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Overview and Literature Review

Opportunities to Commercialize Life Science Technology in Southeast Asia

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Resources Development Foundation
1920 N Street, N.W., Suite 400
Washington, D.C. 20036

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I. Introduction

The application of life science technologies has had a profound impact on the world's health care, agricultural, food and beverage and specialty chemical industries. In addition, there is little doubt in the minds of industry analysts that emerging biotechnologies could have an even greater impact on these commercial sectors in the future. Up to now, however, the commercial application of these technologies has largely been a phenomenon of the industrialized countries of Western Europe, North America and East Asia. Can similar opportunities be realized through the commercialization of appropriate life science technologies in developing countries?

This paper will attempt to answer the question based on an assessment of available literature sources in combination with the experience of the authors. The primary purpose of this paper is to identify the important issues and needs that must be addressed to enhance local private sector participation in the commercialization of life science technologies in developing countries. This initial task establishes the questions that will be addressed in subsequent tasks.

The life science technologies of primary interest for the purposes of this review are those that are immediately or are soon-to-be applicable and that can be adapted and commercialized by the private sector in developing countries. Of the various R&D activities under way in developing countries, only those that have the potential to provide immediate or near-term commercial benefits in developing countries were considered. The following industry sectors and life science technologies were considered during the preparation of this paper:

- Agricultural crop improvement - including conventional plant breeding, molecular- and cell-based genetic manipulations, and molecular diagnostics; also included were microbial inoculants for improving nutrient availability and uptake;

- Integrated pest management - including the use of insect, fungal and nematode predators as well as microbial control agents and purified toxins derived from these organisms;

- Bioconversion of plant material - for energy, fertilizer, animal feed, and food and specialty chemical production;

- Microbial fermentation and immobilized enzyme technology - for the production of specialty chemicals;

- Human and animal health care - including mammalian cell culture and recombinant DNA technology for the production of vaccines and animal growth hormones and hybridoma technology (to produce monoclonal antibodies) and recombinant DNA technology (to produce nucleic acid probes) for molecular diagnostics;

- Algae culture - including both macroalgae or seaweeds and microalgae, for animal feed, food products, or specialty chemical production; and

- Aquaculture - of marine or freshwater fin fish, crustaceans, or mollusks.

Included in the agricultural crop improvement category is the use of conventional plant breeding (the creation of plant improvements based on successive sexual crosses) as well as emerging technologies for manipulating genetic material at the cellular and molecular levels. Included were the cereals, legumes, root, forage crops, fruits, vegetables, oilseeds, fiber crops, crops for the production of other commodity and specialty derivatives, horticultural, ornamental, and forestry varieties.

Molecular diagnostics based on monoclonal antibodies and nucleic acid probes are now under development in developed countries for the detection of plant pathogens, pesticide residues, crop components, nutrient markers and genetic markers. Such products will play a significant role in agricultural pesticides in developing countries if they are made available at low cost.

The so-called "post-harvest" technologies can also be considered in the agricultural crop improvement category. Included are appropriate storage and processing technology allowing local growers, processors and distributors to take full advantage of the genetic improvements that have been achieved and to receive added value for agricultural products. Research and development involving the bioconversion of plant materials into value-added products can also be considered as post-harvest technology.

Also under consideration in this category were the various interrelated technologies and practices comprising integrated pest management. Integrated pest management utilizes bacterial, insect, nematode and fungal control agents in combination with conventional chemical pesticide products as an alternative to the sole application of chemical agents.

The bioconversion of whole plants, as well as agricultural and food processing wastes is increasingly promising as a source of food, animal feed, fertilizer and specialty chemicals. Bioconversion technologies range from relatively unsophisticated

techniques such as composting to sophisticated biopress technology for reducing the cellulose, hemicellulose and lignin fractions of plant biomass to useful commercial products.

The life science-based health care product sectors offering the most immediate commercial opportunities in developing countries are antibiotics, diagnostic products and vaccines.

Hybridoma technology is available for the production of monoclonal antibodies for incorporation into both standard immunodiagnostic tests as well as in newer tests to detect infectious disease organisms and cancers. Nucleic acid hybridization tests are also available for the detection of infectious and genetic disorders. The underlying technology for monoclonal antibody- and nucleic acid hybridization probe-based tests was developed primarily in the United States and Western Europe but is readily transferable to developing country laboratories. These are relatively new technologies but are already having a profound impact on the medical diagnostic field and represent a rapidly growing market around the world.

Vaccine production requires more sophisticated facilities and their effective distribution requires diagnostic capabilities and an adequate medical infrastructure. However, there are many parasitic and other diseases in developing countries that can be prevented by immunization.

Microbial fermentation for the production of antibiotics, amino acids, oxychemicals, and other specialty chemical products has already been introduced in developing countries on a limited scale. The range of potential products that can be produced and for which there are ready markets, is quite large.

The culture of seaweeds, fin fish, and crustaceans are considered since they represent established business opportunities in a number of developing countries. Furthermore, a number of promising life science technologies are beginning to be introduced that are profoundly improving the overall success of commercial ventures in these areas.

Microbial fermentation, bioconversion of plant material, conventional plant breeding, production of molecular diagnostics for use in human health, mammalian germplasm manipulation, macroalgae culture, and aquaculture are under way on a commercial scale in some developing countries. Most of these technologies were initially developed in industrialized nations and are currently being adapted and transferred to developing countries.

Of the life science technologies under consideration, a number fall into the category of biotechnology, defined here as new and emerging molecular- and cell-based technologies, including genetic engineering. Most biotechnologies will have a medium- (5-10 years) to long-term (<10 years) commercial impact. They include immobilized enzyme technology, mammalian cell culture, microalgae culture and genetic engineering of plants through recombinant DNA technology.

Recombinant DNA technology is already having an impact on health care in industrialized countries through the production of insulin and other therapeutic proteins. Recombinant DNA technology is also used to produce nucleic acid probes, which are beginning to find use in developing country applications as well.

Appendix A provides definitions of the specific life science technologies included in this paper.

The authors focused on the commercial application of life science technologies through indigenous operating companies located in developing countries, as opposed to private sector interests in developed countries per se. Development programs and policies were considered that enhance local private sector participation in life science research and development.

Section IV provides a compilation of the literature sources that formed the basis for this paper review. The literature sources considered in this assessment were categorized as technical reviews, discussions of programs and policies of the international development community, national development programs and policies, industry/economic evaluations and private sector activities, and miscellaneous issues (see Section IV, Selected References).

No attempt was made to provide a comprehensive review of the great body of technical publications covering the various technologies of interest. Technical reviews were included only if they involve applied research that is related specifically to a developing country setting.

II. Summary of Findings Regarding Life Science Commercialization

Research and development involving life science technology is advancing along a broad front in developing countries. However, of the sectors examined in this study, commercialization efforts appear to be making the most headway in agricultural plant improvement, bioconversion of plant material, and aquaculture. Plant improvement and bioconversion technologies have particularly high visibility in developing countries and receive the most attention from national and international research centers and multilateral development organizations. Because most developing countries have economies with dominant agricultural sectors, such technologies have long been recognized as important for countries to achieve greater self-sufficiency and to foster further industrial development.

Table 1 shows the important commercial sectors providing immediate and near-term applications of the technologies in developing countries.

Table 2 shows initial estimates of the commercial development timetable for the technologies under review.

Enhancing the role of the private sector in developing and commercializing life science technologies presents significant challenges to developing countries, where the private sector supports much less R&D than U.S., European, and Japanese firms. Companies in industrialized countries are currently predominant in the development of emerging technology with the greatest long-term potential for future commercial application in developing countries. Indigenous operating companies in developing countries are often blocked from acquiring the technology themselves because they lack the know-how to develop their own expertise in these areas and have little to offer a technology proprietor by way of a joint venture. They are also hindered by lack of capital, often inadequate infrastructural support and lack of market access. In order to be successful, indigenous companies must also contend with local socio-political and economic factors that can present significant barriers.

These realities have created tremendous challenges for the international development community and national agencies that have the task of stimulating and enhancing local business development. While the effectiveness of these institutions is being challenged, their assistance in facilitating the commercialization of appropriate life science technology in developing countries has never been more critical.

Table 1

Immediate and Near-Term Applications of Biotechnology in Important Commercial Sectors in Developing Countries

	Commercial Sector			
	Agriculture for Food	Human Health	Animal Health & Nutrition	Energy
Technology				
Aquaculture	X			
Immobilized Enzymes (Biocatalysis)	X			X
Biomass Conversion	X		X	X
Hybridoma Technology		X	X	
Macroalgae Culture	X		X	
Mammalian Cell Culture		X	X	
Mammalian Germ Plasm Manipulations			X	
Microalgae Culture	X		X	
Microbial Fermentation	X	X	X	X
Plant Cell Culture	X	X	X	
Recombinant DNA (regulatory proteins, enzymes, vaccines, probes)		X	X	

Table 2

Estimated Timetable for Biotechnology
Commercial Development in Developing Countries

	Near-Term (0-5 Years)	Medium Term (5-10 Years)	Long Term (>10 Years)
Technology			
Aquaculture	X		
Immobilized Enzymes (Biocatalysis)			X
Biomass Conversion	X		
Hybridoma Technology	X		
Macroalgae Culture	X		
Mammalian Cell Culture	X		
Mammalian Germ Plasm Manipulations	X		
Microalgae Culture		X	
Microbial Fermentation	X		
Plant Cell Culture	X		
Recombinant DNA (regulatory proteins, enzymes, vaccines, probes)		X	
Recombinant DNA (microbial systems)		X	
Recombinant DNA (plants)			X

Except for crop improvement, little of the life science technology that is being commercialized by indigenous companies in developing countries has been transferred from research and development that was primarily supported by the academic community, public sector foundations, or the international development community. The most promising life science technologies now being exploited by these companies has been transferred through collaborations with private sector interests in more industrialized countries or, less often, developed internally.

Successful indigenous companies with business activities based in the life sciences have often been those that have successfully acquired technology overseas to allow them to exploit regional and international export markets. For instance, even in a world of declining commodity prices and increased protectionism by industrialized countries, some well-managed companies are now successfully employing plant cell and tissue culture, biomass conversion technology and improved shrimp culture technology to develop and produce new products, or add value to old products.

Agricultural Crop Improvement

The so-called Green Revolution has demonstrated that life science technology, effectively applied, results in enormous economic and social benefits in developing countries. The CGIAR system has been the instrumental mechanism for the development, adaptation and transfer of agricultural plant improvement technologies responsible for the Green Revolution. Its principal impact has been on major staple crops including beans, cassava, maize, potatoes, rice, and wheat. The CGIAR system has provided a major conduit for funds from private foundations, national government bodies and the international development community used in building local developing country capabilities. Through the continued expansion of this system and the ongoing efforts of various IARCs to adapt and transfer new and emerging technology, the Green Revolution is likely to continue in many parts of the world. More recently, the emphasis in agricultural crop improvement has begun moving away from the intensive farming practices upon which the green revolution was built. Efforts are now concentrating on technology to reduce the need for chemical fertilizers, herbicides and pesticides while preserving crop yields and soil conditions.

Based on the foundation that has been laid by the international donor community and the CGIAR system, local agricultural plant improvement capabilities are being strengthened. However, little of this valuable technology has been effectively transferred to the private sector. Much of the CGIAR technology is being transferred to growers in developing countries through

government extension programs. However, there is little incentive for growers to apply the technology beyond providing for their own immediate needs. The international agricultural research system has done little to foster business enterprise formation or to improve the financial and other incentives necessary to foster sustained development. Farmers have done little to incorporate agricultural technology improvements even where the private sector is offering new products. Hybrid seed companies have been formed in the Philippines, Thailand, and other developing countries, but the hybrid seed market remains small and underdeveloped. Developing country-based companies providing plant propagation services based on tissue culture have experienced very slow demand growth.

A number of indigenous companies are developing and marketing cut flowers and other ornamentals, fruits, vegetables, and other value-added varieties for regional and international markets. These areas are minimally served by the international and national research centers which have concentrated development activities on staple food crops. The IARCs have been steadfast in maintaining a narrow focus to their investigations although they would clearly be of great utility if they were to broaden their mandate to include high value cash crops, renewable energy crops and post-harvest technology. However, appropriate technology in these areas is available and is being developed and transferred through the private sector although the level of private sector effort remains quite low. Developing country biotech firms are usually undercapitalized and have received little R&D support from the development community.

The available literature contained very little relating to the commercialization of monoclonal antibody- or nucleic acid probe-based products for plant improvement applications. However, these areas have become very important in plant improvement research and have great commercial promise.

Integrated Pest Management

Efforts involving integrated pest management are highly fragmented and will require significant additional research and development input before many commercial products emerge. While there is little information on this topic available in the open literature, the authors believe that the development of biological pesticides will provide highly specific, cost effective ways to provide crop protection in developing countries. One product has already been developed and marketed in a developing country and more are likely within the next few years. Integrated Pest Management is a relatively new concept and is just now beginning to be fully understood. However, there is room for tremendous improvement in the integration of efficient, environmentally safe

crop protection and cropping strategies along with improved, disease-resistant cultivars. The result will be lower production costs and higher yields for both small land holders and corporate growers.

Bioconversion of Plant Material

The available literature covers the production of useful by-products such as fertilizer and livestock feeds from biomass sources in some detail, but the discussions usually center on relatively small-scale operations. Technology is, however, under development by companies in both industrialized and developing countries for the large-scale production of organic fertilizers, livestock feeds and aquaculture feeds from readily available raw materials.

Technology is also under development around the world for the large-scale production of livestock and aquaculture feeds from agricultural and food processing waste, yeast, and micro-algae. A lack of affordable, nutritious livestock feeds has been a major barrier to the successful development of the dairy and beef industries in developing countries. Meat and dairy products are becoming increasingly important as protein sources to feed the domestic populace.

Aquaculture to produce fin fish and shrimp is a major source of food in developing countries, and in many cases represents a highly profitable export business. Up to 60% of the production cost for cultured marine shrimp is for the complex feeds employed. Most intensive aquaculture feeds in use are formulated from expensive ingredients many of which must be imported. However, technology is available that can increase the self-sufficiency of local growers and significantly improve profitability.

Microbial Fermentation

Microbial fermentation is one of the most fundamental life science technologies and the area with the most widespread commercial applications. Microbial fermentation is a relatively proven technology and in many cases is amenable to immediate commercial application in developing countries. Traditional microbial fermentation can be viewed as a mature technology. Interest in its application in developing countries is based more on factors such as the rising price of petroleum-based feedstocks and the desire of nations to become more self-sufficient in the production of important chemical and specialty products than it is the consequence of scientific breakthroughs.

While some efforts are currently under way by indigenous operating companies in countries such as India and Indonesia to develop microbial fermentation processes for specialty chemical production, most of these efforts are dominated by U.S., European, and Japanese companies, which establish local subsidiaries or joint venture operations.

Ethanol production in Brazil has demonstrated how the ample availability (sugarcane) of a raw material in a developing country, coupled with a large domestic market can form the basis for establishing pre-eminence in a growth industry, leading ultimately to penetration of foreign markets. Brazil has also been diversifying into other ethanol-derived and fermentation chemicals.

Most biomass energy installed capacity consists of relatively small-size plants, with substantive technology improvements having been made over the last few decades. Although most countries have far less experience with alcohol fermentation than Brazil, its application is still widespread and provides a basis for countries to branch out into other fermentative processes. Other technologies, such as anaerobic digestion, are still highly developmental. R&D is needed in such areas as plant design and scale optimization, capital and input cost reduction and technology adaptation to regional needs.

Human and Animal Health Care

Little if any technology involving mammalian cell culture and recombinant DNA technology for the production of vaccines and other products has been transferred to local operating companies in developing countries. However, genetic engineering, mammalian cell culture, and support programs in microbiology, molecular genetics and immunology have been undertaken by universities and national research programs in a number of developing countries including Brazil, India, Thailand, Indonesia and the Philippines. In the long term, some of this technology will probably be transferred to selected indigenous companies, primarily by multinational and biotechnology startup companies. However, the health care private sector is currently very weak in most developing countries. In many countries there is a critical need for basic analytical services and health care personnel and these needs must first be met before a viable vaccine and diagnostic market can be developed.

Basic health care technology, equipment and facilities are now being made available in developing countries around the world through the World Health Organization, USAID, JAICO and other public sector development organizations. Furthermore, many developing country governments have put into place effective

mechanisms for acquiring and distributing health care products. What is sorely lacking, even in the more advanced of the countries, is a well trained work force of professionals and support personnel to implement these national programs.

A major limitation to the development of human therapeutic products in developing countries based on biotechnology is the lack of an adequate R&D base to support product development and innovation or clinical analysis, in combination with small, underdeveloped markets. With the exception of human insulin, current and anticipated biotechnology products (e.g., interferons, lymphokines, growth hormone, tissue plasminogen activator) represent non-essential and often heroic therapy in developing countries. Current efforts toward achieving self-sufficiency in drug production is directed mainly at manufacturing and formulating the WHO's list of Essential Drugs. Even for antibiotics, which comprise a significant portion of the Essential Drugs, there is more than enough microbial fermentation capacity available in developed countries to meet demand around the world for some time. A number of countries in Asia and the Middle East have initiated antibiotic production facilities. But even with heavy government support, these facilities are unable to produce at a price that is competitive with the major multinational producers.

The development of molecular diagnostic products is sufficiently advanced in a number of countries such as Indonesia and Thailand, that commercialization by indigenous companies is under active consideration. Monoclonal antibody technology for the production of immunodiagnostic tests for which there is significant demand in developing countries is increasingly available for transfer. However, there are still few university or governmental laboratories and still fewer private companies that have acquired the fundamental know-how and possess the necessary support facilities and staff to yet sustain a product development program in this area. To further complicate the matter, established diagnostic product companies based in developed countries are able to market sophisticated, easy-to-use tests at costs that are a deterrent to local manufacture.

The situation for animal vaccines and diagnostics is largely the same. These businesses are now entirely in the hands of established multinational companies, many of which also market products for human use.

Significant health care product commercialization efforts are currently underway in a number of countries by PATH (Program For Applied Technologies In Health), based in the United States. Their efforts are resulting in limited but tangible progress in matching available diagnostic product technology with indigenous companies capable of undertaking commercial product development.

Algae Culture

Island nations in Southeast Asia and the Pacific often contain excellent coastal resources for the production of commercially valuable seaweeds that are used for the extraction of industrial gums and food additives. There is also a significant domestic and regional demand for seaweeds used in traditional food dishes. The growth and harvesting of seaweeds is traditionally a highly labor intensive activity carried out by local fishermen and growers. Technology involving the cultivation, efficient harvesting and processing of seaweeds is possessed almost entirely by multinational companies based in industrialized nations. Some of this technology is being transferred to local suppliers of FMC's Marine Colloid Division, a major U.S.-based phytocolloids producer in Indonesia.

A number of research institutions and companies in industrialized nations are conducting research and development on the large-scale cultivation of microalgae as a source of organic fertilizer, high protein food and animal feed substitutes, and as a source of specialty chemicals. There are technical hurdles to be overcome in optimizing the cultivation and harvesting of microalgae in order to be competitive with other sources of the same products. A Thai company is developing low-cost algae culture technology using cassava starch plant effluent as nutrient for culturing Spirulina for use as a feed component. A U.S. biotechnology company is currently working with a Malaysian plantation company to field test their microalgae-based fertilizer product. Beta-Carotene and other specialty pigments and fatty acids can also be extracted from microalgae products and can help carry the still relatively high costs of algae culture. If the technology can be further refined and effectively transferred, microalgae culture has tremendous long-term potential in developing countries with the correct climate and infrastructure requirements.

Aquaculture

The integrated, semi-intensive pond culture of marine shrimp is currently one of the most profitable life science-based commercial activities undertaken by indigenous companies in developing countries. Aquaculture companies in Southeast Asia and Latin America are already successful in supplying regional markets as well as U.S., European and especially Japanese customers. Most of the technology involved in building hatchery, feed mill, and processing capabilities was developed by private companies in Taiwan and the United States. The industry is well enough established, however, that good technology and know-how in all of these areas has been acquired and perfected by indigenous companies.

Already successful shrimp culture operations for the production of Penaeus monodon are located in Indonesia, the Philippines and Thailand. However, because of limited know how, post-larvae availability and the high costs for feeds, many operations are struggling to survive or have already failed. Know-how in managing shrimp culture operations is limited but available in these countries for forming efficient, fully integrated systems involving hatcheries, feed mills, grow-out ponds and processing facilities.

Technology improvement involving the control of the shrimp breeding cycle and production of aquaculture feed components from available raw materials is being undertaken by indigenous operating companies but local R&D capabilities need strengthening. Linkages between operating companies and country R&D centers would undoubtedly enhance the rate at which new technology is introduced.

III. Unmet Needs and Suggestions for Further Action

Without effective incentives and support from the public sector, including the international development community, indigenous companies in developing countries will continue to lag behind their counterparts in developed countries and economic growth will continue to stagnate.

Steps that can be taken by public sector agencies and the international development community to strengthen the role of indigenous companies are summarized below:

- Establishment of effective international research programs analogous to the IARCs and focusing on value-added export crops, diagnostic and therapeutic agents, vaccines and industrial biotechnology. Fundamental research related to agriculture and the processing of agricultural products should be undertaken by the existing CGIAR system. A worldwide medical research network comparable to the CGIAR system does not yet exist but there is a core group of capable institutions which could provide the base for a coordinated vaccine and diagnostics development effort.

- Continued support of international research organizations, but focused on more basic research, the solving of technical problems likely to have a significant regulatory impact (e.g., the effect of releasing genetically engineered microbes into the environment) and transfer of know-how to national research programs, universities and companies in developing countries; there should be an effort to lessen dependency on the international donor agencies as national research capabilities are strengthened. National research programs could adopt an applied R&D role and might leverage government funding with corporate funding if the channels existed for joint development efforts.

- Increased emphasis on R&D supported by the international development community that is coordinated with national research efforts and dictated by the business development needs of developing countries.

- Strengthening of national research programs in developing countries focused on specific, local development needs and tied more directly to the needs of indigenous private sector companies. An understanding of private sector needs can be best cultivated by incorporating private sector representatives into the R&D planning and review process. Brazil's alcohol research program which was financed through a $30 million World Bank loan was able to mobilize over $100 million in research funding through industry cost sharing.

- Increased research collaboration between national and international research centers in developing countries and academic institutions and corporations in developing countries through a deliberate effort to integrate private sector R&D capabilities with those of the research centers.

- Allow researchers to accept royalties on technology put to use. Allow indigenous companies to market technology under exclusive licensing agreements as scientists with the private sector should be organized.

A number of problems have arisen to diminish the effectiveness of efforts to build national research capabilities involving life science technologies. The following criteria should be considered in developing truly effective national research capabilities and minimize past problems:

- Development of scientific and technical staff should be a high priority, in addition to research facilities,

- Differentiation between basic and applied research programs with substantial private sector oversight and participation in applied programs,

- Elimination of excessively burdensome administrative burden for approval and initiation of research and development projects, which stifles creativity and leads to delays and discontinuity in research programs,

- Selection of appropriate sites for research facilities that take into account such factors as related educational and scientific infrastructure, proximity to the need or resource base to be addressed, and basic infrastructure (e.g., electricity, transportation, port facilities),

- Qualitative congruence between research budgets and the economic importance of research and development targets,

- Analysis and planning beforehand to determine that research priorities and thrusts are directed toward real needs and opportunities, and regular research reviews by a diverse body of reviewers,

- Development of sustained national funding efforts that are stable and not subject to the fluctuations of funding from the international donor community; incentives need to be provided for national program directors and program beneficiaries to build national support for ongoing funding to sustain research and development efforts over the long term and enhance the viability and independence of local efforts.

- Encourage R&D funders to adopt a strategy of disaggregated contributions to improve project accountability.

In addition to strengthening the effectiveness and interaction of the international and national research organizations, it is important that tax and other incentives be provided to indigenous operating companies in developing countries to develop their own R&D programs. Minimal resources have been devoted to the development of life science technology by private sector companies in developing countries because the returns can be quite small in relation to the high development costs and the risks associated with doing business in these countries. The Western notion that the private sector will automatically champion biotech research with commercial potential does not apply.

Local companies must be provided with opportunities to acquire appropriate technology, either through the public sector network or through collaborations with other private sector concerns. A mechanism should be put in place to facilitate sourcing of technology and management expertise. They also need managerial assistance, market intelligence and market access. A good example of such a mechanism is the Association of Retired Executives that provides experienced management to LDC companies at very low subsidized salaries. Joint ventures with companies based in developed countries can be successful in realizing the commercial benefits from biotechnology if ventures can be identified in which the developing country partner truly brings value to the partnership. This added value can be in terms of proximity to raw materials, low production cost, production know how, and access to local markets and capital. However, the developed country ventures partner must be committed to the actual transfer of know-how to the LDC venture rather than be simply providing limited technology insights to LDC personnel on a "need-to-know" basis.

In the remainder of this section, the authors highlight products arising from life science research and development that represent important commercial opportunities for indigenous companies in developing countries and are now being overlooked. The following sections should be confined to relevant examples of the unmet needs.

Organic Fertilizer, and Animal Feeds from Agricultural Residues and Food Processing Wastes

The productivity and profitability of agro-industries can be greatly enhanced through better utilization of site-generated wastes, yet there are few programs that deliberately target by-product utilization technology development.

A number of indigenous companies are developing technology for the conversion of agricultural residues (e.g., animal manure) and food processing wastes (e.g., sugarcane bagasse, cassava starch waste) into useful by-products on a commercial scale. There is a tremendous need in developing countries for low-cost organic fertilizers and feeds but little discussion on commercially viable operations is available in the literature.

Fabcon Philippines has developed and is now marketing a value-added organo-phosphate fertilizer based on sugarcane bagasse and phosphate rock and utilizing their proprietary large-scale composting technology. This and similar technology under development can be easily transferred to other developing countries. Such technology has great potential to reduce dependence of local growers on imported inorganic fertilizers and can significantly lower crop production costs while building local soils. Fabcon has formed agreements with San Carlos Milling in the Philippines and other indigenous companies in developing countries to develop and market their product in specific applications.

Technology is also under development around the world for the large-scale production of livestock and aquaculture feeds from agricultural and food processing waste, yeast, and microalgae. Lack of affordable, nutritious livestock feeds have been a major barrier to the successful development of the dairy and beef industries in such countries as Indonesia and the Philippines to improve the nutrition of the domestic populace.

Aquaculture to produce fin fish and shrimp is a major source of food in developing countries, and in many cases represents a highly profitable business. Up to 60% of the production cost for cultured marine shrimp is for highly sophisticated feeds. Most aquaculture feeds in use are formulated from expensive ingredients that often must be imported. However, technology is available from a number of sources that can increase the self-sufficiency of local growers and significantly improve profitability.

Value-Added Export Crops

Indigenous companies can build upon the comparative advantage of many developing countries for the cultivation of important tropical plants for export. Promising candidates include selected ornamental plants, tropical flowers, spices, fruits, and vegetables. By selecting sites at upland locations, it is also possible to grow many temperate zone plants (e.g., strawberries, vegetables, carnations, roses) year round.

Many of these plants are vegetatively propagated and readily lend themselves to in vitro cultivation methods that offer tangible cost- and labor-saving advantages over conventional propagation methods. Such technology is under active development around the world and is already in use to produce value-added export crops by a limited number of companies in Asia and Latin America. There is a need for virus-free potatoes, fungus-resistant black pepper and other species in tropical regions. Planting stock must often be imported, a costly undertaking with many storage and handling problems. In vitro cultivation technology is available or under development to address this issue from several developed country companies and at least three developing country companies. Some of these companies have been able to obtain donor funding for their R&D and the substantive results achieved provide initial evidence of the benefits of greater private sector involvement in R&D.

Through the development of low-cost production and processing sites in regions with the necessary infrastructure, lucrative export markets (e.g., North America, Europe, Japan) can often be profitably served.

More attention must be paid to innovative approaches for organizing farmers into entities capable of providing post-harvest processing and transportation infrastructure needed to effectively market cash crops. The application of the "nucleus" or "satellite" farming concept involving contract growers permits large-scale crop production by a centralized processing/marketing enterprise while reducing the investment that is required. Controlled environment farming is of interest to a number of indigenous companies in Asia for the production of fresh vegetables. A number of corporate and forward-thinking diversified crop producers located in developing countries are now employing these techniques.

Any successful operation involving the production of fruits and vegetables for export must be supported by post-harvest technology. For instance, appropriate storage procedures for seasonal fruits are required so that higher prices can be realized during off-season periods. Many developing countries that would otherwise be good candidates for developing the production technology do not currently have this capability. Programs such as the AID-supported Agricultural Technology Transfer program in Thailand have begun to address these mundane but essential considerations.

Molecular Diagnostics for Crop Improvement

Molecular diagnostics could play a major role in improving the productivity and profitability of agricultural operations in developing countries. Rapid analysis of pesticide residues, early detection of plant diseases, and quantification of pest levels provide information useful in determining crop rotation patterns, variety selection, pesticide selection, application timing, and harvest dates. This is an overlooked area when one considers the enormous crop losses borne by both plantations and small farms. (Yields are typically 30-50% below optimum for virtually every crop. New viral and fungal infestations have played havoc with banana, citrus, vegetable and spice crops.) The underlying technology is under active development by biotechnology companies in the United States and Europe. Molecular diagnostics are already being used in research and it is likely that they will be commercialized within the next five years. Successful implementation of this technology could play a major role in the further development of improved varieties of basic agronomic crops as well as value-added export crops.

Plant-Derived Natural Products

There are a number of human and animal healthcare applications with near- and medium-term commercial potential that are only minimally discussed in the literature. Included is the extraction of important steroid precursors, glycosides, alkaloids and other plant-derived medicinals.

In all cases, the appropriate life science technologies involved have already been developed by multinational pharmaceutical companies and are already being transferred to indigenous companies in developing countries, albeit on a limited scale. Indigenous companies in some developing countries (e.g., India, Indonesia) have begun acquiring such technology, usually based on joint ventures with European or U.S. companies. A barrier to the successful transfer of such technology, however, is its proprietary nature and the lack of adequate patent protection in many developing countries.

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APPENDIX A

DEFINITIONS

Algae Culture - The cultivation of seaweeds such as Gracilaria (macroalgae culture) for the production of agar and other industrial polysaccharides. This is a relatively non-intensive operation, usually conducted by individuals on a small scale in coastal regions. Seaweed cultivation was traditionally developed as a source of food and fertilizer. Microalgae culture involves large-scale intensive cultivation of species such as Spirulina for use in human health food products, as a source of fertilizer, or for the extraction of high-value specialty chemicals (e.g., pigments, beta-carotene, eicosapentenenoic acid).

Anther Culture - The culture of pollen mother cells, once they are isolated from anthers, to produce haploid plants for subsequent screening. This technique has the potential to compress breeding cycles, increase selection efficiency, provide for early expression of recessive genes and expose gametoclonal variations.

Aquaculture - A term referring to the numerous intensive, semi-intensive and non-intensive methods used for the production of edible fin fish (e.g., carp, tilapia), crustaceans (e.g., Pineaus monodon) and mollusks (e.g., abalone, oysters).

Bioconversion - The transformation of materials through the action of a living system or an agent (e.g., enzyme) derived from a living system.

Controlled Environment Farming - The production of plants under carefully controlled conditions that regulate temperature, humidity, light intensity, nutrients and other variables to achieve optimum productivity.

Embryo Rescue - The use of plant cell and tissue culture techniques to nurture otherwise abortion-prone embryos through cell division to the eventual regeneration of an F1 (first generation) plant following sexually induced wide hybridization.

Embryo Transfer - Process of surgically or non-surgically implanting viable embryos in recipient female animals (usually cattle, buffalo, goats, sheep, swine) to genetically improve livestock herds; undertaken in combination with superovulation, artificial insemination, embryo collection and sexing, and often, embryo splitting (twinning), and embryo freezing.

Floriculture - Cultivation of flowering plants for sale as potted or cut flowers, or for seed production.

Genetic Engineering - Genetic manipulations at the molecular or cellular level in order to improve genetic traits. The term typically refers to the isolation, characterization, and recombination of nucleic acids.

Hybrid - A heterozygous plant formed by the cross of inbred (homozygous) parental lines.

Immobilized Enzymes - The use of industrial enzymes covalintly or ionically linked to an inert substrate (usually a column or beads) for the bioconversion of organic molecules in flow-through systems.

Immunodiagnostics - Analytical procedures based on an antigen/antibody reaction, incorporating a fluorescent or radioactive label that will indicate either qualitative or quantitative levels of an antigenic substance; usually employed in diagnostic medicine, but with potential also in agriculture.

Integrated Pest Management (IPM) - A system for controlling agricultural pests whereby all available techniques are evaluated and consolidated into a unified program to manage pest populations so that economic damage is avoided and adverse side effects on the environment are minimized. The term generally refers to the integration of biological control (insect- microbial- or nematode-based) with pesticide application and the use of appropriate cropping systems.

In Vitro Conservation - The use of plant cell and tissue culture to produce *in vitro* genebanks. Modification of culture protocols ensure slow growth provides a means of establishing *in vitro* genebanks to form medium-term collections to complement more traditional means of germplasm conservation.

In Vivo Cultivation - Cell and tissue culture.

Life Science Technologies - Technologies derived through the application of biological processes.

Mariculture - Cultivation of marine organisms in their natural habitat.

Molecular Diagnostics - Analytical diagnostic tests based on immunodiagnostic or nucleic acid hybridization procedures. When coupled with a visualization method, such diagnostics provide simple, specific and sensitive detection and quantification methods with a broad range of applications.

Monoclonal Antibodies - Highly specific, purified antibodies produced from hybridomas (the fusion products of antibody-producing lymphocytes and rapidly dividing myeloma cells) that find widespread commercial use in immunodiagnostic tests. They are widely used in research applications and are employed in immunotherapy, targeted drug delivery and bioprocessing (purification).

Nucleic Acid Hybridization - Annealing of complementary DNA strands derived from different sources; nucleic acid probes are single-stranded nucleic acid fragments that can be used diagnostically to determine whether or not the nucleic acid base sequence in a sample corresponds to that which is characteristic of a genetic disorder or the presence of a disease organism; probes can also be used in plant selection work by identifying specific genetic regions.

Pathogen-Free Plant Production - The use of virus-free plant tissue derived from meristem culture. This technique has been used to produce virus-free plants for over 50 species.

Protoplast Fusion - A non-traditional method of gene transfer at the cellular level, resulting from the culture and subsequent fusion of plant protoplasts.

Rapid (in vitro) Clonal Propagation - Plant cell and tissue culture techniques resulting in rapid and reproducible multiplication rates, pathogen-free conditions and the ability to propagate species that are difficult to propagate vegetatively, and production on a year-round basis.

Recombinant DNA Technology - Non-traditional methods of gene transfer at the molecular level for identifying, accessing and transferring useful genes. These techniques can be used to transfer genes via bacterial or virus vectors and direct gene transfer by microinjection or electroporation.

Somaclonal Variation - Variation observed in plants regenerated from tissue culture that has promise in providing cereal and perennial crop germplasm with tolerance to environmental stress and other useful traits.

Vegetative Propagation - The reproduction of plants by means other than through seeds.

APPENDIX B

SPECIFIC BIOTECHNOLOGY R&D ACTIVITIES CONDUCTED BY INTERNATIONAL AGRICULTURAL RESEARCH CENTERS IN DEVELOPING COUNTRIES

Specific examples of activities under way in developing countries to produce or screen cloned material derived through micropropagation include:

- Rapid (*in vitro*) clonal propagation - Centro Internacional de la Papa (CIP) in Lima, Peru, employes culture of single nodes and shaken shoot cultures and production of *in vitro* tubers for multiplication and distribution of potato germplasm.

- *In vitro* conservation of germplasm - now used extensively with cassava, sweet potato, potato and banana at CIP, Centro Internacional de Agricultura (CIAT) in Cali, Colombia, and the International Institute of Tropical Agriculture in Ibadan, Nigeria. India's National Bureau for Plant Genetics Resources has established a National Facility for Plant Tissue Culture Repository, which is involved in the cryopreservation of seeds, anthers, pollen grains, callus and organs. Centro Agronomico Tropical de Investigacion y Ensenanza (CATIE) in Turrialba, Costa Rica plants to develop protocols for *in vitro* cultivation of bananas.

- Pathogen-free plant production - in collaboration with the University of Wisconsin, CIP is developing new *in vitro* methods to ensure pathogen elimination from potatoes that will allow CIP to provide more germplasm more quickly to national programs for breeding and seed production.

- Molecular Diagnostics - immunoassays and nucleic acid hybridization probes are being used to detect viruses such as tungro, grassy stunt and ragged stunt on rice in Asia and Latin America. A nucleic acid spot hybridization test is used by CIP for evaluation of potato spindle tuber viroid from samples collected in the field. Restriction fragment length polymorphisms (RFLPs) are being used diagnostically at CIP to test for genetic stability following micropropagation of potatoes.

The following are examples of the use of emerging technologies in developing countries to generate genetic variation of potential use in varietal improvement programs:

- Embryo rescue - The International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) is using this technique in crossing domesticated peanut with over a dozen wild relatives to create domesticated varieties with resistance to late leaf spot and rust. IRRI has successfully used embryo rescue techniques following wide crosses of domesticated and wild rice resulting in varieties with broad-spectrum resistance to the brown plant hopper, the vector for grassy stunt virus in tropical Asia.

- Somaclonal variation - In collaboration with Rothamsted Experiment Station in the United Kingdom, CIP is investigating the genetic stability of tissue culture methods for propagation and conservation of potato genetic resources. Biochemical analysis is used to evaluate genetic changes associated with somatic variation in whole plants regenerated from culture.

- Anther culture - IRRI is using this technique to support conventional plant improvement programs involving selection of improved varieties of upland rice with rust and blast resistance. CIAT is using anther culture to develop new rice germplasm that is tolerant to cold and can find use in Chile. The next step is to combine resistance to rice blast and iron toxicity with this material for use in southern Brazil.

- Non-traditional methods of gene transfer - in collaboration with Louisiana State University, researchers at CIP have developed a synthetic gene for high-quality protein that they have successfully inserted and expressed in potato using the agrobacterium vector system. In a collaboration with the Weizemann Institute in Israel, CIP is also developing a potato protoplast fusion program to transfer nuclei of one genotype to the cytoplasm of another genotype in order to confer cytoplasmic sterility. This technique will allow for enhanced production of true seed. CIP eventually hopes to genetically engineer potato plants for resistance to viroid and virus infections by inserting gene sequences that interfere with their replication. CIP's primary interest is to insect resistance to potato leafroll virus and potato spindle tuber viroid.

The success of these emerging technologies lies with the effectiveness with which they are integrated with conventional breeding programs. They are of limited commercial value if divorced from the needs and goals of plant breeders responsible for coming up with improved, tested varieties for distribution to growers. The skills of plant breeders in making sexual crosses with plant and carrying out the necessary selection and field

testing will be required regardless of whether new varieties result from cellular or molecular manipulations or sexual manipulations at the whole plant level.

The goal of biotechnology at the IARCs is to enhance the efficiency of established breeding programs and to devise new crop improvement strategies as quickly as possible. The IARCs are important in identifying appropriate applications for biotechnology in agriculture, training scientists from the various national programs, and transferring technologies to national programs so that their expertise does not lag behind that of the industrialized nations and the private sector.

A major role of the CGIAR system is the preservation of valuable germplasm. As a result of several international symposia and meetings, the International Board for Plant Genetic Resources (IBPGR) was established in 1974, with the Food and Agricultural Organization of the United Nations providing the headquarters. Successful long-term storage of germplasm is possible with relative ease for seeds of most cereals, pulses, many vegetables, some oil seed crops, some cash crops such as cotton, sugar beet and flax. However, for many important crops, long-term storage of seed appears to be either difficult or in many cases simply impossible, as with banana, breadfruits, sugar cane, pineapple.

For these vegetatively propagated plants as well as seed producing plants where asexual propagation is becoming increasingly important for improvement (e.g., citrus, avocado, durian, kola, macadamia nut, mango, certain spices, cacao, coffee, rubber) in vitro preservation and conservation is a viable alternative. In 1985, IBPGR established the scientific basis for running an in vitro genebank, including the testing of stability at various stages through the subculturing regime. In vitro storage of germplasm may in some cases be the best solution to problems typically encountered with live collections, especially in the tropics. However, much more work is required to prove this technique as an alternative to conventional methods of vegetative propagation.

An underlying concern of the CGIAR system is the introduction of agricultural cropping and harvesting methods that enhance the ability of small-scale local growers to become more sufficient and that contribute to sustainable agricultural growth. Perhaps of equal importance is CGIAR's work in post-harvest technology. For instance, CIP is conducting research on the storage of potatoes and low-cost processing.

There has been much discussion as to whether the IARCs should confine themselves to more basic or "strategic" research as opposed to applied or "adaptive" research. In reality, most centers engage in the entire spectrum of research activities. For example, CIAT has been conducting research on the basic physiological biochemical processes of importance in cassava. At the same time, they were instrumental in assisting Thailand's Field Crop Research Institute to develop the Rayong 3 cassava variety through the various stages of varietal improvement, from germplasm supplied by CIAT.