechnology is basically rooted in high-tech research and development, it is necessary to safeguard the outcomes of such research through the protection of intellectual property rights. The Republic of China has amended the Plant Variety and Seedling Act to make the law more comprehensive and allow new plant variety rights. This has included pass-

ing regulations for conducting isolated field observation trials of genetically modified organisms (GMOs) as well as the harvesting and direct processing of products of GM species.

Currently, the country's existing laws on biotechnology are in accordance with the TRIPS 27.3 Law of the World Trade Organization, indicating that the country is protecting both inherited resources and traditional knowledge. The protection of intellectual property rights is a core value of the knowledge economy. Not only does it protect the rights of the creator, it also encourages and attracts top-notch talent to participate in innovation and R&D processes, a crucial factor in modern economic development. Consequently, the country's industries have reached a consensus. In the interest of being able to protect farmers' interests as well as providing for research responsibilities, appropriate protection is being established for new crops, livestock, and aquatic organisms.

Acceleration of Capacity Building

The Republic of China has drafted the Field Trial and Biosafety Evaluation Regulations for Transgenic Breeding Flock, the Guidelines for Field Trials of Transgenic Plants, and the Management Regulations for the Field Experimentation of Transgenic Aquatic Organisms to establish a management system for genetically modified organism (GMO) field trials. The country is also planning the establishment of isolated field trial stations for transgenic animals and plants (including aquatic organisms).

Talent is being recruited and training programs strengthened with the aim of assembling a research and development team that can expand and consolidate R&D efforts. For example, biosafety assessment for transgenic crops like rice, tomatoes, broccoli, and papaya and for transgenic pigs is conducted in contained experimental sites. Current regulations stipulate that these transgenic organisms are to be subjected to safety assessment in isolated field trial experimentation before release for large-scale cultivation and marketing. On the other hand, an important goal is to improve crucial technology and research of biosafety assessment for genetically modified crops in accordance with regulations governing the management of imports and exports and the sale and promotion of GMO products. In addition, studies on genetic engineering, functional genomes, microarray analysis, physical mapping, and DNA sequencing will be promoted.

Accelerated passage and implementation of laws relating to the biotechnology industry (for example, laws on managing and inspecting biological pesticides and fertilizers), establishment of effective assessment and management systems, and promotion of accreditation of and cooperation within the international agricultural biotechnology sector are desirable. Consumer safety, maintenance of ecological equilibrium, and benefits to exportation of these products will be ensured through these measures. At the same time, obsolete laws may reviewed to determine if they could be relaxed to encourage local and international investments and thus accelerate improvement of the local agricultural biotechnology industry. This would aid in expanding the market share of the country's agricultural biotechnology products in international markets.

The Republic of China's agricultural technology is excellent. Innovative, market-oriented technology products will continue to be developed, gaps among the core technologies will be made up, and the application of technologies will be expanded. The excellence of selected core products will be emphasized to gain consumer confidence.

The Republic of China will also actively participate in international biotech and product exhibitions as well as organize regular biotech product fairs in the country in order to enhance international cooperation and technology exchanges. The Republic of China is committed to actively contributing to the international agricultural biotech community.

Establishment of Agricultural Biotechnology Parks

The Republic of China is planning to establish a series of agricultural biotechnology parks to concentrate limited resources and provide adequate basic investment conditions to attract both

local and international biotech investors. With such concentration, the development of agricultural biotechnology industries can proceed at an even faster pace.

Currently, the Republic of China has already established the Agricultural Biotechnology Park in Pingtung, the National Flower Park in Changhua, the Taiwan Orchid Plantation in Tainan, the Medicinal and Spice Herb Biotechnology Park in Chiayi, and the Marine Biotechnology Park in Ilan, combining private capitalization and governmental research and development capacity to create a high-value-added industry in agriculture.

The Agricultural Biotechnology Park Establishment and Management Act was enacted in April 2004, a law primarily providing full access to factory facilities and clarifying the amenities and benefits offered to agricultural biotechnology companies.

CONCLUSION AND SUGGESTIONS

In the context of agricultural development in the 21st century, aside from satisfying the traditional needs of the people, the Republic of China's most urgent need is to become internationally competitive while protecting and maintaining its ecosystems. The crucial factor lies in the improvement of technology. Consequently, whether seen from the viewpoint of international trends, national policy, or industrial development, the use of biotechnology is a road that agricultural industries worldwide must travel. In addition to focusing efforts on building infrastructure to attract various sectors of society to become involved in agricultural biotechnology, the Republic of China will focus on the influence and effect biotech has on traditional agriculture and farming villages, making a thorough evaluation and suggesting countermeasures. The Republic of China will also look forward by taking one step further and combining agricultural biotechnology with other domestic industries, such as medicine, food processing, and information technology, thus opening up new fields of application and creating industries that promote public health and welfare.

3. RESEARCH AND DEVELOPMENT PRIORITIES FOR BIOPESTICIDE AND BIOFERTILIZER PRODUCTS FOR SUSTAINABLE AGRICULTURE IN INDIA

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INTRODUCTION

Sustainable crop production depends upon the rational use of chemical fertilizers and pesticides along with organic manures for better soil health. Indian agriculture has undergone dynamic change since the “Green Revolution,” which provided self-sufficiency and ushered in an era of rural prosperity. Production of food grains has increased from 50.82 million tons in 1950–51 to 211.2 million tons through the use of chemical fertilizers, high-yielding varieties, plant protection, chemicals, irrigation, etc. This period was also noted for a 250-fold increase in fertilizer consumption, from 69,000 tons during 1950–51 to 17.4 million tons of NPK nutrients during 2001–02, from 0.5 kg/ha to 91 kg/ha. Consumption of pesticides increased from approximately 160 metric tons in 1949–50 to 64,000 metric tons (2002–03). Excessive use of fertilizers and pesticides has caused a serious imbalance in the nutrient status in soils and in food quality. Nitrate concentration in groundwater and accumulation of heavy metals like arsenic, lead, and cadmium have been reported. The WHO recommends a 10 mg/liter nitrate nitrogen limit in drinking water. One study has shown 773 nitrate-affected villages in Gujarat alone, and about 68% of water samples from 113 villages in the Ludhiana district of Punjab were found to have nitrate levels above permissible limits. At the same time, residues of DDT and Aldrin, etc. have been reported in different food materials, for example, milk. These are matters of serious concern.

While production of food grains increased fourfold, soil and environment health have been affected adversely by the application of 250 times more chemical fertilizers and 400 times higher applications of pesticides than needed. This has prompted a search for biological alternatives such as biopesticides and biofertilizers. Estimates indicate that biopesticides have about a 2.5% share in the Indian pesticide market and may reach 12%–15% by 2006. Similarly, the use of biopesticides and biofertilizers at present is estimated to be USD1.5 billion, and the market is anticipated to grow substantially with greater demands for quality produce free from pesticides and other toxic residues amidst growing public concern towards sustainability.

Excessive and indiscriminate use of agrochemicals resulting in deteriorating soil health has led to reduced profitability from agriculture in spite of the development of high-yielding varieties and superior agrotechnologies. The gaps between expected and actual yields from best agropractices continue to widen, forcing farmers towards urbanization. The major causes are deterioration in soil structure and texture, deficiency in soil microflora and –fauna, and nutritional imbalances. Emphasis is now being placed on overcoming this situation by managing nutritional and biological stresses through organic, cultural, and biological means. Here biofertilizers and biopesticides may play a significant role.

MEETING THE DEMANDS OF ORGANIC FARMING AS A NEW OPPORTUNITY

Consumers’ increased awareness about food safety and environmental pollution has contributed to a clear upward consumption trend in organic food, flavors, aromas, and medicinal herbs

during the past few years. Organic farming, the oldest form of agriculture on earth, offers multiple benefits: price premiums, natural resource conservation (soil fertility, water quality, prevention of erosion, preservation of natural biodiversity), and social advantages (generation of rural employment, improved household nutrition, reduced dependence on external inputs). In addition, organic food, medicinal herbs, spices, and essential oils are assuming greater export potential. There is a huge export market for organic medicinal herbs as a raw material for health care products. These herbs are bound to command considerably higher prices in international markets, where the total world organic market is estimated to be USD22,000 million with an annual growth rate of 20%–30%; it is often considered the fastest-growing agriculture sector. The area under organic cultivation in India has increased substantially. Presently estimated at more than 100,000 hectares (certified), it is expected to expand at a faster rate in the coming years. This will require biological sources as nutritional and pesticide input supplements, and thus there will be a significant demand for biofertilizer and biopesticide products.

BIOFERTILIZERS FOR SUSTAINABILITY

Status in India

Biofertilizers are preparations containing live or latent cells of efficient strains of microbes augmenting the availability of nutrients in a form which can easily be assimilated by plants. In 1983, 100 metric tons of biofertilizer was produced in India; by 2002–03 production had increased almost 100-fold, to 90,000 metric tons. Currently there are 126 biofertilizer units engaged in biofertilizer production, and the government has extended financial assistance to 73 biofertilizer units for commercial production. The Bureau of India Standards (BIS), in consultation with the National Biofertilizer Development Center, has set IS specifications for the following biofertilizers:

<i>Rhizobium</i>	IS: 8268-2001
<i>Azotobacter</i>	IS: 9138-2002
<i>Azospirillum</i>	IS: 14806-2000
PSB	IS: 14807-2000

It is estimated that production of biofertilizers by the existing units is far below the potential demand of about 760 thousand TPA (Table 1).

Table 1. Estimated Potential Demand for Commonly Used Biofertilizers, India

Type of biofertilizer	Demand (tons)
<i>Rhizobium</i>	34,999
<i>Azotobacter</i>	145,953
<i>Azospirillum</i>	74,342
Blue green algae	251,738
Phosphate-solubilizing microorganism	255,340
Total	762,372

Source: National Biofertilizer Development Center (NBDC) Ghaziabad

This estimated demand is based on the cultivated area and the treatment of the total seed sown at the rate of 200g biofertilizer per 10 kg of seed. Although this assumption reflects only the macro-level requirement, if even 50% of the cultivated area is to be brought under biofer-

tilizer application, there will be a wide gap between the actual production and the demand. Current trends indicate that there is a steady increase in demand, especially in the southern states.

Critical Factors Responsible for Effectiveness

Suitability of the species to the target crop or host specificity.

Identification of strains suited to the agro-ecosystem, particularly the soil pH and moisture conditions.

Significant cell count of living organism present in the product, its purity, and its level of contamination.

Conditions of the carrier material in which the culture is packed and the quality of the packing material, which determine the shelf life.

The conditions in which the packed materials are stored, distributed, and kept by farmers before application.

Level of Benefits

The benefits typically obtained are not as visible as those of chemical fertilizers except in some critical conditions. Biofertilizers can add from 20 kg/ha to 200 kg/ha nitrogen depending upon optimum conditions. Pastures and forages respond more than grain crops. Yield increases usually range from around 10%–35%. However, in the vast areas of low-input agriculture and in the context of imparting sustainability to crop production at reduced chemical pollution, these products will be very useful.

BIOPESTICIDES AS NONTOXIC OPTIONS FOR PEST CONTROL

Pests and diseases cause over INR290 billion in crop losses per annum, with *Helicoverpa* alone accounting for around INR35 billion. This has been caused by indiscriminate use of chemical pesticides resulting in the development of alarming resistance in pests and a resurgence of minor pests. Agricultural exports are rejected with increasing frequency because of high pesticide residues. WHO estimates that there are 1 million pesticide poisoning cases globally every year due to high pesticide residues in food chains, including those of cereals, pulses, vegetables, fruits, milk and milk products (including mother's milk), fish, poultry, meat products, and water. Apart from causing significant harm to human and animal health, pesticides also damage non-target beneficials, soil microflora, and crops.

Biopesticides are advantageous because they are ecosafe, they have target specificity, there is no development of resistance, the number of applications is reduced, yield and quality are improved, they have higher acceptability, the value of produce for exports increases, and they are suitable for rural areas. There has been wide acceptance of biopesticides globally, amounting to around a 10% share of the agrochemical market in 2000 with a growth rate of 10%–15% per annum.

Adoption of Biopesticides and Biocontrol Agents in India

To overcome the hazards associated with pesticides, stress is being given to biological pest management through cultural, biological, or organically accepted chemical alternatives. Biological pest enemies such as predators (e.g., *Chrysoperia*), parasitoids (e.g., *Trichogramma*), and biopesticides like *Trichoderma*, *Bacillus thuringiensis*, NPV, etc. are cost-effective and pollution-free inputs for controlling pests and plant pathogens. Botanical pesticides like neem, *Lantana*, etc. are also very effective in checking insect attacks. Current production of biopesticides has increased from 210 metric tons (1996–97) to roughly 902 metric tons (2001–02). Their use is regulated by the Insecticide Act of 1968. There is enough scope for the use of biofertilizers and biopesticides, but unless a high-quality supply is ensured, the confidence of the end user cannot be maintained.

The use of biopesticides and biocontrol agents is on the increase, but not to the desired level of growth, although presently a decrease in chemical pesticide consumption is indicated. Many small entrepreneurs are developing biopesticides and biocontrol agent products, but many of them have little quality consciousness.

Success Stories of Biopesticides in India

Encouraging success stories of biopesticides and biocontrol agents used in agriculture include:

- Control of diamondback moths by *Bacillus thuringiensis*.
- Control of mango hoppers and mealy bugs and coffee pod borer by *Beauveria*.
- Control of *Helicoverpa* on cotton, pigeon-pea, and tomato by *Bacillus thuringiensis*.
- Control of white fly on cotton by neem products.
- Control of *Helicoverpa* on gram by N.P.V.
- Control of sugarcane borers by *Trichogramma*.
- Control of rots and wilts in various crops by *Trichoderma*-based products.

Constraints in Widespread Adoption of Biopesticides

Constraints preventing widespread adoption of biopesticides include lack of knowledge, lack of simple illustrated information and well-executed demonstrations, shorter shelf life of bio-control agents, and inappropriate application technologies and equipment.

Availability of Biopesticides in India

The success stories of biopesticides and biocontrol agents in the areas mentioned above illustrate the possibility of their large-scale adoption in other areas as well. Timely availability of high-quality inputs is essential. The present status of the availability of biopesticides and bio-control agents and related constraints is summarized in Table 2.

Table 2. Availability of Biopesticides, India

Biopesticides/Bioagents	Quantity/annum	Constraints
Neem 300 PPM	Over 1,000,000 L	Quality, stability
Neem 1500 PPM	Over 250,000 L	—
Bt	Over 50,000 kg	—
NPV (liquid)	Over 500,000 L.E.	Quality, stability
NPV (W.P.)	Nil	—
<i>Beauveria</i>	Meager	Quality, stability
Pheromone traps	Over 500,000	Quality, stability
Lures	Over 2 million	Quality, stability
<i>Trichogramma</i>	1 million	Quality, stability
Chrysoperla and other biocontrol insects	Meager	Quality, stability
<i>Trichoderma</i>	Over 500 T	Quality, stability

Necessary Steps to Improve Adoption of Biopesticides

IPM packages by each state to meet local needs, involving industry.

Priority on pest surveillance and monitoring for timely forewarning of pests and disease.

Simplification of registration requirements for biopesticides and biocontrol agents, bringing all of them under the purview of the Insecticide Act.

Promotion of biopesticides in export-oriented commodities like spices, fruits, vegetables, basmati rice, and organic cotton.

Inclusion of IPM methodologies and biocontrol in the curriculum of graduate and post-graduate courses in agriculture universities.

Detailed Examples of Biopesticides

Trichoderma Harzianum as Nematode Inhibitor, Fungicide, and Plant Growth Promoter and a Process for the Isolation Thereof (U.S. Patent No. 6475772, November 2002)

T. harzianum has been used as a biocontrol agent to protect plants against root, seed, and foliar diseases. To make this system of plant disease management more attractive, strains of *T. harzianum* have been identified and shown to provide the benefits of plant growth promotion, resistance to pesticides, effectiveness against phytonematodes, and induction/enhancement of rooting in stem cutting in the nursery.

Streptomyces Strain with Antimicrobial Activity Against Phytopathogenic Fungi (U.S. Patent No. 6,558,980, May 2003)

Streptomyces is one of the potentially most antagonistic microorganisms to act as an effective biocontrol agent. It is nonhazardous and ecofriendly in nature. A novel strain (CIMAP A1) of *Streptomyces*, capable of inhibiting the growth of a wide range of plant pathogenic fungi, including *Rhizoctonia*, *Sclerotinia*, *Pythium*, *Fusarium*, *Curvularia*, and *Alternaria*, has been isolated. This strain seems to have great scope for protection against various kinds of diseases caused by various kinds of fungal pathogens in both agricultural and horticultural crops. Moreover, it has the novelty of showing maximum growth inhibition of dark-spored pathogenic fungi which are cosmopolitan in distribution and can thus be used as a biocontrol agent against several plant-pathogenic fungi. In addition, this new strain multiplies on a simple delivery medium, is cost-effective, and can be exploited commercially.

A Novel Bacillus Subtilis Strain for Promoting Plant Growth and Controlling Plant Disease Caused by Fungal Pathogens

A unique, novel, and highly potent strain of *Bacillus subtilis* has been identified as promoting growth activity in plants and inhibiting the growth of plant-pathogenic fungi. Treatment of plants with *B. subtilis* invariably improved the percentage of plant survival and resulted in significantly higher growth and biomass production in comparison with an untreated control. In addition, it was found useful in inducing rooting in vegetatively propagated crops.

The present strain of *B. subtilis* was able to inhibit the growth of several fungal pathogens: *Rhizoctonia solani*, *Fusarium oxysporum*, *F. samitectum*, *Curvularia*, *Alternaria alternata*, *Colletotrichum acutatum*, *Colletotrichum capsici*, *Colletotrichum gloeosporioides*, *Corynespora cassiicola*, and *Thielavia basicola* *in vitro*.

Use of Albizzia Lebbeck Plant Extract and Bacillus Thuriengiensis Delta-endotoxin Against Lepidopteran Insects (U.S. Patent No. 6455,079, September 2002)

There are many examples of production and application of different preparations from *Bacillus thuriengiensis* delta-endotoxin for plant protection, but there is a possibility of resistance development in the insect population as a result of continued monotonous exposure of the insects to this toxin. In response, a plant-based insecticidal mixture has been developed that when combined with other biological insecticide(s), including *Bacillus thuriengiensis* delta-endotoxin, restricts resistance development against the endotoxin. Further, the mixture is environmentally safe and economically effective at significantly lower dosages. This provides a novel synergistic mixture consisting of an alcoholic extract obtained from the plant *Albizzia lebbeck* together with *Bacillus thuriengiensis* delta-endotoxin acetone powder that can be sprayed on infested standing crops and exhibits potency against lepidopteran insects at a very low dosage.

MARKETING CONSTRAINTS AND STRATEGIES

There is a large market potential for biofertilizer and biopesticide products that can only be tapped through a better understanding of rural markets and product/marketing constraints. Various stakeholders—farmers, government, manufacturers, marketers, and everyone concerned with agricultural productivity—must coordinate their efforts in order to succeed. The quality aspect must be regulated by the government, the manufacturer must identify and develop location-specific strains and improve packaging and logistics, and the marketer must be active in formulating suitable strategies using marketing techniques.

CONCLUSIONS

Successful adoption of biofertilizers and biopesticides, as with any other agro-input, will be based on convincing evidence of efficacy in controlling damage to crops by pests and diseases with a resultant increase in yields coupled with timely availability of desired quantities of high-quality products with an acceptable shelf life at affordable prices. To achieve these objectives, an extensive research and development effort in areas pertaining to production, quality assurance, field application, and knowledge transmission of biocontrol products is of great importance.

Basic R&D priorities for biopesticides include enhanced efficacy of the strains, enhanced tolerance to environmental stresses, enhanced efficacy of the formulations, packaging development, improved/new application technologies, trust-building demonstrations, and nodal quality control laboratories. Biological strains should have improved efficacy, improved spectrum of activity, improved productivity, and multiple modes of action. Cost reduction through use of inexpensive local raw materials is essential. Tolerance to high temperatures and varying pH would give added advantages. The formulation adjuvant needs to be selected carefully by considering the biology of the pests, microbes, and crops involved and should not interfere with the action of biocontrol agents. UV protectants, stabilizers, antioxidants, and efficacy enhancers deserve attention.

Application technologies must be refined to target applications at appropriate sites and to minimize environmental pollution. Well-planned and well-executed field demonstrations with follow-ups should enhance the satisfaction of end-user farmers. Nodal quality control laboratories with proper infrastructure, reference standards and standard test organisms, and human resources need to be established, and state pesticide testing laboratories need to be upgraded.

Biopesticides and biofertilizers will be successfully adopted only when convincing evidence is available that the microbes used provide efficient protection from pests and diseases and sufficiently supplement the nutritional requirements (nitrogen, phosphorus, iron, etc.) of plants. Products should be of high quality with the desired number of propagules present and an acceptable shelf life. Efforts are underway to select low-cost carrier materials that will support the population of desired organisms for a sufficient period. Despite the phenomenal growth in the availability of biopesticide and biofertilizer products during the past few years, their adoption by farmers has not been encouraging, primarily because they do not offer any practical advantage over conventional chemicals and there is a lack of high-quality products, mainly due to the absence of a proper infrastructure and adequate technical expertise. Research efforts therefore should be directed towards development of efficient strains with the right host compatibility, better competitive abilities, and improved tolerance to abiotic stresses. Strains with multifarious activities or consortia of efficient strains with multiple activities like N fixation, phosphate solubilization, and/or biocontrol properties would be the appropriate choice. Such strains, if mass cultured in low-cost formulation and supporting sufficient populations of microbes for longer periods (shelf life), would give added advantage to these biotechnological products. Well planned and well-executed demonstrations with the proper application technology would enhance adoption by end users.

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4. POTENTIAL FOR AGRI-BIOTECHNOLOGY PRODUCTS IN INDIA

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INTRODUCTION

The Indian biotechnology sector is gaining global visibility and is being tracked for emerging investment opportunities. Human capital is perceived to be the key driver for global competitiveness. Biotechnology is a powerful enabling technology that can revolutionize agriculture, health care, industrial processing, and environmental sustainability.

The estimated size of the Indian biotech industry is more than INR2305 billion; specific advantages include low operational costs, low-cost technologies, a skilled human resource base, a large network of research labs, and an abundance of raw materials in the form of plant, animal, and human genetic diversity. The combined annual global market for products derived from bioresources is roughly USD500–800 billion. India is one of 12 global biodiversity megacenters, harboring approximately 8% of global biodiversity in only 2.4% of its land area. The country is also home to two of the world's 25 hotspots. Varied cultural diversity as well as an ancient traditional knowledge system associated with biodiversity represent added assets. Nonetheless, much of this biodiversity is in peril, primarily due to anthropogenic causes. Thus, if the goal of converting bioresources—animal, plant, microbial, and marine—into commercially useful products and processes is to be realized, biodiversity must be not only conserved but also utilized in a sustainable manner. In this context, the absence of a good quantitative information network on bioresources—one that combines remote-sensing data and ground surveys—is a major constraint. The situation is even worse in regard to microorganisms. Field and marine biologists rarely work with molecular scientists, chemists, pharmacologists, or other experts, and there is virtually no bioprospecting industry. While the traditional knowledge base would be the starting point for bioprospecting, ethics and equity should be the guiding principles in benefit sharing.

VISION AND MISSION

Biotechnology as a business segment has the potential of generating revenues of USD5 billion and creating a million jobs through products and services by 2010. This can propel India into a significant position in the global biotech sweepstakes. Biopharmaceuticals alone have the potential to be a USD2 billion market opportunity, largely driven by vaccines and biogenetics. Clinical development services can generate in excess of USD1.5 billion, while bioservices or outsourced research services can garner a market of USD1 billion over this time period. The balance of USD500 million is attributable to agricultural and industrial biotechnology.

India has many assets, including its strong pool of scientists and engineers, vast institutional networks, and cost-effective manufacturing. There are over a hundred national research laboratories employing thousands of scientists. There are more than 300 college-level educational and training institutes across the country offering degrees and diplomas in biotechnology, bioinformatics, and the biological sciences, producing nearly 500,000 students annually; about 300,000 postgraduates and 1,500 Ph.D.s qualify in biosciences and engineering each year. These resources need to be effectively marshalled, championed, and synergized to create a productive enterprise.

India is recognized as a biodiversity mega-country, and biotechnology offers opportunities to convert biological resources into economic wealth and employment opportunities. Innovative

products and services that draw on renewable resources bring greater efficiency into industrial processes, check environmental degradation, and provide a more bio-based economy.

Indian agriculture faces the formidable challenge of having to produce more farm commodities for the growing human and livestock population from diminishing per capita arable land and water resources. Biotechnology has the potential to overcome this challenge and to ensure the livelihood security of 110 million farming families.

The advancement of biotech as a successful industry poses many challenges related to research and development, creation of investment capital, technology transfer, technology perception, patentability and intellectual property, affordability in pricing, regulatory issues, and public confidence. Central to this are two key factors: affordability and accessibility to the products of biotechnology.

The government's National Science and Technology Policy and the Vision Statement on Biotechnology issued by the Department of Biotechnology have mandated significant interventions in the public and private sectors to foster life sciences and biotechnology. There has been substantial progress over the past decade in terms of support for R&D, human resource generation, and infrastructure development. With the introduction of the product patent regime, it is imperative to achieve higher levels of innovation in order to be globally competitive. The challenge now is to join the global biotech league, and India has a clear biotech policy (www.dbtindia.nic.in). Key recommendations include human resource development, infrastructure development and manufacture, promotion of industry and trade, public investment for commercialization, establishment of biotechnology parks and incubators, a regulatory mechanism for monitoring, and public communication and participation.

PROMOTION OF INDUSTRY AND TRADE

The biotechnology sector has witnessed accelerated growth in recent years. With approximately 200 industries, the biotech sector has grown rapidly. Current estimates indicate that the industry grew by 39% annually to reach a value of USD705 million in 2003–04. Total investment also increased by 26% in that time period to reach USD137 million. Exports presently account for 56% of revenue. The biopharma sector occupies the largest market share, 76%, followed by bioagri 8.42%, bioservices 7.70%, industrial products 5.50%, and bioinformatics 2.45%. The bioservice sector registered the highest growth—100%—in 2003–04, with bioagri at 63.64% and biopharma at 38.55%.

The current policy review envisages an annual turnover of USD5 billion by 2010. India must develop its own biotechnological and pharmaceutical products to ensure quality and affordability for global trade. In addition to opportunities in drug discovery and development, there are significant openings to provide services to the worldwide biotech and pharmaceutical industries and to leverage low-cost, high-quality manufacturing with a global discovery potential. Capitalizing on these opportunities would create many valuable new jobs in India, as has been seen in the outsourcing and service industries.

However, to achieve the targeted business volume, several new challenges must be met: developing predictable and enabling policies, increasing public and private support for early or proof-of-concept stage of product development, improving communication among stakeholders in the sector, fostering public-private partnerships, integrating the Indian biotech sector globally, and improving infrastructure. The vision is to maximize opportunities in the area of contract research and manufacturing and to promote discovery and innovation.

The capital-intensive biotech industry has historically relied on venture capital from public and private sources. India needs to provide active support through incubator funds, seed funds, and provision of various incentives in order to develop the biotech sector. Clear government policies for promotion of innovation and commercialization of knowledge will propel its growth.

STRATEGIC ACTION

Innovation

Basic and translational research in key biological processes and new materials will be supported as innovation for tomorrow. Access to the knowledge generated will be improved by supporting knowledge and social networks among stakeholders so that those with appropriate skills can convert the research output into useful products and processes.

Research to promote innovation must be supported increasingly on a cooperative rather than a competitive basis. This requires effective communication among science agencies, research institutions, academia, and industry.

To promote India as a hub of innovation, a network of relevant stakeholders should be developed. Public investment should be used as a catalyst to promote such clustering and networking, as this can lead to enhanced creativity through sharing of expertise, resources, and infrastructure.

Availability of human resources would be ensured at each phase of the product cycle.

Technology transfer capacity should be strengthened.

It is proposed to create several national/regional technology transfer cells (TTCs) over the next five years to provide high-caliber, specialized, and comprehensive technology transfer services, including evaluating technology and identifying potential commercial uses, developing and executing intellectual property protection strategies, identifying potential licensees, and negotiating licenses. Each TTC would service a cluster of institutions in a region or a large city. Optimal delivery of services by the TTCs requires professionals with a background in industry and science, wide networks, an external focus, and high-level licensing skills. The best practices for effective technology transfer will be benchmarked.

The skills of existing technology transfer professionals will be upgraded by a combination of specialized training courses, including linking to important programs redesigning the incentives and career paths for posting.

Scientists and other innovators will be equipped with a better understanding of markets and commercialization pathways, the process of technology transfer, the strategy of protecting intellectual property rights, and industrial licensing.

Fiscal and Trade Policy Initiatives

Biotechnology firms are by far the most research-intensive among major industries. The biotechnology sector invests on average 20%–30% of its operating costs in R&D or technology outsourcing. Government support, fiscal incentives, and tax benefits are therefore critical. These measures will also help to capitalize on the inherent cost-effectiveness of the Indian biotech enterprise. Fiscal incentives already initiated by the government are detailed below.

Direct Taxes

100% wave-off on revenue and capital expenditure.

Weighted tax deduction @ 150% on R&D expenditure to companies engaged in the business of biotechnology.

Weighted tax deduction @ 125% for sponsored research programs in approved national labs, universities, and IITs.

Income tax rebate @ 125% on donations for scientific research made to noncommercial organizations.

Tax holiday for 10 consecutive assessment years to commercial R&D companies.

Accelerated depreciation allowance on new plant and machinery set up based on indigenous technology.

Indirect Taxes

Customs duty exemption for goods imported for R&D and central excise waiver on purchase of indigenous goods for R&D to publicly-funded R&D institutions and privately-funded noncommercial organizations approved by DSIR.

DSIR-recognized in-house R&D units engaged in R&D in the biotechnology and pharmaceutical sector can import specified equipment duty-free.

Interventions suggested for future implementation:

- Exemption of import duties on key R&D, contract manufacturing/clinical trial equipment and duty credit for R&D consumer goods to enable small and medium entrepreneurs to reduce the high capital cost of conducting research.
- Extension of the 150% weighted average tax deduction on R&D expenditure under section 35 (2AB) until 2010, permitting international patenting costs under this provision and enabling eligibility of expenditure incurred with regard to filing patents outside India for weighted deductions u/s 35 (2 ab).
- Enabling lending by banks to biotech companies as priority sector lending. Currently banks are almost averse to lending to young biotech companies. In order to encourage banks to lend and provide banking services to the biotech sector, a significant push through appropriate policy guidelines from the Reserve Bank of India is necessary. Currently, lending to agribusinesses as well as investment in venture funds by banks is categorized as priority sector lending. Biotech as a business has similar characteristics in terms of risk as well as gestation timelines, and it is therefore recommended that lending to biotech also be categorized as priority sector lending.
- Removal of customs duty on raw materials imported into India, where the finished product is imported duty-free. Life-saving drugs imported into and sold in India are exempted from paying customs duty, whereas customs duties are levied on raw materials for diagnostics and other pharmaceutical biotech products manufactured in India. To promote the indigenous manufacturing industry and make it competitive globally, raw materials imported by Indian manufacturers should be eligible for duty drawback.
- Rationalization of import and export of biological material is critical for clinical research and business process outsourcing.
- Procedures for import, clearance, and storage of biologicals, land acquisition, and obtaining environmental and pollution control approvals would be simplified and streamlined with shorter time frame lines through consultations with various central and state government departments.
- As an effective regulatory mechanism has been put in place though recent interventions, Foreign Investment Promotion Board (FIPB) approval for equity investment may no longer be necessary.
- Joint R&D collaboration and generation of joint IP through global partnerships would be fostered.
- International and global trade opportunities would be promoted aggressively to guide biotech R&D investment.
- Efforts would be made to remove hurdles for contract research, especially for input-output norms and taxes on revenue generated through contract research/R&D.
- Promotion of easy access to information regarding legislation and rules and regulations for transboundary movements of biologicals.
- Enhancement of current standards and safety of products.
- Strengthening of efforts to promote acceptance of Indian regulatory data internationally.
- Fostering of research, trade, and industrial partnerships at regional and subregional levels.
- Encouraging a “cluster” approach in operations. One significant feature of the industry is the fluidity and variety of its intercompany relationships, traditionally much greater than

in other industries. It has relied to a considerable degree on contracting and outsourcing, especially “upstream” in R&D through various licensing arrangements and “downstream” through co-marketing agreements.

- Promotion of collaborative knowledge networks. Expanded sharing of information, including creation/use of collaborative knowledge networks (CKN), can greatly enhance a company’s performance under a cluster approach. Managing the many external relationships is complex. Flexible and pervasive communications systems that allow information to flow effortlessly within and between contracting organizations will provide the key to success. Increasingly, IT advances, including web-based approaches, will provide the foundation for these systems.

Public Investment for the Promotion of Innovation and Knowledge Commercialization

Availability of financial support for the early phase of product development to establish proof of principle is the key to sustaining innovation. In this context, it is proposed to institute a Small Business Innovation Research Initiative (SBIRI) scheme through the Department of Biotechnology in 2005–06 for supporting small- and medium-sized enterprises with grants or loans. Companies with up to 1,000 employees will be eligible. The scheme will support pre-proof of concept, early-stage innovative research and provide mentorship and problem-solving support in addition to the grant/soft loan. The SBIRI scheme will operate in the phases of innovation and product development.

SBIRI Phase I

In this stage, funding will be provided for highly innovative, early stage, pre-proof of concept research. Preference will be given to proposals that address important national needs. The maximum amount of funding to an enterprise will be limited to INR50 lakh, with not more than 50% of it as a grant and the remainder as an interest-free loan. For projects to be considered at this stage, a partner from a public R&D institution would be considered important but not mandatory for those companies that have good-quality scientists. This should encourage high-quality scientists to agree to work in small- and medium-sized biotech companies, which is not currently the case. The R&D requirements of the public institution will be met through a grant.

SBIRI Phase II

It is expected that some of the proposals funded with SBIRI Phase I will establish the proof of concept. At this stage, the ability of the project to obtain venture capital funding improves. Such projects will be eligible for Phase II funding. Some projects could be eligible for direct Phase II support. It is proposed to provide soft loans at this stage for product development and commercialization at an interest rate of 2%. The role of a public R&D institution at this stage, too, is critical. The partner in the public institution at this stage will receive the R&D support as a grant.

Small- and medium-sized knowledge-based industries in the biotech sector will be encouraged to avail themselves of equity support from the SME Growth Fund of the Small Industries Development Bank of India (SIDBI).

Code of Best Practice for Disclosure Guidelines

A Code for Best Practice for Disclosure Guidelines for the Indian Biotech Industry will be a part of the General Listing Requirements and Disclosure Guidelines in conjunction with SEBI’s General Listing Rules and Disclosure Guidelines.

REGULATORY MECHANISMS

It is important that biotechnology be used for the social benefit of India and for economic development. To fulfill this vision, research and application in biotechnology must be guided by a process of decision-making that safeguards both human health and the environment with adherence to the highest ethical standards. There is consensus that existing legislation, backed by science-based assessment procedures, clearly articulates rules and regulations that can efficiently fulfill this vision.

Choices must be made that reflect an adequate balance between benefit, safety, access, and the interest of consumers and farmers. It is also important that biotechnology products required for social and economic good are produced speedily and at the lowest cost. A scientific, rigorous, transparent, efficient, predictable, and consistent regulatory mechanism for biosafety evaluation and release system/protocol is an essential ingredient for achieving these multiple goals.

Strategic Actions

The recommendation of the Swaminathan Committee on the regulation of agri-biotech products and of the Mashelkar committee on recombinant pharma products will be implemented in 2005.

It is recommended that an event that has already undergone extensive biosafety tests should not be treated as a new event if it is in a changed background containing the tested and biosafety evaluated "event." Where adequate evidence is available that the recurrent parent genetic background of a notified/registered genotype is nearly restored (through field data/molecular data), only the agronomic performance and the level and stability of the transgene expression may be analyzed by two-year trial data by the ICAR. Even in the case of a structurally altered transgene with no significant modifications in protein conformation, the toxicity and allergenicity tests need not be carried out provided the predicted antigenic epitope remains the same and the level of expression of the transgene is within the defined limits. For the released event, the Department is of the view that there is no need for large-scale trials under the Genetic Engineering Approval Committee, as the biosafety aspects have been already addressed adequately before releasing the "event." Only ICAR trials may address the agronomic evaluation of the crop.

An interministerial group chaired by a reputed scientist will be established in 2005 to address anomalies in regulations and issues that arise from time to time. It is proposed that the administrative support given to this committee be through the Department of Biotechnology. The mandate of the committee should be to vet any changes in policies, procedures, and protocols by departments dealing with regulations in biotech products and processes, resolve issues emanating from the overlapping/conflicting rules in various acts related to regulation of biotechnology activities in R&D, import, export, releases, etc., and to review guidelines, protocols, and standard operating procedures and ensure their dissemination to all stakeholders from time to time.

A competent single National Biotechnology Regulatory Authority is to be established with separate divisions for agriculture products/transgenic crops, pharmaceuticals/drugs and industrial products, and transgenic food/feed and transgenic animal/aqua culture. The Authority is to be governed by an independent administrative structure with a common chairman. The interministerial group will develop suitable proposals for the consideration of the government.

A center for in-service training of all professionals, irrespective of their location, engaged in the regulatory process is to be established by the Department of Biotechnology in close collaboration with other concerned departments and institutions.

All existing guidelines are to be updated in 2005 and made consistent with the recommendations of the Swaminathan and Mashelkar committees. New guidelines on transgenic research and product/process development in animal, aqua culture, food, phyto-pharma, and environmental applications are to be put in place in 2005 by the concerned ministries/departments.

As an interim measure, a special regulatory cell will be created by the DBT to build capacity in the country for scientific risk assessment, monitoring, and management, to foster international linkages, support biosafety research, obtain and review feedback from different stakeholders, and provide support to industry and R&D institutions. This cell will have a solely promotional and catalytic role.

Measures will be taken to build professionalism and competence in all agencies involved with regulation of biotechnology products

Research in support of regulation to safeguard health and the environment shall be supported by the concerned funding agencies to generate knowledge that will guide regulations and bioethics policy.

Concerned ministries will make a vigorous effort to promote acceptance of the Indian regulatory decisions by other trading countries.

CONCLUSION

The spectrum of biotechnology application in agriculture is very wide, encompassing generation of improved crops, animals, and plants of agroforestry importance, microbes, the use of molecular markers to tag genes of interest, acceleration of breeding through marker-assisted selection, fingerprinting of cultivars, land raises, and germplasm stocks, DNA-based diagnostics for pests and pathogens of crops, farm animals, and fish, assessment and monitoring of biodiversity, *in vitro* mass multiplication of elite planting material, embryo transfer technology for animal breeding, and food and feed biotechnology. Plants and animals are being used for the production of therapeutically or industrially useful products, with an emphasis on improving efficiency and lowering the cost of production. However, the emphasis should not be placed on edible vaccines, which are difficult to use in real-life conditions. Nutrition and balanced diet are important health promotional strategies. Biotechnology has a critical role to play in developing and processing value-added products of enhanced nutritive quality and providing tools for ensuring and monitoring food quality and safety.

It has been estimated that if biofertilizers were used to substitute for only 25% of chemical fertilizers on 50% of India's crops, 235,000 million tons would be used. Today about 13,000 million tons of biofertilizers are used—only 0.36% of the total fertilizer use. The projected production target by 2011 is around 50,000 million tons. Biopesticides have fared slightly better, with a 2.5% share of the total pesticide market of 2,700 crores and an annual growth rate of 10%–15%. Despite the obvious advantages, several constraints have limited their wider usage: products of inconsistent quality, short shelf life, and sensitivity to drought, temperature, and agronomic conditions.

From a research perspective, the spectrum of organisms studied has been rather narrow, and testing has been limited in scale, restricted mainly to agronomic parameters. Environmental factors, such as survival in the rhizosphere/phyllosphere and competition of native microbes, have not received sufficient attention. Moreover, results on crops are slow to manifest. Unless there is a policy initiative at the center and the state to actively promote biofertilizers and biopesticides at a faster pace, there is unlikely to be a quantum increase in their use.

A task force headed by Dr. M.S. Swaminathan under the Ministry of Agriculture (2004) has prepared a detailed framework on the application of biotechnology in agriculture that rightly emphasizes the judicious use of biotechnologies for the economic well-being of farm families, the food security of the nation, the health security of the consumer, protection of the environment, and the security of national and international trade in farm commodities. Consistent with this overall vision, the priorities in agri-biotech would be based on social, economic, ecological, ethical, and gender equity issues. The following guiding principles would apply across the sector:

- A comprehensive and integrated view should be developed of r-DNA- and non r-DNA-based applications of biotechnology with other technological components required for agriculture as a whole.
- Use of conventional biotechnologies (e.g., biofertilizers, biopesticides, bioremediation technologies, molecular assisted grading, plant tissue culture, etc.) should continue to be encouraged and supported. A precautionary yet promotional approach should be adopted in employing transgenic R&D activities, based on technological feasibility, socio-economic considerations, and promotion of trade.
- Public funding should be avoided for research in areas of low priority or those that could reduce employment and impinge upon the livelihood of rural families.
- Regulatory requirement in compliance with the Cartagena Protocol, other international treaties and protocols on biosafety, germplasm exchange, and access, and the guiding principles of codex alimentarius will be implemented through an interministerial consultative process.
- Transgenic plants should not be commercialized in crops or commodities where international trade may be affected. However, their use may be allowed for the generation of proof of principle, strictly for R&D, where alternate systems are not available or not suitable.
- In the long-term perspective, basic research for development of low-volume, high-value secondary and tertiary products through the enabling technologies of genomics, proteomics, engineering of metabolic pathways, RNAi, host pathogen interaction, and others should be encouraged. Research and support of biosafety regulations would need support.
- It is proposed to do away with large-scale field testing of released transgenic events and make it compliant with agronomic test requirements.

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5. AGRICULTURAL BIOTECHNOLOGY DEVELOPMENT IN INDONESIA

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INTRODUCTION

Biotechnology has been used to improve product processing and in the development of energy-saving, cost-reducing, nature-oriented, environment-friendly products. In the 21st century, where the pace of technological change has never been so fast, industries must use biotechnology to survive and must be intensively supported by research activities and research networking. Researchers not only have to work harder but also face new ethical and moral issues and changes in consumer protection laws.

The future environment is a changing landscape characterized by technology based on computer networking, which in turn influences the behavior of people moving into an “e-society” and their approach to doing business. Competition becomes global when ideas move freely across borders. Restructuring, always anticipating new technology is essential because of the impermanence of success. Success in the 21st century competitive landscape requires specific capabilities. For Indonesia, it is the ability to manage tropical bioresearch wisely to maintain sustainable industrial development, the ability to build networks to adapt to rapid technological changes, and the ability to fulfill stakeholders’ needs. Furthermore, the approach for collaboration should be based on mutual benefit at every stage, from raw material aspects to downstream industries.

Indonesia has developed largely due to industrial policies that stand in close relationship to macro-policies in which economic considerations are given the highest level of priority. It has been a very good decision for Indonesia to take the steps necessary to promote industrialization based on local resources. Bioresources are among the local natural resources that are ready for utilization. The development of a bio-industry which utilizes biotechnology to process bioresources into products is expected to significantly support the national effort in systematically recovering from the economic crisis.

Biotechnology will be as important to the first half of the 21st century as computers were to the second half of the 20th century. Along with information technology, biotechnology will enhance the quality of human life by overcoming the problems of human health and food shortage and preventing environmental destruction.

ECONOMIC AND COMMERCIAL CONSIDERATIONS

In 1985, the Indonesian government declared biotechnology a priority area for national development. This decision was further promoted after the recent economic crises (1997 up to now), based in part on Indonesia’s unfortunate past experiences with other technological applications, especially air and space technology.

There are very strong links between increases in agricultural productivity and broad-based economic growth in the rest of the economy. Agriculture is an engine of growth in low-income developing countries, including Indonesia, where only the agricultural sector maintained positive growth during the peak period of the economic crisis in 1997.

The contribution of biotechnology to improved economic well-being and performance is much more difficult to measure. It takes essentially three forms: a boost to the performance of industries (including the public sector) for which the application of biotechnology knowledge

could result in improved products, a boost to the performance of industries (including the public sector) for which biotechnology-based production provides a key input, and higher-quality goods and services for households overall.

Agricultural biotechnology is considered to have the most potential for investment, but industries are reluctant to invest in it because of the economic crisis. Some applications of biotechnology in the agribusiness sector with great potential are:

Cell breeding and plant tissue culture involving the development of new clones, disease-free plants, and hybrid plants using embryo breeding and cell fusion. The potential plants for investment are for food (hybrid corn, rice, soybean, and potato), plantation (oil palm, cacao, coffee, pepper, rubber, golden teak wood, etc.), horticulture (mango, banana, durian, leafy vegetables, cut flowers, etc.), and forestry, especially plant species used for pulp and paper production.

Embryo transfer techniques and super-ovulation, embryo fusion (twinning), and low-temperature preservation for animal husbandry. The animals selected are cattle, sheep, buffalos, and pigs.

Diagnostic techniques, using monoclonal antibodies, for early detection of plant and animal diseases caused by virus, bacteria, or fungi that are difficult to detect by conventional methods. Areas of potential importance are in the aquaculture (shrimp, tilapia, carp, seabass, ornamental fish, etc.), poultry, and cattle and sheep businesses.

Vaccine production for the livestock and aquaculture businesses.

Development of bio-industries for the production of food (organic acids, conventional foods, liquid sugars, fermented foods, etc.), feed (poultry and livestock), and enzymes (papain, bromeline, and microbial enzymes from agro-industrial waste materials).

Development of biotechnology for degrading biological waste or byproducts, such as composting, ensilage, etc.

BIOTECHNOLOGY INDUSTRY

As shown in the simplified diagram (Figure 1), biotechnology in the context of industrialization is a technological tool. Together with management and political tools, it should be utilized comprehensively to foster businesses by optimizing the positive synergy among them. Management and political tools for the development of bio-industry would consist of a supportive business infrastructure, institutionalization of financial backup, and the implementation of special incentives for research and development activities.

Biotechnology may be considered an input for industrial development, some aspects of which are shown schematically in Figure 1. Bio-industry is an economic activity which provides response to demands under certain conditions. The quality of the product and its cost and delivery are very much dependent upon the conditions of supply, the business environment, and policies.

Biotechnology as a technological tool is required to develop bio-industry and to shift the main orientation of natural resource utilization from depending on its surplus (factor-driven based on comparative advantage) to processing natural resources for making products (innovation-driven based on competitive advantage). It has the characteristic that all modern industries expect: being relatively less capital-intensive. The resources used are recycled and renewable and in harmony with a sustainable environment. The emergent, strategic, and innovative properties of biotechnology could be promoted, especially the effect of bringing the product, not the commodity, to the marketplace both domestically and globally.

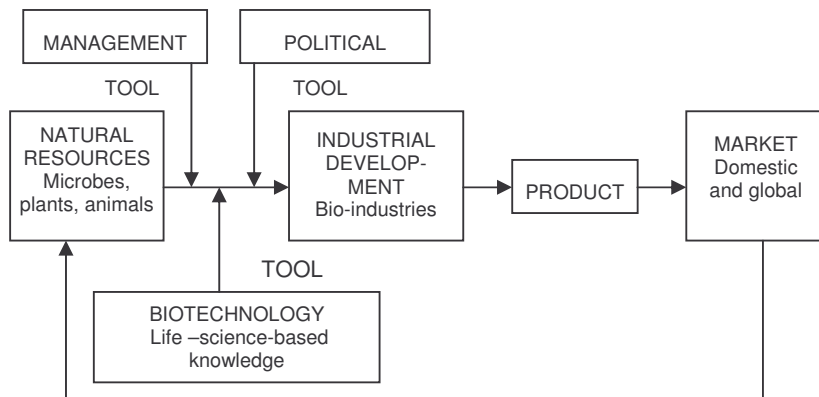


Figure 1. Diagrammatic Illustration of the Links between Markets, Biotechnology, and Natural Resources

Based on the utilization of biotechnology, bio-industry is well placed to become a strategic industry. Some bio-industry products for therapeutic use, such as antibiotics, vaccines, diagnostics, etc., and agricultural applications related to crops and livestock have found good markets in Indonesia. Bio-industry products such as biopesticides and biofertilizers are becoming preferable to chemically-derived products due to environmental and ecological concerns.

The strategic approach of biotechnology development for industrialization in Indonesia will be addressed from two levels: macro and micro approaches. On the macro level, the first element is positioning biotechnology in terms of technology capacity and the industrial stage of development. Worldwide competition among research institutes and business enterprises in the field of biotechnology is severe. To be significantly competitive, the specific area of biotechnology to be focused on should be determined with care. The second element is national capacity building, including the development of human resources, small- and medium-sized enterprises for the domestic market, and large-sized ones with the possibility of entering the global market under joint ventures, foreign direct investment, or licensing.

The strategy for the development of biotechnology on the micro level focuses on upgrading or improving technology processes (fermentation and downstream processing, cell and tissue culture, and biological development), upgrading the supporting knowledge (molecular biology, biochemistry up to the molecular level, physiology, biomaterial sciences, bioengineering, etc.), benefiting from and making maximum use of the rapid advancement of genomic research and bioinformatics for more advanced research and development of better products, and maximizing synergy through networking among related research institutes by sharing experiences and establishing complementary programs. Potential benefits of agricultural biotechnology include higher crop yields, reduction in fertilizer and pesticide use, tolerance of adverse climatic conditions, greater use of marginal lands, fewer adverse environmental impacts, identification and elimination of diseases in food animals, and better food quality and nutrition, including restoration of micronutrient deficiencies. Some potential applications are:

Food and Agriculture

Genetic transfer of traits in transgenic plants by recombinant DNA technology: herbicide tolerance, insect resistance, viral disease tolerance, fungal disease tolerance, product quality improvement, and male sterility traits. Production of metabolites/chemicals, improvement of nutritional traits, stress-resistance properties, etc.

Business Potential for Agricultural Biotechnology Products

Animals

Embryo transfer and embryo splitting, recombinant DNA technology, gene transfer for generating disease-resistant animals, production of new and improved vaccines, more effective gender control, and manipulation of egg composition from cholesterol-rich to cholesterol-free, etc.

Aquaculture and Marine

Selective breeding and brood stock management, genetic characterization of hatchery breeds, production of recombinant GH and IGFs and development of protocols for growth enhancers, and cell culture and terrestrial agriculture.

Biotechnology will affect international trade, with varying impacts in different areas of application. Though more biotechnology research takes place in the health sector than in all other sectors, the impact on trade flows will be greater in agriculture. Trade in agricultural products has more than ten times the value of trade in pharmaceuticals; therefore shifts in agriculture trade would have more important implications. Social repercussions of shifts in international trade would be more important in the case of agriculture than in the case of health products.

Biotechnology has also opened the door to the greater use of biodiversity in agriculture. Half of the gains in agricultural yield come from genetic natural material. The products of agricultural biotechnology will reach USD100 billion. Two drugs derived from the rosy periwinkle alone have earned USD100 million per annum for Eli Lilly, an American pharmaceutical company.

In addition, biotechnology is currently widely used to improve the efficiency of key production processes, particularly in food processing, drinks, and detergents. Major new applications will emerge in industries such as textiles, leather, pulp and paper, oil refining, metals and mining, printing, environmental services, and specialty chemicals. However, biotechnology ventures typically require more start-up capital than electronics or software-based ventures and have longer product development lead times. Thus from the perspective of a potential entrepreneur, the ideal strategy would be to conduct as much development work as possible within the incubator organization before starting the new venture.

APPLIED MICROBIOLOGY FOR AGRICULTURE

One of Indonesia's potential domestic biotechnological resources is microbial. Research in this area relates primarily to the application of the best selected native microbial isolates to facilitate better growth performance of plants and/or animals. In food crops, the use of vesicular-arbuscular mycorrhizae, rhizobium, bradyrhizobium, and azospirillum has been proven beneficial in promoting nutrient efficiency and yield of rainfed rice, soybean, and peanut on acid soils. Bioconversion of cellulose material, i.e., rice straw, has been found to be accelerated by the use of cytophaga and trichoderma as activators. Several native strains of *Bacillus thuringiensis* have been identified as effective in controlling army worm, Asian corn borer, rice stem borer, cotton bollworm, and sugarcane borer.

Development of biofertilizers consisting of effective nonsymbiotic N-fixing, phosphate-solubilizing, and aggregate-stabilizing microbes, of bioinsecticides composed of entomophogenic fungus, *Beauveria bassiana*, of biopulping activators using white rot fungi, and of microbially induced flavoring agents are major activities in the application of microbial technology in the estate crops area. Antagonistic fungal isolates have also been recognized as effective in controlling the white-rot disease of rubber and the pod-rot disease of cacao.

Some biotechnological products have been launched and commercialized in Indonesia and treated as biofertilizer and biopesticide.

Biofertilizer Emas

The function of this fertilizer is to increase the efficiency of fertilizer application (N, P, and K). The bioactivator of this biofertilizer is bacteria: *Azospirillum lipoferum*, *Azotobacter beijerinckii*, *Aeromonas punctata*, and *Aspergillus niger*. It is used mostly for estate crops.

Biofertilizer RhiPhosan

This biofertilizer is used to improve the nitrogen fertilizer from the air and to promote the liquidation of P and C fertilizer in the soil. It can also produce photohormonal Indol Acetate Acid (IAA), which will increase root growth. Its bioactivators are *Bradyrhizobium japonicum* and *Aeromonas punctata*. It is used mostly for secondary crops and cover crops.

Organic Decomposer OrgaDec

OrgaDec is a bioactivator that decomposes the organic materials in a short period of time and is antagonistic to some root diseases. It consists of *Trichoderma pseudokoningii* and *Cytophaga sp.* *OrgaDec* is used mostly to decompose organic material with a high cellulose content (cocoa and palm tree waste, paddy straw, leaves, bud, and other materials).

Plant Regulator NoBB

NoBB consists of a plant regulator which can stimulate the function of cambium for cell fission and recovery of latex vessels. It also helps in the recovery of the skin of the rubber tree from Brown Bast. *NoBB* can be used to increase the productivity of rubber estates.

Biofungicide Greemi-G

Greemi-G consists of two green microbes (*Trichoderma harzianum* and *Trichoderma pseudokoningii*) which can be used to manage the impact of *Ganoderma* for palm oil trees, JAP for rubber and *Phytophthora* for cocoa.

Bioinsecticide BioMeteor

The bioactivator of this product is *Metharhizium anisopliae*, which can manage plant pests in soil, such as *Dorystheness sp.* (bokor tebu) and *Xystrocera festiva* (bokor sengan).

Bioinsecticide NirAma

NirAma consists of the bioactivator *Paecilomyces fumosoroseus*. It is used mostly to manage plant pests such as *Heliopectis antonii*, fire worm, *Ectropis bhurmitra*, *Antitrygodes divisaria*, *Hyposidra talaca*, *Metanastria hyrta*, *Homona coffearia*, *Poecilocorys sp.*, *Spodoptera litura*, and *Meloidogyne sp.*

In summary, it can be seen that there are many biotechnology products based on applied microbiology in Indonesia, all of which together constitute a small but growing industry. The production and marketing experience gained from this aspect of biotechnology can provide a basis for the expansion of more modern biotechnology applications.

6. AGRICULTURAL BIOTECHNOLOGY STATUS IN THE ISLAMIC REPUBLIC OF IRAN: PROGRESS, PRODUCTS, LIMITATIONS, AND FUTURE

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INTRODUCTION

The Islamic Republic of Iran is one of the largest importing countries for agricultural products. As shown in Table 1, agricultural productivity is not sufficient; a revolution is needed. Many years ago it had been the aim of Iranian researchers to try to reduce this dependency on imports and achieve food self-sufficiency. These endeavors were successful to a limited extent, for example, in 2004 self-sufficiency in wheat production was attained. However, agricultural production strategies, based primarily on old-fashioned methods, were not sufficient to meet the challenges. With the rapid developments in biotechnology and genetic engineering techniques, many scientists in Iran hoped to solve the country's food problems more rapidly and efficiently. Now, elsewhere, biotechnology-derived agricultural products are multiplying in number and area grown and are considered by many to be a remedy for overcoming world food shortages.

Table 1. Agricultural Materials Imported in 2003 and Their Value, Iran

	Material	Quantity (Mt)	Value (USD 1000)		Material	Quantity (Mt)	Value (USD 1000)
1	Barley	6,374	980	12	Cottonseed oil	2,447	1,496
2	Maize	3,089,731	437,880	13	Linseed oil	3,678	386
3	Oilseed	845,560	234,833	14	Olive oil	922	740
4	Potatoes	33,189	3,362	15	Palm oil	126,970	60,055
5	Rapeseed	432	2,009	16	Rapeseed oil	19,974	12,369
6	Rice	945,729	276,316	17	Soybean oil	923,384	514,508
7	Soybean	828,000	225,041	18	Sunflower oil	117,856	789,382
8	Wheat	406,365	168,466	19	Chicken meat	5,175	4,460
9	Wheat flour	2,345	600	20	Hen eggs	2,345	4,988
10	Sugar	406,365	81,210	21	Dry milk	8,341	24,411
11	Textile fibers	8,797	38,254	22	Cottonseed oil	2,447	1,496

Source: FAO

AGRICULTURAL BIOTECHNOLOGY PRODUCTS READY FOR THE MARKET

Biofertilizers

Phosphate Biofertilizer

This product is the result of a 12-year study of phosphate-dissolving bacteria. These bacteria occupy the plant root region and cause release of the phosphorous from insoluble minerals and organic soil compounds and result in an increase of available phosphate for the plant. About 80% of chemical phosphate fertilizers convert into an insoluble form in the soil very quickly. This means that more than the necessary amount of phosphorous must be added to the soil, re-

sulting in increased cost and environmental contamination due to fertilizer residues. Phosphate biofertilizer can decrease phosphate chemical fertilizer usage by 50% while increasing the yield by 10%–50%, thus eventually doubling the benefit to farmers.

Nitrogenous Biofertilizer

Economic, health, and environmental problems have resulted from the use chemical nitrogen fertilizers, demonstrating the importance of alternative plant feeding methods. Countries using biological nitrogen fixation (BNF)—China, India, Vietnam, the Philippines, Canada, the U.S., Russia, Argentina, Brazil, and Cuba—have shown that it has not only theoretical and experimental but also has practical applications. After seven years of research, Iranian researchers have produced nitrogen fertilizers containing native rhizobacters as a nitrogen fixative. These bacteria can increase N-uptake in native rice cultivars by 69%.

Biopesticides

Pests reduce crop yield worldwide by 10%–20% annually. About 23,000 tons of chemical pesticide were used on Iranian farms in 2002 and 2003 to protect crops against pests. Of this amount, 8,000 tons were used solely against insects. Because of both the harmful effects of chemical pesticides and the economic cost, biopesticides are considered to be a viable alternative. Bt-derived pesticides are the most conventional and environmentally friendly. In Iran, Bt-derived Cry proteins are produced on a large scale as a biopesticide, which has been shown to effectively control one of the most important rice pests, the green rice caterpillar (*Naranga aenescens*).

Bt-transgenic Rice

According to FAO statistics, Iran is the third-largest rice-importing country (926,000 tons annually). An effort has been made to compensate for this deficiency through classic agronomic and breeding methods. However, there is an emerging opinion that new genetic engineering technologies should be adopted to complement these methods. In 1997, a Bt gene, developed in cooperation with more than 20 scientists from India, Malaysia, the U.S., and Australia, was transferred into Tarom Molai rice cultivar, an Iranian rice, to achieve rice lines resistant to green rice caterpillars (*Naranga aenescens*) and striped stem borers (*Chilo suppressalis*). After 12 years, these efforts resulted in several Bt-transgenic rice varieties. Three-year field trials proved that the insect resistance gave higher yields (10%) compared to the unmodified control. The most important characteristic of this transgenic rice is that it expresses Cry 1Ab protein only in its green tissues (not in seed) and kills only striped stem borers and green rice caterpillars, with no harmful effects to humans or live farm organisms, as shown in data collected when the transgenic rice was fed to mice and chickens. It has been estimated that Bt-transgenic rice cultivation will prevent the loss of 200,000 tons of rice yield due to pests and result in a benefit to Iranian rice producers of about USD125 million.

***In vitro*-produced Pistachio Seedlings**

The pistachio is native to Iran; more than 380,000 ha are devoted to this invaluable plant. The average yield of 1000 kg/ha annually is lower than the yield of other competing countries (2500 kg/ha). This inefficiency is the result of a lack of adequate research. Having access to highly productive and homogeneous pistachio seedlings is very important in increasing the yield. Micropropagation via tissue culture techniques has been adopted to accomplish this, which has resulted in highly productive stock tolerant of environmental stress. The results have been very satisfactory, and there are now optimized micropropagation protocols for large-scale production of root stocks from several pistachio stocks. This is a two-month process, as opposed to the year required to produce pistachio seedlings using traditional methods. It is possible to produce more

than 100,000 root stock plants per year from each initial explant. Utilization of this technology will require private sector investment.

AGRICULTURAL BIOTECHNOLOGY PRODUCTS IN THE PIPELINE

Bt-transgenic Cotton

An estimated 400 tons of chemical pesticides are used on 150,000 ha of cotton fields to protect against pink bollworm (*Pectinophora gossypiella*). Attempts to produce cotton lines resistant to this pest resulted in Bt-transgenic cotton. Laboratory bioassays and greenhouse trials have demonstrated its resistance. Field trials and biosafety tests must still be undertaken before it can be released in the field. Estimates are that cultivation of this transgenic cotton will increase edible oil production by 3,000 tons and textile production by 9 million tons annually.

Chitinase-transgenic Cotton

Verticillium wilt (*Verticillium dahliae*) is an important fungal disease of cotton in North Iran and causes 15%–20% of the damage in this region. A cotton line has been developed that is able to express the chitinase enzyme in its tissue. This enzyme digests fungal cell walls and so prevents serious damage. Bioassays and experiments have confirmed its efficacy, and field trials are beginning.

Virus-free Potato Minutubers

In 2001, a project was designed to produce virus-free potato minutubers via tissue culture techniques. Now optimized protocols for large-scale production of minutubers are available. Since more than 90% of maternal potato seed is imported, this procedure will save more than USD120 million annually and also guard against infection by exotic pathogens.

CONSTRAINTS ON THE COMMERCIALIZATION OF AGRICULTURAL BIOTECHNOLOGY PRODUCTS

Popularization

There have been some protests against biotechnology-derived products. Convincing the consumers that these products, now available, are safe to consume will not be easy and will require the effort of both government agencies and scientists.

Privatization

Every idea needs investment to support commercialization, and the best investors are in the private sector. Unfortunately, in the Islamic Republic of Iran the private sector is in its infancy. Also, the preference for investing in biotechnology industries is not as strong as for other industries like petroleum, electronics, and construction. It will be necessary to educate investors on this new industry and demonstrate that its benefits are worthwhile. Success in other countries will be helpful in convincing Iranian investors.

Biosafety Challenges

This is a common problem with biotechnology worldwide. These concerns arise primarily from political, not scientific considerations. However, public awareness-building is likely to be very effective, especially in a society that includes many uneducated people. Fortunately, the situation is changing to some extent.

PROSPECTS

The Islamic Republic of Iran imports more than 97% of its required edible oil. This is an unfortunate fact that should shift the country's focus to oilseeds. A large canola project is currently in progress that is projected to release transgenic canola before 2008. As can be seen in Table 1, more than ever there is a need to invest in livestock. Transgenic fish, which have shown a 30-fold growth rate in other countries, are a first step. Improving the use of molecular marker techniques in cattle breeding projects is another important goal.

CONCLUSION

Agricultural biotechnology is experiencing rapid progress in the Islamic Republic of Iran. Its growth depends largely on how successfully a suitable background can be prepared. Public media and educational organizations can play an effective role in familiarizing society with agricultural biotechnology products and in the public perception of them as safe and beneficial. The private sector participation has great potential in the commercialization of agricultural biotechnology products. However, there is a need to put in place appropriate government policies to encourage both scientists and private investors. Success in recruiting private investors from other countries will likewise be helpful.

7. STATUS OF AGRICULTURAL BIOTECHNOLOGY IN THE ISLAMIC REPUBLIC OF IRAN

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INTRODUCTION

The agricultural sector of the Islamic Republic of Iran has made considerable achievements in supplying food commodities, largely attributable to increased production capabilities and the availability of resources, including 37 million ha of arable land, 118 billion cubic m of available water resources, diversified climate conditions and the potential for producing diversified tropical and cold-climate crops, renewable natural resources (forests and rangelands of 102.4 billion ha, 2,700 km of coastal water), and skilled manpower and producers. However, the condition of basic resources has gradually worsened, and their sustainability is in question. About 8.1 million ha of the 12.4 million ha of forests are at risk of severe degradation and require protection; only 10.5% of the 88.6 million ha of rangelands are considered good, and 49% are poor to very poor.

Use of ground water resources exceeds the natural recharge rate and has resulted in a reduction in groundwater levels. Most of the reservoirs are at risk of water scarcity. Large sections of the cultivated area are under-irrigated; average irrigation efficiency is 38%, so that significant renewable water resources are not available for plant consumption. Salinization and waterlogging add to the problem, and overuse of chemicals to control pests threatens human health.

Biotechnology may provide a way to end the overuse of basic resources and enhance their sustainability.

HISTORY OF BIOTECHNOLOGY IN IRAN

Biotechnology consists of a group of technologies that use biological elements. This valuable modern science, only recently developed, has brought about significant changes. Iran started using modern biotechnology about two decades after the developed countries, that is, from the mid-1990s, but only in the past five years has this technology been seriously considered. As a result of poor investment and a lack of clear objectives and policies, the country is still preparing the groundwork for using biotechnology to address economic needs.

After the war with Iraq ended, the government allocated funds to improve biotechnology, with these goals:

- Supporting established research centers, such as the Pasteur Institute of Iran and the Razi Research Institute, in carrying out research in biotechnology.
- Establishing the National Research Center for Genetic and Biotechnology Engineering.
- Constituting the Biotechnological Research Center in the Organization of Industrial and Scientific Research.
- Conducting biotechnological research in the Biochemistry and Biophysics Research Institute at Tehran University.
- Founding the Biotechnology Committee in the Scientific Research Council in order to prepare a national biotechnology plan and create an atmosphere of cooperation among those involved in biotechnology research and production.
- Founding biotechnology departments in research institutes such as the Seed and Plant Improvement Research Institute, the Forests and Rangelands Research Institute, industrial universities, and science, agriculture, and medical colleges.

- Establishing the Agricultural Biotechnology Research Institute in Karaj.
- Establishing the Agricultural Biotechnology Research Institute in Esfahan.

At the same time that biotechnological research centers were being established, academic and educational centers began to design formal biotechnology courses.

MAJOR ACHIEVEMENTS IN AGRICULTURAL BIOTECHNOLOGY RESEARCH

Razi Research Institute

Activities of this institute are considered “traditional” biotechnology. It has been a pioneer in research, mass production, and localizing the technology of vaccine and serum production. In addition to producing human vaccine, the institute produces some 3.3 million doses of livestock vaccine and 350 thousand doses of fowl vaccine each year.

Research Center for Agricultural Biotechnology

Activities of this center are considered “modern” biotechnology. Despite the fact that this institute was established only recently, it has had significant achievements.

Production of Transgenic Cotton

Each year some 150 thousand ha of farmland are allocated to cotton cultivation. Almost 400 tons of chemical pesticide are used for pest eradication. If production is increased at the same time that transgenic cotton resistant to cotton pod worms is introduced, costs will decrease and there will be less use of chemical pesticides, resulting in less environmental pollution.

Production of Transgenic Rice

Introduction of transgenic rice resistant to some pests and fungal diseases concurrent with increased production may lead to a decrease in costs and eventually less environmental pollution due to decreased use of chemical pesticide. This year, transgenic rice is being cultivated in 2,000 ha of the country’s rice fields; the amount will be increased in future years.

Production of Biofertilizer for Paddy Rice

Because of the high costs of production and distribution of chemical pesticides and the resulting environmental pollution, the Research Center for Agricultural Biotechnology has decided to produce biofertilizers from local bacteria and algae. This will reduce costs for the production and distribution of chemical pesticides and decrease environmental pollution.

Production of Biopesticides to Eliminate Agricultural Pests

Insects cause great damage to plants, reducing crop production by 10%–20% annually. Each year 23,000 tons of chemical pesticides are used to kill agricultural pests, at an import cost of USD35 million. The Research Center for Agricultural Biotechnology has not only produced biopesticides but also proved their effectiveness on rice pests in farm tests. Industrial production of these biopesticides, in addition to preserving the environment and consumers’ health, has reduced the cost of producing crops significantly.

Production of Virus-free Potato Seed

The total area cultivated to potato is about 60,000 ha. Use of contaminated seed increases the spread of viral infections and thus the damage to potato farms. Using uncontaminated seed increases production by at least to 30%; potato production could be increased from 3 million to 4.5 million tons.

Business Potential for Agricultural Biotechnology Products

Production of Pistachio Seedlings Using Tissue Culture

A major project of the Ministry of Jihad-e Agriculture has as its goal the development of areas cultivated with high-quality pistachio and an increase in the yield of pistachio per ha, requiring large numbers of high-quality pistachio seedlings. The Research Center for Agricultural Biotechnology has produced 4,000 pistachio seedlings to date using tissue culture.

Production of Date Seedlings Using Tissue Culture

The majority of the production in the Research Center for Agricultural Biotechnology is being tested in farms and prepared for mass production.

IMPORTS

Trade in transgenic seeds is increasing rapidly throughout the world. Iran, however, is only an importer of some agricultural biotechnology products. In 2002, soybean products (the most cultivated transgenic plant in the world), including raw soybean oil, soybean meal, and soybean seeds, were imported at a value of USD712 million. In the same year, imports of corn and cotton (the second and third most widely-grown transgenic plants worldwide) were at about USD220 million and USD2 million, respectively. Moreover, USD1 billion of edible oil is imported, a portion of which is derived from rapeseed (the fourth most cultivated transgenic plant). In the dairy industry large amounts of enzymes, microorganisms, and starter are also imported.

EXPORTS

Since modern biotechnology got underway only a few years ago, agricultural biotechnology has not reached the mass production stage, and at present all the products are used in the country. Iran does not export any agricultural biotechnology products.

PROGRESS MADE IN BIOTECHNOLOGY

Although agricultural biotechnology is relatively new, significant progress has been made:

Founding of the National Committee of Biotechnology in cooperation with ministries and other organizations.

Founding of the National Research Center for Genetic and Biotechnology Engineering.

Establishing and equipping the biotechnology departments in the Jihad-e Agriculture, Health, Treatment, and Medical Training ministries and the major established research institutes, such as the Pasteur Institute and the Razi Serum-Making Organization.

Creating postgraduate courses at master's and Ph.D. levels in fields relevant to biotechnology.

Training skilled manpower in and out of the country.

Establishing ties and carrying out research projects with advanced countries such as France, Austria and Italy, as well as membership in international organizations.

CONSTRAINTS TO PROGRESS IN BIOTECHNOLOGY

The development of agricultural biotechnology in Iran is constrained by:

- Lack of adequate investment in research and development and failure to apply biotechnology in food production.
- Public unawareness of biotechnology's potential.
- Lack of adequate cooperation among the organizations and ministries involved.
- Uncertainty concerning the outcome of research activities due to the lack of intellectual property and patent laws.

- Absence of adequate methods and mechanisms to move *in vitro* products to production and lack of a link between research products and production practices.
- Unwillingness or inability of the industrial sector to mass produce the products of biotechnological research.
- Deficiency in the management system in some sectors and the presence of often conflicting decision-making units; lack of efficient supervision and control.
- Shortage of adequate skilled and specialist manpower.
- Inadequate scientific relationships among the research, training, and scientific centers in the country and internationally.

PLANS FOR AGRICULTURAL BIOTECHNOLOGY

Medium-Term Plan for Agricultural Biotechnology (2005–09)

Cultivation of transgenic plants amounting to at least 0.2% of the area of these plants under cultivation in the world by the end of the plan period.

Production of forage and supplements of livestock amounting to 0.5% of the need of the country.

Production of biofertilizers and biopesticides amounting to 3% of the need of the country and replacing chemical fertilizers and pesticides.

Production of three kinds of new vaccines against livestock diseases.

Production of biological products usable in the food industry amounting to 10% of the need of the country.

Long-Term Plan for Agricultural Biotechnology in Iran (2010–14)

Cultivation of transgenic plants amounting to 0.5% of the area under cultivation of these plants in the world by the end of the plan period.

Production of forage and supplements of livestock amounting to 10% of the need of the country.

Production of biofertilizers and biopesticides amounting to 10% of the need of the country and replacing chemical fertilizers and pesticides.

Production of at least five kinds of new vaccines against livestock diseases and an export target of 30% of total products.

Production of biological products usable in the food industry amounting to 15% of the need of the country.

STRATEGIES FOR THE DEVELOPMENT OF BIOTECHNOLOGY

Recognizing the existing capabilities and the increasing gap between the technology in the world and that in Iran, and in order to achieve the goals set, guidelines are:

- Preparation of a comprehensive plan for biotechnology training.
- Legislation of intellectual property laws relevant to biotechnology.
- Establishment of national nonprofit centers to verify the quality of biotechnological processes and products.
- Establishment of a national biotechnology information network.
- Preparation of national standards for biotechnological products.
- Legislation of biotechnological moral principles.
- Promotion of public awareness and public acceptance of biotechnology.
- Support for the establishment of private marketing agencies.
- Support for the establishment of organizations investing in biotechnology.
- Allocation of funds and provision of facilities according to priorities.

Business Potential for Agricultural Biotechnology Products

- Facilitation of joint investment of domestic and foreign biotechnology agencies to achieve advanced biotechnology.

Strategies for Industrialization and Production

- Support for biotechnological parks and centers.
- Preparation of mechanisms for transmitting biotechnology from research centers to beneficiaries.
- Support for the establishment of biotechnological consultative and engineering service organizations.

Strategies to Support the Private Sector, Trade, and Markets

- Establishment of biotechnological development zones in order to increase the production of biotechnological products and their export.
- Preparation of the groundwork for exploiting existing capacities in the country and in neighboring countries so as to develop a market for biotechnological products.
- Establishment of an effective presence in local and international exhibitions and conferences in order to develop a market for biotechnological products.
- Creation of effective procedures to attract foreign investment.
- Legislation of customs regulations and establishment of special customs regulations for biotechnological products.

CONCLUSIONS

Because of the Islamic Republic of Iran's capabilities and potential to develop agricultural biotechnology, and considering the government's investment in this field in recent years and the plans to improve it, Iran is likely to have a bright future in this field. This will require:

- Promotion of public awareness and public acceptance of biotechnology.
- Legislation of intellectual property laws relevant to biotechnology.
- Support for the establishment of organizations investing in biotechnology.
- Facilitation of joint investment of domestic and foreign biotechnology agencies to achieve advanced biotechnology.

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8. TRENDS IN KOREAN ANIMAL BIOTECHNOLOGY AND PRODUCTION OF TRANSGENIC LIVESTOCK HARBORING RECOMBINANT HUMAN PROTEINS IN MILK AND URINE

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INTRODUCTION

The Republic of Korea has a large number of government institutes which research genetically modified organisms (GMOs). Although the issue of GM food safety has not been settled, several GM crops are currently being imported as food ingredients as well as for industrial purposes (Rural Development Administration, 2005). On the other hand, many researchers as well as biocompanies are in favor of GMOs that produce useful materials, since the organisms are accepted more easily by the general public when compared with GM food itself (Rural Development Administration, 2005). This report will emphasize the field of animal biotechnology in Korea, which has produced the most promising results.

Therapeutic proteins, especially glycoproteins, are manufactured primarily from cultured animal cells. Production of pharmaceutical glycoproteins in cultured animal cells presents several problems: varying glycosylation levels, high cost of culture media, difficulties in scaling-up, etc. (Dimond, 1996). Fabrication of such proteins in transgenic animals is cost-effective and relatively easy to scale up to match the increasing demand for therapeutic proteins, whose supply is restricted due to bottlenecks in their production. Using established purification systems for the glycoproteins from milk (or urine), production of therapeutic proteins from transgenic animals is highly cost-effective (Van Berkel et al., 2002). Although manufacture of pharmaceutical human proteins from transgenic animals is considered feasible using cost-effective bioreactor systems, only a few existing businesses seem successful in producing such animals (PPL, GTC, Pharming). Only a single product that has completed clinical trials and reached the market, after decades of research, but researchers and the pharmaceutical industry have continued pursuing the technology in the hope of achieving this goal within the next few years.

Transgenic farm animals have many uses in the fields of biotechnology and pharmaceutical development. Researchers and biotechnology firms are attempting to construct a human-like research model explore how a disease develops and reacts to drugs and to test the purity of recombinant human proteins produced by external sources. One of the primary goals in producing transgenic farm animals is to create an animal bioreactor—a pharmaceutical production unit. Using transgenic technology such as microinjection, genes that code for the production of a human protein are inserted into the genome of an animal, which in turn produces the human protein. Production of recombinant human protein is targeted to specific tissues, or organs that produce body fluids, that can be relatively easily collected and purified. Examples of such body fluids are blood, milk, urine, and seminal fluid (Houdebine, 2000).

The first breakthrough in producing a transgenic farm animal came in 1985, when the first transgenic sheep was created (Hammer et al., 1985). The production of transgenic farm animals recently garnered a new name, “pharming,” meaning “the production of pharmaceutical human proteins in transgenic farm animals” (Krimpenfort et al., 1991). There are two major targets for the production of foreign protein from the transgenic animal: milk and urine. Although controlling quality and quantity of production of recombinant proteins in the transgenic animal is diffi-

cult, once they have been produced and cloned, it will be possible to create herds of transgenic animals giving pharmaceutical milk products of identical quality (Reichenstein et al., 2001). However, production using milk has some disadvantages. Producing milk is time-consuming (lactation has to occur) and sex-dependent (sexual maturation has to occur), and the target protein is difficult to purify from numerous other milk proteins. Urine, on the other hand, is continuously produced right after birth and relatively free of other proteins.

PPL in the UK produced “Tracy,” the first transgenic sheep, in 1991 using transgenic techniques in order to produce human protein in its milk (AAT) (Wright et al., 1991). In 1997, PPL announced that transfection of a human blood coagulation factor IX gene to a cell culture prior to nuclear transfer had produced “Polly,” a genetically engineered lamb (Schnieke et al., 1997). In 1997, a U.S. scientist in a Dutch laboratory reported the production of a biologically active human blood coagulation factor VIII protein in the milk of a transgenic pig (Paleyanda et al., 1997).

In 2003, GTC, a biotherapeutics company, announced completion of clinical trials for Atryn, a recombinant human antithrombin for deep vein thromboses (DVTs) and thromboembolisms in patients with a hereditary deficiency of antithrombin (GTC, 2004). GTC submitted a marketing authorization application (MAA) to the European Medicines Evaluation Agency (EMA) for review in early 2004. The submission was accepted in late February 2004, and GTC is planning the commercialization of Atryn. GTC stresses that Atryn is “the first therapeutic protein produced using transgenic technology to be submitted to any regulatory agency anywhere in the world” (GTC, 2004).

TRANSGENIC ANIMALS AS BIOREACTORS

Transgenic Pigs

hEPO Transgene Expression in Transgenic Pig (Saerome) (Source of information: 3 October 1998. National Livestock Research Institute [NLRI], Suwon, Korea. Patents: PCT WO 01/59074, GB2376024 [2004.9.22])

NLRI has been a leader in Korean livestock research since 1906. The Institute has a well-organized research system covering almost every aspect of farm animal research. Although the Animal Biotechnology Division is relatively new, it has focused on current technologies, including the field of livestock cloning and transgenic animals.

Epoetin alfa is used to treat anemia patients and is produced by Amgen, the company dominating virtually the entire EPO market; the drug had a market share of about USD6 billion in 2001. The market share of epoetin alfa has been increasing every year since 1989, the year the USFDA approved its medical use (Datamonitor, 2002). In 1998, it was USD2 billion; by 2001, it had grown to USD6 billion. Its market share is expected to increase further after the expiration of the key patent enables the marketing of various generic drugs of a similar nature. Erythropoietin is used to treat various symptoms of anemia, ranging from anemia associated with chronic renal failure (CRF) to anemia in cancer chemotherapy patients (Tsakiris, 2000). Medicare covers only anemia associated with CRF patients due to the high price of drugs and a supply shortage caused by limited production capacity. In many countries, including the U.S., in some cases where EPO is called for, it is either not covered by Medicare or not administered (Greer, 1999). Listed in Table 1 are the world’s top ten biopharmaceutical products.

Using mouse whey acidic protein (WAP) promoter (Piletz et al., 1981) as expression controller, NLRI scientists designed a human EPO transgenic expression vector and introduced it into pig embryos via microinjection. The founder male was born in 1998. After the identification and analysis of hEPO proteins in its milk, NLRI has been producing TG progeny. Although the purification project is ongoing, a basic foundation has been established that included amino acid sequences, expression level, and activity analysis. Erythropoietin (EPO), a ca. 34 kDa glycoprotein that stimulates red blood cell formation, is produced primarily in adult kidneys (Fisher,

2003). The EPO protein has three N-glycosylation sites and one O-glycosylation site. N-glycosylation is considered the key player in the glycoprotein's activity (Jelkmann, 1992). Not only the number but also the pattern of glycosylation seems important to the stability and activity of the protein. For example, instead of the normal three, Amgen's new EPO product has five N-glycosylations to increase the half-life of the protein (Egrie and Browne, 2001).

Table 1. World's Top Biopharmaceutical Products (1996)

Rank	Product	Company	Business	1996 sales (USD 1,000)
1	Epogen	Amgen	Amgen	1,150
2	Neupogen	Amgen	Amgen	1,017
3	Procrit	Amgen	Ortho Biotech	995
4	Humulin	Genentech	Eli Lilly	884
5	Engerix-B	Genentech	SmithKline Beecham	568
6	Intron A	Biogen	Schering-Plough	524
7	Betaseron	Chiron/Berlex	Berlex/Schering AG	353
8	Epivir	BioChem Pharma/Glaxo Wellcome	Glaxo Wellcome	306
9	Activase	Genentech	Genentech	284
10	Humatrope	Genentech/Eli Lilly	Eli Lilly	268
Total				6,348

NLRI researchers have microinjected cloned transgene constructs into a one-celled embryo which was then transferred to a surrogate sow. The resulting piglets were identified by PCR using genomic DNA from each piglet's tail. In 1998, a transgenic founder was identified out of 47 candidate piglets using PCR and Southern blot analysis, both of which showed positive results for the founder individual. The founder was later named "Saerome," meaning "novel one" in Korean. Transformation efficiency—the percentage of successful transgenic—was about 2% within progeny. The rate was lower, below 0.5%, if one success out of 204 transferred embryos was considered. Since 1999, a transgenic pig herd has been propagated. The gene transfer rate of the transgene reached 70% at F2 generation, as seen in Table 2.

Table 2. Transfer Rate of the Transgene in Generations F1 through F3 of a Transgenic Pig Herd

	Founder	F1	F2	F3
Number of transgenic individuals	1	82	30	34
Gene transfer rate (%)	2.13	17.98	70.18	56.67

The transgene now seems to have stabilized and is being inherited stably by the next generation. The sex ratio of progeny is about one to one, which suggests that the expression of the transgene does not inhibit survival of specific sexes during development. The milk from the transgenic female was examined. In this case study, one sow was milked after delivery for 50 days during the lactation period, and about 880 units of human EPO were found in one milliliter of pig's milk, about 8.8 grams per liter. The molecular weight for the EPO was about 34 kDa, similar to that of natural human EPO. The usual molecular weight of commonly used recombinant human EPO is about 50 kDa, which is a larger than natural EPO. After removal of glycosylation, this EPO showed the same molecular weight as commercial EPO that is identical to

natural EPO without glycosylation. Amino acid sequence analysis showed that the EPO is indeed human EPO, not porcine EPO. Generally the TG pig strain has a relatively high RBC count and hematocrit value. However, it shows a moderate growth rate when compared to a normal pig. The average birth rate is eight and a half piglets per delivery (six of them are usually transgenic). Human EPO production in the milk was confirmed after both the first and second delivery. The possible application of this transgenic pig for other uses besides EPO production, especially the use of male TG pigs, must be considered. There is a possibility that these TG animals consider the human EPO as part of themselves (since a certain amount of hEPO already exists in their plasma but not in that of ordinary pigs). The TG males could be used as animal test subjects for the antigenicity of hEPO gene therapy targeting vectors or the purity of recombinant EPO protein itself. Also, since transgenic pigs show general symptoms of erythrocytosis, they can be used as the model animal for this disease (Shibata et al., 2003). Since Saerome, NLRI has produced a number of transgenic pig lines harboring human genes encoding therapeutic proteins such as human blood coagulation factor VIII or tissue plasminogen activator (t-PA) under regulatory control of mammary-gland-specific promoters (whey acidic protein or beta-casein promoter) or urinary-bladder-specific uroplakin II (UPII) promoter (unpublished data). Several individuals of the transgenic pig line were tested for human protein concentration in their milk or urine. NLRI recently reported the successful creation of transgenic pigs that produce the recombinant human tissue plasminogen activator in their urine (unpublished data). While these pigs are still too young to produce offspring and their recombinant protein products are in the process of analysis, NLRI has already shortened the timelines for the production of transgenic pigs. Still, for the transgenic animal producing human protein, the human EPO transgenic pig line is the only one that is close to mass production. NLRI is now pursuing the goal of bringing the product into manufacturing and clinical trials in cooperation with a new Korean bioventure company, PMG Biopharming.

In addition to NLRI, there are number of leading research forces in the research and pharmaceutical industry.

Transgenic Cattle

Production of Human Lactoferrin in the Milk of the Transgenic Animal (Boram) (Source of information: 30–31 October 1998. The 2nd Korea-Japan Joint Seminar on Animal Biotechnology. Kim S.J. et al. The production of recombinant proteins and transgenic animals. Korea Research Institute of Bioscience and Biotechnology (KRIBB), Taejeon, Korea. *Journal of Biochemistry* (Tokyo) 1999; 126(2): 320–325.)

The Korea Research Institute of Bioscience and Biotechnology (KRIBB) announced that a transgenic cow, “Boram,” that can express human lactoferrin (hLF) in its milk, was generated utilizing microinjection. hLF is a pivotal protein abundant in mother’s milk that confers anti-bacterial functions on babies and elevates their immune responses (Kim et al., 1999). The complete gene encoding the hLF was isolated from a cosmid library and its structure was characterized. The expression level of hLF protein in a transgenic animal ranged from 0.1 to 34 µg per ml. Milk contains a significant number of substances having peptide characteristics that are known to possess biological activity; however, bovine milk doesn’t contain LF. Thus bovine milk containing hLF will be highly effective in maintaining children’s health. KRIBB has four domestic patents and five pending patents regarding the hLF transgenic cow. KRIBB has announced that they are at the stage of mass-breeding transgenic cows and are in the process of technology transfer with Doosan Co., a major Korean food and beverage company.

Transgenic Goats

Production of Human Granulocyte Colony-Stimulating Factor using Goat b-casein Promoter (Meddy) (Source of information: 12 May 1999. Korea Herald Newspaper; 2003 Hanmi Company report. Patents WO0015808, US6635474)

The pharmaceutical company Hanmi has produced the transgenic goat “Meddy” (in collaboration with KAIST, KRIBB, and ChungNam National University) which produced human granulocyte colony-stimulating factor (hG-CSF), one of the hematopoietic factors that control the differentiation of pluripotent stem cells into many kinds of blood cells during hematopoiesis (Ko et al., 2000). It also plays a key role in the stimulation of proliferation and differentiation for other types of blood cells, in addition to granulocytes and macrophages. This is a promising drug for many kinds of disorders related to reduction of neutrophil and other blood cell levels. If the materials derived from the goat’s milk are effective, the price of G-CSF will be decreased. Humans produce on the average only small amounts of G-CSF, which has made the protein extremely expensive for white-cell-deficient cancer patients. The cost of producing G-CSF from genetically altered animals is one-tenth of the cost of obtaining it from mammalian cells, the method commonly used in advanced countries. The hG-CSF gene was subcloned into plasmid pGbc behind the 1.7 kb sequence of the goat b-casein promoter and named pGbc-hG-CSF. The expression cassette of pGbc-hG-CSF was microinjected into fertilized mouse eggs and goat eggs. One mouse and two transgenic goats named Meddy and Serry were identified by PCR analysis and Southern blotting. According to Hanmi, the company has established a method of purifying G-CSF from the milk of transgenic goats and has produced the fourth generation of Meddy, confirming the stable transfer of the G-CSF gene. Currently, one gram of G-CSF costs about KRW 900 million, and the global market for the protein is estimated at USD1.4 billion each year, according to KAIST. The Korean market for the protein is estimated at KRW 15 billion. Each injection of G-CSF (400 micrograms) costs around KRW 260,000. Hanmi is currently working on large-scale breeding of the transgenic goat and is planning clinical trials with purified G-CSF in 2005.

CONCLUSION

Transgenic animal research has received firm support from the Korean government since the late 1990s and will be given a major stimulus in 2005 with the launching of the national grants program. Although the technology has yet to produce a final product, there have been several successfully created transgenic farm animals. It is expected that the first successful product that can undergo clinical trials will be produced within the next few years.

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9. BUSINESS POTENTIAL FOR AGRICULTURAL BIOTECHNOLOGY PRODUCTS IN MALAYSIA

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INTRODUCTION

Biotechnology has been shown to contribute significantly to advances in science and technology as well as to the health, pharmaceutical, agriculture, and biorelated industries. It is said to be the technology of the 21st century that will drive economic and social development. Life-styles in the current and future decades will be increasingly shaped by advances in biotechnology, for example in the health, environment, manufacturing, and agricultural sectors.

In general, biotechnology is a technique or process which uses science related to living things—micro-organisms, animals, plants—for solving problems or making products that are useful to humankind (T.C. Seng, 2003). It has been used for many centuries in food processing, for example in the fermentation process, and in crop agriculture in selecting breeder seeds.

In Malaysia, the biotechnology industry is relatively new, especially in the agricultural sector. However, the government has focused on biotechnology since the mid-1990s, as reflected in the Prime Minister's recent statement: "Biotechnology has a great potential in Malaysia, and it could be the catalyst for new growth areas in the country's economy as well as a source of new wealth and income for the people" (Prime Minister's Department, 2004). Biotechnology has been identified as the new engine of growth for Malaysia. The country's abundant flora and fauna provide potentially rich reservoirs of natural resources for health care applications, food production, and solutions for a clean environment, and it can be useful in many other areas: live-stock farming, the herbal industry, and traditional and modern medicine.

The development of biotechnology as a source of economic growth was championed by Malaysia's former Prime Minister Tun Dr. Mahatir Mohamad. This movement aimed to put Malaysia on the world's biotechnology map. The Malaysian government launched its biovalley initiative in 2003 to provide a more integrated environment for the development of the biotechnology industry, allocating more than MYR100 million (USD26.3 million) for infrastructure and facilities. The biovalley is expected to attract around USD12.0 billion in investment over the next 10 years. By 2010, it is anticipated to house more than 250 new companies that can produce or commercialize biotechnology products, including agricultural biotechnology products.

The concept of the biovalley was modified when the new biotechnology policy was launched in 2005. Under the new strategy, the development of biotechnology will be spread out using the concept of a bionexus network, in which the development of biotechnology will be divided into three main fields: pharmaceutical and nutraceutical, agrobiotechnology, and genomic and molecular biology. The value proposition of the bionexus network is that it will leverage on the facilities, infrastructure, and capabilities of existing universities and research institutes. For example, a Pharmaceutical and Nutraceutical Institute will be established at the present biovalley site at Dengkil. The Institute of Agrobiotechnology is situated at MARDI, Serdang,

and the Genomic and Molecular Biology Institute is situated at existing facilities in the National University Malaysia, in Bangi. Bionexus will link these institutes with industries throughout the country. With this foundation, Malaysia hopes not only to witness the maturing of dedicated biotechnology companies but also to establish industries that can spearhead economic growth in biobusiness in general.

COUNTRY PROFILE

Malaysia covers an area of about 329,758 sq kilometers made up of peninsular Malaysia, Sarawak, and Sabah. Its climate is tropical; the average daily temperature varies between 21°C and 32°C, with high humidity. Malaysia is known for its biodiversity. It is famous for its tropical rain forests, characteristically evergreen and species-rich. Its multiracial population of around 25.6 million is comprised of Malay and indigenous people (64%), Chinese (26%), Indians (8%), and people of other ethnicities (2%).

After 1957, in the early days of independence from Britain, Malaysia was known as an agricultural nation, exporting primary products such as tin, rubber, timber, and spices. As early as the late 1960s, Malaysia started to diversify its agricultural base and venture into industrialization, making the country one of the fastest-growing economies in the Asia-Pacific region. Currently Malaysia's main exports are electrical and electronics products, manufactured goods, and crude petroleum and petroleum-based products. Agricultural produce such as palm oil and palm oil-based products, rubber, timber, and other agricultural products remain important, though their contribution and overall growth have declined.

THE AGRICULTURAL SECTOR IN MALAYSIA

The agricultural sector was historically the backbone of and primary contributor to the economy, the source of food for the Malaysian people. Over the past five decades, however, it has been overtaken in importance by the manufacturing and service sectors. The agricultural sector's contribution to the economy has declined from 18.7% (1990) to 13.5% (1995) and further to 8.7% (2003); it remained at 8.5% in 2004. Its value, however, increased from MYR16.23 billion (1995) to MYR18.85 billion (2000) and MYR20.693 in 2004. The contributions of the various sectors to GDP is shown in Table 1.

Table 1. Contributions to the Economy: Agriculture, Manufacturing, and Services, Malaysia

Sectors	MYR (million)			Average annual growth rate		Share of GDP		
	1995	2000	2004	1996–2000	2001–2004	1995	2000	2004
Agriculture	16,230	18,542	21,137	2.6	2.5	13.5	10.5	8.5
Manufacturing	39,825	66,323	78,558	10.7	8.3	33.1	37.5	31.6
Services	53,303	81,117	142,849	8.8	8.9	44.3	45.8	57.4

Source: Malaysia's Economic Report 2005/2006

The main challenges faced by agriculture are a shortage of land suitable for agriculture, low productivity, high production costs, and a shortage of labor. These supply-side factors have severely constrained food production. As a result, Malaysia currently imports more than MYR13 billion of food, compared to MYR7.5 billion in exports. Most of the food imported consists of temperate fruits and grains (soy beans, corn, and milk-based products).

Following the Asian financial crisis of 1997–98, the government put more emphasis on agricultural development. Malaysia aims to transform the agricultural sector into a dynamic, modern, highly commercial sector with high returns. It is hoped that the agricultural sector will contribute significantly to the economy through new agrobiotechnology-based agricultural prac-

tices. Strategic initiatives are now being put in place to enable biotechnology to play a core role in advancing the agricultural sector. Industries targeted for improvement include palm oil, rice, cocoa, fruits, flowers, ornamentals, vegetables, and the herbal and medicinal industries as well as agro-based downstream industries.

Agrobiotechnology

The policy on agrobiotechnology was introduced in the National Agricultural Policy in 1998 (revised version: 1998–2010). Its goal is to accelerate development of the agricultural sector to complement conventional practices and technologies.

Malaysia relaunched its biotechnology policy on 28 April 2005 with the aim of creating an environment conducive to R&D and industrial development while leveraging on the country's existing areas of strength. The new policy is supported by nine policy thrusts, with agricultural biotechnology development as the first, demonstrating the seriousness and commitment of the government. Malaysia's biotechnology policy is reprinted in Appendix 1.

Information on agrobiotechnology products and marketing is scarce. Current statistics on transgenic crops, GMO crops, crops produced via tissue culture, and other products and involvement by farmers and companies are based on conjecture and projections. In strengthening the economic foundation for the development of agrobiotechnology, the government will provide support in the form of R&D and HRD programs. This includes developing favorable policies on agrobiotechnology funds for research and introducing legislation to regulate access to genetic resources, intellectual property rights, and incentives to companies and investors participating in agrobiotechnology. Joint ventures between the public and private sectors have also been intensified. Projects include the participation of companies and institutions from other countries. Biotechnology in agricultural development has been accorded a higher priority and greater emphasis.

The government recognizes that biotechnology processes such as genetic engineering have the potential to increase production and productivity in the agricultural sector. Malaysia is among the few ASEAN countries that have approved the use of GM food crops as human food and animal feed. It has successfully conducted field trials of GMOs and has developed guidelines for their release. GM activities and products are governed by guidelines formulated by the Genetic Modification Advisory Committee (GMAC), which has published the National Guidelines for Release of Genetically Modified Organisms (GMOs) into the Environment. The National Guidelines have been revised and drafted into a new piece of legislation, the Malaysian Biosafety Bill, which will be considered in Parliament in December 2005. Under these guidelines, commercialization of biotech crops requires GMAC approval for all field evaluations. GMO release into the environment is currently restricted to research fields. Malaysia has also set up a National Biosafety Central Body to be responsible for monitoring biotechnology activities.

The biotechnology industry in Malaysia consists of companies specializing in biotechnology, biopharmaceuticals, bioinformatics, and agricultural biotechnology that focus on a range of products such as tissue culture, diagnostics, vaccine production, and blood bank collection. Companies involved in agricultural biotech are primarily plantation (palm oil), herbal-based, and aquaculture companies. There are currently 20 companies involved in agricultural biotechnology activities and registered with the Biotechnology Directorate, Ministry of Science, Technology, and Innovation. Companies and their main activities are listed in Appendix 2.

ISSUES, CHALLENGES, AND OPPORTUNITIES

Issues and Challenges

The new biotechnology-related industries face a number of issues and challenges. For example, Malaysia still lacks R&D facilities and expertise in biotechnology. In 2003, Malaysia had only 23,262 research personnel, and only 15,000 of them were researchers. Of these, fewer

than 1,000 (0.6%) had an academic background in biotechnology. Through 2003 local universities had produced more than 3,000 graduates in this field of study, but not all are effectively employed as biotechnologists, since employment opportunities in the biotechnology field are still limited in both the public and the private sectors. In 2003, fewer than 100 companies were involved in producing biotechnology products, even fewer in agrobiotechnology. Most of the biotechnology activities, including R&D, were carried out by government institutions.

Public awareness of agro-biotechnology products is also low. In a survey conducted in 1999 by the ASEAN Food Information Center on Malaysians' perception of GMOs, only about 18% of the respondents were aware of food biotechnology and about 50% did not know about biotechnology. A survey by the Far Eastern Economic Review, however, showed that 75% of Malaysians are very concerned about genetically modified food. These studies indicate that either people do not understand what biotechnology is or the issue of GMO is of great concern. In a survey of 1,400 Malaysian Muslim respondents around Kuala Lumpur conducted by the Institute of Islamic Understanding Malaysia (IKIM), results showed that 66.7% had heard of biotechnology but only 52.2% know what it is about (Ministry of Finance, 2004). The survey also showed that while 67% could explain genetically modified organisms (GMOs), genetic engineering, and biopharmaceuticals, only 40% knew what cloning is. This indicates that the acceptance level is low but promising.

Competition in land use is another critical issue in agriculture. Competition with other sectors, especially housing and manufacturing, has restricted increase in the amount of land suited to agriculture from 5,535,000 ha in 1990 to 6,173,000 ha in 2004 (11% increase in 14 years). The limited land suited to agriculture has resulted in low productivity and a higher cost of production. Agrobiotechnology techniques and practices can be used to overcome these issues.

The total workforce in agriculture is expected to decline from 1.5 million workers in 1995 to 980,000 in 2010. With the current land and worker shortages, the cost of production has increased steadily for the past 10 years. Malaysia has lost its competitive advantage to neighboring countries such as Thailand, Vietnam, and Indonesia. It must transform its agricultural sector into a modern and dynamic one through technology and innovation, and biotechnology is one of the alternatives.

Intellectual property rights (IPR), patents, and plant breeders' rights (PBR) are crucial for development in agricultural biotechnology. A patent is a right granted to inventors by the government to prevent others from imitating, manufacturing, using, or selling a specific invention for commercial use during a certain period, usually 17 to 20 years. The patent holder, in turn, is obligated to disclose the invention to the public. Plant breeders' rights are granted to plant breeders by the government to prevent others from producing or commercializing materials of a specific plant variety for a period of about 15 to 20 years. Malaysia has not yet granted patent protection in agricultural biotechnology. This can constrain development, since ownership rights are not guaranteed.

Opportunities

The market potential for halal food (food processed according to Islamic law) is significant. Its global market value was estimated at USD400 billion in 2004. Malaysia intends to tap this market. As a Muslim country, it is a potential hub for the halal market. Current halal food production is relatively limited (around MYR10.9 million annually). There is a great opportunity to explore this market, as the use of biotechnology techniques and practices can advance the manufacturing of food products. Halal food products that can potentially be produced using biotechnology practices, including the production, biogenesis, and modification of foods and bio-ingredients, are natural food or food ingredients, modified palm oil, and feed or feed supplements from herbs.

Malaysia has the second-highest per capita income in the region, with an increase of 8.5% from MYR14,838 (2003) to MYR17,741 (2004). In terms of purchasing power parity, it was

estimated to be around USD10,323, an increase of 9.3% compared to 2003. Domestic expenditure is expected to grow by 4.6%. These indicators show a favorable domestic market potential for biotechnology products, including agro-based biotechnology products. These include health care products, pharmaceuticals, cosmetics and toiletries, food products, and ornamental plants. It was estimated that the total domestic market value for these products is around MYR14 billion (USD3.6 billion). Estimating agrobiotechnology products to be around 10% of this, its value will be around MYR1.4 billion per year (Table 2).

Table 2. Domestic Market Value for Selected Sector Products (estimated, 2004), Malaysia

Item	Value (MYR'000)
Health care (including pharmaceutical products and medical devices)	3,428,000
Nutraceuticals	2,000,000
Aromatics products	50,000
Cosmetics and toiletries	1,400,000
Ornamental plants	100,000
Food (including food supplements)	7,000,000
Total	13,978,000

Source: Zainal Abidin., 2004

The biotech industry is dominated by small- to medium-sized companies. Only a few larger companies are involved in biotechnology; most of them focus on plant tissue culture. Currently there are about 100 companies registered with the Malaysian Biotechnology Directorate under the Ministry of Science and Innovation. Of these, 20 are involved in the agricultural sector. However, there are about 50 companies that utilize biotechnological processes, primarily in food production, herbal products, and pharmaceuticals (Malaysia, 2005). There is still great potential for SMEs and large-scale firms in this industry. The newness of this industry is also an advantage because as a pioneer, a company has the opportunity to spearhead the business.

With 15,000 species of flowering plants, 1,100 ferns, and 100 species of herbal and medicinal plants, Malaysia has a diverse biosource that is still untapped. These flora and fauna can be exploited for health care applications, increased food production, and protection of the environment. The rich biodiversity is ripe for the exploitation of materials to be used as new food ingredients, including nutraceuticals, and for bioprospecting new food biocatalysts and bio-ingredients that will diversify the end uses and enhance the value of food products. There are also many other areas of food processing and production where biotechnology processes can play a role.

More than a million tons of agricultural products are imported and used each year that are produced using agrobiotechnology practices: soybeans, wheat and meslin, malt, maize, and corn. The amount of agricultural produce imported from the U.S., South Africa, Argentina, and Brazil increases every year, as shown in Table 3.

Other agrobiotechnology products produced and marketed in Malaysia include food and health-related herbal products such as tongkat ali (*Eurycoma langifolia*), pegaga (*Centella asiatica*) and anoni, cosmetics and toiletries, aromatics, pharmaceuticals, nutraceuticals, tissue culture plants (oil palm, rubber, orchids, herbal plants), biodiagnostics, industrial enzymes, and bioactive compounds for health care. These products enjoy a large market and can be produced locally. There is tremendous potential for growth in the industrial sector, especially for cosmetics and toiletries, due to the abundance of natural resources like palm oil and herbal plants and other natural biodiversity. The local cosmetics market is valued at approximately MYR1.4

billion with 11% growth (SIRIM, 2004). Malaysia also exports products like beauty cream and skin care items to Singapore, Hong Kong, Thailand, Japan, and Australia.

Table 3. Imports by Selected Commodity of Agricultural Produce (2001), Malaysia

Item	Value (USD'000)
Soya sauce	36,870
Corn (grain)	50,800
Corn (starch)	5,463
Corn (oil)	236,137
Corn flake and prepared food	134,454
Total	463,724

The production of orchids via tissue culture is another example of activities carried out by SMEs with an eye to the potential market. Annual production of orchids via tissue culture alone was been at USD13 million for 2003, of which USD8.7 million was for the export market.

The production of herbal products as food supplements and for medicinal use also shows tremendous market potential. The annual local market for herbal remedies is valued at USD789 million. The strengths and weaknesses of the biotechnology industry are analyzed in Table 4.

Table 4. Strengths and Weaknesses, Opportunities and Threats in the Biotechnology Industry, Malaysia

Strengths	Weaknesses
Strong financial support, R&D facilities, and incentives	Lack of expertise in biotechnology
High priority in biotechnology R&D in government institutions and universities	Private sector is reluctant to invest in R&D and industries based on biotechnology
Government has identified biotechnology as a core technology to be given priority	Lack of molecular and genetic information on crops important to the country
Opportunities	Threats
Increased demand for biotechnology products and services	Opposition to genetically engineered products
Growing business opportunities for specialized agricultural products to meet increasing demand	

INCENTIVES FOR THE BIOTECHNOLOGY INDUSTRY

To spur growth and further development of the biotechnology industry, the government offers attractive investment incentives to local and foreign-owned companies:

- For high-tech companies, pioneer status with full tax exemption of statutory income for five years or an investment tax allowance of 60% on qualifying capital expenditure for five years to be offset against 100% of the statutory income.
- For strategic projects, pioneering status with a full tax exemption of 100% of statutory income for 10 years or an investment tax allowance of 100% on qualifying capital expenditure for five years to be offset against 100% of the statutory income.
- Incentives for R&D.

- Incentives for software development.
- Incentives for export.
- Prepackaged customized incentives packages that cover both tax and nontax incentives.
- General incentives: industrial building allowance, infrastructure allowance, import duty exemptions for raw material components, equipment, and machinery.

Beside those incentives, Malaysia also offers strong value proposition initiatives for biotechnology ventures:

- Establishment of the Malaysian Biotechnology Corporation, a one-stop agency with the primary objective of developing the country's biotech industry that will work closely with ministries and agencies to develop the biotechnology industry. Its functions include catalyzing commercial spin-offs to the private sector, facilitating market-driven R&D and commercialization via funding and industry development services, and advancing R&D and commercialization in agrobiotechnology, health care, and industrial biotechnology.
- Establishment of the National Biotechnology Directorate as a coordinator of biotechnology R&D activities via human resource development and commercialization of biotechnology R&D findings. It also promotes private-public sector participation in national biotechnology programs through collaborative R&D ventures and outsourcing of the private sector R&D requirements to available researchers from universities and government research institutions.
- Establishment of BioNexus Malaysia, a network of centers of excellence based on the capabilities of existing institutions and companies with specific specialization in biotechnology. This will support the biovalley concept established earlier. Three centers of excellence have been identified: the Center of Excellence for Agrobiotechnology in MARDI and Universiti Putra Malaysia at Serdang, the Center of Excellence for Genomics and Molecular Biology in Universiti Kebangsaan Malaysia at Bangi, and the Center of Excellence for Pharmaceuticals and Nutraceuticals, to be established in the biovalley at Dengkil.

The government has also extended attractive tax incentives to further spearhead the modernization and commercialization of the agricultural sector. These include a 100% deduction on capital expenditure, pioneer status, or investment tax allowance. To further expand food production, companies are also provided with an investment allowance or group relief, while their subsidiaries undertaking the projects are given 100% tax exemption until 2010. These incentives also apply to all foreign companies investing in Malaysia.

R&D ON AGRO-BIOTECHNOLOGY: MARDI'S EXPERIENCE

The Malaysian Agricultural Research and Development Institute (MARDI) was established in 1969 with the objective of developing indigenous science and technology capabilities in support of the development and modernization of the national food and agricultural sector. It is a statutory body under the Ministry of Agriculture and Agro-based Industry that undertakes research and development in tropical agriculture (all crops except rubber, cocoa, and oil palm) and livestock.

MARDI set up a Biotechnology Research Center in 2002 as one of its 13 research centers. Prior to this, biotechnology research was conducted under the auspices of the Biotech Science Center, Ministry of Science, Technology, and Environment. The establishment of this center underscores the government's vision of transforming the agricultural sector into a modern and dynamic sector and of exploiting of biological processes. Under the biotechnology program, MARDI has been given the responsibility for coordinating the Plant Biotechnology Cooperative

Center, a mechanism to coordinate, cooperate, undertake research, and commercialize agrobiotechnology.

In the implementation of the national biotechnology policy, MARDI was designated the center of excellence for agrobiotechnology, responsible for developing networks with other public R&D institutions and the private sector, providing infrastructure and facilities, and enhancing human resource development.

Biotechnology research in MARDI is divided into three scopes of study: biological molecule and genetic engineering, bioprocessing, and biodiagnosis and biosafety.

In the Eighth Malaysian Development Plan (2000–05), MARDI allocated more than MYR100 million (USD26.3 million) for R&D in biotechnology programs to generate technologies and techniques that can improve agricultural practices. As of 2004 MARDI has generated more than 50 technologies related to agrobiotechnology, including biosensor kits for pesticide residue, transgenic papaya seed, transgenic rice, seedlings of papaya, orchids, banana, and mangosteen using tissue culture, and use of reproductive biotechnological techniques in cattle (embryo transfer, IVF, embryo sexing, semen and embryo cryopreservation). These technologies are ready to be upscaled and commercialized, and MARDI is open to the possibility of joint ventures or others with both local and foreign firms. MARDI's policy is to encourage local and foreign companies to collaborate in carrying out research and in commercializing its technology.

CONCLUSION

Malaysia has enormous potential and talent. The government has recognized the potential of biotechnology as a key driver for wealth creation and social well-being as well as serving as an economic generator. The industry is expected to generate MYR270 billion of revenue, create 280,000 jobs, and establish 100 companies by the year 2020, when Malaysia aims to be an industrialized nation. Agrobiotechnology is an industry with great potential. The current market value of agrobiotechnology products and its growth point to an encouraging future. In this regard, Malaysia has additional advantages: rich biodiversity, high government support and commitment, and a substantial human resource base can benefit firms both in Malaysia and in other countries that have the intention to invest in Malaysia.

Malaysia's doors are always open to companies and R&D institutions wanting to jointly explore its resources for the benefit of all parties. The government is always open to new ideas and will provide support to ensure the success of these new ventures.

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APPENDIX 1

NATIONAL BIOTECHNOLOGY POLICY

The Philosophy of the Policy

The National Biotechnology Policy envisions that biotechnology will be a new engine for Malaysia, enhancing the nation's prosperity and well-being. The Policy aims to build an environment conducive to R&D and industry development while leveraging on the country's existing areas of strength.

The National Biotechnology Policy is underpinned by nine policy thrusts.

Thrust 1: Agriculture Biotechnology Development

Transform and enhance the value creation of the agricultural sector through biotechnology

Thrust 2: Health Care Biotechnology Development

Capitalize on the strength of biodiversity to commercialize discoveries in natural products as well as position Malaysia in the biogenetics market.

Thrust 3: Industrial Biotechnology Development

Ensure growth opportunities in the application of advanced bioprocessing and biomanufacturing technologies.

Thrust 4: R&D and Technology Acquisition

Establish centers of excellence in existing or new institutions to bring together multi-disciplinary research teams in coordinated research and commercialization initiatives. Accelerate technology development via strategic acquisitions.

Thrust 5: Human Capital Development

Build the nation's biotech human resource capability in line with market needs through special schemes, programs, and training.

Thrust 6: Financial Infrastructure Development

Apply competitive lab-to-market funding and incentives to promote committed participation by academia, the private sector, and government-linked companies. Implement sufficient exit mechanisms for investments in biotech.

Thrust 7: Legislative and Regulatory Framework Development

Create an enabling environment through continuous reviews of the country's regulatory framework and procedures in line with global standards and best practices. Develop a strong intellectual property protection regime to support R&D and commercialization efforts.

Business Potential for Agricultural Biotechnology Products

Thrust 8: Strategic Positioning

Establish a global marketing strategy to build brand recognition for Malaysian biotech and benchmark progress. Establish Malaysia as a center for contract research and contract manufacturing organizations.

Thrust 9: Government Commitment

Establish a dedicated and professional implementation agency overseeing the development of Malaysia's biotech industry under the aegis of the Prime Minister and relevant government ministries.

The implementation of the National Biotechnology Policy encompasses three main phases:

Phase 1 (2005–2010): Capacity building

Establish advisory and implementation councils.

Establish Malaysian Biotechnology Corporation.

Educate and train knowledge workers.

Develop legal and IP framework. Business development through accelerator program.

Build Malaysian branding.

Create initial jobs and industries in agricultural biotech, health care biotech, industrial biotech, and bioinformatics.

Phase 2 (2011–2015): Science to Business

Develop expertise in drug discovery and development based on natural resources.

Develop new products.

Acquire technology.

Intensify investment promotion.

Intensify spin-off of companies.

Strengthen branding.

Develop capability in technology licensing.

Create knowledge-intensive jobs.

Phase 3: Global Presence

Consolidate strengths and capabilities in technology development.

Further develop expertise and strength in drug discovery and development.

Strengthen innovation and technology licensing.

Promote global Malaysian companies. It is intended that by 2020 Malaysia will be a global player in biotechnology and at least 20 global Malaysian companies will be generated.

Table 5. Summary of Targets of the National Biotechnology Policy, Malaysia

	Phase I (2005–2010)	Phase II (2010–2015)	Phase III (2015–2020)	Total
Policy objective	Capacity building	Creating business out of science	Turning Malaysia into global player	Biotechnology for wealth creation and social well-being
Creation of employment	40,000	80,000	160,000	280,000
Establishment of companies	25	25	50	100
Contribution to GDP (%)	2.5	4.0	5.0	5.0
Compounded annual growth (%)	32.8	21.7	14.7	23.7

Source: The National Biotechnology Policy

APPENDIX 2

COMPANIES INVOLVED IN AGRICULTURAL BIOTECHNOLOGY ACTIVITIES IN MALAYSIA AND THEIR PRODUCTS

Comapany	Main activity	Products
Agricultural Chemicals (M) Sdn Bhd	Formulation of agrochemical, supply sprayers, consultancy, training in ACm Agile Crop Management system	Agricultural chemicals, agricultural equipment, consultancy and advisory services, landscaping, horticultural supply
Applied Agricultural Research Sdn Bhd	Research activities (agronomy—oil palm, plant protection, plant forestry, information tissue culture); seed production, quality control, routine testing	Oil palm tissue culture plants, oil palm seed, esigel
Borneo Samudra Sdn Bhd	Plant oil palm and process fresh fruit bunches from oil palm	Crude palm oil kernel, oil palm germinated seed, clonal material
Best Farm Co.	Development of one processing factory to produce latest beverage product from herbs/nutritional supplements	Herbal nutritional supplement, personal care, organic fertilizers; supplying tongkat ali root and extract, kacip fatimah leaves and extract, misaim kucing and pegaga
Borneo Tree Seed and Seedling supplies Sdn Bhd	Development and propagation of improved exotic tree species for use in large-scale forest plantation	Ten tree species of different seed
Guthrie Biotech Laboratories Sdn Bhd	Production and research of clonal oil palm.	Clonal oil palm
Golden Hope Research Sdn Bhd	Production of oil palm, rubber, cocoa, coconut planting material; R&D activity on breeding, especially tissue culture and agronomy	Oil palm, rubber, cocoa, coconut planting materials
Felda Agricultural Services Sdn Bhd	Manufacturing and sale of oil palm seeds, oil palm seedlings, fresh fruit bunches	Oil palm seeds and seedlings, fresh fruit bunches, oil palm's leaf and soil sampling
H.R.U. Sdn Bhd	Production and sales of DxP oil palm planting materials	DxP oil palm seeds and seedlings
R.E.Fuel Sdn Bhd	Production of EFB fibre for use in various industries, such as pulp and paper	Oil palm biomass utilization solution
Melaka Institute of Biotechnology	Commercialization of biotechnology products, services produced by MIB	Seaweed farming using foreign technology, bioinformatics, essential oil and tissue culture
(continued on next page)		

Business Potential for Agricultural Biotechnology Products

Melaka Biotech Holding Sdn Bhd	Investment in biotech-based projects (seaweed farming, herbal planting, production of plant through micro propagation and tissue culture)	Seedling/ plantlets, dry seaweed, plant extractions, bioconsultation, DNA marking, biotraining
Marditech Corp. Sdn Bhd	Technobusiness due diligence studies, food production and process development, environment assessment and quality services, intellectual capital management	Newcastle disease vaccines (fow fox vaccines, swine fever vaccines), Killed vaccines
Malaysian Agri-Hitech Sdn Bhd	Production of microbial products in agriculture sector	MyCOgold—beneficial soil fungi, biofungicide, biopesticides
IOI Corporation Sdn Bhd	Cultivation of oil palm, rubber	Plantation—fresh fruit bunches, crude palm oil, palm kernel, lates concentrates, oil palm seeds and seedlings
INproser Konsortium Sdn Bhd	Production of animal feed through enzymatic conversion of palm kernel expeller	Orgafeed, manostel, manoase
United Plantation Berhad	Cultivation of oil palm and coconut	Crude palm oil, palm kernel, copra
TH Group Berhad	Echnology and health care services	
Sasaran Ehsan Utama Sdn Bhd	Production of oil palm seed	Oil palm seed and seedlings

10. BUSINESS POTENTIAL FOR AGRICULTURAL BIOTECHNOLOGY PRODUCTS IN THE PHILIPPINES: THE NATIONAL AGRICULTURAL RESEARCH SYSTEM EXPERIENCE

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INTRODUCTION

Biotechnology is regarded as one of the most potent means for resource-rich, cash-poor nations like the Philippines to become active players in the global market. It is considered a sunrise industry. As a tool, it could revitalize ailing commodity industries such as coconut and sugar cane through the development of “unique,” “green,” and “healthy” biotech products that can be the result of both modern and conventional biotechnologies.

STATUS OF AGRI-BIOTECH PRODUCTS

Conventional Biotechnology

In the Philippines, most agri-biotech products that have reached the market result from conventional biotechnologies, including biofertilizers, biopesticides, tissue cultured planting materials, enzyme products, vaccines, and diagnostic and detection kits (Table 1). Most of these products were developed by the University of the Philippines at Los Baños–National Institute of Biotechnology and Molecular Biology (UPLB–BIOTECH), funded by the government. Commercialization was done primarily by UPLB–BIOTECH, with limited private sector participation. Table 1 shows selected commercialized biotechnology products perceived to have high market potential that were presented during a recent business forum for R&D in biotechnology (Jamias, 2004).

Table 1. Selected Commercialized Agri-biotechnology Products, Philippines

Category	Name/ product	Purpose	Developed by	Commercialized by
Biofertilizer	BIO-N	Uses <i>Saccharum spontaneum</i> L. to fix atmospheric nitrogen in a form usable by rice and corn plants	UPLB–BIOTECH/1989	UPLB–BIOTECH/1990 TLRC Demand is high; more entrepreneurs are needed
Bioremediation	Bio-Quick	Rapid composting using <i>Trichoderma harzianum</i> and use of compost as fertilizer; hastens decomposition of farm wastes from five to six months to three to five weeks	UPLB–BIOTECH	UPLB–BIOTECH Already adopted by farmers and cooperatives nationwide
(continued on next page)				

Business Potential for Agricultural Biotechnology Products

Growth hormones/ regulators	COCOGR OE	From coconut water or milk, it promotes plant growth; used in tissue culture of ornamental plants and vegetable production	UPLB– BIOTECH/ 1989	UPLB–BIO- TECH/1994
Tissue Culture	Banana tissue culture	Provides clean planting materials within a shorter period at minimum cost	PCARRD	Entrepreneurs and SCUs in Regions 2, 4, and 11
Animal vaccine	HEMOSEP -WC	Contains or increases resistance against <i>Pasteurellosis</i> in domestic animals (swine, cattle, and poultry industries)	UPLB– BIOTECH/ 1989	UPLB–BIO- TECH/1994 Biologics Co./1994
	Biovac-FC	Contains <i>P. multocida</i> serotype A adsorbed on aluminum hydroxide gel; protects chickens against fowl cholera	UPLB– BIOTECH	UPLB– BIOTECH
	Biovac-HS	Contains <i>P. multocida</i> serotype B; protects cattle, carabaos, and goats against HS	UPLB– BIOTECH	UPLB– BIOTECH
	Biovac-IC	Contains <i>H. paragallinarum</i> serotype A with aluminum hydroxide gel as adjuvant; protects chicken against IC	UPLB– BIOTECH	UPLB– BIOTECH
	Hemosep- WC	Protects cattle and carabao against the dreaded <i>Hemorrhagic Septicemia</i> (HC) disease	UPLB– BIOTECH	UPLB– BIOTECH
Detection kit	Pathogens	Detects <i>Salmonella</i> and <i>E. coli</i> contamination in food, water, and animal feeds utilizing DNA technology through PCR	UPLB– BIOTECH	UPLB– BIOTECH
Diagnostic kit	Plant pathogens diagnosis by ELISA	Diagnoses the following plant pathogens: papaya ringspot virus, citrus tritessa virus, greening disease of citrus or leaf mottling, maize dwarf mosaic virus, peanut stripe virus, cymbidium mosaic virus, tobacco mosaic virus-orchid strain, anthurium blight organism, banana bunchy top virus, banana bract mosaic virus, banana mosaic virus, abaca bunchy top virus, abaca mosaic virus, mango anthracnose organism, potato virus X, Y & S, potato leaf roll virus, red tide bacteria, red tide bacterial toxin, red tide toxin from mussels, ochratoxin, zearalenone	UPLB– BIOTECH	UPLB– BIOTECH
Enzymes	Cellulase	Used as feed additive, in coconut oil extraction, ethanol production, hydrolysis of wood and agricultural wastes	UPLB– BIOTECH	UPLB– BIOTECH
	Lipase	Fungal lipase from <i>Rhizopus</i> sp.; modifies coconut oil to produce high-value products such as b-monoglyceride, glycerol, fatty acids, and others	UPLB– BIOTECH	UPLB– BIOTECH
(continued on next page)				

Business Potential for Agricultural Biotechnology Products in the Philippines

	Pectinase	Utilizes locally-produced pectinase in extracting essential oils from leaves of patchouli, lemongrass, and citronella and from ilang-ilang flowers	UPLB–BIOTECH	UPLB–BIOTECH
	Proteases	From <i>Bacillus sp.</i> and <i>Monascus sp.</i> ; can be used as bread improver, as feed additive, and in coconut oil production	UPLB–BIOTECH	UPLB–BIOTECH
	Papain	Proteolytic enzyme; can be used in breweries, pharmaceutical, and personal care industries	SECURA	SECURA Clients find product of high quality
	Bromelain	Proteolytic enzyme which can be used in breweries, pharmaceutical, and personal care industries	SECURA	SECURA Clients find product of high quality

Source: UPLB–BIOTECH and SECURA flyers/brochures, various years

BIO-N

This is a microbial-based fertilizer composed primarily of bacteria isolated from the roots of talahib (*Saccharum spontaneum*) which reportedly replaces 30%–50% of the nitrogen fertilizer requirements of rice and corn and enhances vegetables production. It is popular among farmers. Ten mixing plants have been set up in major corn-growing provinces, and the Technology Livelihood and Resources Center (TLRC) has begun commercializing it. Demand is high, and more entrepreneurs are needed. The required investment is about USD12,000 (PHP54/USD1), with 302% average annual return.

Enzymes for Virgin Coconut Oil (VCN) Extraction

VCN is popular for its health and diuretics effects (Kabara, undated). Using enzymes, coconut oil can effectively be extracted without the use of heat, producing more high-quality virgin coconut oil for potential export. Enzymes can also be utilized to derive more quality essential oils from plants, which can decrease imports (currently USD226 million annually). The required capital investment is about USD92,500 (equipment, administrative and marketing costs). With an average net income of USD176,000 a year and a return on investment of 2.08%, the investor can break even in about six months.

Biotech Microbial Rennet

This technology produces cheese with improved taste, smell, texture, and shelf life compared to cheeses made with animal rennet. Cost is also reduced by 80% compared to imported rennet. The required investment in building and equipment is USD1,500. With net sales of 1,192 liters, the investor attains a net profit/cost ratio of 5.6 with a payback period of 3.5 years.

Biotech Detection Kits

To detect salmonella and *E. coli* contamination in water, food, and animal feeds, these kits use polymerase chain reaction (PCR)-based DNA technology that makes detection faster, more specific, and more accurate, with greater reliability. With an investment of USD157,500, an entrepreneur can have a net present value of USD320,500 and recover total investment within three years.

Hemorrhagic Septicemia (HS), Fowl Cholera (FC), and Coryza Vaccines (Cr)

Vaccines using monoclonal antibodies can provide a more specific and effective defense for cattle, carabaos, and fowl against septicemia, fowl cholera, and infectious coryza. The re-

quired investment in equipment to produce 1,162 liters is USD170,500. The benefit/cost ratio is 1:1.9.

Tissue Cultured Planting Materials (Banana, Orchids)

The most common application of tissue culture technology is for banana and orchids. Large private sector companies use tissue cultured banana for their planting materials. A growing number of SMEs and community-based enterprises (CBEs) are engaged in commercializing tissue cultured planting materials for banana and orchids and benefit from government-supported projects and training programs. There is a need, however, to rationalize the proliferation of tissue culture laboratories and maintain only a limited number in strategic locations (National Fruits R&D Team, 2002). A tissue culture facility for banana with 15,000 plantlets/month capacity will provide an 84% internal rate of return (IRR). It has a three-year payback period and 15% net present worth (NPW), with USD19,500 opportunity cost of capital.

While some agri-biotech products have met with a degree of success in the market, most remain on the shelf. The major obstacles to commercialization have been the traditional production orientation of publicly-funded R&D, scientists' desire to keep their technology to themselves, research managers who lack entrepreneurial and technology management skills, inadequate incentives for extension agents to promote products, the lack of clear IPR policy and guidelines, and limited public-private sector partnerships.

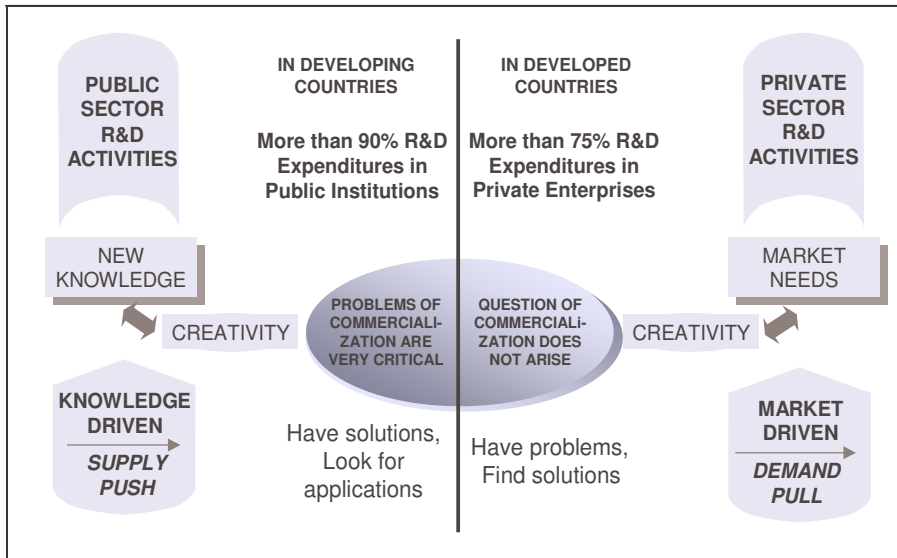
The advent of globalization will necessitate a shift in the technology commercialization paradigm by the Philippine National Research System (NARS) from the traditional supply-driven and production-oriented approach to a more market-driven and private-sector-led approach (Figure 1). The problems in commercialization associated with the former must be avoided and an increase in private sector investments in R&D encouraged following the latter.

Modern Biotechnology

Modern biotechnology utilizes transgenic approaches to plant and animal improvement as a result of a lack of suitable conventional approaches to dealing with a particular agronomic problem or need (e.g., *Papaya Ringspot Virus*).

Not all modern biotechnologies generate transgenic or so-called genetically modified organisms (GMOs). Ongoing modern biotechnology projects and tools—for example, molecular mapping, marker-assisted breeding, and bioinformatics—are already being applied with many plant and animal gene pools to generate improved varieties and other industrial applications which are not transgenic and hence outside the restrictions of current biosafety regulations.

The government has supported modern biotechnology since 1997, particularly work on transgenics for selected economically important crops—corn, papaya, mango, and coconut. The work has expanded to include other crops and other traits, the majority of which are in the research stage (Table 2). Only Bt corn produced by Monsanto has been commercialized since 2002.



Source: Sharif, 1995

Figure 1. Technology Development and Commercialization Approaches

Table 2. Major Modern Biotechnology Initiatives, Philippines

Commodity	Trait	Status
Corn	Asiatic corn borer resistance	Approved for commercial planting on December 4, 2002 (Peczon, 2004)
	Roundup herbicide resistance	Approved for commercial planting in 2005 (Sarmiento, 2005; www.prnewswire.com)
Rice	Vitamin A-fortified	Field testing (Resurreccion, 2005)
	Bacterial leaf blight resistance	Field testing (SEARCA-BIC, 2002); negotiating with UCLA (Resurreccion, 2005)
	Stemborer tungro	Field testing (SEARCA-BIC, 2002); for negotiation with Danforth (Resurreccion, 2005)
	Blast	Field testing (SEARCA-BIC, 2002)
Cotton	Cotton bollworm resistance	Field testing (Felix, 2005)
Papaya	Papaya ringspot virus (PRSV) resistance	Contained field testing; for field testing by end of 2005 (Felix, 2005)
	Delayed ripening	Research (PCARRD, 2003)
Mango	Delayed ripening	Research (PCARRD, 2003)
Banana	Banana bunchy top virus (BBTV) resistance	Research (PCARRD, 2003)
Coconut	Modified medium chain fatty acid for high lauric acid content	Research (PCARRD, 2003)
(continued on next page)		

Sweet potato	Sweet potato feathery mottle virus (SPFMV) resistance	Research (PCARRD, 2003)
Eggplant	Fruit and shoot borer resistance	Research (ABSP II and IPB, 2005)

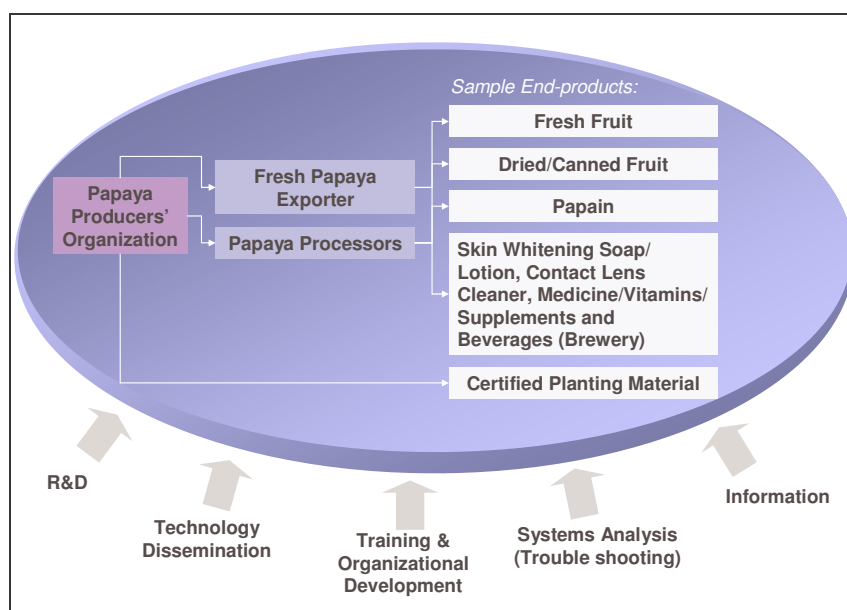
SETTING THE STAGE FOR COMMERCIALIZATION

The majority of publicly-funded research is still production-oriented and not commercially viable. There is a growing concern that agricultural research should address not only the production of raw materials but also associated focal and downstream industries. Value addition commands higher market prices and margins. Continuous innovation through R&D is imperative to keep up with market preferences and changing demands.

Over the past two decades, the Philippines has experienced several challenges in embracing modern biotechnology but has nonetheless achieved a number of milestones necessary to set the stage for the growth of an agricultural biotech industry.

The Research, Development and Extension (RDE) Paradigm

To enable a shift towards a market-driven approach, an appropriate technology commercialization model has been adopted, albeit to a limited extent (Figure 1), since 1997 when the Philippine National Research System (NARS) formulated the Philippine Biotechnology Agenda for Agriculture and Forestry (PAFBA I: 1997–2002). This approach considers diversified end products for certain markets (for example, fresh papaya and mango with a long shelf life for export to nontraditional markets such as Europe and Canada, coconut oil with high lauric content), the particular industry (as against the particular commodity traditionally addressed by the NARS), the role of research and development, enabling mechanisms, and support industries in place. Figure 2 shows the potential application of the model for the papaya industry.



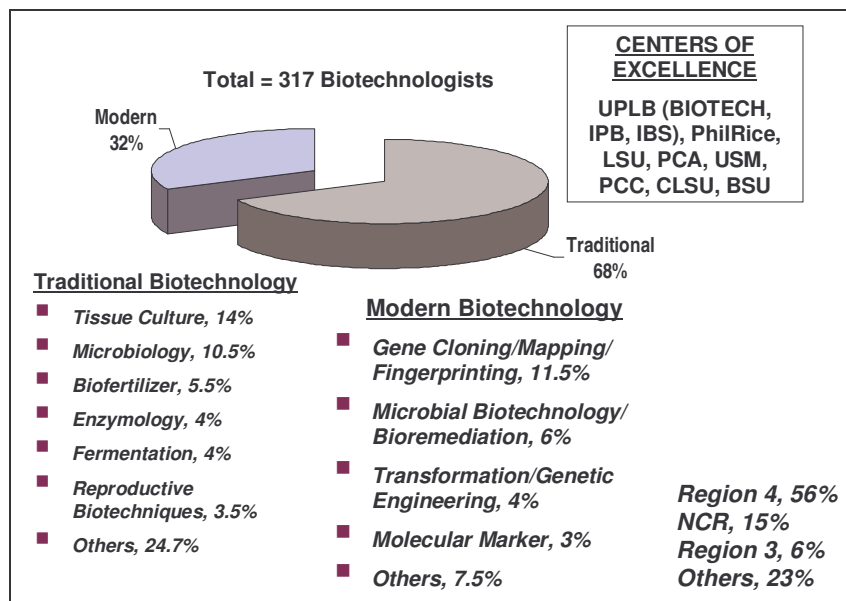
Source: Modified from Sharif, 1995

Figure 2. Papaya: Diversified Market Approach

In PAFBA II (2002–10), the economic potential of the technologies proposed for R&D was used as the “killer”/discriminating criterion in biotechnology research prioritization for the NARS. The most recent crafting of Agriculture 2020 led by the National Academy of Sciences and the Philippine Council for Agriculture, Forestry, and Natural Resources (PCARRD) adopts the industry cluster approach, which looks at the entire supply chain (e.g., feedgrain-livestock-poultry cluster). This industry cluster approach considers the global competitiveness of Philippine products in terms of cost and price.

Core Competencies

The Philippines has developed core competencies in manpower and infrastructure (Figure 3) for developing and evaluating its own biotechnology products and those from other countries. This was begun during the creation of BIOTECH in 1979 and has expanded to date into several centers of excellence around the country, with about 300 scientists working on both traditional (68%) and modern (32%) biotechnologies. Competencies in traditional biotechnologies relate to tissue culture, microbiology, biofertilizer, enzymology, fermentation technology, and reproductive biotechniques. In modern biotechnology, these skills are related to gene cloning, mapping, bioremediation, genetic engineering, molecular markers, and bioinformatics, among others. Bioinformatics is a relatively new field, and only very few scientists are competent enough to maximize the use of this tool as well as teach it to others. The centers of excellence in modern agricultural biotechnology include UPLB–Biotech, UPLB–Institute of Plant Breeding, UPLB–Institute of Biological Sciences, Philippine Rice Research Institute, Leyte State University, Philippine Coconut Authority, University of Southern Mindanao, Philippine Carabao Center, Central Luzon State University, and Benguet State University. Government support through the Department of Science and Technology (DOST) and PCARRD jumpstarted the work on priority transgenic crops in 1997, upgrading the scientists’ skills in transformation/genetic engineering. The University of the Philippines and other academic institutions offered degree programs in molecular biology. Specialized laboratories (BL2) or contained facilities were supported through project funds.



Source: PCARRD, 2003

Figure 3. Core Competence in Philippine Agricultural Biotechnology, 2002

Regulatory Environment

Two major regulatory milestones have been the establishment in 1990 of the National Committee on Biosafety of the Philippines (NCBP) under Executive Order 430 and the issuance in 2002 of Department of Agriculture (DA) Administrative Order No. 8: Rules and Regulations for the Importation and Release into the Environment of Plants and Plant Products Derived from the Use of Modern Biotechnology.

The NCBP formulated biosafety guidelines for conducting research and field testing involving living organisms in 1991, and they are considered the strictest in the world (Galvez, 2005; Colmo, 2005; BMARC, 2005). Institutional Biosafety Committees were established, and material transfer agreements were required of collaborating institutions. Licensing agreements were brokered by the International Service for the Acquisition of Agri-biotech Applications (ISAAA). To date the NCBP has approved a number of applications for research and a limited number for field testing. The DA has approved several events regarding importation of GM products, with Bt corn the first to be allowed for importation for direct use as food and feed, in 2002.

Figure 4 shows the process flow and major key players. NCBP, DA-Bureau of Plant Industry, DA-Science and Technology Review Panel, DA-Bureau of Agriculture and Food Products Standards, DA-Bureau of Animal Industry, Department of Environment and Natural Resources (DENR), Department of Health-Bureau of Food and Drugs, and the Department of Trade and Industry are involved in regulating biotechnology products. Mandatory GM labeling, more of a consumer choice than a regulatory issue, has been proposed by some legislators/senators and is now being discussed in public hearings. GM labeling has a major impact on the growth and sustainability of SMEs as it increases production cost by around 10%–12% (Estabillo, 2005).

Intellectual Property Rights

Laws have been passed concerning the protection of the rights of sources or stewards of biodiversity—the raw material for biotechnology—and generators of biotechnology products and related processes. EO 247, considered to be a landmark instrument, addresses benefit sharing from biodiversity use. However, its guidelines were too restrictive for researchers and were later superseded by Republic Act 9147, the Wildlife Resources Conservation and Protection Act of 2001, which redefines bioprospecting to exclude scientific and academic research. EO 247 and RA 9147 are the country's response to the threat of biopiracy, ensuring that benefits accrue to the appropriate stakeholders.

The Intellectual Property Code of the Philippines (RA8293), signed into law in 1997, and the Plant Variety Protection (PVP) Law, enacted in 2002, support technology innovators and generators. At the institutional level, the Department of Science and Technology (DOST) has formulated IPR guidelines for technologies generated through its competitive grants program, acknowledging its ownership of these technologies and sharing the benefits through royalties among the research institutions and the researchers and scientists. The DOST-Technology Application Institute provides patent assistance to scientists; however, approval of such patents can take more than a year. The Philippine Intellectual Property Office acknowledges that only very few scientists apply for and become patentholders. The long approval process, the system of reporting technologies generated by publicly-funded research, and limited knowledge about the value of IPR protection are major constraints in IPR management in the NARS.

Process	Regulation	Specific concern	Agency involved	Requirement
Biotech products (BP) ↓	EO 240	•Import for contained use	•NCBP	•Permit
Laboratory evaluation ↓	EO 240	•Use of GMO in lab experiments •Lab facilities	•NCBP Committee	•Permit
Greenhouse evaluation ↓	EO 240			
Contained field trial ↓ ↓ Imported BP	EO 240	•Limited release in field	•DOST, DENR, DA •BPI implements monitoring	•Certification
Commercialization	AO 8	•Import for direct use		•Permit
—Food safety	RA 3720	•Evaluate protein (identify, function, dietary exposure, nutrition, digestibility, toxicity, allergenic factor)	•DA-STRP, BAFPS, BPI, BFAD	•Expertise •Laboratory
—Feed safety		•Feeding trial •Nutritional equivalent	•BAI	•Expertise •Laboratory
—Env. safety ↓		•Susceptibility to insects/disease •Impact on beneficitation/non-target organisms •Out-crossing	•DENR	•Expertise
Market •local •foreign ↓	RA 7394	•Monitoring	•DTI	REGULATORY
Consumer's acceptance •labeling •risk communication ↓ Utilization •seed •food •feed •others	RA 7394	•Labeling •Risk communication •Ethical clearance	•DTI	CONSUMER'S CHOICE

Source: Faylon et. al., 2003

Figure 4. Process Flow of Regulating Biotechnology Products

The guidelines for the implementation of the Plant Variety Protection Law were formulated in 2004. The law recognizes plant breeders' rights; breeders include individuals who have generated varieties using the required criteria.

Public Acceptance

Public acceptance of modern biotechnology was clearly attained last year when the Philippines joined for the first time the mega-country group producing agricultural biotech products. The Philippines now ranks 14 among mega-countries producing agricultural biotech products (Table 3). This was made possible by the contributions of the various advocates for modern biotechnology and the growing policy support provided by the government. The advocacy activities paved the way for a more open and transparent dialogue among key stakeholders—government, the private sector, academia, NGOs, and farmers. It also blocked the passage of bills and resolutions in Congress attempting to impose a moratorium on activities related to biotechnology and GMOs. Particularly in 2000, during the height of anti-biotech sentiments, Senate Report No. 397 recommended that the proposed moratorium on activities related to biotechnology and GMOs would in effect stifle the impetus of human innovation and inventiveness and exclude the Philippines from the tide of technological advances now prevalent elsewhere in the world.

Table 3. Mega-countries Producing Agricultural Biotechnology (Bt corn) Products

Country	Million hectares (planted to Bt corn)	Percent
USA	47.6	59
Argentina	16.2	20
Canada	5.4	6
Brazil	5.0	6
China	3.7	5
Paraguay	1.2	5
India	0.5	1
South Africa	0.5	1
Uruguay	0.3	less than 1
Australia	0.2	less than 1
Romania	0.1	less than 1
Mexico	0.1	less than 1
Spain	0.1	less than 1
Philippines	0.1	less than 1

Source: Philippines Today, 2005

Among the different actors who played major roles in biotechnology advocacy were, in no particular order, the various professional groups and nongovernment organizations, such as the Biotechnology Coalition of the Philippines and the Philippine Maize Farmers Association, private companies like Monsanto Philippines and Pioneer-Dupont, regional and international organizations like the Southeast Asia Regional Center for Agriculture-Biotechnology Information Center and the International Service for the Acquisition of Agri-biotech Applications, public research institutions such as the University of the Philippines National Institute of Molecular Biology and Biotechnology and Institute of Plant Breeding, and government departments such as the DOST–National Academy of Science and Technology and the Philippine Council for Agriculture, Forestry and Natural Resources Research and Development (PCARRD) as well as the Department of Agriculture DA–Biotechnology Implementation Unit

Policy Support

The key government policy support that set the stage for the application of modern biotechnology was direct funding support for R&D and capability building. Five projects in genetic engineering were approved by former President Fidel V. Ramos in 1997. From 1998 to 2002, a

total of USD2.31 million was spent on biotechnology, 61% of which came directly from DOST and 33% from PCARRD. Similarly, biotechnology became a major component of the Agriculture and Fisheries Modernization Act (R.A. 8435 AFMA, 22 December 1997). From the total appropriation of USD370 million for the first year of implementation, the law stipulated the allocation of 10% for research and development, 4% of which was to be used to support the biotechnology program. In 2001, the administration of President Gloria Macapagal-Arroyo explicitly recognized the safe and responsible use of modern biotechnology as a means to achieve food security and a sustainable environment. In addition, in a cabinet meeting held in February 2005, President Arroyo approved the formation of a biotechnology industry cluster proposed by former DOST Secretary and DTI-BOI Governor Ceferino Follusco, now active in the private sector. In March 2005, DA Secretary Arthur Yap agreed to lead the agri-biotechnology industry cluster.

Public-Private Sector Collaboration/Partnership

The Philippines is in a learning mode with regard to public-private sector partnership in agricultural biotechnology. The following initiatives have rallied private sector participation in biotechnology R&D and commercialization:

Establishment of the 22-hectare UPLB Science and Technology Park (UPLB-STP) in 1993 to commercialize UPLB-generated superior biotechnologies.

Creation of the Biotechnology Association of the Philippines, Inc. in 1996 to unify the private sector's dispersed efforts on health, environment, and industrial biotechnology in coordination with the Department of Trade and Industry.

Linkage with the International Service for the Acquisition of Agri-biotech Applications (ISAAA) to provide proprietary "goodwill" technologies of regional importance through a networking mode (i.e., PRSV and SPFMV resistance for papaya in 1997 and sweet potato in 2003, respectively).

Establishment of the Biotechnology Coalition of the Philippines (BCP) in 2001 to advocate for the safe and responsible use and advancement of modern biotechnology, as well as an expansion of its membership to include the agricultural biotechnology sector.

Conducting two workshops at the Department of Science and Technology in 2002 to initiate the formation of biotechnology industry clusters.

Packaging of PAFBA II with involvement from the private sector in brainstorming, determining core competence, framework formulation, and research prioritization.

Meetings held in 2005 by PCARRD, PCASTRD, and BCP to facilitate the creation of bio-industries by acting as a buffer for scientists, entrepreneurs, and investors.

With the current R&D budget constraints faced by the NARS worldwide and the CGIAR Centers and the challenge of making an impact on the livelihood of the rural poor and the sustainability of the environment, public-private partnership is no longer an option but a necessity. R&D investment has been 0.30% of GVA, far below the 1% recommended by the World Bank for developing countries and one of the lowest in the Asian region. Partnerships with the private sector on research areas with market potential could swing the balance from primarily public sector investment to one that will increase private sector investment from 5% to 15% (DOST-GAINEX, 1995). Such partnerships, though, must be guided by a strong IPR policy and require special skills in IP management that have yet to be acquired and applied by most scientists and research managers in Philippine NARS.

COMPETITIVENESS OF AGRI-BIOTECH PRODUCTS

While the Philippines is the first country in Asia to commercialize a biotechnology product of a multinational company, Monsanto's Bt corn, its experience is still limited. Studies on social, economic, and other related issues have been done by Gonzales (2004), Yorobe et al. (2004),

and Batiquin and Cruz (2004). This section discusses the competitiveness of modern agri-bio-tech products using two cases: Bt corn produced by Monsanto, a private multinational company, imported by the Philippines since 2002 for direct use as food and feed, and transgenic PRSV papaya, still in the testing stage, for which work began in 1997.

Bt Corn

After rice and coconut, corn is one of the major commodities produced in the Philippines both for food and livestock feed. Corn production has been erratic. A decrease in area devoted to corn production coupled with an increased demand from the livestock sector has prompted the government to import additional supplies. Feed comprises around 70% of the cost of raising chickens and hogs, and about 2.5M mt goes to feed production annually.

The Asiatic corn borer (ACB) is the most destructive of the insects that attack corn plants. Losses due to ACB have been reported to be as high as 80% (Rejesus and Javier, 1985); damage can vary depending on the season and time of planting. The common control method is through the use of chemicals. Nonchemical methods such as detasselling and biological control (through the use of *Trichogramma*) have been ineffective.

Bt corn is an alternative to chemical sprays for controlling ACB throughout the growing period. It has been adopted by the U.S. South Africa, and other countries from which the Philippines imports corn. The government approved the propagation of Bt corn and its importation for direct use in December 2002, after almost six years of trials and safety evaluations. The Philippines is the first country in Asia to commercialize Bt corn. From an initial 126 hectares in 2002, the total area planted to genetically-modified Bt corn in 2005 is projected to be 100,000 ha (Table 4). Although Bt corn seeds were originally imported, Monsanto is now operating a seed production plant in southern Philippines. The commercialization of Bt corn (Monsanto's Yieldguard 818 and 838) has caused some controversy, for example, with respect to biosafety, health risks, local farmers' competitiveness, and relative economic advantage of Bt over non-Bt corn.

Table 4. Area Planted to Bt Corn, Philippines

Year	Area planted (ha)
2002	126
2003	24,000
2004	54,688
2005 (projected)	100,000

Source: del Rosario, 2004; *Philippines Today*, 2005

Two studies (Gonzales, 2004; Yorobe et al., 2004) have reported the superiority of Bt corn over non-Bt corn. Gonzales (2004) compared performance of Yieldguard corn with ordinary hybrid corn, covering two seasons and at least five corn-producing provinces during the initial phase of Bt commercialization using five impact indicators of global cost competitiveness under import substitution and export trade: yield, farm production cost, net farm income (profit), subsistence level carrying capacity ratio, and resource cost ratios. The study estimated that under an import substitution scenario, YieldGard corn production was more cost-competitive by 17% than ordinary hybrid corn production. Likewise, under an export trade scenario, YieldGard production had a global cost-competitive edge over non-Bt corn production of 16%. At high yield levels of 5 mt/ha, YieldGard corn production, as reflected in the analysis, can be globally cost-competitive as an export (Table 5).

Despite the bright prospect for transgenic corn demonstrated in this study, Yieldguard corn adoption faces constraints: lack of information on how or where to access Bt corn seeds, lack of technical knowledge on how to maximize the benefits from transgenic corn, high cost of Bt corn

seeds, and perceived health and environmental hazards. As other corn transgenics enter the country, adoption of a particular variety may depend on the cost-competitiveness of the seeds. Gonzales (2004) recommends information/education campaigns, techno demos, and workshops on integrated pest management, proactive financing to cover the cost of fertilizer and seeds, providing the needed public and private investments in infrastructure and back-up services in strategic corn-producing provinces, market-matching activities and linkages with the livestock-poultry subsectors to increase the efficiency and global competitiveness of the feedgrain-livestock-poultry industry cluster, and a sustained, ongoing system of evaluation and socio-economic impact assessment of YieldGard and other transgenic technologies to help technology generators and the public in strengthening the strategic position of Bt corn as the key result area in developing a globally competitive feed corn-livestock industry cluster.

Table 5. Comparative Global Competitiveness (Import and Export Trade Scenario) of Bt versus non-Bt Corn, 2003

Trade scenario	Global competitiveness (RCRS)*						Performance ratio (Bt/Non-Bt)		
	Bt			Non-Bt					
	Low yield ^a	High yield ^b	Both yield levels	Low yield ^a	High yield ^b	Both yield levels	Low yield ^a	High yield ^b	Both yield levels
All provinces, wet season 2003									
Import	0.35	0.22	0.26	0.47	0.29	0.35	0.74	0.76	0.76
Export	0.35	0.22	0.26	0.47	0.29	0.35	0.74	0.76	0.76
Only Isabela, dry season 2003–2004									
Import	0.37	0.20	0.23	0.37	0.23	0.25	1.00	0.90	0.92
Export	1.47	0.93	1.01	1.44	1.02	1.08	1.02	0.91	0.93
^a yield <= 4mt/ha ^b yield > 4mt/ha *Resource Cost Ratio (RCRs) was used as indicator of global competitiveness. Globally competitive if RCR < 1, neutral if RCR = 1, globally uncompetitive if RCR > 1. Note: A performance ratio (Bt/Non-Bt) less than one implies that Bt corn is more globally cost-competitive than non-Bt corn.									

Source: Gonzalez, 2004; data from STRIVE Corn Survey, 2003–04

PRSV Papaya

Papaya is widely consumed in the Philippines, along with banana, pineapple, and mango. As the world's ninth-largest fresh papaya exporter, the Philippines enjoys a market share of 1.4% valued at USD1.8 million per year. Local cultivars/strains grown in-country are Solo, Cavite Special, Legaspi Special, Morado, DMPI, and hybrid Sinta (Table 6). The cultivars Solo and Sinta are mainly intended as dessert fruit for the export and domestic market, respectively. DMPI is canned as tropical fruit cocktail. Major markets for Solo papaya are Japan, with a comparative share of 74.10%, and Hongkong, with 21.46%. Other importers of Philippine fresh papaya are Taiwan (0.91%), Singapore (0.71%), New Zealand (0.68%), Saudi Arabia (0.68%), UAE (0.59%), South Korea (0.55%), China (0.18%), South Africa (0.10%), and others (0.05%). Production ranged from 85,000 mt to 100,000 mt from 1990–2003. The area harvested grew from 6,000 ha in 1990 to 9,000 ha in 2003. The yield increased minimally, from 14mt/ha in 1990 to 15mt/ha in 2003 (Payot, 2005; DA–NAFC–Philippine Genetics, Inc., 2002; National Papaya R&D Committee, 2004). In general, papaya production, area harvested, and demand have been increasing. Yield, however, increased only minimally, while export has been continuing but is

erratic. Of an average volume of 109,525 mt per year, 92% goes to domestic consumption as food, 6% is processed/wasted, and only 2% is exported (Payot, 2005).

Table 6. Papaya Cultivars/Strains, Philippines

Cultivars/ strains	Weight	Grown in	Principal use	Market	PRSV resistance
Solo	About 0.45 kg	Large farms in Mindanao	Dessert fruit	Export and domestic	Susceptible
Cavite Special	More than 3 kg	In Cavite and neighboring provinces	Dessert fruit	Domestic	Susceptible
Legaspi Special	More than 3 kg	In Legaspi (Albay) and neighboring provinces	Dessert fruit	Domestic	Susceptible
Morado	–	In Mindanao	Canning	Export	Susceptible
DMPI (devel- oped by Del Monte Philip- pines, Inc.)	–	In Mindanao	Canned tropical fruit cocktail	Export	Susceptible
Hybrid Sinta (released by UPLB–IPB in 1995)	1.2–2 kg	In Luzon	Dessert fruit	Domestic	Moderately resistant

Source: Tabulated from Payot, 2005

In 1984, the *papaya ringspot virus* (PRSV) outbreak created havoc in the flourishing papaya industry. PRSV reduces total production by 35%–41% and reduces yield by as much as 90%–100%. Once an area has been infested, PRSV is there to stay: no eradication effort yet has been successful. All the Philippine cultivars/strains are susceptible to PRSV except for Sinta, which is moderately resistant. Biotechnology's contribution is to produce PRSV-resistant papaya, developed locally, although the gene construct is imported, with PCARRD holding the license. It is currently undergoing contained field testing and is set to be commercialized by 2007. Public acceptance of this GMO, however, promises to be a tough challenge.

Laude (2002) showed that cash costs comprise the bulk of production costs (75%); chemical inputs such as fertilizers and pesticides (36%) and hired labor (35%) contributed 71%. Varying price and cost-competitiveness of the GM papaya over the non-GM papaya were also reported. Using export parity prices, the analysis revealed greater-than-one price ratios for Solo GMO, non-GMO, and Sinta papaya, which implies that these fruits are price-competitive on the export market. Moreover, the non-GMO Solo papaya appears to be more price-competitive by 15% over the GMO Solo and the non-GMO Sinta (Table 7). Laude observed that there was unfortunately bias in the world market against the GMO papaya. In fact, the price ascribed to the GMO papaya is almost half that of a non-GMO papaya's border price. On the other hand, a non-transgenic Sinta papaya has about the same border price as that of a Solo GMO. Despite this, the Sinta papaya can still obtain a better price when exported than when sold locally, that is, if the export market reacts positively to Sinta.

Table 7. Price Ratios for Export Competitiveness by Variety (2000–01), Philippines

Variety	Export parity	Domestic wholesale	Price ratio*
Non-GMO Solo	59.16	30	1.97
GMO Solo	33.66	20	1.68
Sinta	33.66	20	1.68
*Price ratio = export parity price/domestic wholesale price; competitive if price ratio > 1			

Source: Laude, 2002

As far as global cost-competitiveness, the *ex ante* domestic resource costs (DRCs) and resource cost ratios (RCRs) of Solo and Sinta papaya show possibilities of export competitiveness regardless of the presence or absence of the PRSV disease. For instance, the RCRs for both Solo GMO and non-GMO papaya regardless of yield group and port of export were less than one. This reveals the country's competitive advantage in producing quality papaya for export. The Solo non-GMO papaya was more cost-competitive by 42% than the Solo GMO papaya (Table 8).

Table 8. *Ex ante* Resource Cost Ratios (RCRs) of Solo and Sinta Papaya for Export by Port, by Biotechnology Delineation, and by Yield Group (2000–01), Southern Mindanao

Parameter	Low		High	
	Non-GMO ^a	GMO ^b	Non-GMO ^a	GMO ^b
Solo Papaya for export (Manila Port), Southern Tagalog				
DRC (P/HOUSD)	28.83	49.51	27.69	48.13
RCR*	0.57	0.97	0.54	0.94
Solo Papaya for export (Davao Port), Southern Mindanao				
DRC (PHP/USD)	24.50	41.85	23.36	40.46
RCR*	0.48	0.82	0.46	0.79
Sinta Papaya for export (Manila Port), Southern Tagalog ^c				
DRC (PHP/USD)	42.66	-	42.10	-
RCR*	0.84	-	0.83	-
^a 31.36% disease incidence ^b 0% disease incidence ^c 17.14% disease incidence *Resource Cost Ratio (RCRs) was used as indicator of global competitiveness. RCR=DRC/OER; globally competitive if RCR < 1, neutral if RCR = 1, globally uncompetitive if RCR > 1; official exchange rate (OER) used was PHP51 = USD1.				

Source: Laude, 2002

THE WAY FORWARD

Challenges

Successful adoption and commercialization of modern biotechnology products will depend on increased awareness by the general public of product benefits and safety and the market orientation of the key players from research to enterprise building, which will require special skills in technology management in general and market intelligence, market-led R&D, market-based regulatory, market matching, and market retooling in particular. While the policy environment has been put in place through relevant laws and other policy instruments, the lack of limited expertise to successfully implement, monitor progress, and evaluate impact will remain a challenge. The current limited policy support on price, transport, microfinancing, and technical

assistance may have to be adjusted to provide an environment more conducive for the prospering of the biotech industry. A new generation of highly innovative, forward-looking, enterprising scientists and research managers will have to arise. Strong public-private sector partnerships guided by clear IPR policy and other appropriate incentives should be encouraged and supported to attract private sector investment in R&D and to commercialize technologies successfully. Recent advances in ICT and global developments with respect to trade are realities which the Philippine NARS should view as opportunities for new knowledge generation (such as functional genomics) and application of modern biotechnology to develop high-quality marketable products.

Present Initiatives

Government will have to consider its R&D leadership in areas where it has competitive advantages and provide funds for technology acquisition (through licensing) to fast-track technology adoption, as it did in the case of Bt corn, for which the technology is already available for commercialization, or for PRSV papaya, for which the gene construct is available for developing a transgenic using local varieties. The current database on the performance of Bt corn will have to be enhanced by 2007 to include other corn transgenics in the pipeline for a more informed policy-related decision-making process.

Since agricultural extension has already been devolved to local government units, an aggressive education and communication program on biotechnology for local government units will have to be developed, supported, and sustained. The formation of bio-industry clusters and e-business should be led by the private sector, jointly supported by the government and the private sector, capitalizing on the strength and experience of academia, research institutions, and development-oriented NGOs.

Future Prospects

The future of the agricultural biotechnology industry appears bright. The Philippines must strategize by focusing on products where it has a competitive advantage and expanding its world market share of competitive products through downstream processing, related-services provision, and overseas company joint ventures.

The role of the government must be to provide policies conducive to the growth of the biotech industry, setting direction and providing basic infrastructure; that of academia lies in basic and strategic research and education; the private sector must be concerned with applied R&D and commercialization; farmers must engaged in primary production and primary processing; and the development-oriented NGOs must concentrate on farmer retooling and organizing so that the latter can be globally competitive producers and traders. In the Asia-Pacific area, regional partners/countries will be active in sharing experiences, adopting good agricultural practices, and strategically planning as a regional bloc how to compete for international trade, thereby aiding economically weaker member countries and strengthening further the roles of all member countries.

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11. STATUS OF PUBLIC RICE BIOTECHNOLOGY RESEARCH AND DEVELOPMENT AND COMMERCIALIZATION IN THE PHILIPPINES

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INTRODUCTION

Rice is the most important economic crop in the Philippines, contributing an average of 15.5% to the country's gross value added in agriculture, 13% to the consumer price index, 3.5% to the gross domestic product, and 3.3% to the gross national product. As the country's staple food, rice accounts for from 35% of the average calorie intake of the population of 82 million to as high as 60%–65% for households in the lowest income quartile. Average annual rice consumption has been estimated at 103 kilograms per capita. In recent years, rice sufficiency has been synonymous with the food security policy (<http://www.da.gov.ph>). A buffer stock of 60 days' worth is maintained through import to ensure food security.

The demand for increased rice production is necessary to meet the immediate needs of an ever-growing population in the midst of a decline in the supply of water for irrigation of rice fields, a plateau in rice yield, and the prevalence of ever more virulent rice pests and diseases (Gonzales, 2003).

Modern agricultural biotechnology would seem to offer a solution to these problems. It has the potential to produce more nutritious, better-tasting, higher-yielding, more pest- and disease-resistant rice varieties in a relatively short period of time compared to conventional rice breeding (PhilRice, 2004). It is one of the strategies that will be used in the next decade to tackle the challenges of a rapidly increasing population and increased global competition.

For modern agricultural biotechnology to be immediately useful, however, it must be commercialized. But since modern agricultural biotechnology can be considered intellectual property, commercialization can only be done within a favorable legal and institutional framework. Further, because of the possible consequences of biotechnology modernization, products of modern biotechnology might not be enjoyed fully until uncertainties regarding the risks to human health and the environment are minimized and managed, if not eliminated. A responsive regulatory system is therefore also an essential component of this precautionary approach in dealing with the products of modern agricultural biotechnology.

This paper will discuss the existing legal and institutional frameworks for public modern agricultural biotechnology research and development (R&D) and commercialization in the Philippines, with a focus on rice and the Philippine Rice Research Institute (PhilRice).

THE EXISTING LEGAL AND INSTITUTIONAL FRAMEWORK ON PUBLIC RICE BIOTECHNOLOGY R&D AND COMMERCIALIZATION

The Philippine Constitution states that “science and technology are essential for national development and progress.” The state is mandated to give priority to research and development, invention, innovation, and their utilization, to promote science and technology education, training, and services, and to support indigenous, appropriate, and self-reliant scientific and technological capabilities and their application to the country's productive systems and national life.

Pursuant to this constitutional mandate and also consistent with the Constitution's incorporation clause, the government has signed international treaties concerning agricultural biotechnology: the Convention on Biological Diversity, signed on June 12, 1992 and ratified on October 8, 1993 (recently, the Philippine Congress passed into law the Wildlife Conservation Act which, in effect, puts into law the provisions in the convention), and the Cartagena Protocol on Biosafety, signed in May 2000 (not ratified to date).

In anticipation of the advent of modern biotechnology, the government issued Executive Order No. 430 creating the National Committee on Biosafety, tasking it with evaluating applications for testing biotechnology products.

In December 1994, the Philippines ratified the General Agreements on Tariffs and Trade (GATT), including the provision on Trade-Related Aspects of Intellectual Property Rights (TRIPS). The Congress also ratified the country's World Trade Organization (WTO) membership. Subsequently, the Congress enacted the Intellectual Property Code of the Philippines pursuant to the TRIPS Agreement, which took effect on January 1, 1998.

To demonstrate the government's resolve to modernize agriculture utilizing biotechnology, the Agriculture and Fisheries Modernization Act was enacted in 1997 mandating the use of biotechnology as a tool in modernizing agriculture and increasing productivity.

Administrative Order No. 8 was issued by the Department of Agriculture in 2002, setting forth for the rules on laboratory testing up to commercialization and even importation of products of modern agricultural biotechnology (<http://www.da.gov.ph>). In the same year Congress enacted the Plant Variety Protection Act, which provides protection to newly developed transgenic plant varieties.

These and other laws, legislation, and rules provide the legal and institutional framework for commercialization of agricultural biotechnology in the Philippines.

THE STATUS OF PUBLIC RICE R&D AND COMMERCIALIZATION IN THE PHILIPPINES

Few public or private research institutions in the Philippines conduct modern agricultural biotechnology research. Most modern agricultural biotechnology R&D is conducted by the public sector. The private sector, mostly multinational companies, imports agricultural biotechnologies.

The major public institutions engaged in modern agricultural biotechnology R&D are the Institute of Plant Breeding (IPB) and the National Institute of Microbiology and Molecular Biology (BIOTECH) at the University of the Philippines Los Baños (UPLB), the National Institute of Molecular Biology (NIMB) of UP-Diliman, the Philippine Coconut Authority (PCA), and the Philippine Rice Research Institute (PhilRice). The International Rice Research Institute (IRRI) is among the international public institutions engaged in modern agricultural biotechnology. The Bureau of Agricultural Research (BAR) of the Department of Agriculture and the Philippine Council for Agriculture Forestry and Fishery Research and Development (PCARRD) of the Department of Science and Technology (DOST) coordinate and fund R&D in modern agricultural biotechnology conducted by these and other institutions.

The private sector, however, also dynamically takes part in the promotion of biotechnology. The International Service for the Acquisition of Agri-biotech Applications (ISAAA), which has its Southeast Asia Center based in the country, is a nonprofit international organization that works for the delivery of biotechnology benefits to developing countries through the promotion of technology transfer. One of the leading private companies conducting field trials and commercializing agricultural biotechnology is Monsanto Philippines, through its Bt corn.

The Philippine Rice Research Institute (PhilRice)

PhilRice, a government corporation attached to the Department of Agriculture (DA), is the national agency for R&D, with a mandate to lead, unify, and strengthen the manpower capabilities and improve the facilities of agencies involved in the national rice R&D program and to serve as a vital force in attaining and sustaining the country's goal of self-sufficiency in rice and in promoting greater access by farmers to agricultural technology (PhilRice, 1995).

PhilRice coordinates the R&D activities of more than 60 public agencies through its national rice R&D network, which includes experiment stations of the DA and state colleges and universities strategically located in rice-producing areas in the country. Figure 1 presents the map of the rice R&D network.

R&D Programs

PhilRice has implemented eight new programs: Transplanted Irrigated Lowland Rice, Direct-Seeded Irrigated Lowland Rice, Hybrid Rice, Rice for Adverse Environments, Rice-Based Farming Systems, Rice and Rice-Based Products, Policy Research and Advocacy, and Technology Promotion and Development.

Manpower

Since 1987, PhilRice has pursued a manpower development program to boost rice R&D, with a focus on expertise in agricultural biotechnology and related fields. This manpower build-up is funded by the Philippine government, the Rockefeller Foundation (RF) for Ph.D.s in biotechnology, the Japanese government through the Japan International Cooperation Agency (JICA), and International Rice Research Institute (IRRI). To date, 32 PhilRice and R&D network staff members have earned their Ph.D.s, and 75 others have earned their M.S./M.A. degrees. In addition, 11 Ph.D. and 17 M.S./M.A. candidates will complete their studies soon. All in all, there are about 2,000 personnel involved in rice R&D, excluding those of IRRI.

Laboratories and Facilities

The main laboratory facilities of the Institute were provided by the Japanese government through JICA in 1991. The facilities include research laboratories for plant physiology, soil analysis, chemistry, food technology, molecular genetics, genetic transformation tissue culture, entomology, and plant pathology. A medium-term germplasm bank and several greenhouses are also included.

Biotechnology R&D and Commercialization

Rice biotechnology research is undertaken in the genetics and tissue culture laboratories. Equipment in these two laboratories has been provided through an initial JICA grant, JICA Technical Assistance, ARBN, RF, and funds from the Philippine government. The present biotechnology facilities include laboratory areas for transgenic work, anther culture, and molecular marker analyses (Beronio and Payumo, 2004).

Rice biotechnology research is integrated in the five component programs: transplanted irrigated lowland rice, direct-seeded irrigated lowland rice, hybrid rice, rice for adverse environments, and rice and rice-based products. These programs are directly involved in the development of varieties suited for specific locations and conditions and rice-based products (Sebastian and Obien, 2000).

Specifically, the biotechnology R&D currently being pursued includes utilization of molecular marker technology for assessing the diversity of germplasm resources, for fingerprinting or establishing genetic identity of specific genotypes, for identification of appropriate parental materials for breeding purposes, for tagging agronomically important genes, and for pyramiding

Map of Rice R&D Network

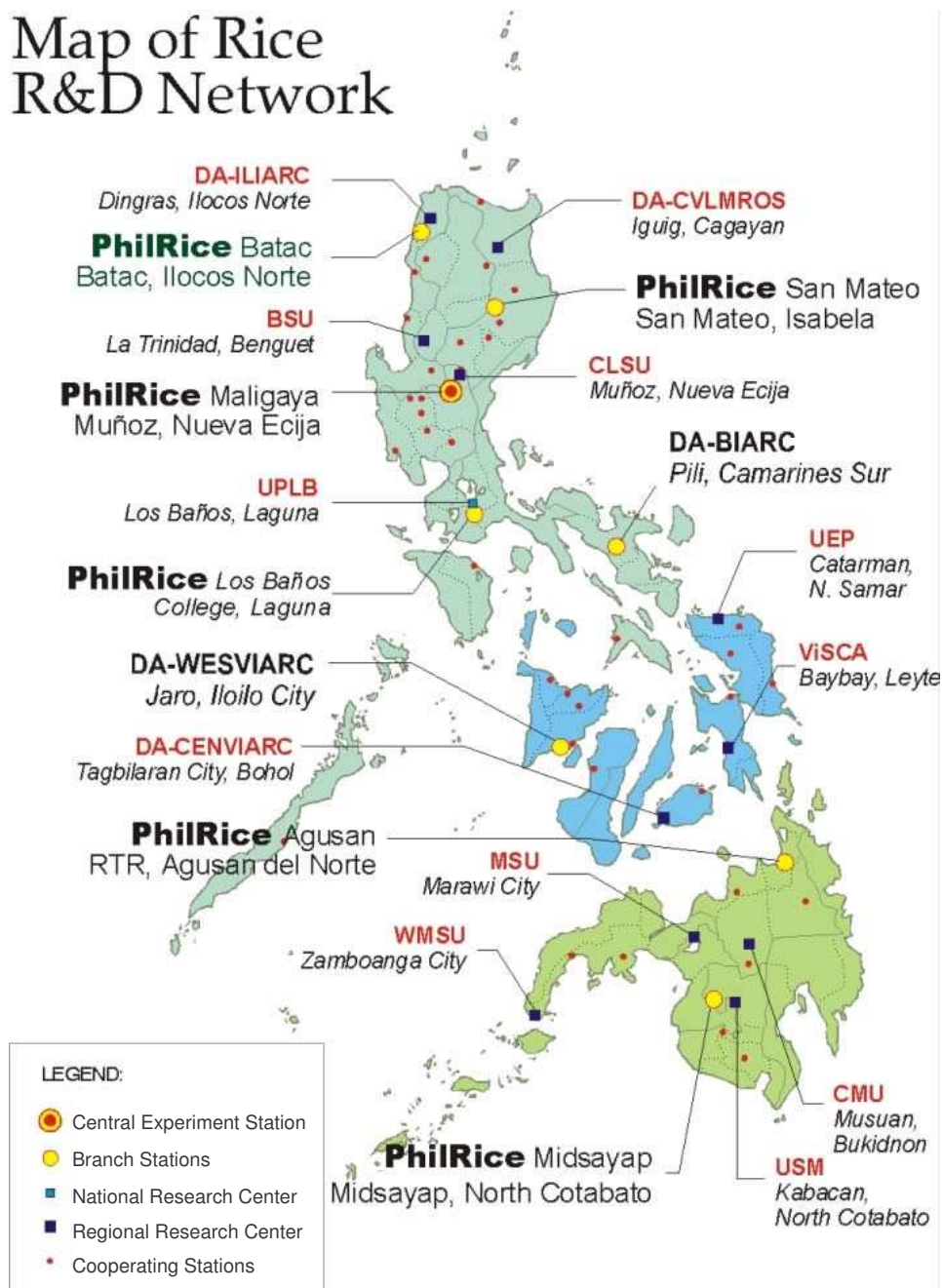


Figure 1. Location of R&D Stations of PhilRice

different bacterial blight resistance genes; *in vitro* culture to facilitate line purification, production of stable lines adapted to adverse environments, and induction of useful mutants/variants; genetic transformation for introducing genes such as *Xa21* for bacterial blight resistance, *proteinase inhibitor 2* for stemborer resistance, *Hva1* for drought and salinity tolerance, and *chitinase/glucanase* for fungal disease resistance; and DNA marker tagging and cloning of genes involved in aroma, tungro resistance, fertility restoration, and salinity tolerance (Obien and Sebastian, 1997).

The targets of genetic engineering at PhilRice are presented in Table 1. Other activities include evaluation and utilization of Golden Rice lines as donors of betacarotene biosynthetic genes for transfer into popular Philippine commercial varieties through conventional breeding as well as evaluation of transgenic plants that are designed to resist tungro viruses by over-expressing certain genes. The National Committee on Biosafety of the Philippines and the local Institutional Biosafety Committee (IBC) play active and important roles in ensuring that biosafety protocols and precautions are strictly followed in the conduct of research involving genetically modified plants.

Table 1. Targets of Genetic Engineering Research at PhilRice, Philippines

Target	Transgene	Source	Status
Bacterial blight resistance	<i>Xa21</i>	<i>Oryza longistaminata</i>	Laboratory, screenhouse, field
Fungal disease resistance	<i>Chitinase and glunase</i>	Alfalfa and rice	Laboratory and screenhouse
Stemborer resistance	<i>Proteinase inhibitor 2</i>	Potato	Screenhouse
Abiotic stress	<i>Hva 1</i>	Barley	Screenhouse
Improved F1 hybrid seed production	Candidate <i>Restorer of fertility</i> gene	Rice (IR64)	Laboratory and screenhouse
Vitamin A rice	<i>Phytoene cyclase and desaturase</i>	Daffodil, <i>Erwinia</i>	Screenhouse
Tungro resistance	Transcription factors	Rice	Screenhouse

Another variety produced in PhilRice is the *Wagwag*. It is an improved traditional variety, tissue culture derived and already released as a commercial variety, NSIC Rc130. Popular varieties, like AR32 containing pyramided genes for bacterial blight resistance, are nearing commercialization but already well known in the farmers' fields.

The Secretary of Agriculture has recently approved the establishment of the Agricultural Biotechnology Center at PhilRice, tasked primarily with coordinating biotechnology R&D under the Department of Agriculture.

PhilRice Intellectual Property Policy

PhilRice is probably the only government agency in the Philippines with a fully functioning, beneficial, effective IPR policy. Enacted in August 2004, it states that while it will protect its own IP, it will also recognize and protect the IPR of others. It also advocates proactive generation, protection, and commercialization of IP.

In the same year, PhilRice also established, staffed, and funded its Intellectual Property Management Office (IPMO). The IPMO handles capability building of PhilRice staff on IPR, conducts prosecution of IPR applications, helps negotiate in-licensing and out-licensing of IPR, and collects and distributes royalties. In its first year of existence it filed numerous applications for patents, utility models, copyright deposits, etc., facilitated the disbursement of royalties, and

caused more than 97% of all PhilRice staff to issue undertakings for confidentiality and prosecution of generated IP.

PhilRice is thus in a position to effectively commercialize the modern agricultural biotechnology it generates.

CONCLUSION

Except for Bt corn, which has been commercialized by a multinational company, prospective agricultural biotechnology products are in R&D or are undergoing laboratory and confined testing. It will take perhaps one to five years to have them in the field. By then, the necessary institutional and legal framework for commercialization will be in place.

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12. BUSINESS POTENTIAL FOR AGRICULTURAL BIOTECHNOLOGY IN SINGAPORE

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INTRODUCTION

The agriculture biotechnology or agri-biotechnology industry in Singapore is modest in comparison to other Asian countries such as China, India, or the Philippines which have been classified as one of the 14 biotech mega-countries (growing 50,000 hectares or more of biotech crops) by the International Service for the Acquisition of Agri-biotech Applications (ISAAA) (Clive James, 2004) because they produced 5%, 1%, or less than 1% of 81 million ha of global biotech crops respectively in 2004. However, agri-biotechnology development in Singapore has been uniquely featured as one of the case studies in the guidance report “Western Australia’s Strategy to Build Its Biotechnology Capacity” because of its strong government leadership in supporting agri-biotechnology development, despite having little agricultural industry.

The agri-biotechnology sector was profiled for development in 1991, with Singapore adopting a vision of a knowledge economy powered by ideas and innovation under the establishment of the National Technology Plan(s).¹ Today, it has been subsumed under the broader industry sector of life sciences, which also includes pharmaceuticals, biotechnology, medical devices, and food sectors. Life sciences, a knowledge-intensive and high-value-added industry, has been identified by the Economic Development Board (EDB) as the fourth pillar of Singapore’s manufacturing sector, alongside electronics, chemicals, and engineering. The agri-biotechnology business sector in Singapore is also anticipated to grow in tandem with the other subsectors of the life sciences.

Embracing the capital-intensive and high-risk agri-biotechnology industry for fast economic returns in Singapore, where agricultural land resources are limited, is a significant challenge, especially when the neighboring countries with low land costs, like China and India, are also entering into the agri-biotechnology business. With the extensive support of knowledge, infrastructure, and a regulatory framework that the government has formulated to drive the agri-biotechnology sector since the 1990s, numerous agri-biotechnology R&D activities are being undertaken, particularly in the areas of genetic transformation, molecular breeding, vaccine and diagnostic technology, genomics, and bioinformatics for the improvement of agricultural novelty, yield, quality, nutritional content, and stress resistance (against environmental stress and diseases).

Singapore, a country that imports many of its commodities, produces a small proportion of its agri-food (i.e., 31% of hen eggs, 7% of fish, and 5% of vegetables for domestic consumption)

¹ NTP, NSTP, and NSTP 2000. The National Science & Technology Board (NSTB) was established in 1991 to spearhead the two national master plans that outlined Singapore’s strategies for science and technology (S&T) development: the National Technology Plan (NTP) in 1991 to develop key resources in technology, manpower, and skills to meet industry needs and the National Science and Technology Plan (NSTP) in 1996, which envisioned “an innovative and enterprising society that embraces science and technology to develop a thriving knowledge economy and good quality of life.”

but is nonetheless a major player in the world ornamental fish and orchid trade, with values of SGD33 million for orchids and SGD72 million for ornamental fish for export to markets worldwide. In 2003, agriculture contributed to about 0.1% of Singapore's GDP, or about SGD159 billion.

The development of the agri-biotechnology sector is aligned with the goal of increasing food supply and addressing the food safety issues that will have an impact on the national economy. Agri-biotechnology needs to be applied appropriately and integrated vertically into the intensive farming system of Singapore to achieve high farm productivity and efficiency. In addition, these applications can also be used to facilitate food supply, food safety, and agri-trade. As in many other countries, the biosafety of agri-biotechnology remains a growing public concern. The development of agri-biotechnology business in Singapore will have to take into consideration the social economic aspect for safe, quality agriproduce.

A*STAR is the national body spearheading biotechnology development, with a broad focus on life sciences. The Agri-Food and Veterinary Authority of Singapore (AVA) is the national regulator of a safe food supply and animal and plant health and a facilitator of agri-trade and agriculture development. The application of biotechnology in agriculture is driven by AVA together with key R&D institutes. AVA has a key role in partnering with the agri-biotech R&D institutes and the private sector in charting the development of agri-biotechnology business in the context of facilitating food production, enhancing a safe food supply, and maintaining vibrancy in agri-trade.

AGRI-BIOTECHNOLOGY ACTIVITIES AND PRODUCTS

The development of agri-biotechnology is focused on both food (leafy vegetables, rice, marine foodfish) and nonfood-based products (diagnostic kits, vaccines, ornamental fish, and plants) (Table 1).

Several products have been commercialized to date, such as nonfood ornamental fish (trademarked GloFish), while many potential products are in the pipeline awaiting approval from the relevant approving authority. The trademarked GloFish was developed by a Singapore scientist, Dr. Zhiyuan Gong from the National University of Singapore (NUS), who licensed the tropical fluorescent zebrafish as pets to Yorktown Technologies, L.P. in Florida, U.S. in 2004. The fish were sold as pets in Taiwan for about USD5 apiece in January 2004 and subsequently in Malaysia and Hong Kong after approval was obtained from U.S. authorities.

MNC agri-establishments like Dow Chemical Company, Syngenta, and Bayer Cropscience, which have regional manufacturing bases in Singapore, are involved primarily in the distribution of agricultural chemicals. Food companies such as Nestlé and Kellogg utilize agricultural crop products that may be derived from gene technology and are of concern to the food authority or consumers. Such concern has warranted the companies' attention on food safety assurance in accordance with the various regulations of importing countries concerning genetic manipulation (GM)-derived products and local consumer preferences and needs.

Table 1. Agri-biotechnology Activities and Products Developed, Singapore

Agri-biotechnology/ product	Commercial values	Establish- ment/ collabora- tive party	Develop- mental stage	Challenges/ issues
(continued on next page)				

Business Potential for Agricultural Biotechnology in Singapore

Trademarked GloFish with genetic-engineered glow gene of a jellyfish and sea anemone	Bioluminescent ornamental fish	NUS	Patent filed in U.S. and product is commercialized by U.S.-based company	Consumers' concern on environmental impact after market release
Genetic engineering of resveratrol (stilbene synthase gene) producing red lettuce	Functional food (cancer and heart diseases prevention)	NIE; academic	Patent filed; not commercialized	Rigid biosafety evaluation by GMAC
Genetic engineering of firefly luciferase gene in orchid	Bioluminescent ornamental plant	NIE/IMCB; academic	No patent filed	Reason unknown
Quantitative Trait Loci (QTL) mapping project on tilapia and salmon broodstocks; application of GenTrack as enhanced traceability system	Accelerated breeding and safe food	TLL/GenoMar ASA (Norway) (R&D research institutes)	Ongoing R&D	–
Asian leafy vegetables and rice (molecular techniques in variety screening)	Disease-resistant varieties	TLL/AVA	Ongoing R&D	–
GMO testing methods	New techniques for detection of GM contamination	TLL/AVA	Ongoing R&D	–
Fish and animal (livestock and poultry) diagnostic kits and vaccines	Protection of fish and animal health	TLL/AVA	Ongoing R&D	–
AFLP DNA fingerprint profiles	Software package for protection of biological materials and biodiversity management, plant breeding (e.g., novelty of a new tropical cultivars)	TLL	–	–
(continued on next page)				

Orchid biotechnology—genetic transformation (new transformation systems, developmental genes for flower development)	Improve floral traits in orchids	NUS	Ongoing R&D	—
<p>NIE: Natural Science Academic Group, National Institute of Education, Nanyang Technological (University (http://cf2001.sngs.sch.edu.sg/Cyberfair/orchid_grex/grex_glow.html)</p> <p>IMCB: Institute of Molecular and Cell Biology</p> <p>NUS: National University of Singapore (http://www.dbs.nus.edu.sg/research/focus/biotech.htm)</p> <p>TLL: Temasek Life Sciences Laboratory (www.tll.org.sg)</p>				

In the case of Nestlé, its food safety and quality policy is that it respects the responsible use of gene technology for food production based on sound scientific research and that food ingredients derived from GM crops will be used where appropriate. Such ingredients must also undergo safety evaluation by international scientific bodies like WHO, FAO, and OECD. Nestlé does not use GM-derived food ingredients in Singapore, and it maintains stringent quality control to prevent such contamination to its input grain supply (personal communication). It has established a traceability system to document its U.S. grain suppliers and farmers in accordance with the requirements of the EU market.

CREATION OF AN AGRI-BIOTECHNOLOGY SECTOR

The government has taken a leading role in supporting the development of an agri-biotechnology sector and supports an active approach in coordinating biotechnology strategies and funding programs and establishing supporting infrastructures to kick-start agri-biotech R&D and commercialization. The establishment of the Institute of Molecular Agrobiotechnology (IMA) in 1995 heralded the advent of agri-biotechnology. The institute was operated in collaboration with the Chinese Academy of Sciences and the Chinese Ministry of Agriculture with the objective of developing Singapore as a world-class center in agri-biotechnology research through the clustering of high-caliber scientists. With the investment arm of Imagen Holdings, IMA was poised to capitalize fully on possible avenues for collaboration, joint ventures, and new agri-biotech business opportunities.

In 2002, IMA's agri-biotectchnology activities were streamlined to team up with the National University of Singapore (NUS) and the Nanyang Technological University (NTU) with a new focus on life sciences. IMA was renamed the Temasek Life Sciences Laboratory (TLL) and tasked with undertaking cutting-edge research in molecular biology and genetics in the broad fields of life sciences. Currently, there are 15 research groups working in the areas of cell biology, developmental biology, pathogenesis, and bioinformatics (Table 1). It is using a comprehensive approach, in close cooperation with industry and AVA, in harnessing agri-biotechnology's strength and revitalizing its potential under the broader scope of life sciences in this region.²

² TLL will help to develop the knowledge infrastructure and R&D human capital in Singapore through joint appointment of research fellows and collaboration in teaching and research; collaborate with the AVA, other research institutes, hospitals, and foreign companies; and undertake a global drive to hire world-class scientists to build its R&D capabilities in basic and applied research. It will create intellectual property to proactively help translate research into application through successful partnership with local and international life sciences companies. It will create a new cluster of knowledge-intensive industries in the broad areas of biotechnology. The commercialization strategy includes licensing and establishing research collaboration agreements with local and international partners as well as forging alliances with established research organizations; identifying parties

Since 2003, AVA has been working closely with TLL, NUS, and other tertiary research institutes on agri-biotechnology to develop key applied upstream farming technology in specific areas of food crop research, plant biotechnology, animal and fish health research, fish biotechnology, and aquaculture in the following agri-food areas:

Vegetable: identification of genes for abiotic and biotic stress resistance in Asian leaf vegetables, downstream field testing, molecular diagnostics for leafy vegetable diseases, and GMO testing for food crops.

Rice biotechnology: disease resistance.

Aquaculture biotechnology: molecular selective breeding of fish, molecular diagnostics and vaccines for food fish and shrimps, genetic transformation of indigenous foodfish for improved traits.

Animal biotechnology: molecular diagnostics and vaccines against zoonotic diseases or those of food safety concern.

These projects will help Singapore build long-term capacity for platform technologies as well as human and intellectual capital that can benefit both agri-biotechnology and the life sciences as they cover diverse and broad areas of platform technologies development.

Other tertiary academic institutes like Temasek Polytechnic are also involved in agri-biotechnology R&D, working in close partnership with the industry and AVA in shaping the agri-biotech sector.

SUPPORTING INFRASTRUCTURE

Under a major government initiative of the NSTP, Technopreneurship21 (1999), a framework providing comprehensive support for cultivation of innovation and entrepreneurship was constructed to ensure that the value from the knowledge creation (from industrial sectors, including biotechnology) is extracted, protected, and exploited. These initiatives range from increasing the availability of equity financing to soft and hard infrastructural support enabling technopreneurial businesses to grow. The lead government agency in this initiative, NSTB (now A*STAR), has been working closely with state agencies such as EDB, Jurong Town Corporation (JTC), and the Housing Development Board (HDB) and with various industry sectors over the years to realize this vision.

Science Park and Incubators

The Science Park, established in 1981, together with incubators designed by government, provides the high-quality infrastructure essential for industrial R&D, as well as an environment conducive to interaction between industry, academia, and research groups. The Technopreneur Assistance Center established within the park provides a range of technical, business, training, and shared facilities. Other support for early-stage companies includes financing for innovators, venture capital, and a patent application fund, as well as state agencies providing productivity,

with a complementary fit to harness respective strengths in forming mutually beneficial partnerships, such as working with local small- and medium-sized enterprises (SMEs), to provide R&D consultation and technology transfer to assist these companies to move up the technology ladder, and with multi-national corporations (MNCs) such as Bayer CropScience (French-German) and Delta & Pine Land Company (U.S.) on R&D in cutting-edge scientific discovery; exploring various avenues to commercialized projects in animal health, fish, and plant biotechnology as well as drug discovery with a number of potential industrial partners. TLL is also investing in life sciences that have limited private sector participation due to their long gestation period and high risks, both directly in companies and indirectly through venture capital funds invested in overseas firms with the strategic intent of generating spin-offs for local life sciences and biotechnology industries through technology transfer and other forms of collaboration.

quality, and design services. All of these have offered life science companies a quick start-up in addition to the support of the advanced telecommunications infrastructure and powerful computing resources known as bioinformatics. Today, the Science Park houses some 180 local and MNC tenants within the 270,000 sq m gross floor space and an Innovation Center of 2,000 sq m with 29 start-up companies from the different industrial sectors, i.e., information technology, electronics, chemicals, materials, and biotechnology.

AVA and EDB have also developed the Agri-Bio Park (APB) located next to the Lim Chu Kang Agrotechnology Park in northwest Singapore. Land in lots of one hectare can be allocated on 30-year leases for agri-biotechnology activities. This will further strengthen Singapore as a center of excellence in tropical agro-technology. In addition, Agri-food and Technologies Pte. Ltd. (ATP), a private arm of AVA, was incorporated in October 2000 to further support regional developing agribusiness, including the agri-biotechnology business. Agri-biotech companies interested in investing in Singapore or in this region for product development, commercialization of laboratory findings, and production of agri-biotechnological materials can avail themselves of its consultancy, training, and certification services.

INVESTMENT FINANCIAL SUPPORT

In support of a large-scale financial commitment to the life sciences and biotechnology sector, the government has created a number of mechanisms—PharmBio Growth Fund, Singapore Bio-Innovations and Life Sciences Investments—to provide funds to the private sector to upgrade technologies and form joint ventures with leading international biotechnology and pharmaceutical companies. It has channeled more than SGD1.7 billion into biotech funds and has allocated SGD1.5 billion for biotech R&D and SGD2 billion to attract investment in local and foreign in biotech start-ups. This risk-sharing environment also includes numerous investment and start-up assistance schemes—SEEDS, Patent Application Fund PLUS, Enterprise Investment (Technopreneur) Scheme, Venture Capital—and programs—Growth Financing Program³—for innovation, R&D, and intellectual property managed by EDB.

Manpower Development Programs

Keeping up with local talent as well as attracting more global talent is key to maintaining a knowledge-based economy. Talent will include the whole spectrum of researchers, entrepreneurs, investment bankers, analysts, venture capitalists, and patent and corporate lawyers. The government is adopting an open-door policy to draw in talent from around the world.

Continuing efforts under the NSTP, driven by then-NSTB, now A*STAR, and other government agencies such as EDB include the launch in April 2000 of a five-year Life Sciences Manpower Development Program costing SGD60 million to increase the pool of talent to propel Singapore's push into the life sciences. The initiatives include offering postgraduate and Ph.D. scholarships, a fellowship program, and an exchange program to create a cluster of 245 life science experts to support the newly-developed sector.

Favorable Intellectual Property (IP) Regime

Protection of intellectual property (IP) is key to a thriving biotechnology business that fully taps into the value of the technology developed. The Patents Act of Singapore contains no restriction to the patentability of plants and animals or other biotechnological inventions such as DNA or living tissues as long as the bio-intervention does not contradict public morality. However, the IP regime does not contain many incentives to preserve and maintain traditional knowledge of local and indigenous communities or to provide developing countries with access to technologies in a just and equitable manner. This is being addressed under the recent ASEAN

³ http://www.sedb.com/edbcorp/sg/en_uk/index/investors/assistance_schemes/for_innovation.html.

initiative to establish the Framework Agreement on Access to and Fair and Equitable Sharing of Benefits Arising from the Utilization of Biological and Genetic Resources (“the Agreement”).

Even though it is in compliance with international treaties, the current Singapore IP regime was further strengthened when Singapore acceded in 2004 to the UPOV convention (for the protection of new plant varieties) under the requirements of U.S.-Singapore Free Trade Agreement. Granting the breeder of a new variety the exclusive right to exploit it will encourage investment in plant breeding and contribute to the development of agriculture, horticulture, and forestry. Plant breeders who formerly had limited monopoly rights are now accorded better protection to commercialize new plant varieties derived from biotechnology as well as from traditional breeding methods. This IP regime will give agri-biotechnological interventions exclusive protection in Singapore should they be developed and patented there.

Robust Regulatory Framework/Biosafety

As in many countries, biosafety regulation of agri-biotechnology on genetically modified organisms (GMOs) and released agri-biotech products derived from GMOs is a key concern that must be strengthened to ensure food and public safety and for the benefit of agri-trade. There is a need to safeguard public and environmental safety while allowing for the commercial use of GMOs and GMO-derived products by companies and research institutions in compliance with international standards (CODEX, FAO, Cartagena Protocol, etc.).

Singapore established the multi-agency national Genetic Modification Advisory Committee (GMAC) in 1999 to oversee and advise in this matter. The key initiatives of GMAC lie in establishing biosafety regulations and guidelines for the conduct of GMO research and the commercial release of GMO-derived products and in facilitating public education and creating awareness on GM issues. Members of GMAC are drawn from regulatory agencies such as AVA, National Parks Board (NParks), Ministry of Health (MOH), A*STAR, and the Attorney General Chambers (AGC); academic and research institutes such as the NUS, Nanyang Technological University (NTU) and (NIE), TLL, and the Institute of Molecular and Cell Biology (IMCB); and consumer interest groups such as the Consumers Association of Singapore (CASE).

Two guidelines, one covering release of GMOs (Singapore Guidelines on the Release of Agriculture-Related GMOs, August 1999) and the other covering research on GMOs (Singapore Biosafety Guidelines for Research on GMOs), have been released. The latter is in its final draft stages and currently available to the public at GMAC’s website as a working draft (<http://www.gmac.gov.sg>).

As an advisory committee, GMAC leverages on the regulatory powers of various national agencies, including AVA, MOH, and the National Environment Agency (NEA), to oversee safe movement, transfer, and containment of GMOs relevant, respectively, to food/feed, human health, and environment. The AVA is the approving authority for the import and release of agriculture-related GMOs and GM foods in Singapore. Under AVA’s Animals and Birds Act and Control of Plant Act, importers are required to seek approval from AVA before importing agriculture-related GMOs. GMAC will evaluate applications to import or release GMOs through expert panels to ensure that food safety and environmental issues have been assessed and found to be satisfactory. AVA will take into consideration GMAC’s evaluation before permitting the import or release of the GMOs.

Thus far, GMAC and AVA have allowed the sale of GM corn, soybean, and canola oil after reviewing the risk assessments of the specific products and the safety tests conducted by Monsanto or other companies involved and ensuring that the products meet the safety criteria set by the Singapore Guidelines on the Release of Agriculture-Related GMOs, guidelines established to ensure safe movement and use of agriculture-related GMOs and to address issues related to food safety based on the concept of substantial equivalence, especially in the area of risk assessment in relation to human health and the environment. In addition, GMAC and AVA take into account prior approvals by the authorities of the country from which the specific product

originates. To further strengthen biosafety regulations, a bill to deter misuse of biological agents and toxins and to instill confidence in life science research has been drafted (www.moh.gov.sg) and following public consultation will be passed in late 2005.

Enhanced Biosafety and Genetically Modified Food Testing Network

To ensure an effective and balanced approach in regulating agricultural products derived from biotechnology that will help to facilitate agri-trade within the ASEAN region, Singapore had taken the lead since 1997 in harmonizing the GM regulations within ASEAN, with the support of the Senior Officials Meeting–ASEAN Ministers for Agriculture and Food (SOM–AMAF).

Working hand in hand with the ASEAN member countries, Singapore organized the ASEAN Workshop on Regulations for Agricultural Products derived from Biotechnology in 1998 to establish baseline data on national regulations implemented by various ASEAN countries and the workshop to establish an ASEAN Task Force on the Harmonization of Regulations for Agricultural Products Derived from Biotechnology (ATFHRAPB) to draft harmonized guidelines. The ASEAN Guidelines on Risk Assessment of Agriculture-Related GMOs (hosted on the website of the ASEAN Secretariat—www.aseansec.org) were completed and adopted by AMAF in 1999. The Guidelines address the need for each country to establish its own National Authority on Genetic Manipulation (NAGM) and the roles and responsibilities of this authority in regulating agricultural GMOs. While the guidelines cover the procedures for notification, approval, and registration of agriculture-related GMOs, they do not address questions of liability, compensation, labeling, and socio-economic issues. They focus on a science-based approach to the evaluation of applications for release of agriculture-related GMOs. Since then, SOM-AMAF has supported extensive activities on public awareness of GMO issues in ASEAN.

Singapore has identified two key areas of current needs: capacity building in biosafety—risk assessment and management of agriculture-related GMOs—and testing capability of GM food, both locally and in the region due to its extensive reliance on imported agri-food and agri-products and the forecast for increasing agri-biotechnology activities in Asian countries such as China and India. Using the ASEAN guidelines as a scientific basis for evaluating GMOs, an extensive educational process was begun in 1999 following the formation of GMAC. Singapore, in close partnership with the International Life Sciences Institute (ILSI),⁴ has collaborated with international food safety authorities such as Health Canada, the Australia New Zealand Food Authority (ANZFA), and the U.S. Food and Drug Administration and between 2000 and 2004 organized a series of workshops on safety and risk assessment of agriculture-related GMOs for the 10 ASEAN countries in Malaysia, Indonesia, Singapore, and Thailand. This has created a cluster of at least 80 experts—policymakers, food regulators, and public and private researchers—for GM assessment and management within ASEAN.

The ASEAN Genetically Modified Food Testing Network was established in 2003 with the objective of helping ASEAN member countries to better utilize the expertise and available resources in the region and to gain better access to information on developing testing capabilities for GM food. This GM food testing network will see the adoption in the coming years of reference methods and materials that are internationally recognized for use in GM food testing in ASEAN and resource sharing and expertise exchange between ASEAN and external agencies

⁴ The International Life Sciences Institute (ILSI), headquartered in Washington D.C., is a nonprofit worldwide foundation established in 1978 to advance the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. ILSI collaborates with leading international health and development organizations in projects that encourage global cooperation. It has non-governmental organization (NGO) status with the World Health Organization (WHO) and a special consultative status with the Food and Agriculture Organization (FAO) of the United Nations. ILSI Southeast Asia is one of 15 overseas branches of ILSI. Established in 1993, it serves as a regional branch currently overseeing programs in the ASEAN region as well as Australia and New Zealand.

such as the European Commission Joint Research Center and the International Life Science Institute. A GM food testing laboratory has been established in the AVA as part of the SGD30 million Veterinary Public Health Center.

CURRENT ISSUES AND CHALLENGES

There is rising regional competition from neighboring agricultural countries that have low-cost land and labor, especially China and India, who are now also the leading Asian players in agri-biotechnology. China, for example, has intensified its investment in biotechnology research and can leverage on Hong Kong's financing capabilities. Singapore has the capacity and infrastructure to undertake advanced R&D in agri-biotechnology. The challenge is to move into cutting-edge and novel agri-biotechnologies that will impact not only Singapore but also tropical agri-biotechnology, especially in the area of food safety, where it has a good reputation. There is also the constant challenge to develop its own talent as well as attract and retain talent in Singapore to sustain the newly developing agri-biotech sector.

The domestic market for agri-biotech products is small. Local agri-biotech developers will have to adopt sound marketing tactics for overseas markets to ensure full exploitation of the agri-biotech product's potential. To facilitate the commercialization and marketing of agri-biotech products in the global market, the government will need to harmonize its regulations beyond ASEAN. At this juncture, there is still a lack of global agreement, mainly between EU and U.S. markets, on the labeling of biotech ingredients in food besides the stringent requirement for product traceability imposed by the EU. The threshold limits of the different markets in the U.S., Japan, and the EU have yet to be harmonized, while Singapore is still waiting to take its cue on labeling requirements from recommendations of the CODEX Alimentarius International Committee. The outcome of the labeling issue will have implications for the cost of agri-biotech business and trade in the region. While domestic consumers generally will want their food to be labeled, the challenge is to also ensure consumer confidence in the food through education, transparency, and easy access to GM information.

Commercial release of China's biotech (Bt) rice is awaiting regulatory approval, likely in 2005, and its adoption will provide a significant stimulus to global acceptance of biotech food, feed, and fibre crops. Since rice is a staple in the Asian diet, there is an urgent need to further improve Singapore's biosafety system and testing capability to better regulate the rice supply and the GM rice trade within the region.

CONCLUSION

Singapore has the potential to become an attractive and vibrant center for global business and technological activities involving agri-biotechnology in Asia, which consists primarily of agricultural countries. Agri-biotech products' potential can be realized with enhanced market demand and marketing strategies and mechanisms. The market's receptivity to agri-biotech products will depend largely on its maturity, and this will require extensive consumer education to address biosafety concerns. Locally, the government, through GMAC, has been actively involved in public awareness programs such as a Public Forum on Bioengineered Foods (www.gmac.gov.sg/news/2005_01_25.html) and the distribution of educational brochures about GM foods (www.gmac.gov.sg/news/2004_11_22.html). Market demand is also boosted by confidence in Singapore's strong leadership role in harmonizing biosafety regulations within ASEAN (i.e., under ASEAN GM initiatives) in the context of food safety assurance.

Beside Singapore's strategic geographical location, it has an extensive business network supported by efficient logistics to facilitate food and agri-trade distribution. Singapore has good accessibility to global markets and can be positioned as a regional headquarters, exporting biotechnological services to the entire Asian market. When free trade agreements with countries such as the U.S., Japan, Australia, and New Zealand and the European Free Trade Association

have been negotiated, companies based in Singapore will gain access to even more of the world's markets.

In addition, Singapore is well known for its strong capital, technology, and manpower infrastructures, which will help to move ideas to the marketplace quickly. Its committed multi-disciplinary governmental involvement in developing, facilitating, and growing business may further encourage agri-biotech investors to consider high-risk agri-biotechnology investment. With its limited agriculture land resources, Singapore might consider providing agri-biotech consultancy, financial, and trading services rather than a production base by leveraging on its strong network with the Asian biotech mega-countries such as China and India. Collaboration could be in the area of agri-biotech rice, which if approved by China has great potential. However, limited agricultural space does not preclude R&D in agri-biotechnology. Singapore's advantage in this context lies in its disease-free, credible environment for agri-biotech research. Moreover, its strong relations with nearby Asian biotech mega-countries should be tapped for research resources like commercial field trials, for which space and funding in Singapore are limited.

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13. BUSINESS POTENTIAL FOR AGRICULTURAL BIOTECHNOLOGY PRODUCTS IN THAILAND

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INTRODUCTION

Thailand's National Biotechnology Policy Framework

The National Biotechnology Policy Committee, chaired by the Prime Minister, approved Thailand's National Biotechnology Policy Framework (2004–2011) in December 2003. Biotechnology is expected to play a vital role in the country's development by 2011, in keeping with the government's policy and the national agenda encompassing sustainable competitiveness, health care for all, income distribution, and a self-sufficient economy. Emphasis will be placed on applying core technology to accelerate development in areas such as agriculture and food, medical care, protection of the environment, new knowledge creation for the development of higher-value-added products as well as helping to promote high-value biotechnology businesses and creating new types of services where modern technology is required. The six goals for biotechnology development are: emergence and development of new biobusiness (Figure 1), biotechnology promoting Thailand as the kitchen of the world (Figure 2), Thailand as the health community and health care center of Asia, utilization of biotechnology to preserve the environment and to produce clean energy (Figure 3), biotechnology as the key factor for a self-sufficient economy (Figure 4), and development of a qualified human resource system. Goals related to agricultural business are primarily the first and second.

Emergence and Development of New Biobusiness

The potential of biotechnology will be utilized to encourage investment in research and development and the establishment of new biotechnology companies with two main objectives: emergence of over 100 new biotechnology companies and investment by the private sector in biotechnology R&D amounting to at least THB5 billion per year. The new biobusinesses can focus on many new opportunities, for example, the production of high-value-added products, such as medical diagnostic kits, supplementary food, and seed, or service businesses, especially molecular-level detection/analysis for medical care and public health, agriculture and food export, biosafety, and bioterrorism/bioweaponry. Venture capital will help to expand investment in biotechnology businesses. Knowledge-based business, including investment in bioinformatics research for new drug development and gene research for the improvement of crop plants and livestock, will be the future-oriented focus. Key strategies are:

To construct/develop infrastructure such as biotechnology parks to attract both domestic and overseas investments as well as provide user services in research and development.

To set forth clear policy to settle controversial issues, for example, enacting laws on the protection of bioresources and establishing policy on the development of safe GMO products.

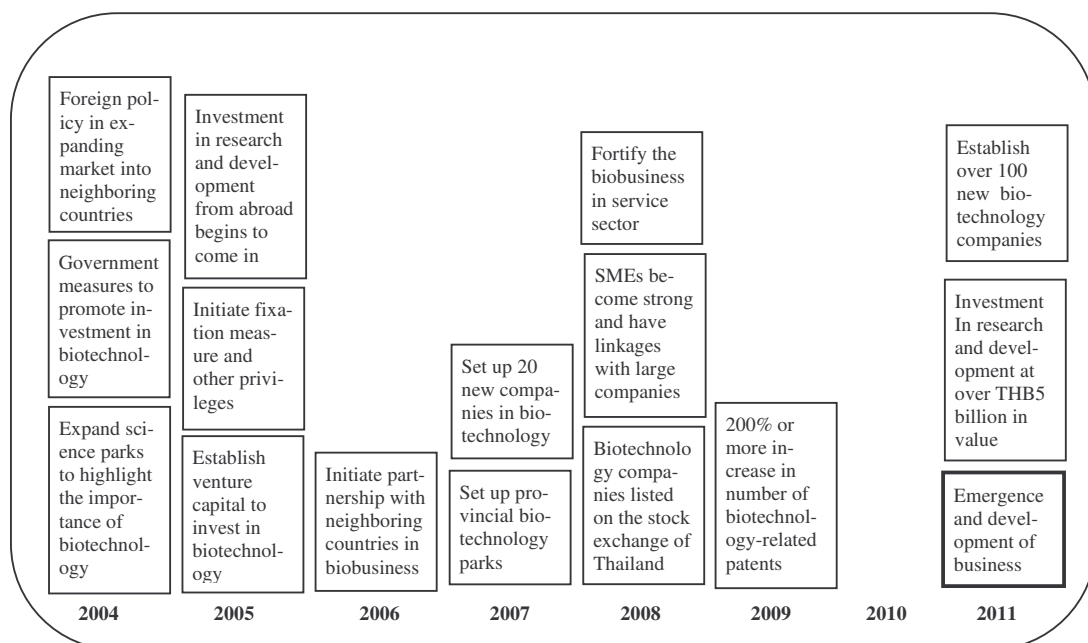


Figure 1. Milestones for New Biobusiness

To create an environment and incentives like tax privileges for venture capital to invest in biotechnology, which requires longer periods than other industrial technologies for returns on investment.

To promote investment in research, development, and innovation.

To support the listing of biotechnology companies on the Stock Exchange of Thailand.

Biotechnology Promoting Thailand as the Kitchen of the World

This will be achieved by maintaining and enhancing Thailand's competitiveness in the agriculture and food industries, which will increase export value up to THB1.2 trillion and improve the export value of processed agricultural products from 12th in the world into the top 5 by 2011. Key strategies are:

To promote agricultural research to include more biotechnology components.

To formulate clusters of high-value-added manufacturing in the supply chain, such as the shrimp industry, the seed industry, and important goods. Biotechnology is to be applied as a core component in increasing productivity, breeding plants and livestock to suit the cultivating environment, reducing chemicals, developing and using the potential of biotechnology for quick, precise, and specific detection and diagnosis in managing food and seed safety by setting up a biotechnology laboratory to certify the quality and standard of products exported as well as inspection of imported products.

To expedite development of new lines of marine products to provide alternatives to existing products (shrimp).

To develop technology and service businesses in post-harvest and packaging technology to prolong the shelf life of agricultural products.

To conduct research to collect the scientific data needed for risk assessment of food and agricultural products for export, which will eventually enable Thailand to set standards for products of which Thailand is the leading exporter.

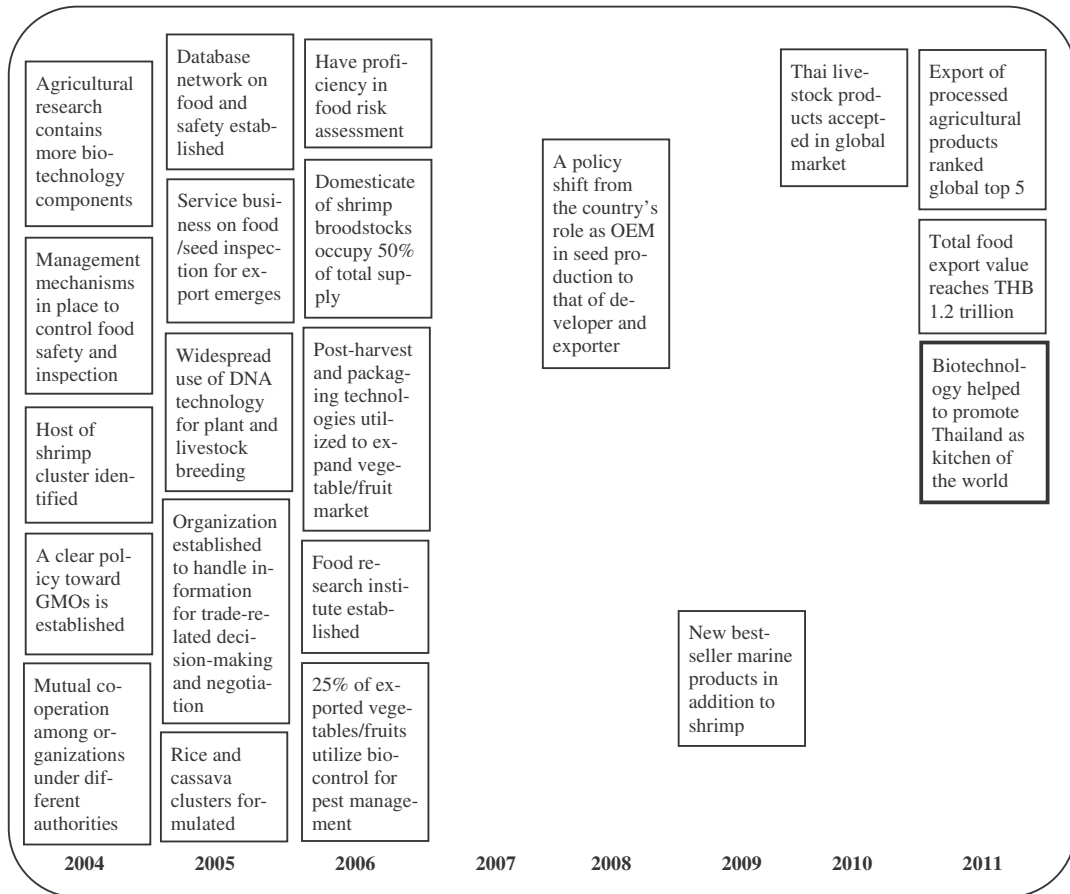


Figure 2. Milestones for Promoting Thailand as the Kitchen of the World

To prepare and utilize (scientific) data in decision-making, establishing key measures, and negotiating or solving trade barrier problems.

Regulatory Framework and Existing Laws Related to Agricultural Biotechnology, Business, and Products (including GMOs)

Agricultural biotechnology is relatively new in Thailand; the existing laws, mainly under the Ministry of Agriculture and Cooperatives, that are summarized in Table 1 have been implemented provisionally until new specific laws are issued. In addition, there are two guidelines: Genetic Engineering and Biotechnology for Laboratory Work and Genetic Engineering and Biotechnology for Field Work and Planned Release, approved in 1992 and implemented under the National Biosafety Committee (NBC) established in 1993. These guidelines were reviewed and published as Biosafety Guidelines for Work Related to Modern Biotechnology or Genetic Engineering in November 2004. Regulations for food containing ingredients derived from GMOs were drafted in 2002 by the Food and Drug Administration (FDA). They became a Ministerial Notification in 2002 and have been in force since May 11, 2003. Only GM soybean and corn are imported for food and feed production. The threshold level is 5% of DNA or protein from each of the top three ingredients, and each ingredient should be more than 5% by weight of product. The product should be labeled as Genetically Modified, for example, Gene-

Business Potential for Agricultural Biotechnology Products

tically Modified Soybean. This year (2005), the Ministry of Natural Resources and Environment is drafting the Biosafety Law. When finished and approved, it will be the first law that is specific to this modern technology.

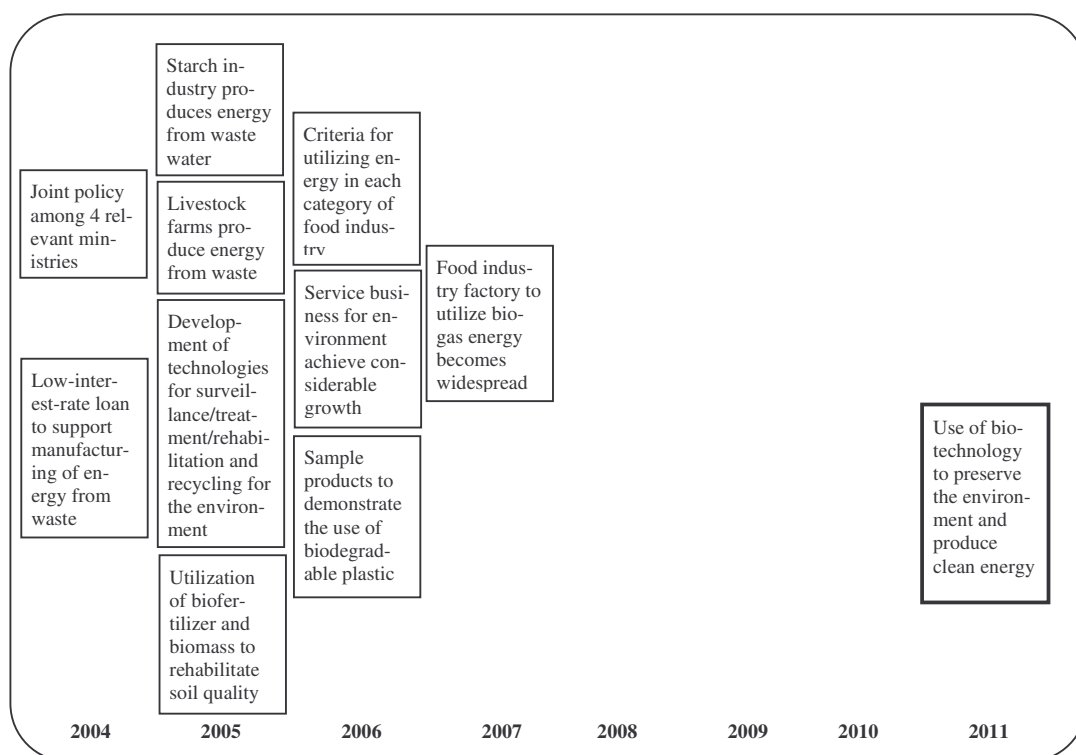


Figure 3. Milestones for Preserving the Environment and Producing Clean Energy

Table 1. Existing Laws Related to GMOs, Thailand

Issued by	
Department of Agriculture, Ministry of Agriculture and Cooperatives (MOAC)	Plant Variety Act B.E. 2518 (1975) Plant Quarantine Act B.E. 2507 (1964) amended 2542 (1999) Plant Variety Protection Act B.E. 2542 (1999) Fertilizer Act B.E. 2518 (1975)
Department of Livestock, MOAC	Animal Feeding Quality Act B.E. 2509 (1966) Animal Disease Control Act B.E. 2505 (1962) Animal Pathogen and toxin Act B.E. 2525 (1982)
Department of Fisheries, MOAC	Fishery Act B.E. 2490 (1847) Fishery Act (No.3) B.E. 2528 (1985)
(continued on next page)	

Food and Drug Administration, Ministry of Public Health	Food Act B.E. 2522 (1979) GMOs labeling: Ministerial Notification (2002)
Ministry of Natural Resources and Environment	Hazard Substance Act B.E. 2535 (1992) Enhancement and Conservation of National Environment Quality Act B.E. 2535 (1992)
Ministry of Justice	Copyright Law B.E. 2521 (1978) Patent Law B.E. 2522 (1979) Intellectual Property Right Act B.E. 2536 (1993)
Department of Agriculture , Ministry of Agriculture and Cooperatives (MOAC)	Plant Variety Act B.E. 2518 (1975) Plant Quarantine Act B.E. 2507 (1964) amended 2542 (1999) Plant variety Protection Act B.E. 2542 (1999) Fertilizer Act B.E. 2518 (1975)
Department of Livestock, MOAC	Animal Feeding Quality Act B.E. 2509 (1966) Animal Disease Control Act B.E. 2505 (1962) Animal Pathogen and toxin Act B.E. 2525 (1982)
Department of Fisheries, MOAC	Fishery Act B.E. 2490 (1847) Fishery Act (No.3) B.E. 2528 (1985)
Food and Drug Administration, Ministry of Public Health	Food Act B.E. 2522 (1979) GMOs labeling: Ministerial Notifica- tion (2002)
Ministry of Natural Resources and Environment	Hazard Substance Act B.E. 2535 (1992) Enhancement and Conservation of National Environment Quality Act B.E. 2535 (1992)
Ministry of Justice	Copy right Law B.E. 2521 (1978) Patent Law B.E. 2522 (1979) Intellectual Property Right Act B.E. 2536 (1993)

POLICIES ON CROP GENETICALLY MODIFIED ORGANISMS (GMOs)

In 1999, a subcommittee on policy concerning biotechnology products under the National Committee on International Economic Policy developed policy and strategies on biotechnology products.

Crop Production

GM crops may not be grown commercially unless they have been proven safe for the environment and human health. GM seed is permitted for research purposes only.

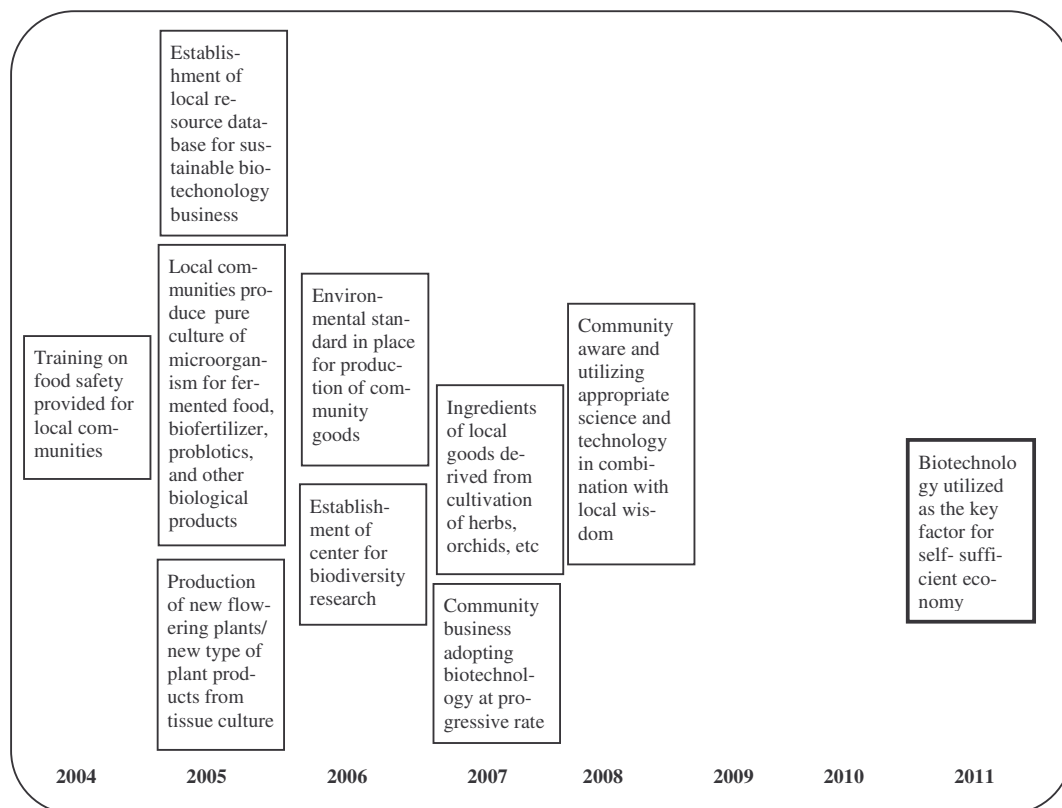


Figure 4. Milestones for Biotechnology in a Self-Sufficient Economy

Export

Importers and exporters determine by agreement whether they need to certify or label their products. If they need to certify or label the products, the relevant authorities must issue them a certificate.

Import

For GM seeds, import must be regulated by the Department of Agriculture (DOA), Ministry of Agriculture and Cooperatives (MOAC) under the Plant Quarantine Act; it is allowed for research purposes only. For GM grain, only soybean and corn used in the food and feed industries are allowed to be imported as long as there is no evidence of any environmental or human health danger.

Information Distribution

Information related to GMOs and biosafety is to be released to the public to assist in their understanding. The policy has been revised by the Working Group on Measures Concerning Production and Trade of Biotechnology Products assigned by the Subcommittee on Policy Concerning Biotechnology Products. The draft policy on genetically modified food and agricultural products (2002–2006) was completed in February 2001 and consists of six topics:

Policy on Production

Thailand has not yet produced genetically modified plants, animals, or microorganisms or used genetically modified organisms in production processes for trade unless scientifically sound evaluation has been conducted to guarantee the biosafety of activities.

Policy on Human Resources and Technical Development

Supports developing and strengthening the capacity of research and production using genetically modified technology for food and agricultural products to ensure self-reliance, effectiveness, and competitiveness and takes into account the issue of safety for consumers and the environment. Promotes development of knowledge and experience for those associated with monitoring genetically modified food and agricultural products in research, laboratory analysis, biosafety evaluation, and risk assessment.

Policy on Biosafety Evaluation

Biosafety evaluations and risk assessments of genetically modified food and agricultural products are to be carried out on a scientifically sound basis using basic transparent procedures.

Policy on Trade

Importation and domestic distribution of genetically modified food and agricultural products are subject to prior biosafety evaluation and risk assessment. Supporting preparation for the export of genetically modified food and agricultural products guarantees that their safety has been certified and is in accordance with rules, regulation, conditions, and demands of trading partner countries.

Policy on Public Relations

Promotes collecting, analyzing, and promoting the compilation and dissemination of news and information on scientific issues, trade, governmental regulations, and procedures and findings on genetically modified food and agricultural products in Thailand and other countries and distributing this information to involved parties and the general public to ensure correct understanding of issues. These activities are carried out in an objective and transparent manner.

Policy on Participation

Supports partnerships between the public and private sectors, both domestically and internationally, in the implementation of policies related to genetically modified food and agricultural products and provides support for the formulation of clear guidelines on genetically modified food and agricultural products.

The research and development policy of “giving the public choices” was introduced in 2005. Research and development in genetic engineering as well as biosafety are considered vital, as is capacity building in both areas. This will be accomplished through cooperation and networking between institutes. Alternative approaches to adding value to existing crops, such as cut flowers and oil-containing crops, are also encouraged. Lastly, public education about GMOs will be promoted. Universities are encouraged to participate.

**STATUS OF RESEARCH AND DEVELOPMENT OF
AGRICULTURAL BIOTECHNOLOGY**

Although biotechnology has been commonly used in the food and pharmaceutical industries, it has only recently been seen as a tool for agricultural improvement. Traditionally, research and development of agricultural biotechnology was done primarily by the public sector—universities and government organizations. Funding was primarily through government organizations, including the Ministry of Agriculture and Agriculture Cooperatives, the Ministry of

University Affairs, the Thailand Research Fund, the National Research Council, and the National Science and Technology Development Agency. Science and technology investment (R&D) was approximately 0.52% of GDP in 2004. National agricultural research systems (NARSs) can be divided into three types according to market size for agricultural biotechnology products, level of research, breeding programs, participation of the private sector, and any regulatory framework for biosafety and intellectual property rights (IPR) (Byerlee and Fischer, 2001). Using these criteria, the Thailand NARS is considered a type II with considerable capacity in applied plant breeding and biotechnology research as well as the capacity to acquire and apply molecular tools developed elsewhere. Thailand also has an existing regulatory framework for agricultural biotechnology and IPR law. Thailand's agricultural biotechnology research is focused on curing diseases and dealing with insect infestation and environmental stress using genetic modification, DNA markers, breeding, and biocontrol. Local crop varieties such as papaya, tomato, and pineapple have been genetically engineered with gene/DNA from local strains of pathogens or other genes with desired characteristics in order to produce crops with disease resistance or herbicide resistance. Other research programs include determination of molecular markers in rice, tomato, cucumbers, and orchids, development of insect-, drought-, and disease-resistant rice within one variety via pyramiding of the necessary genes, and production of monoclonal and polyclonal antibodies against plant viruses. Recently, some of this technology has been in demand in the private sector, particularly molecular markers and disease diagnosis. In animal-related biotechnology, there are programs for the development of disease diagnostic products and animal production techniques. Although technologies such as embryo transfer, *in vitro* fertilization, and embryo sexing are known to some scientists, there are still technological and economical limitations to their use. Recently, Thailand has become a new market for bull semen with high import value. This procedure is seen as an inexpensive way to improve the genetics of domestic cattle.

AGRICULTURAL BIOTECHNOLOGY BUSINESS IN THAILAND

The agrobiotechnology business in Thailand is still in an initial phase. It is divided into three main areas: disease diagnosis, biocontrol. And tissue culture.

Disease Diagnosis

Thailand has a special interest in supporting local discovery and innovation in both agricultural and health-related areas. Diagnostic kits have been developed for several important plant and animal diseases. From late 2003 on, bird flu was reported in a number of Asian countries, including Korea, Japan, Taiwan, Vietnam, and Thailand. The disease initially infected only chickens, ducks, and wild birds. Later, there were reports of human deaths in many countries, including Thailand. With this urgency, the avian influenza virus test kit was developed in 2004 with the cooperation of the National Science and Technology Agency and INNOVA Biotechnology. It has been widely used in both the public and the private sectors.

In the agroindustry, chilled and frozen shrimp was among the top ten export products of Thailand (Tables 2 and 3). The Shrimp Biotechnology Business Unit (SBBU) was established in 1999 under the National Center for Genetic Engineering and Biotechnology (BIOTEC) to assist the shrimp industry. SBBU conducts its own research and contracts research, training, and consulting as well as commercializing diagnostic kits (EZEE Gene) for important viral diseases in shrimp, including White Spot Syndrome Virus, Infectious Hypodermal and Hematopoietic Necrosis Virus, Monodon Baculovirus, Taura Syndrome Virus, and Yellow Head Virus/Gill Associated Virus. Most of the test kits are stripped kits, simple and portable. Others are PCR-based. The income is returned to the investor, BIOTEC, and royalties go to inventor, Mahidol University. Recently the technology was transferred to a private company, Farming IntelliGene Technology Corp. For plant diseases, monoclonal antibodies for detection of Tomato Yellow Leaf

Curl Virus (TYLCV) were developed, commercialized, and proven to be useful to several seed companies in viral detection. This has greatly reduced the cost of importing antibodies without compromising the quality and reliability of the tests.

Table 2. Top Ten Export Products in 2003 and 2004, Thailand (million THB)

Items	2003	2004
Computer accessories	665,950	724,168
Electronic appliances	267,350	339,897
Automobile accessories	172,073	240,534
Plastic and products	140,988	186,435
Electronics circuits and accessories	186,001	199,358
Garments	114,091	124,201
Rice	73,621	102,264
Gems and jewelry	104,241	106,300
Seafood	71,408	76,858
Rubber and products	70,188	84,432
Other	1,793,078	2,100,047
Total	3,326,014	3,922,410

Source: Thai Customs Department

Table 3. Export Products in 2003 And 2004 by Category, Thailand (million THB)

Category	2003	2004
Agricultural products	285,466 (8.58)	333,301 (8.50)
Seafood and related products	73,028 (2.19)	71,345 (1.82)
Forestry related products	7,897 (0.24)	10,521 (0.27)
Mining	50,687 (1.52)	62,993 (1.61)
Industries	2,757,911 (82.9)	3,369,416 (85.9)
Others	151,025 (4.54)	74,834 (1.91)
Total	3,326,014 (100)	3,922,410 (100)

Source: Thai Customs Department

Biocontrol

The use of commercial microbial insecticides such as *Bacillus thuringiensis* (Bt) is common in many countries. In Thailand, similar practices started in 1996 when the Department of Agriculture approved the use of *Trichoderma harzianum* as the first registered biofungicide under the trade name of UNIGREEN UN-1 (Uniseed Co. Ltd.). There are currently two companies producing *Trichoderma* and *Ketomium* (for *Phytophthora* control) commercially.

Plant Tissue Culture

Cut flowers, particularly orchids, have become an important source of revenue for Thailand. Thailand is the world leader in exporting *Dendrobium*, a tropical orchid. In order to obtain flower uniformity while tracking global trends, a number of production technologies have been introduced into the cut flower industry: micropropagation, hybridization, induced mutation, and induced polyploidy. The pioneering work was done in public universities and a few public

research laboratories and later adopted by the private sector. The technology has since been refined and further developed. Micropropagation is most widely used in the Thai cut flower industry, used for the commercialization of many cut flowers: orchids, gerberas, carnations, chrysanthemums, anthuriums, cucumas, red ginger, torch ginger, lilies, and calla lilies. Several varieties are results of somaclonal variation during micropropagation.

CONCLUSION

It is clear that development of agricultural biotechnology products is still in the initial phase and that strategic improvement is needed. The major issues, such as the weak link between the private and public sectors, lack of a proactive plan for upgrading local technical capability, and high levels of technology transfer, urgently require solutions. The ratio of R&D to GDP is still low compared with other countries, such as Singapore, Japan, and the U.S. The percentage of private R&D is also low, indicating a low level of R&D for commercial purposes. The Thai government has developed five main strategies in its S&T action plan: enhancing the competitiveness of the private sector, reforming the educational system to create human resources, employing performance-based management, adjusting R&D funding systems, and expanding ICT facilities. The Plant Variety Protection (PVP) Act was implemented in 1999 to protect new as well as indigenous and traditional plant varieties.

There are several good signs for the future, including the establishment of new companies using local technologies and agricultural biotechnology projects initiated by the private sector. Multinational companies are expanding their presence and continuity. Nevertheless, it is clear that Thailand's enormous potential is not being fully realized. Several issues urgently need solutions and/or good management, such as communication with the public for better understanding of agricultural biotechnology, particularly on GMO issues, and communication with nongovernmental organizations (NGOs).

For research organizations, with their important role in agriculture biotechnology development, there are issues of research priorities, acquiring technology as well as producing their own technology, providing technical support where and when needed, and working closely with the private sector. They also need to expand their sources of funding to include regional and international organizations. In the private sector, more effort in both information-sharing and financial support is required to drive business development.

As for government, there are several issues at both policy and technical levels awaiting solutions, including providing a quality workforce for the business establishment, providing career paths for those who graduate in agriculture/biotechnology, recognizing the needs of private companies to protect their intellectual property, and assessing priorities. Successful public-private partnership will rely on defining goals, identifying mutual assets, segmenting the markets for each partner, and recognizing and accepting the differences in values and goals.

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Part IV

Appendices

1. LIST OF PARTICIPANTS, RESOURCE SPEAKERS, AND SECRETARIAT

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2. PROGRAM OF ACTIVITIES

Date / Time	Activity
<i>Mon., 23 May</i>	
Forenoon	Opening Session Presentation and Discussion on Topic I: <i>Why Agricultural Biotechnology? Opportunities and Challenges</i> by Dr. William P. Pilacinski
Afternoon	Presentation and Discussion on Topic II: <i>Global Status and Trends of Commercialized Biotechnology in Crops</i> by Dr. Paul S. Teng Presentation and Discussion on Topic III: <i>Commercial Application of Plant Biotechnology</i> by Dr. Hsin-Sheng Tsay Presentation and Discussion on Topic IV: <i>Commercial-scale Production of Valuable Plant Biomass and Secondary Metabolites Using a Bioreactor System</i> by Dr. Sung Ho Son Panel Discussion: <i>International Regulations and Intellectual Property Rights Issues on Agricultural Biotechnology Products</i>
<i>Tues., 24 May</i>	
Forenoon	Presentation and Discussion on Topic V: <i>Development and Application of Biofertilizers in Taiwan</i> by Dr. Chiu-Chung Young
Afternoon	Presentation of Country Papers by Participants Continuation of Presentation of Country Papers by Participants Presentation and Discussion on Topic VI: <i>Frontiers and Advances in Transgenic Biotechnology of Animals and Fishes</i> by Dr. Jen-Leih Wu Panel Discussion: <i>Global Status and Trends of Commercialized Biotechnology in Livestock, Poultry, Aquaculture, and Fisheries</i>
<i>Wed., 25 May</i>	
Forenoon	Presentation of Country Papers by Participants Presentation and Discussion on Topic VII: <i>Current Status of the Transgenic Approach for Control of Papaya Ringspot Virus</i> by Dr. Shyi-Dong Yeh Presentation and Discussion on Topic VIII: <i>Commercialization of Agricultural Crop Biotechnology Products</i> by Dr. Paul S. Teng
Afternoon	Visit Tai Mushroom Farm at Wufeng County

Thurs., 26 May

Forenoon	Visit Taida Horticultural Company (Orchid Farm)
Afternoon	Visit Asian Vegetable Research Center; Southern Taiwan Science Park

Fri., 27 May

Forenoon	Visit National Museum of Marine Biology and Aquarium
Afternoon	Visit Taiwan Banana Research Institute

Sat., 28 May

Forenoon	Summing-up Discussion
	Closing Session