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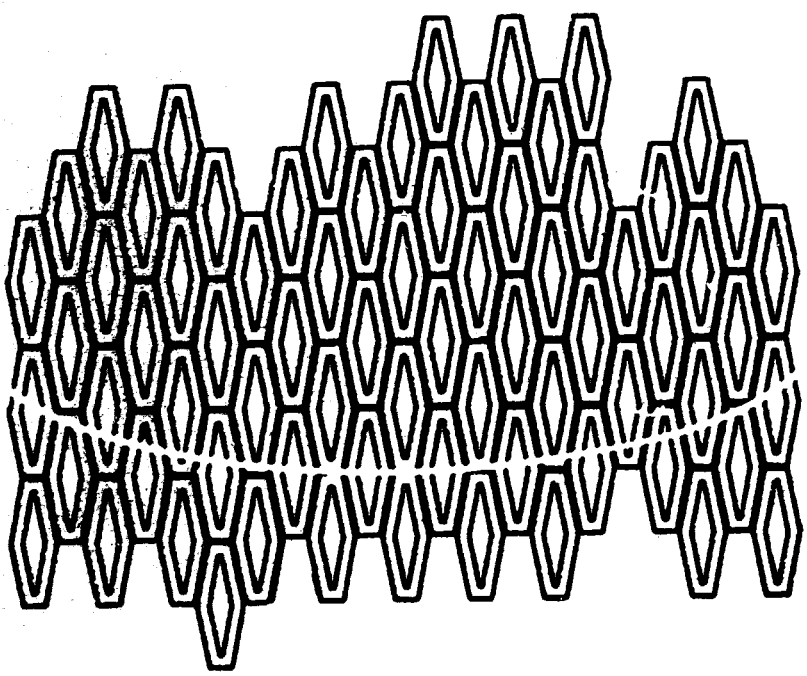
ISSUES IN THE COMMERCIALIZATION OF BIOTECHNOLOGY



General Studies Series

ISSUES IN THE COMMERCIALIZATION OF BIOTECHNOLOGY

Proceedings
of the Expert Group Meeting on the
Commercialization of Biotechnology

Vienna, Austria
28 October-1 November 1991

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The following acronyms and abbreviations have been used in this report:

AIDS	acquired immunodeficiency syndrome
ARCI	Astra Research Centre India
BCIL	Biotech Consortium India Limited
BOD	biological oxygen demand
BST	bovine somatotropin
BT	Bacillus thuringiensis
CAD	computer-aided design
CNRS	Centre national de recherche scientifique
CRP	chronic renal patient
DBT	Department of Biotechnology (India)
DNA	deoxyribonucleic acid
EFB	European Federation of Biotechnology
EFTA	European Free Trade Association
EGF	epidermal growth factor
ELISA	enzyme-linked immunosorbent assay
EPA	Environmental Protection Agency (United States)
EPO	erythropoietin
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration (United States)
FELAEB	Federation of Latin American Biotechnological Enterprises
FOS	flash-out system
GATT	General Agreement on Tariffs and Trade
GEMs	genetically engineered microorganisms
GMO	genetically modified organism
GNP	gross national product
GRAS	Generally Recognized As Safe
HIV	human immunodeficiency virus
HSV	herpes simplex virus
ICGEB	International Centre for Genetic Engineering and Biotechnology
IDRC	International Development Research Centre (Canada)
IFN	interferon
IITA	International Institute for Tropical Agriculture (Nigeria)
IL	interferon-local
ISAAA	International Service for Acquisition of Agro-Biotech Applications
LDCs	least developed countries
LF	lactoferrin
MNCs	multinational companies
MPKSN	National Council for Scientific Research and Development (Malaysia)
NGO	non-governmental organization
OECD	Organisation for Economic Co-operation and Development
OTA	Office of Technology Assessment (United States)
PADCT	programme for supporting scientific and technological development (Brazil)
PCR	polymerase chain reaction
PRATAB	Programme of Policy Research and Technical Assistance in Biotechnology
RFLP	restriction fragment length polymorphism
RIA	radioimmunoassay
RNA	ribonucleic acid
SK	streptokinase
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNCSTD	United Nations Centre for Science and Technology for Development
WHO	World Health Organization

CONTENTS

INTRODUCTION

The Expert Group Meeting on the Commercialization of Biotechnology was held by the United Nations Industrial Development Organization (UNIDO) from 28 October to 1 November 1991 at Vienna. The overall objectives of the Meeting were (a) to review both general and product-oriented policies and programmes in developed and developing countries related to the commercialization of biotechnology in selected areas, focusing on health care and food processing; (b) to identify the elements for success and constraints for bringing products to markets; and (c) to propose modalities for promoting the application of biotechnology, in particular through international cooperation.

CONCLUSIONS AND RECOMMENDATIONS

Human resources

Given limitations on the availability of relevant skills, capabilities, training and experience in all of the necessary fields of science, technology, engineering and management in the continuum of research through development to commercialization of biotechnology in developing countries, it is recommended as follows:

(a) Maximum utilization of existing resources and programmes in specialized institutions should be made to provide broader exposure and training in biotechnology, which should include engineering, technology and, in particular, management, in addition to scientific training. UNIDO should facilitate the coordination of resources and programmes for such training;

(b) Innovative mechanisms should be implemented to permit collaboration with expatriate residents in developed countries, as well as local specialists from other sectors, to ensure the full complement of skills necessary for biotechnology commercialization.

Collaboration

There is inadequate collaboration between the various sectors such as academic, financing institutions and industry, the interaction of which is a prerequisite in the development of commercial biotechnology. It is recommended as follows:

(a) Countries should develop appropriate incentive mechanisms to encourage active involvement of scientists in product commercialization;

(b) Countries should allow scientists to gain rewards from the commercialization of technologies developed by them in public institutions, and provide adequate support in securing patent rights;

(c) UNIDO should promote the concept of development parks by encouraging, in the first instance, the International Centre for Genetic Engineering and Biotechnology (ICGEB) to consider setting up such infrastructure adjacent to its centres. This should include process engineering and physical facilities to take development beyond the concept stage. Such development parks could then be set up in many of the developing economies with models suited to local needs and requirements;

(d) The Trust Fund mechanism of UNIDO should be used by companies and institutions for commercialization of research results.

Financing

Adequate financing is an essential element for the development as well as the commercialization and sustainable market entry and diffusion of biotechnology-based products. Traditional risk capital, such as venture capital, is not yet commonly adopted in developing countries: public equity markets for technology-driven companies are also not readily available. It is recommended as follows:

(a) Creative methods should be established for providing seed capital in developing countries. In addition, other means and modes of financing should be sought;

(b) The consortium approach should be fostered as one means of providing capital, encouraging university-industry-investor linkages and maximizing the utilization of existing infrastructure resources;

(c) In order to be attractive to investors, research programmes should have a product focus;

(d) UNIDO should coordinate and disseminate information concerning funds available to developing countries for the commercialization of biotechnology;

(e) UNIDO should seek funds from international sources as well as from industry, in order to assist developing country enterprises;

(f) UNIDO should assess projects on request from individual enterprises in order to improve their chances for funding;

(g) As convertible currency may be critical for the acquisition of specialty reagents, inputs, equipment and spare parts to jump-start commercialization, researchers should actively recruit corporate sponsors or Trust Fund support early in the development process.

Science, technology and industrial policy

Government policies need to be adjusted in line with entrepreneurial development in the world. It is recommended as follows:

(a) Research and development priorities should be focused on selected areas according to each country's competitive advantage;

(b) Government departments should play a more pro-active role in science-based enterprise development, with appropriate incentive mechanisms to promote public-private interface, technology transfer from abroad, university-industry links, tax policy and financial incentives;

(c) Policies should facilitate the recognition that ecological/environmental costs are no longer to be considered external to projects or products;

(d) UNIDO should cooperate with developing country Governments in the formulation of industrial policy guidelines for biotechnology development.

Regulatory policy

It is recommended as follows:

(a) Coordination should be established at the national level on regulatory issues;

(b) Regulations should be scientifically based, flexible and commensurate with risks;

(c) Regulators, industry, policy makers, consumer groups and the general public should be kept up to date on regulations;

(d) Collaboration should be encouraged at the national level between academics, industry and government staff in the field of regulation;

(e) UNIDO should take a more active role by promoting international cooperation for the adoption of common principles of safety guidelines for biotechnology applications;

(f) UNIDO should collect and disseminate appropriate information regarding regulations or guidelines applied in other countries;

(g) UNIDO should facilitate the training of regulators.

Intellectual property rights

It is recommended that developing countries should devise appropriate strategies on intellectual property rights and patents as this will be an enabling factor in creating an environment for the unrestrained development of science-intensive commercial enterprises.

Information

Timely access to high-quality, reliable information is a serious constraint to the development of appropriate research and industrial programmes in developing countries. It is critical that information should be made available to the public on biotechnology developments. It is recommended as follows:

(a) The information services of UNIDO and others should be strengthened and extended to provide the information in an appropriate form for utilization by researchers and enterprises in developing countries;

(b) National-level information systems should be established for the specific users in each country;

(c) Specific efforts should be made in developing countries to widely disseminate information in order to increase consumer awareness of biotechnology developments and their implications for and benefits to society;

(d) Networks of individuals or institutions within countries and between countries should be established to promote information exchange and other activities.

Infrastructure

It is recommended as follows:

(a) Infrastructure should be strengthened by national Governments to enable the development of internationally competitive biotechnology enterprises as well as marketing and distribution channels for biotechnology products;

(b) Requests for support for international funds aimed at strengthening appropriate infrastructure should be presented by national Governments and institutions as an integral component of biotechnology development proposals.

Socio-cultural factors

In order to overcome the general aversion to financial risk that exists in many developing countries, it is recommended that mechanisms to encourage risk ventures, incorporating attractive financing options, should be established.

To address issues related to the public acceptance of biotechnology and its products, it is recommended that UNIDO should integrate components on consumer aspects of the commercialization of biotechnology in its information and seminar activities.

Promotion

It is recommended that UNIDO should take steps to establish a promotion service for the commercialization of biotechnology and constitute, if need be, a task force of experts for advice.

7/8

Part One

REPORT OF THE MEETING

I. BACKGROUND

Modern biotechnology has acquired a new dimension over the past two decades with phenomenal advances in biomedical sciences. These advances have resulted in new techniques which facilitate the introduction of desirable traits in existing biological species with unprecedented speed and precision. Universities are important sources of these innovations. Both the public and private sectors of industrial and nations, having realized early on the enormous potential of these techniques, have undertaken intensive R&D by establishing firm linkages with universities and have been successfully commercializing the products of biotechnology.

Most developing countries are aware of the advances in biotechnology and its great potential for contributing to rapid economic development, to sustained health care and nutrition and to industrialization. However, for several reasons they are lagging behind in full development of biotechnology and its application to commercialization.

UNIDO has been active in strengthening the developing countries in biotechnology and its applications through ICGEB. In addition to engaging in research with a view to advancing basic knowledge in the field, ICGEB is also keen to liaise with industry to bring the research outputs into meaningful products for commercialization. ICGEB has an elaborate programme, initiated about five years ago, in human resources development through a network of activities which includes seminars, colloquia, workshops and funding of collaborative research projects and bioinformatics. UNIDO has also promoted the establishment of a regional biotechnology network in Latin America.

It is against this background that UNIDO organized the Meeting, which, it was hoped, would play a catalytic role in helping countries, particularly the developing ones, to strengthen the research-industry linkages that would facilitate commercialization of biotechnology products.

II. ORGANIZATION OF THE MEETING

Agenda of the Meeting

The Meeting was opened by the Deputy Director-General of the Department for Industrial Promotion, Consultations and Technology of UNIDO, who briefly reviewed UNIDO initiatives in biotechnology, including the establishment of ICGEB and the development of a voluntary code of conduct for the release of genetically modified organisms into the environment for industrial applications. This was followed with a brief speech by Mr. Hara, President of Seiko Instruments, Japan, highlighting the importance in innovations in biotechnology for industrial development. The keynote address, which gave a worldwide perspective on biotechnology, was by Steven Burrill.

The first two days of the Meeting were largely devoted to presentations on health care and food processing/agro sectors, with special reference to aspects of successful commercialization in developed countries and opportunities available in developing countries in these areas. Those presentations form chapters IV-XII of these Proceedings. Presentations were also made on the second day of the Meeting on education and training requirements necessary for the application of biotechnology to these areas and on the

safety issues connected with the introduction of biotechnology-based products. Those presentations form chapters XXV-XXVIII of these Proceedings.

Country-specific experiences from the Asian, South-East Asian and Latin American regions in the commercialization of biotechnology-related products were covered in the presentations of the third day of the Meeting. They form chapters XIII-XXIV of these Proceedings.

Group discussions were held on the fourth day of the Meeting concerning the key elements that contributed to the success of commercialization in industrialized nations, constraints facing the developing countries and modalities for the promotion of commercialization.

Participants adopted conclusions and recommendations on the final day of the Meeting.

Participation

The Meeting was attended by 34 experts from 19 countries, both North and South. The experts were affiliated with Governments, academia and industry. They are listed in the annex to this chapter.

Summary of discussions

The scientific programme started with a keynote address covering an overview of the global scenario for present and future prospects of commercialization of biotechnology, the essential elements that made companies succeed and the issues to be considered for product development and discussed the impact of government policies on biotechnology growth. A sound research and technology base, teamwork, financial strategies and acceptance of a product in the market were among the elements that contributed to the success of biotechnology industry. In that context, it was felt to be important for developing countries to involve relevant expatriates in the building of healthy biotechnology industry in their home countries. Several participants, while emphasizing the value of expatriates, observed that there was a great need on the part of the countries to appreciate such intellectual capital and for devising attractive terms seeking their active participation.

The keynote address was followed by some 15 presentations from participants on commercialization aspects, regulatory issues and training opportunities in the areas of health care and food processing.

Participants agreed that advances in biotechnology had opened up new horizons to health care and agro-industry. Successful commercialization was already evident in biotechnology-based medicinals and agro-products. The biotechnology industry was just beginning to unfold and was expected to grow at a rapid rate in the 1990s.

There was an increasing trend in the West for technology to flow from academia to multinational companies through direct links, skipping in the process the entrepreneurial set-up. However, it had been argued that for developing countries and even for industrialized nations, entrepreneurial intermediaries were important sources of venture capital.

An ideal example of how to start a small company with an initial venture capital and the successful ventures of a leading pharmaceutical company in the

AIDS field were among the presentations in the health area. The key for success was to possess proprietary technologies targeted to large market segments. The point was well made that it was the quality of the personnel and the conducive environment of the company and not the size of the budget that determined its success. A suggestion had been that companies in the developed countries should establish manufacturing facilities in developing countries, as the demand for the products increased. That seemed to be true of vaccines, particularly the recombinant ones. Developing countries might achieve rapid success if they promoted tie-ins of their companies with large multinationals, as was illustrated by Astra Research Centre India. It was pointed out that in many developing countries, expertise in gene technology was available in arriving at a candidate compound, but to bring it to commercialization, which involved a gamut of preclinical and clinical studies, collaboration with a multinational was desirable. In contrast, it should be kept in mind that in certain projects such as the production of large-volume low-cost proteins by transgenic cows, the initial high-tech part was to produce transgenic animals, which could be done in a developed country; isolation and purification of the proteins involving downstream processing could be done in a developing country. The concept of using transgenic animals in making commercially viable biologicals seemed very attractive since they tended to secrete the product in their milk, which facilitated relatively easy isolation and purification of the products.

It was emphasized at the Meeting that the biotechnology industry in the field of agriculture would have a lasting beneficial effect on the average citizen. The industry should take due note of market needs and consumer perception and strive for employing cost-reducing technologies for success of commercialization. The Governments in developing countries should acquire profitable technologies for rapid commercialization, even by licensing them on a phased payment basis.

Consumer acceptance and regulatory issues were covered in depth at the Meeting. The ethical and environmental considerations might hinder a real take-off of biotechnology industry. It was agreed that those novel technologies should be employed in a manner that promoted environmentally sound development, keeping socio-economic needs, country-specific issues and a balanced safety policy in view. A risk-based regulation should be the norm, with logical reasoning rather than empirical methodology. Any regulation should reduce risks without inhibiting innovation. Public acceptance of a product was a prerequisite and the Governments should develop appropriate biosafety review structures essential for technology transfer for commercialization.

In the context of regulatory issues, it was worth noting that the biosafety guidelines and a voluntary code of conduct developed by UNIDO on behalf of the Informal UNIDO/UNEP/WHO/FAO Working Group laid down the minimum commonly accepted principles on the subject. They aimed at promoting innovation and commercialization of biotechnology products in an orderly manner that was conducive to consumer acceptance.

It was recognized that an enormous amount of information had accumulated on the biotechnology industry and there was a great need not only to prepare data banks but also to process the information into packages designed to help the user. The importance of developing a techno-economic intelligence (INTEL) programme for biotechnology was emphasized at the Meeting.

The importance of human resources development in the application of biotechnology, particularly in the developing countries, was considered vital by the participants. That could be done by strengthening centres active in this area, such as ICGEB, and conducting course programmes, preferably under university auspices. It was observed that some training centres for biotechnology at the research level were available in several developing countries but no such organized activity existed to accelerate industry skills. Therefore, a need had been felt for providing training in the private sector in fields such as bioengineering, with emphasis on downstream processing technologies.

Presentations of case-studies by some 12 participants from countries of Latin America and Asia revealed several opportunities, constraints and methods in promoting the commercialization of biotechnology products. Among the constraints identified in these countries were political instability; economic and financial difficulties; shortage of investment resources; lack of support from Governments by way of customs duty exemption on equipment and bioreagents and tax incentives; general paucity of experience of investors; and inadequate scale-up skills to bring products to markets. However, efforts were being made to overcome those constraints, and countries such as Argentina, Brazil, Cuba and India were forging ahead with the application of those technologies in industrial development. Concerted efforts were made in those countries to increase human resources in biotechnology; to bridge university-investor-industry links; to promote regional cooperation; to form alliances and networks with industries of developed countries; and to establish mechanisms for raising venture capital. It was apparent that much needed to be done in most developing countries in exploiting natural resources; making traditional technologies more competitive; promoting product-oriented research in universities, with equity participation and profit-sharing concepts applicable down to the level of scientist to retain the best talent; orienting research to meet the needs of industry; building strategic partnerships; and designing appropriate cost-effective biotechnological methods. It was vital that those technologies should be applied judiciously without posing threats to established export markets from those countries.

The Meeting underlined the urgency of international cooperation in promoting commercialization in developing countries. That could take the shape of forming information networks; science and technology capability strengthening, including research, bioprocessing, manufacturing and safety; and facilitating technology transfer. A suggestion worth pursuing was to establish science parks or development parks around centres engaged in biotechnology and genetic engineering research in order to make Governments, investors and industry aware of the commercial potential of biotechnology.

Wide-ranging conclusions and recommendations emerged from group discussions on the key elements for success, constraints facing countries and modalities to promote the commercialization of biotechnology products. Several specific recommendations were made by the experts to UNIDO to assist developing countries in rapid industrialization through biotechnology, the implementation of which would entail substantial inputs from UNIDO.

III. KEYNOTE ADDRESS: BIOTECHNOLOGY, A WORLDWIDE PERSPECTIVE

G. Steven Burrill*

Major developments

Some of biotechnology's most important promises have now been kept in the area of products. Sales of Epogen, a product of the United States based company Amgen in the kidney dialysis market, topped the US$ 300 million mark in 1991 and could easily break the US$ 500 million mark in a year or so. In addition, Amgen's product Neupogen reached US$ 50 million in sales in its first month of market activity.

At the same time, other important new products have broken through the United States Food and Drug Administration (FDA) logjam, including Actimmune, Ceredase, Leukine, Intron A (for hepatitis C), Centoxin and Calgene's anti-sense gene for application with tomatoes. In addition, the first genetically engineered bioinsecticides were approved. In fact, more products were approved in 1991 than in all of the previous eight years combined.

The financial picture is also good with booming initial public offerings and secondary markets in the United States raising over US$ 3 billion in new capital. In addition, the stock market reflects a capitalization up 75 per cent from the prior year to over US$ 35 million for publicly held biotechnology companies.

These developments are summarized in table 1.

Table 1. Major developments

Blockbuster products
- Epogen and Neupogen
- New therapeutics clear FDA
- Bioinsecticides approved
Capital markets
- Initial public offering markets boom
- Market up 75 per cent, to $35 billion
Large acquisitions/strategic alliances
- Cetus/Chiron
- US/US biotech transactions

Moreover, total product sales are growing, approaching $4 billion for the year ended 30 June 1991, a 38 per cent increase. Biotechnology companies are on a stronger footing. For instance, Amgen may soon become the first biotechnology company to rank in the Fortune 500. Biotechnology's future looks solid, with more than 120 new biologics in clinical trials and more than 20 awaiting regulatory approval. All of the indicators point to the fact that the biotechnology industry has moved from "promise" to "reality".

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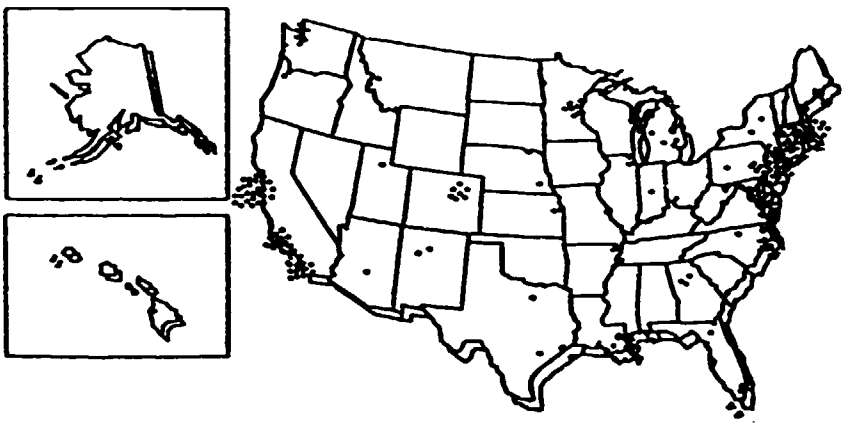
*Ernst Young, San Francisco, California, United States.

The geographical distribution of United States-based biotechnology companies is shown in figure 1.

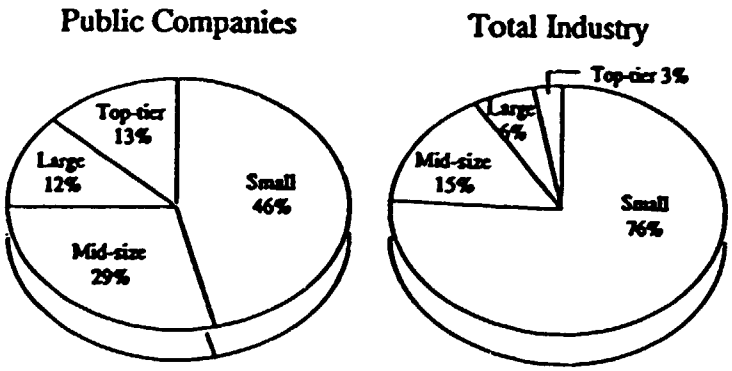
Figure 1. Location of public biotechnology companies in the United States, 1992



Source: Ernst and Young.

Generally speaking, the companies are located near areas of academic excellence. About 1,100 biotechnology companies exist in the United States today. A demographic look reflects the picture seen in figure 2.

Figure 2. Industry concentration, by size

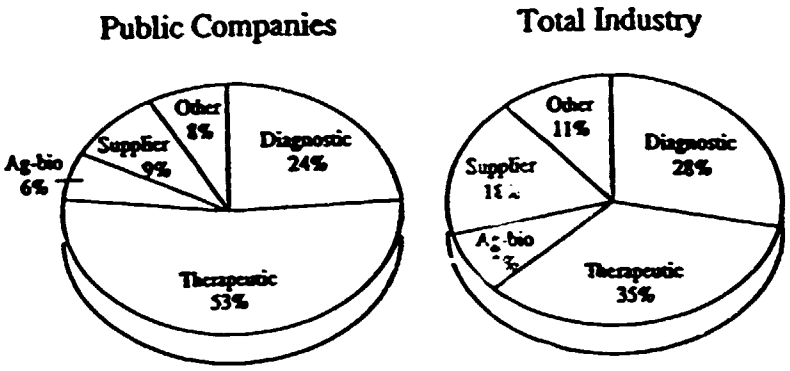


Source: Ernst and Young.

It is noted that the higher percentages of mid-size, large and top-tier companies are the public companies, as compared to the overall industry. At the same time, the largest percentage of public companies (46 per cent) are still small, nearly half of them having under 50 employees.

Because of their economic and health care potential, the therapeutic companies are more attractive to the public equity markets and therefore represent a high percentage of public companies (figure 3).

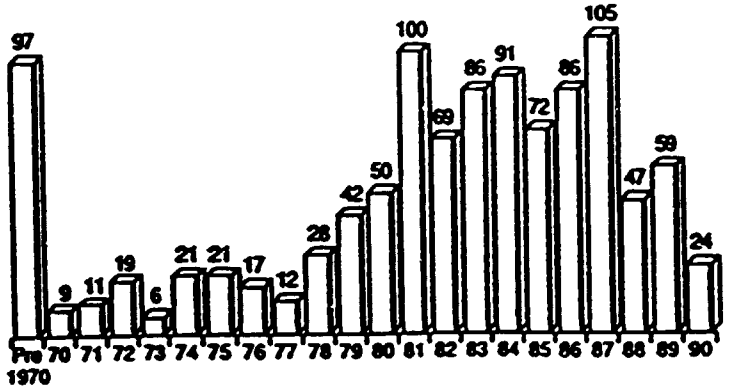
Figure 3. Industry concentration, by market segment



Source: Ernst and Young.

The number of companies established every year is depicted in figure 4. As the figure shows, start-up activity peaked in 1987 as capital was generally available. It has dropped considerably since then, reflecting the impact of the stock market crash in 1987. The lack of an initial public offering market greatly affected the ability of venture capitalists to raise new funds and their propensity to invest, beginning with the October 1987 crash.

Figure 4. Number of companies founded, by year



Source: Ernst and Young.

The following are the financial highlights of 1991 (table 2):

- Total revenues for the United States biotechnology industry reached a record US$ 5.8 billion in 1991, a 23 per cent increase from 1990.
- Product sales approached US$ 4 billion in 1990/1991, a 38 per cent increase from the previous year. These sales were driven by the 11 biotechnology-derived products receiving regulatory approval.
- Asset growth for public companies increased by 25 per cent, twice the increase in assets for the total industry. This largely excludes the January-June 1991 cash offerings (about US$ 2 billion).
- Since the number of employees follows funding, the growth in employees for public companies exceeded increases in the number of employees for the total industry, up 14 per cent for public companies compared to a 6 per cent increase industry-wide.

Table 2. Financial highlights
(Billions of United States dollars)

	Public companies			Total industry		
	Current	Prior	% Change	Current	Prior	% Change
Sales	$ 2.9	$ 2.3	26	$ 4.0	$ 2.9	38
Revenues	3.8	3.1	23	5.8	4.7	23
Assets	7.3	5.9	25	12.3	11.0	12
Employees	33,000	29,000	14	70,000	66,000	6

Source: Ernst and Young.

The status of Western biotechnology activities is summarized below.

A review of biotechnology activities in the United States shows the following:

- Strong funding support for the National Institutes of Health
- The United States spent $6 billion on biotechnology research in 1990
- De facto government policy hinders reaping of rewards
- Capital base is short-term-oriented
- The United States lead is slipping to Japan and Europe
- Science-driven, entrepreneurial and innovative, but largely in small companies

In contrast, biotechnology activities in the United Kingdom:

- The United Kingdom has been slow to take advantage of academic excellence
- United Kingdom academic talent is linking with United States marketing/ entrepreneurial expertise
- British Bio-technology Group PLC and Celltech Ltd. rival United States drug and diagnostic products

Biotechnology activities in Germany:

- Government's Biotechnologie 2000 research budget is DM 1.5 billion for 1990-1994
- Germany's "new" genetic technology laws allow relatively free manufacture of tissue plasminogen activator, Il-2 etc.
- Heavy opposition from the Green Party

Biotechnology activities in France:

- Strong pharmaceutical, chemical and agricultural industries
- Birth of entrepreneurship
- Good academic science (Institut Pasteur etc.)

Biotechnology activities in the European Community in general reflect:

- Europe has 6 of top 10 drug companies and 7 of top 10 chemical companies worldwide
- Pouring capital into acquisitions and joint ventures to access foreign technology
- Venture capitalists invested US$ 100 milllion this year, up from US$ 80 million last year
- European Commission has 10-year plan to put US$ 1.2 billion into research
- Europe's biochemical market is expected to grow to US$ 480 million in 1993, up from US$ 329 million in 1988
- European Community biotechnology could equal 2 million new jobs by 2000 with coordinated policy

In Japan, biotechnology activities reflect:

- Strong support from pharmaceutical, chemical, food, energy and agricultural companies
- Strong government support
- Over 500 Japanese companies use biotechnology
- Japanese companies are targeting European and United States biotechnology companies for investment and technology exchanges
- Dominance of world biotechnology by the year 2000 is a national priority
- By 2000, the Japanese biotechnology market is expected to reach Y15 trillion, up from several hundred billion now

On the world scene, the activity is principally in the areas listed in table 3.

Table 3. Top five market segments
(Percentage share)

Medical/pharmaceutical	36
Fermentation	31
Diagnostics, food and facilities/equipment	19
Agricultural	7
Enzymes	7

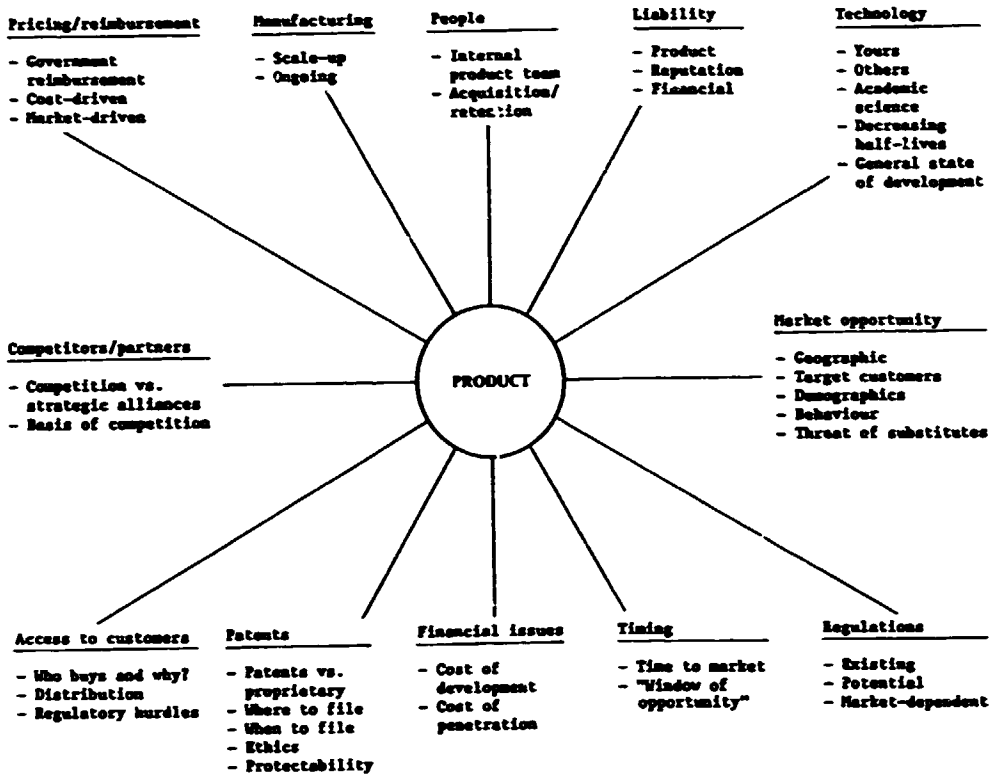
Issues in developing biotechnology companies and a biotechnology industry

Historically, this industry has been driven by its science. There is a common implicit assumption that every piece of science "deserves" a company. In fact, this is not true. Science does not equal business.

Generally, the issues in product development are much more complex than just the technology and its development. These are indicated in figure 5.

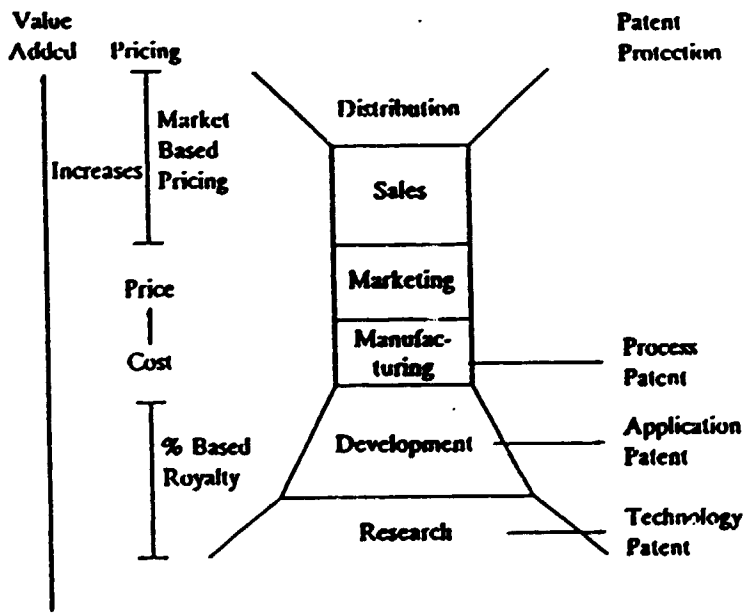
As technology develops, a "flow" moves upward, from research to development, to product definition, then production, marketing, sales and distribution (figure 6).

Figure 5. Issues to consider in product development



Source: Ernst and Young.

Figure 6. The flow of biotechnology products



Source: Ernst and Young.

For the development of an industry, one can recognize the following essential ingredients of biotechnology growth: culture, capital and environment.

First, the culture:

- Local entrepreneurial heroes. People who are recognized by their success, i.e. people whom others wish to emulate
- Social acceptance. A societal acceptance of risk taking and, more importantly, failure. One needs to accept failure as a part of the cost of success
- And, finally, a belief that biotechnology holds the key for future development

Second. the industry needs a capital base, both intellectually and financially. Financially, the key players are venture capitalists, investment bankers and intermediaries assisting in the financing equation. Increasingly, strategic alliances between big and small companies are providing some of that capital base.

Finally, the following elements are important in providing optimal environment:

- Proximity to innovative technology (university research facilities)
- Infrastructure of attorneys, accountants, construction contractors/real estate and experienced managers
- Government support
- Private support

Several key elements will be involved to achieve realization:

- Desire to make it happen
- Concentration on a few market segments
- Focus on existing companies/market segments
- University interface
- Entrepreneurial culture
- Access to capital
- Development of infrastructure

However, worldwide the industry is not without its issues. These include:

- Capital formation
- Technology transfer
- Patent/intellectual property protection
- Regulatory environment
- Education
- Role of Governments
- Reimbursement/pricing
- Research funding
- Foreign encroachment

Capital formation

Historically, the industry has been financed through the following:

- Grants and gifts (including government)
- Research contract/collaboration
- Venture/private capital, private capital
- Public equity capital
- Strategic alliances

Government policies have to deal with:

- Technology transfer, be it encouraged or discouraged
- Research funding - the degree of absolute funding for science and technology development
- Regulatory delay cost, a negative factor in capital formation (the cost of excessive regulation can be detrimental to overall capital formation)

Finally, Governments can impact capital formation through various tax incentives, including:

(a) Capital taxation differential for long-term capital formulation

(b) R&D tax credits (to offset taxes otherwise payable)

(c) Loss utilization pass-through to investors to provide a source of capital

Technology transfer

Encouraged or discouraged, and what is the role of academia, the Government and the private sector.

In some countries, an implied conflict of interest exists if the public sector transfers technology to the private sector. Yet, it is the private sector's role to develop products and technologies and build business, not generally a public sector role. Also, in this age of modern technology, it is important to understand the significance of our technology transfer via the fax, that is the free flow of information worldwide on an almost instantaneous basis. Government policy does impact technology transfer. It is important for Governments to take a position.

Patent and intellectual property protection

First, it is important to recognize that there are different systems worldwide, with conflicting issuances, issuance delays (increasing the backlog) and legal systems that may be cumbersome, expensive and time-consuming. Government policy has much to do with protecting intellectual property, with effective patent and trademark offices, and recognizing its implications on international trade.

Regulatory environment

Each country has its own appropriate regulatory environment. This plays a key role in the development of the industry, either to assist or act as a deterrent. In the United States, the principal regulators include:

- FDA (Food and Drug Administration)
- USDA (Department of Agriculture)
- EPA (Environmental Protection Agency)
- State and local governments

Various foreign Governments also impact on United States companies. Government policy can cause regulation to become cumbersome, expensive and time-consuming. In many countries, a conflict exists within the regulatory environment to determine whether the regulators' duty is to keep reasonably unsafe products off the market or to get reasonably safe ones to market.

Education

Overall, there is an insufficient supply of technically trained people to meet the needs of the biotechnology business. In every country foreign students play a key role. Education should be available to all and secured through individual initiative; Governments must provide a framework to ensure that education systems are adequate.

Roles of Government

Governments are intimately related to the development of this industry, not just through its regulatory structures, but also through its concern for the environment, agriculture/food supply and health care.

Additionally, although sometimes less obviously, use permits for the construction of facilities play a critical role. Generally speaking, Governments tend to pursue their own ends. Some view biotechnology as an offensive strategy, i.e. building new products to develop a new "economy", while others view it defensively, i.e. its impact on existing industry.

Reimbursement/pricing

Governments also tend to promote biotechnology companies' success through their purchasing power.

- Who buys the product?
- What are the payment/reimbursement mechanisms?

How health care is delivered and paid for (central health ministries etc.) also matters:

- Cost substitution
- Rationing
- Role of health maintenance organizations and preferred provider organizations

Governments are large buyers of many of the biotechnology industry's products. Their intention is often to lower overall cost.

Research funding

Governments spend large amounts of money on research, principally through their national health ministries. However, Governments around the world (exception: Japan) are increasingly reducing research expenditures to balance the budget.

Foreign encroachment

Finally, nearly every country has a biotechnology policy, either directly or indirectly.

What makes biotechnology companies succeed?

The keys to a biotechnology company's success are management, market-place/market dynamics, technology and finance.

Management

We have moved from individual champions to balanced teams. No longer is it possible to just build a company around a single Nobel-prize-winning scientist. Companies need to provide dual career paths, one for those in technical or scientific tracks and one for those in management. Frequently, the most accomplished scientists have tried to be turned into managers, without much success.

Therefore, my first law emerges:

> Burrill's First Law
> "Stars lose ... teams win"

Market-place/market dynamics

Secondly, market dynamics not just the science, is a key:

- What are the market dynamics?
  - New markets versus better solutions in existing markets
  - Competition
  - Distribution channels
  - Market segmentation
- What is the window of opportunity?
  - Technology versus other solutions
  - Timing

Ergo, my second law:

> Burrill's Second Law
> "The acceptance of a product in the market-place
> ultimately determines the company's success"

Technology

Another key is the technology:

- Is it patentable?
- How protectable is it?
- What is the product life-cycle?
- Other solutions to the problems

What is the distinctive competence uniqueness?

- New technology to solve old problem
- New technology to solve new problem
- Better technology
- Cheaper product

A third law emerges:

> Burrill's Third Law
> "The key to technology is the barrier to entry"

Finally, the key to individual company success is to provide a capital base. To recognize that the capital markets are very fluid, one must understand the market conditions for financing choices that constantly fluctuate.

One needs to set some finance selection criteria based upon the following:

- The strategic goals of the company
- Stage of development of the company and R&D progress
- Amount and timing of requirements
- Risk/return sharing
- Market conditions
- Cost of financing (not just the cost of the transaction, but the strategic cost as well)

Financing choices:

- Equity (private or public)
- Contracts/grants
- Debt (convertible or standard)
- Joint ventures
- R&D partnerships
- Strategic alliances, such as R&D collaboration, technology licenses manufacturing, marketing and equity

The financing choices are many, but essentially, the key law emerges:

> Burrill's Fourth Law
> "Financing strategies dictate business strategies"

An analysis of this industry reflects the fact that the way a company is financed dictates the business strategy.

Finally, a summation law - as a key to biotechnology success:

> Burrill's Fifth Law
> "Tactics are more important for success than strategy"

Annex

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Part Two

TECHNICAL PAPERS SUBMITTED TO THE MEETING

A. Commercialization issues: health care

IV. DEVELOPMENT STRATEGIES OF BIOPHARMACEUTICAL PROGRAMMES IN TANOX BIOSYSTEMS

Tse Wen Chang*

Introduction

This paper discusses the experience and strategies for developing biopharmaceutical programmes in Tanox Biosystems, a relatively young company. Such experiences are to be shared with experts and officials from developing countries who have keen interests to develop biotechnology industries in their countries.

Biopharmaceuticals are natural biological substances, such as growth or regulatory factors, antibodies or their derivatives, that are produced from gene splicing, cell fusion, gene transfer and other modern methods of molecular or cell biology. These substances are a major class of biotechnology products and the first to make a major impact on our societies. Among the main facts concerning the development of pharmaceutical products is that it usually costs in excess of US$ 100 million and takes eight or more years to bring a prospective product from conception to the market. Biopharmaceutical research is being actively pursued by most international pharmaceutical companies and many newly established small biotechnology firms.

Although Tanox Biosystems, Inc. is located in the United States, in many respects the obstacles and challenges the company has faced, and will continue to face, in its struggle to develop into a successful entity are similar to those the developing countries are facing in developing a competitive, productive biotechnology industry. For Tanox these challenges include establishing proprietary technology positions, recruiting talent for research and clinical and manufacturing process developments and financing the product development activities from the research stage through to the product's commercialization.

Brief background and current status of Tanox Biosystems, Inc.

Tanox was founded in 1986 in Houston (Texas) by two scientists/R&D managers, Drs. Nancy T. Chang and Tse Wen Chang, who had been working in the biotechnology industry for six years and had recently been hired as associate professor and professor, respectively, by the Baylor College of Medicine. The founders provided funds for the seed capital and in early 1987 completed the first phase of the research laboratories. In mid-1987 the company received one round of venture capital financing; since then there has been no such major financing.

The company now has 36 full-time employees, including 18 with Ph.D. or M.D. degrees, two with law degrees and two with M.B.A. degrees. Most of the remaining employees, including those who specialize in quality control, drug

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regulatory compliance and manufacturing processes, hold M.S. or B.S. degrees. The company is located within a few miles of the Texas Medical Center, which has been the company's most important source of human resources.

The company's therapeutic products currently under development are based on antibodies or peptides. The antibodies are chimeric, humanized or authentic human antibodies, which are produced by genetically engineered cell lines in large-scale cell cultures. The peptides are synthesized chemically. The four lead products being developed all target very large markets, ranging from several hundred million to several billion United States dollars. In collaboration with Ciba-Geigy, the company now has an anti-HIV chimeric antibody product in Phase I/IIA clinical studies. Phase I/II clinical studies are targeted to begin on a chimeric antibody product for allergic rhinitis and asthma in mid-1992. There are also two very promising products for rheumatoid arthritis and for treatment of cancers, which are likely to be ready for clinical trials by the end of 1993.

Tanox is also developing proprietary generic technologies to make efficacious immunotoxins or immunoconjugates and produce effective adjuvants to be used in vaccines. While these various programmes may appear diffuse, they have a common theme and technical base.

People who are familiar with Tanox often comment that companies of comparable age and size do not usually achieve the development stage and the portfolio of biopharmaceutical programmes such as the company has. Because it has advanced expeditiously through the efficient use of time and human resources (which equate with funds), the founders and company managers have been able to maintain a strong influence on the management of Tanox and continue to build it into a successful pharmaceutical company.

The generation of proprietary technology

Because the development of a pharmaceutical product is so lengthy and costly, the trend in the industry is not to undertake development unless a very favourable patent or proprietary position is expected for the product. By establishing a good proprietary position, a "small player" has a chance to pursue big opportunities. The holder of a valuable patent or patent application can often successfully establish a new company, even though it may take ten years or longer to derive revenues from product sales. Proprietary technology or product opportunities are probably the most important assets of young, aspiring pharmaceutical companies. They provide the necessary bargaining chips in financing, corporate partnership arrangements and other business development activities.

Building on interest in immune system functions, the company has focused development on proprietary products to treat diseases affected by abnormalities of the immune system. These diseases include AIDS; IgE-mediated allergies, including allergic rhinitis and asthma; autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and more than twenty other diseases caused by autoreactivities, as well as cancers. While certain treatments are available for certain patients inflicted with these diseases, efficacious treatments for the majority of patients are lacking. Therefore these diseases offer some of the most exciting, lucrative and competitive areas for pharmaceutical innovation.

Unlike most of the drugs used for allergies and autoimmune diseases to treat disease symptoms, Tanox's approaches target the source, i.e. the immunological mechanisms causing the diseases. The proprietary foundation for Tanox (with about 50 United States patent applications and many foreign ones) has now been built after several years of vigorous efforts. The company's biopharmaceutical programmes have the following characteristics: (1) they are novel; (2) they target large markets; (3) manufacturing of the products is feasible; and (4) the pharmacological mechanisms are understandable and convincing.

Product/project portfolio

The products for HIV prevention and treating IgE-mediated allergies are chimeric antibodies, having constant regions derived from human antibodies and antigen-binding regions from murine antibodies. One potential exciting application for the HIV-neutralizing antibody is in preventing the infection of newborn babies by their HIV-infected mothers. In the United States, there are about 12,000 babies born to infected mothers in a year; in Africa, the number is much larger. Statistics indicate that about 30 per cent of these babies become infected, with most of the infections probably occurring perinatally. Administration of Tanox's HIV-neutralizing antibodies may significantly alter these dismal statistics.

The company's allergy product can also be an equally important new product for treatment of the millions of persons affected with IgE-mediated hypersensitivities. The anti-allergy antibody binds to circulating IgE and to IgE-producing B cells, but not to IgE bound by IgE.Fc receptors on the surface of mast cells and basophils. The anticipated pharmacological mechanism of this therapeutic is to deplete or down-regulate IgE-producing B cells, thereby suppressing IgE synthesis. Because IgE is believed not to be essential for immune defense, the product may treat allergy effectively without any adverse side effects.

The immune system produces five classes of antibodies, namely IgM, IgD, IgG, IgA and IgE. They mediate different immune mechanisms and are involved differently in the pathogenesis of autoimmune diseases and immediate-type hypersensitivities. For example, IgG, but not IgA, IgD or IgE, is conspicuously involved in most autoimmune diseases. To be able to control antibody production in a class-specific or isotype-specific fashion is most desirable. Tanox has invented and substantiated the idea of targeting the isotype-specific portions of the membrane-anchoring peptides of membrane-bound immunoglobulins for the isotype-specific regulation of B cells. Antibodies specific for epitopes on these peptide segments bind to B cells but not to the large amounts of secreted antibodies in circulation. Tanox currently is developing several product applications for autoimmune diseases based on this technology.

Tanox is also developing a family of immune enhancers, which can specifically stimulate lymphocytes, including tumour-infiltrating lymphocytes. These products can potentially be used to treat a large range of tumours. In addition, Tanox is developing novel molecular conjugate technology that can be used in cell-entry-facilitated drug targeting. Another technology being developed is a potent and safe adjuvant that can be employed for a large number of vaccines. Our new technologies, when successfully developed, are applicable to a broad range of drugs and vaccines and may be licensed to other companies.

The control of development costs

To share the substantial cost of our first two products and with much confidence in their rich project portfolio, Tanox decided to collaborate with a reputable pharmaceutical company to develop the AIDS and allergy products. In a corporate partnership, the small firm usually gives up most of the marketing rights and thus a share of the big potential of a successful product, but it also shares the development costs and risks and thereby obtains security and stability to advance to the next stage of development.

Tanox chose Ciba-Geigy for this corporate partnership and after several years of this relationship, the choice proved to be a sound one. By having much of the responsibility in this collaboration, Tanox has been able to actively and speedily participate in the development of the products. Tanox is producing the products for clinical trials, to which it contributes actively in the clinical plans. For the allergy project, Tanox also retains significant manufacturing and co-promotion rights. Even if only these first two products are successful, Tanox can grow into a significant company. In addition, the experience which the company gains in clinical trials and manufacturing will enable it to better carry out the development of future projects.

It is generally believed that a larger R&D budget will produce better results, although this is not necessarily true. While large budgets permit the assembly of technical groups of different skills and disciplines to develop an identified product candidate, major scientific discoveries require the concentration of research efforts with large budgets. For a start-up company developing its own products, it is important to nurture a stimulating, non-distractive environment for its researchers. Overfunding can often result in broad-based general scientific inquiry, which distracts from the focused effort that is better suited for start-up companies.

Tanox has now reached a stage at which several new products have been conceived and identified. These projects are now beginning to enter the development phase. The risks of rapid growth have decreased as Tanox has progressed, and the company is now ready to raise more funds to assemble teams for the development of various products. Also, because Tanox has a demonstrated record of performance over the past few years, it can obtain financing on terms better than it could several years ago. Thus, the company hopes to develop the autoimmune disease and cancer projects mostly on its own. If this can be accomplished, Tanox will be able to receive a better return on the projects than it would from licensing them early in their development to big pharmaceutical companies.

The enormous manufacturing challenge

Only a small number of biopharmaceuticals, such as human growth hormone, tissue plasminogen activator and erythropoietin, have been marketed. A great number more are pending approval by governmental regulatory agencies. An even greater number of products are being developed. Most of these products will serve niche markets; some will provide the needs for very large populations of patients. The drugs that can effectively treat cancers, autoimmune diseases, neurological diseases, allergies and certain infectious diseases, each of which affects more than 50 million people, are yet to be developed, manufactured and marketed.

The consumption of tissue plasminogen activator (used to dissolve blood clots of heart attack patients), as estimated from sales revenues, is in the range of 10-20 kg for 1991. For a drug that is used by 50 million patients at an annual rate of usage of 100 mg per patient, the yearly requirement would be about 5,000 kg. It is clear that just producing a drug that can effectively treat one of the foregoing prevalent diseases will be an enormous manufacturing challenge. To meet this challenge requires continuing advances in developing higher-yielding production cell lines, more efficient but easier-to-operate bioreactors for large-scale cell cultures and equipment for medium recovery and protein purification. It is predicted that in 10 years time the highest growth of jobs for college graduates majoring in biology and chemistry will be in biopharmaceutical manufacturing. It is also likely that as the scales of manufacturing become larger and the processes become adapted for automation and easier operation, the costs of biopharmaceuticals will go down and become more affordable for patients outside the primary markets of the United States, Europe and Japan.

Prospects for international cooperation

Because drug development is so costly and lengthy, it has been the strategy of drug companies to gain governmental regulatory approvals and to market globally. The typical approach of a fledgling biotechnology company with attractive product candidates is to establish marketing arrangements with large international pharmaceutical companies, which have distribution systems in most regions of the world. To reap better returns, the small companies may reserve their local regions for their own marketing and sales. For example, United States companies often reserve the United States or North American market for themselves. Tanox plans to use a similar strategy for some of its products under development.

Drug companies have also traditionally established marketing arrangements with foreign drug or trading companies that only have regional distribution systems. This may be especially attractive when marketing a drug in a developing country. The interaction between such local drug or trading companies and the foreign biotechnology companies with strong technologies may lead to technology transfer and local product manufacturing. As the demand for biopharmaceuticals increases and the scale of manufacturing expands, it will probably be attractive for the drug developers in the industrially advanced countries to establish manufacturing facilities in developing countries. Tanox will seriously consider such arrangements when the clinical trials of its products advance to Phase III, at which time the company will have a better understanding of the efficacy of its products and hence have more confidence in estimating product demand.

Conclusion

The biotechnology industry started to evolve about 15 years ago. Since then public sentiment has fluctuated and technologists and entrepreneurs are often caught up in public emotion. Sometimes one makes unrealistic projections and sometimes one gets frustrated for not being able to deliver the expected. Planners and builders must take a long-range view of the changes that have taken place and that may occur in the future. It is very clear that in the past 10 or 20 years, biology-related technologies have been advancing at very rapid, even breathtaking, speeds. It is becoming convincing that the biotechnology industry can become a major industry in 10-15 years. Tanox hopes that, although it is a late starter, it can become a significant factor

in the biopharmaceutical evolution. A developing country considering the establishment of programmes based on biotechnology should recognize that biotechnology will have a great impact on medicine, food and the environment, and can become an important part of its citizens' lives.

V. BIOTECHNOLOGY AND AIDS RESEARCH

Jan Mous*

Recent estimates of the World Health Organization (WHO) indicate that to date there have been more than 1 million adult cases of acquired immunodeficiency syndrome (AIDS) and that at least 8-10 million adults worldwide have been infected with the human immunodeficiency virus (HIV). In addition, approximately 1 million infants have been born with HIV infection and the pandemic is spreading. In sub-Saharan Africa and South-East Asia in particular, the rate of new infections is rising steeply. According to WHO, by the year 2000 there could be up to 40 million men, women and children infected with HIV, most of them living in developing countries. In these countries the AIDS toll will have potentially disruptive demographic, social and economic consequences.

The isolation and the sequencing of the human immunodeficiency virus genome in 1984 marked the beginning of a worldwide combat by the biological sciences against the lethal virus. This genetic information and the available methods and techniques of modern biotechnology boosted the progress towards a better understanding of the life cycle and pathology of HIV. In addition, application of biotechnology enabled the rapid development of novel and more accurate diagnostic tests, of new antiviral compounds and innovative therapeutic approaches for the treatment of AIDS, and of potential vaccine candidates. A few examples described below serve to illustrate the successful application of gene technology to applied AIDS research.

The diagnosis of HIV infection

Accurate identification of individuals exposed to the AIDS virus is important in screening asymptomatic blood donors and in clinical situations related to AIDS or AIDS-associated diseases. The common screening tests used today do not detect the immunodeficiency virus itself but the antibodies which are formed in the blood as a reaction to the infection. "First generation" assays used antigens extracted from the live virus, a dangerous procedure for the staff involved in the production of such diagnostic proteins. Roche was among the first companies to develop anti-HIV screening tests based on genetically engineered HIV proteins produced in bacteria with no infectious potential. The strategy used was to join conserved regions of different genes from both HIV type 1 and HIV type 2. These were the genes coding for a protein from the core of HIV-1 known as nucleocapsid p24 and for the transmembrane envelope proteins of HIV-1 and HIV-2. This artificial hybrid gene was then inserted into *E. coli* bacteria to produce a fusion protein consisting of conserved parts of HIV-1 and HIV-2 antigens. This fusion protein has proven to be a very sensitive probe for the detection of antibodies present in HIV-1 and HIV-2 infected patients. Several thousand sera were tested in different centres throughout Europe, demonstrating a clinical sensitivity of 100 per cent for HIV-1 and HIV-2 positive samples. The commercial version of this antibody detection system, anti-HIV-1/HIV-2 EIA Roche, was launched in 1989.

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Several procedures have been developed for the direct detection of the HIV virus in peripheral blood, including co-culture experiments for in vitro propagation of virus and the use of a nucleocapsid antigen (p24) assay. Successful culturing of virus from seropositive individuals and those with a documented infection is often difficult to reproduce and, in addition, costly and time-consuming. The direct viral antigen assay is not very sensitive and is compromised by the sequestering of viral antigen in immune complexes. The introduction of the polymerase chain reaction (PCR) methodology greatly improved both sensitivity and reproducibility of the diagnosis of HIV in clinical samples. With PCR, tiny bits of genetic information in the form of proviral DNA or viral RNA can be amplified into large quantities of accessible, analysable material. The commercially available HIV-PCR test kit (VAL-I.D. PCR^{SM}) can detect one cell infected by HIV from among 10,000 normal, uninfected cells. This extreme sensitivity allows the identification of HIV genetic material in infected individuals prior to the generation of antibodies during the so-called seronegative window. Alternatively, it can be used to resolve the infection status of individuals with ambiguous or indeterminate serological status, for the screening of neonates born to HIV-infected mothers and to determine the type of virus present.

Drug discovery opportunities

For the discovery and development of new therapeutic agents for HIV-related disease, three major directions can be envisioned. The first is the development of antiviral agents directed against HIV, which is the primary cause of the disease. A second focus is upon agents that can upregulate the patient's depressed immune system. The third is the identification of novel pharmaceutical agents that can be used in the treatment of opportunistic infections that occur in AIDS patients. The two strategies generally employed to achieve these goals are random drug screening and rational drug design. In both cases gene technology plays a key role, either directly by providing new pharmaceuticals, so-called protein drugs, or indirectly by making available the necessary tools to develop "smart screens" for inhibitors of crucial enzymatic activities, regulatory proteins or receptor/ligand interactions.

Anti-HIV agents

The current concept in the discovery of antiviral agents is the specific targeting of a drug to a function that is unique to the virus, usually an enzyme or another protein whose synthesis is directed by a viral gene. In the case of HIV, a number of such proteins is being exploited as potential targets. One is the viral envelope protein, gp120. The first step in the HIV infection cycle involves the binding of the viral envelope protein gp120 to the cell-surface receptor CD4, present on helper T-lymphocytes and monocytes/macrophages. Vaccine strategies are mainly focused upon the possible prevention of this interaction. For drug discovery the high affinity binding of gp120 to CD4 also offers various therapeutic possibilities. One strategy has been to identify the gp120 binding site on CD4 and design synthetic peptides which mimic the binding domain. Another approach has been to express soluble forms of the CD4 protein or molecule fusions with toxins or immunoglobulins to block HIV infection and selectively kill HIV-infected cells. As an alternative approach we produced large amounts of recombinant gp120 and soluble CD4 to design a gp120/CD4 binding assay. This system allows high-flux screening of drugs and microbial broths to identify new compounds that can interfere with the binding of HIV to its target cells.

Since HIV is a retrovirus, its genetic information is carried in the form of RNA. Once inside the cell, the RNA is converted to DNA, which can then be permanently integrated into the host cell chromosomal DNA. Therefore, the virus can enter a "latent" phase, where the viral genome is harboured within the cells' chromosomes for lengthy periods of time until, by mechanisms not fully understood, activation can occur. Large amounts of new virus are then made and shed into the circulation, which ultimately leads to infection of many new cells. Attempts to break this infectious cycle can involve interventions in early stages before the viral information becomes permanently integrated, or in later stages to prevent viral activation, expression or assembly of progeny virus.

The pol gene of HIV encodes the enzymes reverse transcriptase, RNAseH and integrase, which are essential for the production of viral DNA and for its integration into the host chromosome. The viral enzyme protease, also encoded by the same pol gene, mediates maturation of viral particles by processing the gag and gag/pol precursor proteins to release the polypeptides essential for virion structure and to provide the active enzymes described above. All these critical enzymes are attractive targets for the design of specific inhibitors as potential antiviral therapeutics. Hence, these different enzymes were overexpressed in E. coli bacteria and purified as biologically active enzymes. These recombinant enzymes were then used for screening inhibitory substances, for evaluating drugs obtained by rational design and for crystallization studies to allow molecular modelling of lead compounds. This strategy resulted in the identification of novel candidate drugs with high antiviral potency in cell culture, some of which already entered clinical trials.

Worldwide accessibility to new HIV/AIDS diagnostics, drugs and vaccines

The efficient application of modern technology, plus the firm commitment of the research-based pharmaceutical companies, has led to the unprecedented rapid development of accurate diagnostic tests, of new antiretrovirals, of new drugs for AIDS-associated opportunistic infections and cancers and of promising vaccine candidates. Since these new diagnostics, drugs and vaccines for HIV/AIDS will probably be under patent, the initial level of pricing is likely to make these products, even if technically available, unaffordable to most of those in need in many developing countries, especially if costs must be covered by public sector/government resources. However, it is highly desirable that persons in developing countries have access to vaccines to prevent HIV infection or, if infected, to accurate diagnostic methods and to drugs that delay disease progression. Initial regulatory approval of new antivirals and drugs for opportunistic infections are likely to be based on studies conducted in populations in industrialized countries; however, research would be needed in populations in developing countries to verify the anticipated benefit. It is generally held ethical to conduct drug and vaccine research in developing countries only when some provision is made to ensure continued access of the product not only to the study participants, but to the broad population in which the trial was conducted. To tackle these problems, WHO has taken the initiative to intensify the contacts with the pharmaceutical industry in order to work out plans and proposals to improve the accessibility, the affordability and the delivery systems of new diagnostics, drugs and vaccines to the people in the developing world.

VI. A UNIQUE EXPERIMENT IN STRATEGIC ALLIANCE: ASTRA RESEARCH CENTRE INDIA

S. Anand Kumar*

The burgeoning research in molecular biology, cell biology, biophysics and immunology in the developed world has kindled hopes of immense possibilities for novel technological developments. It has raised expectations in the third world that their utilization will benefit mankind for the alleviation of suffering from disease (1, 2). However, in developing countries like India, scientific research is primarily a state-sponsored activity restricted to university laboratories and government-run research institutes. Industrial corporations in India do not have research facilities or competent personnel to transform original scientific findings to useful products, or even to adapt new technological innovations. Thus scientific endeavour has remained élitist "pure" science. Although the priority given to education during the past four decades, with the emphasis on science and technology, has produced a large number of competent personnel, many have migrated to the developed countries due to limited opportunities at home. These expatriate scientists are associated with laboratories in the developed countries engaged in front-line science, some of whom are in leadership positions. An academic network of contacts between Indian scientists at home and abroad has maintained a level of awareness with respect to the latest developments and trends in the rapidly growing areas of biological sciences. Yet in spite of the generous support from the Government of India, no major technological breakthrough is apparent (3). The reason is that the publicity is built on the myth in the characterization of biotechnology as an inexpensive small enterprise (4). A sum as high as $240 million is estimated to be the average cost and a period of 12 years, to comply with all the regulatory requirements in the United States to bring a genetically engineered product to the market (5).

Unrestrained excitement and many unfulfilled expectations have led to the realization that strategic partnering or alliance is an effective tool in taking up the challenges of integrating scientific innovation with the focus of industry (6, 7). The process of discovery to product development involves interdisciplinary teamwork. Therefore collaborative agreements between R&D companies pooling their resources and expertise have become the norm in today's world of biotechnology industry (8). In this context, the developing countries stand to gain by a self analysis of strengths and weaknesses in each venture and striking strategic alliances with suitable R&D units in the developed countries. Astra Research Centre India (ARCI) is a unique institution where such an alliance with AB Astra of Sweden is the operational motif in its goal to develop novel diagnostics, therapeutics and prophylactics for diseases afflicting large populations.

The idea of setting up the research centre was based on the realization that India had much to offer in scientific talent and competence, particularly in the areas of molecular biology, biophysics and biochemistry. ARCI is registered as a non-profit-making society. Its governing board, chaired by Professor Sune Bergstrom, discoverer of prostaglandins and recipient of the Nobel Prize for physiology and medicine, is composed of distinguished

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scientists, five of whom are nominees of AB Astra and the others are nominees of the Government of India. The association with AB Astra gives this centre a unique opportunity to collaborate with the research units of the product companies of AB Astra as an equal partner. Expertise available within each group is utilized to accomplish tasks in highly focused, time-targeted projects. A state-of-the-art laboratory with an efficient administration has been set up. A competent scientific staff has been assembled, and the centre is now poised to embark on challenging projects. In choosing projects, several factors are considered, which include the medical need for the product, competition from other companies, financial implications and feasibility based on expertise available. Coordinated teamwork is highly emphasized to accomplish tasks in a predetermined time-frame. Material resources and personnel are channelled to support projects of priority. Progress in each project is reviewed by peers and experimental priorities are determined. All personnel are evaluated annually and the advances in their career are decided on the basis of productivity.

As a beginning, ARCI initiated projects for the design and development of diagnostic procedures using immunological and DNA probe based methods for some diseases for which the methods available were not suitable for clinical and epidemiological purposes. Novel methods were developed for the detection of malarial parasites in human blood samples using DNA probes and non-radioactive procedures, Shigella and/or enteroinvasive E. coli by detecting the presence of a virulence-specific antigen, detection of specific antibodies against Taenia solium in cerebospinal fluid and the sero-detection of antibodies against a specific epitope of M. tuberculosis specific protein. The procedures are transformed into user-friendly prototype kits taking into account the background of consumers and the facilities available to them in a developing country like India. Currently, double blind studies are in progress to evaluate the efficacy of the procedures under field conditions. Long-range projects towards rational drug design and research in close collaboration with the laboratories of the product companies of AB Astra are ongoing, with the objective of developing novel antibacterials and antimalarial agents.

Although ARCI is only four years old, a successful effort has been made to transfer technology to a venture-fund-supported company. The infrastructure, which includes the ready availability of the tools of modern biotechnology research (restriction enzymes, DNA-modifying enzymes etc.), is crucial to the success of biotechnology development in the developing world. During the first two years, processes for the preparation of these tools were developed at ARCI, which have been transferred to a small company, Bangalore Genei Pvt. Ltd., formed by two enterprising scientists-entrepreneurs. The company is in its second year of successful manufacture and marketing of nearly 100 products.

Entrepreneurs like Dr. P. Babu, Managing Director of Bangalore Genei Pvt. Ltd., formerly Professor of Genetics at the prestigious Tata Institute of Fundamental Research in Bombay, should be highly commended. Technological progress in the developing world is only possible if more scientists like him take up entrepreneurial initiatives.

The example of the Astra Research Centre India is indicative of a novel way by which developing countries can harness the wealth of their competent scientists. Scientific research is a viable business idea and it should be promoted to attract investment and partnership from industrial houses of the

developed world. Alliances and partnerships will certainly lead to technological progress, to the benefit of both. A major impediment to such alliances is the policy on intellectual property rights, particularly in India. Investment in research by private industry is directly linked to protection of property, particularly when the investments are high. Even if the Government is the investor, it is prudent to protect the rights because the fruits of the intellectual endeavour should earn returns on the investment. It is particularly poignant to note the increasing number of expatriate scientists from the developing world as inventors in patent applications to European Patent Office, Paris Convention Treaty and the United States Patent Office.

Biotechnological innovations in the developing world can be brought to fruition through partnership agreements, combining expertise and sharing of information. Thus, contractual research holds a great promise for the developing world in the service sector industry.

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VII. BIOTECHNOLOGY DEVELOPMENTS IN HEALTH CARE

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Objectives

The objectives of this presentation are as follows:

(a) To review the current position of biotechnology in health care, especially the pharmaceutical industry;

(b) To explain why the market evolved in this way;

(c) To determine what are the implications of this situation for academia and the developing world.

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Chronology of the development of biotechnology in health care

Since the publication of Cohn and Boyer's work almost 20 years ago, biotechnology has developed rapidly with initial optimism and was replaced in the mid-1980s by the reality of the market-place. Specifically, tissue plasminogen activator (tpa), the keenly anticipated "clot buster" drug, was commercially disappointing, as it is difficult to show any clinical benefits over streptokinase, an established product costing less than 10 per cent of the price.

However, in the early 1990s further optimism persists, fuelled by the success of Amgen with two products, erythropoietin and granulocyte colony stimulating factor. There is continued investment in research in biotechnology and it seems clear that the commercial impact of biotechnology on the pharmaceutical industry will be profound, with most, if not all, new products entering the market in the second half of the decade having some biotechnology pedigree. Currently, the products are either proteins, polypeptides or small molecules emerging from the sort of rational drug design programmes made possible by the advances in cell biology accompanying the biotechnology revolution. Beyond the year 2000, new technologies, notably gene therapy and antisense, are likely to give rise to a range of higher advanced and potentially exciting commercial products.

Biotechnology products in 1991

The diagnostics industry, with its short product development time-scales and easier regulatory environment, has been quicker to adopt biotechnology.

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Monoclonal antibodies are used routinely in diagnostic kit development. Gene probes and gene amplification technologies, such as PCR, are poised for explosive growth. In pharmaceuticals around a dozen products are on the market, including the following:

(a) Hormones: insulin and growth hormone;

(b) Cytokines and related products: and interferon and IL2;

(c) Colony stimulating factors: erythropoietin, G-CSF and GM-CSF;

(d) Vaccines: hepatitis A and B;

(e) Tissue plasminogen activator.

There is a large regulatory pipeline, with around 150 products from 70-80 companies in clinical development. A large community of biotechnology start-ups, especially in the United States, is continuing to grow by 50-100 new companies per year, and some biotechnology majors are emerging, notably Amgen, Genentech and Chiron. Finally, multinational pharmaceutical companies are investing heavily in biotechnology, both through in-house research and, importantly, through strategic alliances with specialized biotechnology companies.

Drivers of commercialization of biotechnology in health care

The reasons that biotechnolcgy has been commercially exploited in health care rather than in other areas are as follows:

(a) Biotechnology has enabled a major advance in the understanding and treatment of disease;

(b) Health care companies are generally highly profitable and used to investing larger sums of money over long periods in searching for innovative products which are necessary to sustain their growth and profitability;

(c) Especially in the United States, there is a highly developed financial community willing and able to invest in such high-risk, high-return ventures.

To date, the role of academia has been as a provider of the enabling technology and, importantly, the entrepreneurial scientist. Governments are generally more prominently seen as regulators, but some, notably the Japanese, have been investing strategically in biotechnology research in the hope of giving their country a leadership position in biotechnology. The pharmaceutical industry has been slow to recognize the potential of biotechnology, and without the support of United States financial institutions it is difficult to see how biotechnology could have made the progress we see today.

Technology transfer today

The conventional model of technology transfer is of a start-up company being set up to exploit technology developed in academia. These companies are generally obliged to collaborate with pharmaceutical multinationals in order to develop and market products. All three participants generally benefit from

this, although ultimately the system favours the established pharmaceutical company, which can sustain the long-term development and can have a portfolio of collaborations to diversify the risk.

This model of technology transfer has developed because the bulk of investment in biotechnology has and continues to be from financial institutions, and they prefer to set up companies led by committed individuals with a personal stake in success and which can be sold as a way of recouping investment.

However, the model has some potential disadvantages. Setting up a company is expensive, and it is inefficient to invest in duplicating the development, regulatory manufacturing and commercial skills already possessed by the pharmaceuticals industry.

The companies may also be undercapitalized and are vulnerable from the need to focus on a few products. This leads to poor product flow, signalling problems in the future, even if they are successful in commercializing the lead products. They are also highly vulnerable to adversities such as regulatory hold-ups or technological obsolescence.

Future models of technology transfer

Whilst today's pattern of technology transfer will still continue to be important, other models will also exist in future. We foresee pharmaceutical companies becoming the major investor in biotechnology, and they take their returns not by selling stock in a company but by making profits on products developed from that technology. This will lead to more direct collaboration between companies and academia. The existence of a small but increasing number of biotechnology majors, e.g. Amgen, Chiron and Genentech, who have realized the stated goal of all biotechnology companies in the mid-1980s "to become fully integrated pharmaceutical companies", introduces a fourth player. They will collaborate with academics and entrepreneurial companies to maintain product flow and development of their technology base and will also continue to form strategic alliances with pharmaceutical companies to provide full access to the market-place.

Academics throughout the world are becoming much more commercial in their approach, fuelled both by need - as governments reduce funding - and opportunity. They increasingly understand how to work with companies, especially the need to communicate well, meet deadlines and be accountable, and they have established better commercial arrangements for technology transfer, allowing all parties to benefit from commercial success.

The lesson of this analysis is that, in future, financiers and, increasingly, pharmaceutical companies are the key to success. They need commercially exploitable technology, the right vehicle for exploitation and commercial attitudes. Around the world Governments and academics need to respond to these needs by providing investment in basic research and encouraging transfer of technology into established and start-up companies.

B. Commercialization issues: food processing/agro products

VIII. FROM ROMANCE TO REALISM: OPPORTUNITIES AND ISSUES IN COMMERCIALIZING BIOTECHNOLOGY IN THE FOOD INDUSTRY

K. Venkat*

Introduction

Biotechnology is ushering in a new era in the history of mankind. Its impact is widely recognized to be far-reaching. It is expected to radically change the way we do things, be it in human health care, animal husbandry, agriculture, food processing or environmental management. Although the thrust of the first generation of modern biotechnology has understandably been in high-value/low-volume human therapeutics, the grass-roots impact of biotechnology is likely to be realized in a much broader and more significant way in agriculture and food processing. Biotechnology can influence every facet of food production and distribution, from the farmer to the consumer.

"Modern" biotechnology owes its origins to the fundamental discoveries and inventions made in the mid-1970s, which allow one to isolate, clone and express genes abundantly. Genes of interest can thus be transferred from one species to another. Success of this genetic engineering approach has been demonstrated in a wide variety of applications. Many of these developments have already been translated into commercial practice, particularly in human health care products. A number of business issues have had to be dealt with and resolved before the successful reduction of the technology into commercial products. These include patent/legal issues, government regulations, such as those mandated by the United States Food and Drug Administration (FDA), consumer acceptance and market development.

Commercializations in the agriculture/food area lag significantly behind those in the human therapeutics and diagnostics areas since the potential barriers to enter the market-place are even more challenging. For instance, many more federal agencies and regulations, in addition to FDA, are involved, including the Environmental Protection Agency (EPA) and the Department of Agriculture (although the United States agencies are cited here, similar organizations and regulations are operative in other countries). Consumers' "fear of the unknown" presents an even more formidable problem when it comes to food products.

This paper analyses selected examples of biotechnology-derived agriculture/food products from the developed world which are already in the market-place or are close to commercialization to provide insights into:

(a) Factors contributing to successful commercialization;

(b) Related issues which must be addressed early on;

(c) Costs and benefits;

(d) Market positioning;

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(e) Consumer perceptions;

(f) Potential pitfalls.

Based on this analysis, commercialization modalities applicable to developing countries are developed and recommended.

Biotechnology-derived products in food and agriculture

While a spectacular array of applications of biotechnology is being contemplated and worked on, they may be conventionally grouped into the following categories:

Agronomic improvement in the field

These relate to the imparting of specific traits to field crops and include such applications as disease resistance, herbicide resistance and the like. Also included here are improving crop yield, as well as tailoring the composition of the desired crop materials, such as increasing specific amino acid levels in corn and altering the composition of rapeseed oil.

Improving the economics of agricultural inputs

The most noteworthy target in this category is the provision of adjuncts to nitrogen fixation and ultimately tailoring major crops to fix atmospheric nitrogen so that the external supply of conventional nitrogenous fertilizers can be obviated.

Improvements in animal husbandry

Preventive vaccines for such diseases as foot and mouth disease in cattle, improving yield through the chronic administration of growth hormones (for instance, bovine somatotropin and fish growth hormones), are examples of this category. Use of embryo transfer technology to breed elite animal varieties also falls under this umbrella.

Food processing aids

Development of the next generation of food processing enzymes through the employment of genetic engineering is a major endeavour in this area. These include both novel enzymes as well as significant cost reductions in existing enzyme applications. Rapid detection of food-borne pathogens, such as salmonella, through DNA probe technology is another commercial objective.

Food ingredients

Cost reductions of ingredients already in use and development of novel functional ingredients are both targets in this category. A substantial decrease in the cost of sweeteners such as aspartame, through genetic engineering, is already in the commercial arena. Development of novel polysaccharides and food gums is being actively worked on. A new generation of food flavours, ingredients and natural colours through improvements in tissue culture technology is also being pursued. That the latter represent "natural alternatives" to chemically synthesized counterparts may present a unique market positioning opportunity in the developed world. The use of novel protein hydrolysates to achieve important functionalities, such as fat mimetics, represents yet another emerging commercial opportunity.

The basic technology involved in many agriculture applications is genetic engineering, which has been particularly successful in conferring single gene traits, such as disease resistance, into crop plants. Cell fusion and cell selection technologies, including somoclonal variations, have been gainfully employed as adjuncts for this purpose. Where a desired trait is a multigenic one, the underlying problem is far more complex. The exact biochemical pathway leading to the culmination in a desired trait, such as increased solids level in a tomato fruit, is yet to be achieved since the exact genes involved in the pathway are not clearly delineated in such cases. Attempts have been made to resort to the identification and cloning of the likely genes responsible through brute force methodology, such as restriction fragment length polymorphism (RFLP) technology. However, this has produced very limited success.

A particularly exciting technology, useful in reducing and/or eliminating undesirable functions, is antisense technology. It has been used, for instance, to turn off food processing enzymatic activities such as polygalacturonase in tomato.

Selected commercial examples

Genetically engineered heat stable starch liquefaction enzyme

Enzymatic depolymerization of native starch suspensions with α-amylase enzyme is the starting point for the multibillion-dollar corn wet-milling industry in the United States. It has been used in this industry for many decades and is a relatively simple enzyme produced as an extracellular protein by different organisms. The liquefaction reaction is carried out at temperatures above 105° C, and the half-life of the enzyme is limited at these temperatures. A more stable enzyme preparation could catalyze the same reaction with a lesser dosage and thus result in reduced enzyme cost. This objective has been achieved by introducing a thermostable-amylase gene from a thermophilic bacterium to a *Bacillus* species.

Originally developed by CPC International, a major player in the United States corn wet-milling industry, this development has already been commercialized. Although CPC could have retained this as a proprietary development for its exclusive internal use, the competitive advantage to be gained from reducing the enzyme cost is somewhat limited. In other words, it accounts for less than 1 per cent of the finished product value. Therefore, CPC licensed the technology to a separate entity, Enzyme Biosystems Corporation, for its production and supply to all companies in the corn wet-milling industry, thus generating a higher revenue for the product to the benefit of the entire industry.

The choice of *Bacillus* as the host organism greatly simplified the regulatory approval process since the same genus has had extensive use as a source of non-engineered α-amylase for a long time. In addition, the FDA classifies *Bacillus* as a GRAS (Generally Recognized as Safe) organism and as such does not require extensive studies to establish its safety.

This is an example of a relatively modest cost-reduction-driven genetic engineering success. Even though the unit cost reduction is relatively small, it still amounts to a meaningful level of total savings, enabling it to be commercially viable. Fewer consumer issues were involved here since the enzyme itself is used in extremely small quantities in processing corn starch

and it is totally denatured in subsequent processing steps, i.e., the enzyme itself is not the final product nor does it appear in its active form in the final product.

Bovine growth hormone

Bovine somatotropin (BST) is an endogenous growth hormone in cattle. By boosting its level, through exogenous introduction, it is possible to improve the growth and performance of such animals, particularly dairy cattle. Essentially, it results in increased milk yield in dairy cows by as much as 15 per cent on a sustained basis. It is also possible to alter the body mass of such animals wherein the ratio of fat to protein is decreased. With the ever-increasing demand for reduction of saturated fats in the Western diet, such leaner animals would have a market appeal.

The BST gene has been successfully cloned and expressed in large quantities in bacteria. Extensive field trials have established increased milk yields, and independent safety studies have indicated no adverse effects from the consumption of milk product. Nevertheless, BST commercialization is bogged down in a quagmire due to a number of external factors.

The principal challenge to commercial acceptance is the very genesis for the development of the project in the first place, i.e. is there a market need? The Western world is awash in a deluge of excess milk and dairy products. Therefore the value of producing an even greater excess is being debated. Although the size of the dairy herd would eventually be reduced to maintain the appropriate market equilibrium (fewer cows producing the total milk demand), this issue has become an emotive one among many dairy farmers. Several leading dairy states in the United States have banned the use of BST in spite of its endorsement by FDA. Leading food processors such as major ice cream manufacturers have also independently and unilaterally decided not to use milk from BST-infused cattle. This is clearly a case of not satisfactorily managing market perception issues. Furthermore, the cost of BST is significant, about $0.50 per animal per day.

Monsanto is the leading developer of BST and the company has already expended millions of dollars in trying to bring it to the United States market-place. The other players in this and other growth hormones are American Cyanamid and IMC (International Minerals and Chemicals). Whether this product will ever see the sunshine of the market-place is still open to debate. It appears to have a questionable need, equivocal economics, strong political opposition and almost belligerent consumer non-acceptance. However, BST could be a boon to both Eastern Europe and many developing countries.

Aspartame intermediate

Aspartame is a major non-caloric sweetener extensively used in the Western world. It is a methyl ester of a dipeptide derived from L-aspartic acid and L-phenylalanine and nearly 200 times sweeter than sucrose. Since its introduction in 1982, worldwide sales of aspartame have grown to be over $800 million per year, replacing sugar in a wide variety of food products, most notably in diet soft drinks.

Aspartame is an expensive sweetener, costing between $50 and $80/lb, depending upon a number of factors. Nearly 40 per cent of the cost of production is attributable to L-phenylalanine cost, which is primarily

produced through classical fermentation. By applying r-DNA technology, the efficiency of the fermentation process has been dramatically improved. A commercial collaboration between a small biotechnology company (Biotechnica International) and a major food processor (H. J. Heinz) developed this improved process. The entire aromatic amino acid pathway was manipulated and the concerted expression of all the genes in the pathway optimized. This results in a substantial increase in product yields, conversion efficiencies and reduced fermentation cycle time. The genetically engineered E. coli represents an interesting application of biotechnology in that the manipulated genes are all native to E. coli and no foreign genes from other species are involved. The improved process leads to a cost reduction of over 50 per cent. It is a relatively simple process, easy to scale up, and employs a clean, well-defined medium. The process is entering the final stages of commercialization.

This is a good example of a cost-driven process development.

L-phenylalanine produced by recombinant E. coli is indistinguishable from L-phenylalanine from any other source; the fact that only E. coli genes are involved and that the recombinant organism is completely destroyed at the end of the fermentation cycle significantly facilitates the regulatory status of this process. Traditional scale-up methodologies could be employed to easily translate the process to commercialization levels.

A similar process has been developed and implemented for the production of L-aspartic acid. Although the cost reduction is not as great as in the case of L-phenylalanine, it is still meaningful.

Insect resistance in cotton plants

Insect attack of cotton plants is perhaps the major reason for reduced yields of cotton around the world. A number of lepidopteran insects are involved in causing damage, and the particular species varies, depending upon the location and climate. Multiple sprays of chemical insecticides (up to 10 sprays per season) are used to control these insects. In some developing countries, such as India, nearly 50 per cent of all insecticides are dedicated to insect control in cotton. Such extensive and repeated use of chemical insecticides has led to the evolution of resistant mutants that are no longer susceptible to control by chemical agents. The environmental burden caused by these chemical insecticides is also heavy.

An alternative approach to the use of chemical insecticides has been made possible through the application of genetic engineering technology. In essence, it confers an insect resistance trait to the cotton plant. It is well known that the protein toxin produced by naturally occurring Bacillus thuringiensis (BT) is an effective bioinsecticide. When sprayed, it is known to control certain types of insects on plants. By isolating and introducing the BT protein gene into the cotton plant, it can be made to resist attack by a number of insects, including lepidoptera. The protein can be expressed throughout the plant; upon ingestion of any part of the cotton plant, the attacking insect is killed off. This is a superior approach to indiscriminate spraying of insecticides in that the resistance is contained within the plant itself.

A number of United States and West European companies have been working on insect-resistant plants via the BT toxin technology. A major United States

company has successfully demonstrated the technical feasibility and commercial utility of this approach. An important factor contributing to this accomplishment is the ability to amplify the gene expression level by several orders of magnitude so that adequate protein levels are present throughout the plant. A close collaboration between the company and a major United States university facilitated this accomplishment.

BT toxin itself has been extensively studied and it is devoid of mammalian toxicity. Extensive field trials of transgenic BT-cotton plant varieties have been conducted in multiple locations over at least two growing seasons. The field effectiveness of the genetically engineered plants has been successfully demonstrated. Appropriate town meetings to win the confidence and concurrence of the local populace were conducted prior to the field trials. There were a number of informed discussions and deliberations among opinion leaders as well as the public at large concerning the approach being taken. This was in addition to obtaining the necessary approvals for field tests from the United States Department of Agriculture. Environmental activists and lobbyists who generally tend to block the introduction of new technology or products into the environment have become surprisingly supportive in this case as they view the *in situ* insect resistance trait to be environmentally more benign than the use of recalcitrant chemical insecticides.

In addition to proving the effectiveness of this approach in actual field performance tests, extensive studies are under way to ensure the safety of cotton seed oil for human consumption and cotton seed as an animal feed.

The insect-resistant cotton plant is projected to be far more cost-effective than the use of chemical insecticides; as much as 40-50 per cent savings is possible. A long-term question that remains is whether new resistant mutant insects would arise and if so what would be the efficacy of this approach. One partial answer might reside in the use of different types of BT protein genes isolated from other species. In fact, a second-generation BT gene with a different mode of action is already being developed.

Widespread commercial use of insect resistant cotton plants in the United States is awaiting appropriate regulatory approvals, which is not expected for another three to four years despite the fact that there is an overwhelming acceptance of the transgenic plants by several cotton farmers.

Recognizing the value of this approach to many developing countries, the large United States company in question is actively embarking on a programme to license the use of this technology to some of these countries. Several commercial issues need to be addressed before such a technology transfer could be made:

(a) Although protected by major patents in the United States and Western Europe, the technology protection is far less in the developing world. Some of the countries are not signatories to international patent agreements and covenants. Considering that the BT toxin gene is ubiquitously present throughout the plant, the gene is potentially accessible to any interested parties;

(b) Hundreds of millions of dollars have been invested by the company in bringing the technology to the point of commercialization. Reasonable returns on this investment must be realized;

(c) The insect resistance trait must be transferred to individual varieties of interest in the particular country;

(d) Despite the successful demonstration of the technology, there is some reluctance on the part of individual countries to make an up-front payment;

(e) The potential application of this technology to other crops and the value associated with them have to be ascertained.

Notwithstanding these issues, a commercial license is being discussed between the company and a major developing country. The creative approach being followed here, while not yet finalized, involves the licensing of the BT gene and the associated technology for the country in question for an affordable sum of money spread over many years and triggered by meeting specific commercial milestones. The arrangement also calls for the training in the United States of selected scientists from the country in question to enable them to assimilate all the details and intricacies of the technology in a "hands on" fashion, so that this knowledge can be translated into tailoring the indigenous cotton plant varieties to incorporate insect resistance. This approach can be a model for transferring advanced genetic engineering applications to address pressing problems in the developing world in an efficacious and cost-effective fashion.

Bioinsecticides

A different means to utilize BT toxin technology is to employ the toxin directly as a spray, i.e. instead of chemical insecticides. In fact, BT-based bioinsecticides have been used in this manner for certain insect control applications for many decades. However, its effectiveness is often limited. By amplifying the amount of the toxin protein through genetic engineering, it can be enhanced. This is the basis of development being pursued by a number of companies.

Among the new United States companies following this route are Mycogen, Ecogen, Crop Genetics and Calgene. Mycogen's version of BT insecticide is now commercialized.

Perhaps the single most potential impediment to the commercialization of the BT insecticide spray was the approvals required to conduct the necessary field trials. The idea of deliberately releasing a genetically engineered organism into the environment was challenged by environmental and consumer activist groups at every turn. This became a highly charged political issue, and it required major efforts to satisfy these groups before field trials could be conducted.

Mycogen used an interesting tactic to allay the fears about the environmental release issue. Its BT toxin is contained within the bacterial cell where it is fixed following the completion of fermentation when the cells are killed. Thus, only non-living cells are released into the field in the form of a spray (although the toxins's effectiveness remains unaltered). As the green movement gathers momentum, this type of BT insecticide has won consumer/environmental activist endorsement.

The successful commercialization of BT insecticides was thus facilitated by an improved product form, careful addressing of environmental issues (and

in fact turning them to BT's advantage) and providing better economics through improved performance of the product achieved via genetic engineering.

Microbial rennin

Rennin is a protease used in cheese manufacture. The traditional source of this enzyme is animal tissue (typically isolated from calves' stomachs). Its supply fluctuates widely and, consequently, its price. A recombinant version of rennin has been successfully developed and commercialized. Pfizer and Genencor (in collaboration with Hanson in Scandinavia) are the leading developers. Pfizer's product has already been approved by FDA and is commercial. The latter's version is awaiting approval in the United States, although it has already reached the market-place in certain European countries.

The major economic benefit of this product is price stabilization since the genetically engineered rennin is not subject to the vagaries of the animal-based commodity market. It is also slightly less expensive than animal-derived rennin.

This is yet another example of a cost- and supply-driven product being successfully brought to the market-place. Rennin is considered a processing aid, and as such the FDA regulations are a bit simpler. However, recombinant rennin has to go through the entire gamut of toxicity and safety testing.

Engineered tomato

As mentioned earlier, antisense technology has been successfully employed to substantially reduce undesirable enzyme activities in the tomato fruit. Calgene and ICI are two key companies involved in attempting to commercialize these developments. The advantages are better ripening control, improved field handling and transportation characteristics and enhanced yield in processing. This development has yet to win FDA approval. Key questions surrounding the approval process are the safety of finished products and effective testing protocol to assure the same. Appropriate market positioning would be necessary to convince the consuming public about the safety of the products. Ultimate economic parameters have also yet to be firmly established.

This is an exciting application of antisense technology which could be a precursor to a number of similar applications in other fruits and vegetables. However, the factors mentioned above have to be worked out for each case to ensure its commercial viability.

A related example is the application of tissue culture and related technologies (non-genetically engineered) to improve the organoleptic and textural properties of selected vegetables. Spearheaded by DNA Plant Technology Corporation, such vegetables are being test-marketed in a joint venture with DuPont under the brand name Vegisnacks. These products do not require FDA approval as no gene transfer is involved. The purported advantages are improved taste and colour parameters. Whether the consumer is willing to pay a premium for this remains to be seen. Clearly this development is market-driven. While an interesting concept, it is perhaps of little interest to the developing world.

Factors critical to successful commercialization

The foregoing examples illustrate the unique application of modern biotechnology techniques to commercial targets. There are a number of hard

business issues that must be addressed carefully and resolved prior to commercialization. These issues would be equally important in the third world as well, as these technologies are translated to appropriate applications there. Discussed below are the specific aspects of some of these key factors.

Market need

It is imperative that the market need for a specific application is understood and established a priori. It could manifest itself in the form of a cost-reduced product, improvements to an existing product, such as a chemical insecticide, unique new products and applications, price stabilization etc. The size of the potential market and barriers to entry would dictate the extent of affordable research and development cost. Market positioning and dealing with consumer issues, real and perceived, is of paramount importance. As exemplified by the BST case, it is easy to underestimate opposition from different constituencies.

Development cycle time

The genetic engineering industry is fraught to a certain degree with the "herd mentality". Since a number of companies pick and work on similar targets, establishing early market presence is of vital importance. In addition to their internal resources, companies that exploit external relationships with academics and strategic alliances with market-oriented partners stand to gain substantially. In fact, the latter are becoming more of a norm, e.g. a developer of an advantageous trait, such as insect resistance, works with a seed production and distribution company to ensure early and ongoing market knowledge and access to an established distribution system. To develop and implement a true vertically integrated chain s becoming less attractive, particularly since getting to the market-place first is a powerful competitive advantage.

Patent/legal issues

There is an enormous backlog in biotechnology patent applications. It takes considerable time and expense to work one's way through the system. Unlike pharmaceutical products, agricultural/food applications tend to have less comprehensive patent protection. This is further exacerbated by the fact that the patented entities are often present in plants in the open field and as such are readily accessible (as illustrated in the case of the BT resistant cotton plant). A number of approaches are being pursued to ensure that such intellectual property is properly protected, including the imprinting of a genetic signature and the use of hybrid seeds. While these are of some value, their ultimate utility has yet to be tested in real life cases.

Field testing

It is meretriciously appealing to project optimistic commercialization timetables based on limited greenhouse and field tests. But these tests always take longer in real life. Notwithstanding the time and effort required to obtain necessary approvals for field trials, it is imperative to conduct extensive and thorough multigeneration field evaluations. Teaming with and/or employing first-rate plant breeders is a prerequisite for achieving successful completion of this phase. In addition to proving the efficacy of the improved trait, there must be no significant changes in all the other agronomic traits, such as field yield, i.e. the engineered trait should be a valuable addition

to the existing commercial traits. Even when approved for commercial use, market penetration takes time and tends to proceed in successively increasing segments and it is certainly seldom an overnight conversion. An appropriate field sales force must be deployed to convince and win the confidence of the farmers. An exciting technology alone does not represent a winning ticket.

Costs and benefits

While intuitively obvious, the economic benefits must be real and convincing. In the case of agricultural applications, improved traits should guarantee adequate economic incentives to the farmer. For instance, if a herbicide-resistant tomato variety saves about $100 per acre net in reduced weed control cost, the grower expects to capture at least 50 per cent of the net savings. This in turn should enter the overall economic equation of a given product to keep potential returns in a realistic perspective.

The thermostable α-amylase example shows that in spite of improved functional properties and reduced enzyme usage it may not translate significantly to the bottom line since this enzyme accounts for less than 1.0 per cent of the cost of the finished product.

Managing the regulatory approval process

It is easy to underestimate the extent of field trials and other testing required to get through the regulatory hurdles. Although the regulatory process is progressively becoming systemized and to some extent simplified, there are still areas where the regulations are not clearly defined. Early dialogue with the regulatory authorities and working with them closely is an essential ingredient for success.

Consumer issues

Food products are chosen by consumers on a daily basis. As such it represents a complex set of realities and perceptions. Careful education of not only the consumers but also the key opinion leaders in a credible fashion is an absolute requirement for market-place success. Clearly, there is no single correct way to do this. Each product and application must be approached on an individual basis. Involving representatives of the affected constituencies and proactively seeking their counsel and incorporating their inputs into the overall development plan is a must. Continual follow-up and timely responsiveness are also critical elements.

Opportunities and development strategies for third world countries

Biotechnology-derived products and applications represent a dramatic opportunity for the developing countries, particularly in the food/agriculture sector. Fruits of this technology can be managed to benefit the populace at the grass-roots level. Agriculture applications such as disease-resistant crop plants can be introduced without major capital investment requirements. In addition to capturing the obvious benefits of the technology in terms of reduced costs of plant disease control, other benefits such as drastic pollution reduction and foreign exchange savings are obtainable. Food processing developments can similarly be harnessed to produce and possibly export value-added food products.

While the Governments of the developing world as well as international organizations such as UNIDO have definitely recognized the potential benefits

of biotechnology and have clearly instituted many projects and programmes, a concerted effort should be mounted to move the early fruits of this technology to the commercialization front. Agricultural developments of the type described here are excellent candidates to transfer to the developing world now. They can, in effect, provide a jump start to push biotechnology to practical utility. Properly planned and executed, they can be complements to existing biotechnology programmes in these countries. In the short term, selected technologies and specific applications can be licensed from the developed countries as a means of accelerating commercialization. The following are suggestions and recommendations to consider in this regard:

(a) License and internalize single gene trait genetic engineering applications such as disease resistance;

(b) The licensing agency can be a government body, a private entity or a consortium of private companies;

(c) If appropriate, form a joint venture with the appropriate industrialized country company;

(d) Stage payments over a period of time, tied to the accomplishment of specific, measurable and meaningful commercial milestones;

(e) Make arrangements to train local scientists/technicians to incorporate the technology to local varieties etc.;

(f) Leverage local strengths, such as the ability to conduct extensive (and possibly less expensive) field trials;

(g) Protect local germplasms and leverage them as part of technology licensing considerations;

(h) Local production and export of hybrid seeds could also be part of such considerations;

(i) Review and modernize patent and trade-secret laws and regulations;

(j) Where appropriate, simplify the regulatory approval process without unduly sacrificing the necessary rigour.

Emphasis may be gradually shifted to indigenous technologies and products over the medium to long term. To speed up commercialization of internally developed technologies and applications, a variety of traditional and novel mechanisms can be considered, such as:

(a) A new breed of entrepreneurialism should be encouraged;

(b) Provide start-up venture capital to initiate a commercial project;

(c) Capitalize on outside management talent to support and encourage technology-based ventures;

(d) Encourage local private industry involvement in biotechnology projects at an early stage, emphasize commercialization and promote university-industry collaborations;

(e) Form a variety of strategic alliances with developed country companies and academic/research institutions; balance basic and applied research programmes;

(f) Strive to implement and showcase one or two commercial successes at an early stage;

(g) Provide a forum for an on-going dialogue between industry and academia;

(h) Harness developments in food processing technology via similar collaborations/licensing/joint-venture routes;

(i) Invigorate and stimulate projects and programmes to develop and commercialize value-added products.

Clearly, there is no one correct approach. A portfolio of approaches and initiatives is needed. Biotechnology is still in its infancy; some early commercial successes are needed to sustain the momentum of development and its propitious translation to practical value.

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IX. PRODUCTION OF BIOMEDICAL PROTEINS IN TRANSGENIC DAIRY COWS

Herman A. de Boer*

Introduction

Several proteins of biomedical importance have been synthesized via recombinant-DNA methods in various cell culture systems. Bacterial, yeast, fungal and mammalian cell cultures have been used for this purpose. The choice of the most suitable expression system depends primarily on the protein to be produced. As a general rule, complex proteins (such as tissue plasminogen activator, erythropoietin and factor VIII), requiring specific post-translational modifications, have been successfully produced in mammalian cell cultures, whereas simpler proteins (such as insulin, growth hormones and cytokines) have been successfully produced in bacterial and yeast fermentation systems. Production systems based on expression of cloned genes in bacteria or yeast are much more efficient than systems based on expression in mammalian cells. In the latter system it is relatively difficult to produce large quantities of the protein. As a consequence, the production costs of such proteins on a per gram basis are very high. Such systems are therefore not suitable for high-volume low-price proteins. Mammalian cell culture systems and bacterial systems are also unsuitable for the production of proteins with a nutritional function.

Expression of biomedical and nutritional proteins in milk of transgenic dairy cattle

Transgenic dairy animals, in particular cows, are likely to be highly suitable for the production of novel biomedical and nutritional proteins because a single cow can produce per year more than 10,000 l of milk containing as much as 340 kg of proteins (mainly caseins) at costs close to $0.01/g. Cows are such cheap protein producers due to their large capacity for protein synthesis and the secretory system in their mammary gland combined with low feed costs and the high efficiency of modern dairy farm management. In addition, cows are easy to multiply using natural mating procedures complemented by artificial insemination and embryo transfer procedures. In comparing transgenic cows to other r-DNA-production routes, it should be noted that bovine mammary epithelial cells are not only more cost-effective than cultured cells, but they are also able to produce continually over 300 days per year. Moreover, since milk can be collected several times a day, the time between actual synthesis of the protein and its harvest can be as short as a few hours, in contrast to fermentation systems. Also, the cow has a genetic stability that is higher than cell-culture-based production systems. Consequently, the frequency of amino acid substitutions due to mutations in the gene encoding the protein product will be lower than that in tissue culture systems.

In terms of downstream processing, production in milk of transgenic animals has the advantage that most heterologous proteins will end up in the whey fraction after caseins are precipitated using a simple acidification or enzymatic procedure. Such a purification procedure can be easily scaled

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up, also in developing countries, using techniques common in the dairy industry.

Many biomedical and/or nutritional proteins can be considered as candidates for production via the milk gland of dairy cattle. High volume, low cost proteins are obvious candidates due to the very low maintenance costs of cows. Human serum albumin is such an example of a biomedical protein. In table 1, a number of candidate proteins are listed along with the equivalent volumes of human blood plasma that would be required to obtain similar quantities.

Table 1. Advantages of transgenic animals in processing biological products

Protein	Estimated U.S. market per year a/	If expression level is: (g.l)	Number of animals needed (10,000 l/ animals	Human blood plasma levels (mg/l)	Equivalent volume human plasma b/ (l)
Factor VII	-	-	-	0.5	-
Factor VIII	120 g	0.01	1.2	0.1	1.2×10^6
Factor IX	-	-	-	5	-
Protein C	100 kg	0.1	100	5	20×10^6
Fibrinogen	200 kg	1.0	20	4 000	0.5×10^6
AT III	800 kg	1.0	80	200	4×10^6
Albumin	100 000 kg	2.0	5 000	50 000	2×10^6

a/ Based on 100% recovery.

b/ About the same for the European market and the Asian market.

Whether the production method of choice for a particular protein will indeed be the cow depends on a variety of economical and technical factors. Moreover, the economical considerations will depend on the local (bio)technological infrastructure. Thus, the considerations to be taken into account for selecting between tissue-culture-based manufacturing processes and transgenesis will be different for a developing country than the considerations to be applied in the developed world. This may be especially true for low volume, high priced proteins. As mentioned above, in developed countries such proteins are usually made in factories containing cell-culture fermentation systems. These production systems require a large amount of high technology and highly trained and specialized operators. The establishment of such tissue-culture systems in a developing country may be very difficult, not only from a technical and economic point of view, but also because of limitations on the

number of personnel with the proper skills. Thus developing countries may consider using transgenic animals as "bioreactors", since such bioreactors renew and multiply themselves by generating their own progeny. High technology is only needed at the very beginning and is only required for the generation of the transgenic founder animals. Once the founders are made, the transgene is inherited to the offspring in simple Mendelian fashion. For high volume, low cost biomedical proteins, dairy animals are economically attractive in both the developing and the developed countries.

Thus the actual production phase does not require high technology. This is particularly true when it concerns proteins that have a nutritional purpose and biomedical proteins that need to be taken orally, as these proteins, when produced in milk, require relatively little or no purification; concentration of the whey fraction in combination with procedures common to the dairy industry will suffice. Good examples of such proteins are those with a bacteriostatic and/or bacteriolytic function and which can serve a biomedical and nutritional function. An example of such a protein is (human) lactoferrin.

That heterologous proteins can be produced in the mammary gland of various mammals has been amply demonstrated, and a high level of up to 30 g/l in milk has been demonstrated (see e.g. Bio/Technology 1991, 9:844-847).

The case of lactoferrin

Lactoferrin (LF) is a member of a group of proteins that play a role in the general defense system of man and animals. This and other antimicrobial proteins are generally found in secreted fluids (milk, tears, sweat, saliva, vaginal secretions and sperm) and in the cells of the immune system that are specialized in the killing of invading pathogens. Apart from its bacteriostatic function, lactoferrin also plays a role in the transfer of iron from mother to child via the milk. There is reason to believe that this protein exerts its bacteriostatic action by two different mechanisms, i.e. titration of free iron from the environment, thereby reducing its availability for organisms with a high iron demand such as *E. coli* and secondly by direct interaction of LF with the bacterial (outer) membrane. This interaction causes membrane destabilization and increases its permeability for other compounds, among which are lysozyme and several classical antibiotics that normally do not act on gram negatives (1).

Recent data indicate that LF is also able to bind to the lipopolysaccharide (endotoxin) component of the outer membrane of gram negative bacteria (2). This activity is of particular interest as endotoxin is an important mediator of septic shock caused by systemic infection. Prevention of death of mice caused by intravenous injection of a lethal dose of *E. coli* cells with LF has been demonstrated (3). Whether this effect in mice is indeed caused by endotoxin neutralization and whether these results will also apply to other animals and to humans, remain to be demonstrated.

Utility of transgenic technology for developing countries

These activities of LF and related bacteriostatic and bacteriolytic proteins could be of special interest for developing countries in particular if it appears that in a clinical setting LF and other proteins with an antibiotic function are active in combating bacterial diarrhoea, a disease that kills about 5 million children annually worldwide. If effective, formulations containing such proteins could be used on a continual basis in order to help

prevent the disease. It will also be of importance to examine whether such antibiotic proteins will have a beneficial effect on the gastrointestinal infections often associated with AIDS.

The possibility of administering antibiotic proteins that are normally present in mothers milk to infants, children and patients would offer a distinct advantage over classical antibiotics, as treatment with those compounds is undesirable for various reasons, among which is the danger of developing resistant pathogenic strains. It is hard to imagine that such problems will arise by consuming a protein that all breast-fed infants have consumed in large quantities during the first months of their life. Obviously, a lot of studies in the clinic and the field still need to be done in order to establish the efficacy of these interesting proteins.

In order to be able to carry out such studies, large amounts of these proteins are required. This can obviously best be done via the milk of transgenic dairy animals, as the milk of human donors is relatively scarce and insufficient to undertake clinical studies on a statistically sound basis. The birth of the world's first two transgenic calves harbouring the LF gene containing mammary-gland-specific regulatory sequences is an important first step towards this goal. The technology underlying this new development in animal breeding has been described (4) and its potential impact on the industry has been highlighted (5, 6). Milk may shake up the industry indeed.

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X. VISIONARY REGULATIONS: AN ESSENTIAL COMPONENT FOR SAFE TECHNOLOGY TRANSFER AND COMMERCIALIZATION

Terry L. Medley*

Introduction

Biotechnology, defined as any technique that uses living organisms or substances from those organisms to make or modify a product, to improve plants or animals, or to develop microorganisms for specific uses (1), is a practical not theoretical science. The practical sciences are differentiated from the theoretical by their purposes or ends. Aristotle gave further definition to the practical sciences by contrasting their purposes and ends to those of the theoretical sciences. Whereas the end of theoretical sciences is knowledge, the end of practical sciences is not merely to know, but rather to act in the light of that knowledge (2).

A national implementation strategy for biotechnology in agriculture should focus on solving important scientific and agricultural problems, effectively using the funds and institutional structure available to support research and training researchers in new scientific areas. However, to be a comprehensive and truly meaningful national strategy, it must place equal importance on efficiently transferring technology (3). The national strategy must assure successful technology transfer for expanded development and commercialization of the products of biotechnology. In February of 1991, the United States President's Council on Competitiveness issued a report on national biotechnology policy (the summary of its recommendations is presented as the annex to this chapter). The report describes the competitive status of American biotechnology and outlines the goals of Administration policy to support free-market development of biotechnology products. It examines three critical policy areas: support for science and technology; risk-based regulation of health and safety; and access to capital and financial resources and protection of intellectual property rights (4).

This paper will discuss some of the current regulatory policies and issues in regard to the commercialization of agricultural biotechnology products. It will focus on the facilitation role of regulations in technology transfer rather than the normally attributed role of constraining or impeding technology development or commercialization. Specifically, it will offer recommendations on a philosophy, on risk-based policy and on public acceptance.

Philosophy

Biotechnology offers new ideas and techniques applicable to agriculture (5). Biotechnology, as a tool, offers tremendous potential to improve agricultural productivity, decrease our dependence on synthetic chemicals and enhance our ability to produce food on marginal lands (6). Crucial to enhanced productivity, efficiency and environmental acceptability is innovation. The successful safe transfer and utilization of agricultural products of biotechnology should be the result of this innovation (7).

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In order to facilitate safe technology transfer and commercialization of agricultural biotechnology products, the regulations must be based upon logical reasoning rather than empirical methodologies. The philosophy at the United States Department of Agriculture (USDA) concerning the regulation of agricultural biotechnology products is based upon logical reasoning and several principles contained in two National Research Council studies on the introduction of genetically engineered organisms into the environment (8, 9). Two of these principles are as follows:

(a) There is no evidence that unique hazards exist either in the use of r-DNA techniques or in the transfer of genes between unrelated organisms;

(b) The risks associated with the introduction into the environment of DNA-engineered organisms ... [are] ... the same in kind as those associated with the introduction into the environment of unmodified organisms and organisms modified by other genetic techniques (10).

Utilization of these principles enables USDA to ask the most appropriate questions about the biology of the organisms being reviewed (11).

Equally important to safe technology transfer and commercialization of agricultural biotechnology products is the focus of the regulatory philosophy. Therefore, the focus must logically be a visionary one and not one of hindsight, i.e. the perception of events after they have occurred.

For example, in the area of food production, we must have a visionary focus. By the year 2000, we will have a world population of 6 billion, an increase of 1 billion people. Eighty per cent of that increase will be in the less developed countries. The population is now foreseen to double in the next 30 to 40 years, to about 10 billion people. Those 10 billion will require at least double the amount of food we are currently producing with an additional 20 per cent more to improve the diet. The greatest increase will occur in developing countries (12, 13, 14, 15).

The ability of the world to provide agricultural products depends very simply on the total available arable land and its productivity. The limitations of the total amount of land can be estimated and are finite, but limits on its productivity are bounded only by our creativity and willingness to use the results of that creativity.

The regulatory philosophy and its focus will either aid or hinder the acquisition of knowledge and its safe use. The acid visionary test would require our vision to be at least 20/20, and we must guard against diplopia - subjecting agricultural biotechnology products to double review (16).

Risk-based policy

Achieving the desired goals of expanded development, safe technology transfer and commercialization of agricultural biotechnology products requires that a high priority be placed on utilization of appropriate oversight structures. Oversight refers to the application of appropriate laws, regulations, guidelines or accepted standards of practice to control the use of a product based on the degree of risk or uncertainty associated with it. In the area of regulations and the implementation of mandatory review requirements, it is of paramount importance that these requirements be balanced and commensurate with risk (17).

If structured and administered properly, regulations can facilitate rather than impede expanded development, safe technology transfer and commercialization of agricultural biotechnology products (18). Regulations should prevent or at least mitigate risks and not inhibit innovation and product development. Development of regulations that neither overregulate nor underregulate is a most formidable task for any national authority (19).

Specifically, the national authority must ensure that the regulatory structure adequately considers health and environmental safety standards as biotechnology is transferred from the laboratory to the field to the marketplace. The exact nature of the regulatory structures implemented will have a direct impact on the potential contribution to the country's economy. It will also directly impact the competitiveness of the country's agricultural producers in both domestic and world markets (20, 21). For agricultural biotechnology, as in many other high technology industries, national regulatory structures are a critical determinant of the time and the cost to bring a product to market. The cost of testing to meet regulatory requirements, the potential for delay in regulatory approval and the uncertainty associated with possible imposition of extensive restrictions or outright disapproval of new agricultural biotechnology research or product could present substantial barriers to product development (22).

To avoid unnecessary burdens on biotechnology, the national authorities in the United States have sought to eliminate unneeded regulatory burdens from all phases of developing new biotechnology products. This includes laboratory and field experiments, product development and eventual sale and use (23). To provide guidance in determining the level and type of necessary oversight or regulatory review, the following four principles of regulatory review were developed:

(a) Federal government regulatory oversight should focus on the characteristics and risks of the biotechnology product, not the process by which it is created;

(b) For biotechnology products that require review, regulatory review should be designed to minimize regulatory burden while assuring protection of public health and welfare;

(c) Regulatory programmes should be designed to accommodate the rapid advances in biotechnology;

(d) In order to create opportunities for the application of innovative new biotechnology products, all regulation in environmental and health areas ... should use performance standards rather than specifying rigid controls or specific designs for compliance (24).

In the establishment of risk-based regulations, the technique or process by which an agricultural product is modified should not be the sole litmus test for the determination of risk. Although knowledge about the process used is useful in assessing the characteristics of a modified organism, use of new molecular techniques does not a priori establish risk (25). The goal of the above principles is to ensure that regulations and guidelines affecting biotechnology are based solely on the potential risks and are carefully constructed and monitored to avoid excessive restrictions that curtail the benefits of biotechnology to society (26).

Public acceptance

As commercial biotechnology enters the 1990s, there are of course uncertainties, but there are also many certainties. The first certainty is that biotechnology is fundamental. The exploration and manipulation of life structures and processes at the molecular level and the application of the knowledge gained represents a genuine revolution for society at large, a revolution that is just beginning to unfold. This industry is necessary and permanent (27).

A second certainty is that an array of powerfully innovative products will be introduced in the early 1990s by the larger segments of the industry - therapeutics, diagnostics, agriculture and instrumentation - and perhaps by the smaller segments such as bioremediation. The wave of technology development in the 1970s and 1980s will be followed by a wave of product introductions in the 1990s (28). For example, the impact of biotechnology on veterinary medicine and animal health is already significant, and it continues to grow at an exponential rate (29).

There is less certainty as to when public anxiety surrounding certain applications of biotechnology will calm. However, public acceptance of applications of biotechnology is a prerequisite for technology transfer and commercialization utilization of the products of agricultural biotechnology. Regulatory systems must include procedures that ensure that the opportunity for meaningful public participation in decision-making is available (30). Participation is essential to public acceptance of biotechnology.

The general public can learn enough about biotechnology to either be comfortable or uncomfortable with it and make informal decisions on it. When feeding the public appetite for exotic tales of our technological future, one tends to arouse equally exotic fears (31). One must continue to feed the appetite but not arouse the fears. The public must be made to be comfortable, not uncomfortable.

There are an array of effective ways to accomplish this task. Two principles that should underlie the approaches chosen should be expounded upon:

(a) When writing about your technology, remember your audience as well as your goal;

(b) Risk communication is an interactive process of exchange of information and opinion.

There is something magical about the written word. Thoughts that appear in print are deemed true or at least more credible. Accompanying this awesome power is an even greater responsibility - accountability.

Dr. Francis Crick offers the following advice on responsible scientific writing for the lay public:

> "Anyone writing on scientific matters for the lay public must try to avoid a number of hazards. He must not use excessive technical jargon or dwell too much on the many scientific details, or his readers will desert him. Especially, he must avoid oversimplification, or the science will become vacuous. In addition, he must not try to side-step difficult political, religious and ethical problems,

otherwise his writing will smack toomuch of the ivory tower. And yet he will do no one a service if, in an attempt to grab readers, he sensationalizes the issues involved" (32).

In 1989, the United States National Research Council published a report on improving risk communication. The report was intended to "significantly improve the understanding of what the problems are in risk communication, particularly the risk communication activities of government and industry". The report provided some extremely helpful recommendations to significantly improve the risk communication process. The report concluded as follows:

> "Risk messages can be controversial for many reasons. The hazards they describe are often themselves centers of controversy. Frequently, there is enough uncertainty in the underlying knowledge to allow different experts to draw contradictory conclusions. Experts are frequently accused of hiding their subjective preferences behind technical jargon and complex, so-called objective analyses. Often a message that is precise and accurate must be so complex that only an expert can understand it. Messages that non-experts can understand necessarily present selected information and are thus subject tc challenge as being inaccurate, incomplete, or manipulative".

There is a crucial distinction between risk messages and the risk communication process. Risk communication is an interactive process of exchange of information and opinion among individuals, groups and institutions. However, do not be misled by this principle of risk communication. Improved risk communication will not always reduce conflict (33).

Regulatory requirements for agricultural biotechnology products must be scientifically defensible. However, public perception must be adequately addressed for efficient technology transfer and commercialization.

The national authority must determine and balance the appropriate form and extent of meaningful public participation. For example, how should the public interest in reviewing the scientific data underlying a decision be balanced against industry's interest in protecting confidential information? What role, if any, will technical advisory committees play in the decision-making process? (34)

It is the author's opinion that public perception underlies public acceptance, which in turn is necessary for efficient technology transfer. "Technology transfer is basically a cultural, attitudinal, and institutional process that in the main cannot be regulated or directed by legal mandate (35)."

Conclusion

In most industrialized countries, it is often alleged that regulations governing biotechnology will impede and slow development. However, if the technological advances that are an outgrowth of a tremendous public and private investment are to be of the greatest benefit, the development of appropriate and effective regulatory structures is a necessity (36). In discussions with scientists and decision makers from developing countries, the author perceived a strong aversion to placing a high priority on regulatory or biosafety review. The preferred priority is that of technology acquisition. Biosafety issues are seen as unnecessary barriers to acquiring and applying technology (37).

However, if technology transfer, expanded development and commercialization of agricultural biotechnology products are the desired results, an appropriate biosafety review structure is essential. Without the appropriate biosafety review structure, those in the international development community will be hesitant to transfer experimental products for testing and development. Both demonstrate a need for a structure that is visionary and proactive, based upon sound scientific principles and responsive to public needs.

Annex

THE PRESIDENT'S COUNCIL ON COMPETITIVENESS REPORT ON NATIONAL BIOTECHNOLOGY POLICY: SUMMARY OF RECOMMENDATIONS

1. SCIENCE AND TECHNOLOGY - Building for the 21st Century

Council on Competitiveness Actions

1-1 To foster competitiveness and the commercialization by the marketplace of discoveries, including new biotechnology research, each agency should vigorously implement the provisions of the Technology Transfer Act, as amended. Agencies should inform university administrators that seeking commercialization of research in cooperation with U.S. industry is an important element in Federally-supported university research.

1-2 To ensure the highest ethical standards by participants in the government regulatory process while facilitating the interaction between scientists and industry, guidelines should be developed to require full financial disclosure of relationships between Federally-supported or employed scientists and commercial entities when the scientist is involved in a clinical trial of an associated product.

1-3 The Federal government should facilitate the training of a sufficient number of scientists and engineers at the graduate, doctoral and post-doctoral levels in science and engineering fields, including those related to biotechnology. Programs should foster multi-disciplinary training, such as through biotechnology centers, and the training of women and minorities.

1-4 Federal immigration policies should consider the value of retaining our competitive edge in areas such as biotechnology by putting greater emphasis on a prospective immigrant's skills. The provisions of the Immigration Act of 1990 should be fully implemented to allow those who can make a major contribution in important fields to enter the country, and to encourage those who are here to stay.

Initiatives for Further Study by the Biotechnology Working Group

1-5 Federal funding allocations for biotechnology research within the fields of agricultural, biomedical, energy, and environmental research should be examined and areas of opportunity identified for support.

1-6 While Federal research programs should continue to have increased support for basic sciences as the top priority, further attention should be given to the need for funding to support the development of enabling and scale-up technologies. The Biotechnology Working Group should identify means within existing programs to encourage the development of these generic, pre-competitive technologies that benefit all firms.

2. RISK-BASED REGULATIONS - Protecting Safety Without Unnecessary Burdens

Council on Competitiveness Actions

2-1 The Administration should use the Four Principles of Regulatory Review to guide agencies in determining the level and type of necessary oversight or regulatory review. The goal of these principles is to ensure that regulations and guidelines affecting biotechnology are based solely on the potential risks and are carefully constructed and monitored to avoid excessive restrictions that curtail the benefits of biotechnology to society.

2-2 The Administration should publish in final form the "Principles for Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits."

2-3 The Administration should oppose any efforts to create new or modify existing regulatory structures for biotechnology through legislation. Any necessary adjustments can be accomplished through policies and regulation based on the Four Principles of Regulatory Review.

2-4 Agencies that oversee biotechnology products and research should adopt guidelines and regulations that are consistent with the Four Principles of Regulatory Review and the "Principles for Federal Oversight of Biotechnology."

2-5 The Biotechnology Working Group should prepare an oversight policy. Under the auspices of the Council on Competitiveness, a policy statement describing the Administration's oversight of new biotechnology research and products not in the 1986 Coordinated Framework should be prepared and published for public comment no later than spring 1991.

Initiatives for Further Study by the Biotechnology Working Group

2-6 The Biotechnology Working Group should consider proposals to remove regulatory burdens by improving interagency coordination, streamlining the regulatory agencies' evaluation processes, periodically reevaluating regulations, addressing problems with state and local laws, and exploring whether non-tariff policies are being applied in such a way as to create technical barriers to trade.

3. A FLOURISHING FREE MARKET FOR BIOTECHNOLOGY - Providing Capital and Financial Resources and Protecting Intellectual Property Rights

Council on Competitiveness Actions

3-1 The Administration should continue to oppose fundamental legislative changes to the Orphan Drug Program that undermine the economic incentives to produce new drugs for rare diseases. The FDA should develop administrative proposals to address concerns about the definition of "disease" used in the program to avoid overextension of the program to treatments that are not "orphan."

3-2 The Administration should support passage of legislation to provide necessary process patent protection for products, such as those in the biotechnology area, which can be protected only through process patents.

Initiatives for Further Study by the Biotechnology Working Group

3-3 The Biotechnology Working Group should continue to examine tax issues that affect biotechnology and recommend ways of reconciling the need to remove barriers to growth and innovation generally with the other objectives of tax policy.

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XI. RESEARCH NEEDS FOR COMMERCIALIZATION OF FOOD BIOTECHNOLOGY IN DEVELOPING COUNTRIES

William Edwardson*

The food-processing sector in developing countries

The food-processing sector in developing countries is characterized by a duality: a few large-scale, often sophisticated corporations pack raw commodities for export and process products derived from these, existing alongside thousands of informal, family and small-scale enterprises that market raw, prepared or processed produce mainly for domestic consumption. Although the domestic population represents a high-volume market, the low levels of disposable income in developing countries and the limited infrastructure available for food handling means that there is only a small market for processed products. Most food is handled in the raw state, which inevitably leads to significant losses in quantity and quality, seasonally fluctuating supplies and hence often relatively high prices for scarce and perishable products. The more modern food processing plants are generally producing standard products such as bread, biscuits, dairy products and canned meats, or are producing products developed in industrialized countries under a license arrangement which allows use of the process or formulation and the right, in some cases, to use the international brand name (soft drinks, confectionary, breakfast cereal, baby foods etc.). These are generally high-cost products targeted at the high-income sector, with little produced for export.

Thus the food industry carries out little research and development despite often being the major employer of the limited number of food professionals of each particular country. These technical staff are principally involved with production and quality control. Innovation means copying or importing from abroad. The public sector research and development infrastructure at universities and national technological research centres is inadequate and underbudgeted and has little relationship with the private sector, large or small. This means that the opportunities for technical change are very limited and are essentially in the hands of the private sector - those that have the contacts and the necessary capital to import technology independently.

This situation needs to change if the food industry is to develop the great potential it has in processing for domestic and export markets, to increase the value-added and contribute to employment and income generation. Innovation has to be promoted and experimented with, as well as the most effective arrangements to bring this about: strategic alliances with private and public sector groups at the national or international level, vertical linkages between producer groups and processors and marketers (at home or abroad), investment from public and private funds etc.

Opportunities or needs for improvement

All of this has been known for years. There is evidence of major developments in the export agro- and aqua-industrial sectors in several developing

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countries in recent years, mainly due to the demand in international markets for tropical fruits and shrimps. The sustainability of these sectors is questionable, due to the lack of local research and technical services available to these new industrial sectors. This is not said in order to undermine the contribution that individual entrepreneurs and technical specialists are making in these pioneering developments, but what is needed is a commitment to develop the necessary services and technical skills and technology which will facilitate the development of more sectors not only for export, but also for the largely untapped domestic food markets.

It is here that food biotechnology could at this moment provide a technological jump to stimulate the development of the food sector. There are immediate opportunities to contribute to increase production of raw materials, custom-designed for particular characteristics or levels of desirable constituents; to reduce process time or energy requirements and therefore costs; to improve the separation of desired constituents; preservation of products; and to improve food quality assurance through rapid testing for pathogens or toxins. If applied to the tremendously varied natural resource base of tropical developing countries, the potential for development of the food sector is impressive, not only on economic grounds but also in motivating innovation in this essential sector of most developing countries.

There is a long list of constraints and barriers that will limit these developments: the point is that there are many new opportunities already available or evolving. The task before the developing countries is to choose those that are appropriate and feasible for their situation and facilitate their acquisition and adoption by local industry. This is not a simple technology transfer process. It is no longer tenable that all researchers in the public sector in developing countries (and developed, for that matter) have the luxury of carrying out research where there is no direct and explicit linkage with the ultimate user of the results - industry (new or established). Biotechnology is developing so fast that researchers in conjunction with investors, entrepreneurs and managers must come together in the adaptation of technology to local resources so that new products or improved processes are tested and put into production as quickly as possible. There is already some movement in this direction as biotechnologists are becoming employed by the private sector or, more significantly, are going into business themselves, as we have seen occur in developed countries. This is of course nothing new as traditionally, once they are professionally trained, many LDC graduates enter their family's business or, once they have accumulated capital from their wider family, go into business for themselves. The difference is that in the biotechnology field they carry on research.

IDRC experience in research for development in the food-processing sector

The International Development Research Centre (IDRC), in Canada, is a public corporation which finances applied research in developing countries aimed at improving the lives of the poor. Projects are identified, executed and managed by indigenous researchers.

While the IDRC has a number of specialist divisions dealing with social sciences, health, information, communication and earth and engineering sciences, the work of the Agriculture, Food and Nutrition Sciences Division, particularly in the Post-Production Systems Program, focuses on the improvement of the food sector.

The Post-Production Systems Program deals with all activities after farm production or fish capture and so includes harvesting, threshing, drying, storage, processing, marketing and consumer issues relating to quality characteristics etc. The IDRC approach is to encourage researchers to consider how the whole food system operates and how the solution of the problem they have identified will improve the situation; or what other opportunities for improvement exist, or are most needed in order that the desired benefits of income, employment or food are delivered to the target beneficiaries, i.e. the rural poor. This is not always possible and is certainly not immediately apparent to researchers who are, in the main, trained in a narrow discipline, such as chemistry, engineering, agronomy or food science, with little contact or knowledge of rural contexts. Thus most projects have experimented as much with a methodology to improve problem definition, research design, field testing and participation of target beneficiaries, as with specific scientific studies such as drying rates, equipment design, product development etc. This has meant that multidisciplinary teams and often more than one institution have become involved throughout or at particular stages of the projects. As there has been little experience of these approaches in research institutes in the past, this has been a process of learning by doing. The major IDRC activity is in the area of agro-industry development in rural areas, where the objective to minimize losses of crops or fish has been expanded to that of generation of additional income and employment through development of a processing enterprise which delivers a stable product for an identified market. The research activity thus incorporates commercialization considerations right from the start, as the target is the identification of a feasible enterprise for the produce from the rural areas.

Projects have evolved to four stages:

(a) Prefeasibility. Market research to identify which product types and forms are required, at what price and by whom (rural/urban consumers, other processors); community studies to determine volumes of produce, seasonality, organizational and social constraints, current marketing situation; initial laboratory work on product or process development for the promising options to assess yields, technical problems, estimates of costs of production; identification of the most feasible options from technical, economic and social points of view;

(b) Pilot plant. Design and test products, processes and equipment; optimize processing operations in terms of yields, costs and quality; testing of products with consumers and markets; adjustments; detailed feasibility;

(c) Pilot enterprise. Establishment of a pilot or commercial-scale plant in the target location; implementation of processing operations, quality and process control and enterprise management; test-marketing; monitoring of yields, costs, sales, cash flow, management and organizational conditions; adjustments for financial viability;

(d) Commercial production. Transfer to operation by community group or entrepreneurs; periodic monitoring as required.

The above are described in some detail in order to illustrate that the innovation process in such development projects is very slow and inefficient, as it has been our experience that attention only to technological research has and will have little effect on its own. Commercialization issues of how

technology will be used, where, at what scale, with whom and for whom and how will its costs be covered, must continually be assessed and taken into account throughout the project.

This approach to technological innovation in developing countries has not been easy and has not been widely adopted, as we have seen in the Post-Production Systems Program and in other technological fields supported by IDRC. Since the public sector research system has little relationship to private sectors needs (or to a very small percentage) and the private sector, for confidentiality reasons, prefers not to involve the public institutions, the output of public system research is rarely utilized and there is little contribution to development, except in the knowledge generated and the experience of researchers. This situation has been of concern to IDRC and other donors as it became clear that IDRC support was not impacting development in any major way, particularly for poor target beneficiaries. Hence IDRC's recent interest to support experimentation at the pilot enterprise stage and the commercialization stage of projects, with technologies and results from projects that have been already funded, as well as a concerted effort to ensure that researchers have spent enough preliminary study and thought in the prefeasibility phase on how the commercialization of the anticipated results could take place.

Therefore, the Centre's aim is to harness biotechnology for development. The opportunity raised by rapidly evolving biotechnology is that of dynamizing the innovation process, particularly in the food sector, as major changes in food systems are possible. There must be a shift from public sector led research in developing countries to a stronger role for the private sector, its opportunities and needs. Greater initiatives in the policy area are needed in the promotion of new enterprises in food biotechnology. The emphasis up to now on the scientific research component, the training of scientists and the establishment of research centres must be balanced by attention to broadening of industry's skills in the acquisition of technology and access to information assisted, where possible, by government programmes and policies. This too will need manpower development at this level.

Potential contribution of biotechnology

Definition

For the purpose of this paper a conceptualized definition of food biotechnology has been borrowed:

> Food biotechnology is the technology dealing with the application of the principles of food science for (a) the preservation of active food biosystems such as post-harvest fresh fruit and vegetables and post-mortem fresh muscle systems such as seafood; (b) the production of useful metabolites in food commodities containing active metabolic and degradative enzymes and contaminated with viable environmental organisms and plant cell cultures; (c) the creation of food products through fermentation of food systems; (d) analysis of food constituents and food toxicants using bioactive systems.

Potential applications in LDCs for the food sector

A list of potential applications of biotechnology in food processing includes the following:*

(a) Production of custom-designed raw ingredients. Biotechnology offers the potential to manipulate crops so as to increase the added value for the food processing industry. Custom designed commodities will have characteristics such as increased solids content, increased levels of specific amino acids and decreased level of saturated fatty acids to improve processing or nutritional attributes;

(b) Production of high-value food ingredients by cell cultures. Production of high-value products such as essential oils, growth hormones, food flavours or colours and alkaloids for medicinal purposes. Secondary metabolites will be produced economically by plant cell suspension cultures, with the added advantage of allowing the control of quality, availability and processing consistency of the ingredients;

(c) Fermentation and enzymology. Biotechnology will improve the flavour, quality, nutritional factors and yield of food and feeds, using genetically modified microorganisms and enzymes. Genetically modified food-grade microorganisms will improve bacteriophage resistance, the production of fat-modifying enzymes, or production of the natural preservative bacteriocin to help in avoiding losses due to spoilage or contamination and change dietary components. Modified enzymes will have application in several areas, from the production of beer chill-proofing to debittering of fruit juices and flavour development;

(d) Natural ingredients. The demand for natural products is favouring the use of microbial metabolites as natural ingredients in food, including biopolymers, surfactants and antioxidants. In the long-term, genetic engineering will be used to improve these components;

(e) Animal biotechnology. The use of growth hormones to increase milk production and feed value efficiency is the best-known example, coupled with the extraction of bioactive components from animal blood, milk and eggs;

(f) Waste management technology. Conversion of waste to high-value products, amino acids and antibiotics for animal consumption will increase the efficiency of food processing plants. Examples include biomass utilization for biofuel production and treatment of food-processing by-products as feedstocks;

(g) Diagnostic tools and rapid detection methods. Rapid screening methods for the early detection of pathogenic or spoilage microorganisms, toxins and chemicals in food will be based on detection kits incorporating DNA probes and monoclonal antibodies as an efficient alternative to classical microbiological techniques. These methods will have an impact on quality control and standardization in the food industry throughout the world.

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*Food Technology, S. Harlander, September 1989, pp. 196-203.

Constraints

The food sector in developed and developing countries is characterized by certain factors that make it less attractive to biotechnology investments than, for example, the pharmaceutical sector. These factors are as follows:

(a) A low value-added component for current and possible biotechnology derived products, which will have to compete with conventional products;

(b) Advantages will be in reducing costs, increasing yields and consistency of quality;

(c) Organisms involved are highly complex biological organisms (plants and animals);

(d) Engineering operations are complex and present technical and economic difficulties;

(e) The issues of industrial intellectual property are less straightforward;

(f) Regulatory concerns can be substantial;

(g) Consumer acceptance and reluctance to ingest products containing recombinant organisms or foods modified by recombinants.

IDRC experience to date: Where are we?

IDRC support to food biotechnology activities has be ⁻ recent, exploratory and minor. Biotechnology on a much broader front has been supported in a number of areas across the Centre. Individual projects have been supported on a number of topics (see table 1).

Table 1. IDRC activities in biotechnology

Description	Latin America	Asia	Africa	Global
Policy analysis and priority setting				
Biotech market entry and industrial policy				X
Biotech strategy in food and health sectors	X			
Assessment of bioengineering capabilities	X			
Technology perspectives	X			
Regional reports on agriculture biotechnology	X	X	X	
Product process development				
Earth and engineering				
Biotransformation and bioprocessing	X	X		

continued

Table 1 (continued)

Description	Latin America	Asia	Africa	Global
Health science				
Botanical products	X	X	X	X
Vaccines	X	X	X	
Diagnostics	X	X	X	X
Agriculture (plants)				
Cell tissue culture	X	X	X	
Biological pesticides and pest resistance	X	X	X	
Biological nitrogen fixation	X		X	
Monoclonal antibodies		X		
Germplasm conservation and selection	X	X	X	
Access to technology and transfer				
Information sources and systems				X
Collaboration options with Canadian institutions				X
Transfer (TSAAA)				X
Intellectual property rights				
Plant-related (keystone) IPR				X
Biodiversity				X
Utilization of research results				
University/productive sector linkages	X	X	X	
Positive/negative impact, biosafety				
Impact of patenting on farmers			X	
Participation at international forums				
Meeting on biotech for food production			X	
Meeting on biotech for improvement of crops			X	
Tissue culture for conservation of biodiversity and plant genetic resources		X		

Policy analysis and priority setting

IDRC is funding activities in the following areas:

(a) Biotechnology market entry and industrial policy. This is a comprehensive global study, which incorporates three Latin American country case studies;

(b) A strategic study is under way in Mexico to develop methodology for priority setting and for research, development and policy implementation in

biotechnology that have the greatest potential for delivery of the benefits of improved processed food production, income and employment generation in the food and health sectors. This should lead to specific proposals in these sectors;

(c) An assessment of the capabilities and needs in engineering aspects of biotechnology implementation in Latin America that would facilitate the transfer of results from laboratory to pilot plant to industrial scale;

(d) A project on technology perspectives looks at issues of new technologies in development in order to formulate a long-term scientific and technological strategy for the region. The section on biotechnology focused on the agro-industrial sector.

Laboratory level product/process development

The main emphasis at IDRC is currently at the level of product and process development:

(a) Biotransformation of agricultural waste for the production of pharmaceutical end-products in Cuba. This project is an example of collaboration between a Canadian public institution and that of a developing country;

(b) A project in Bangladesh is developing technologies utilizing microbes in the processing of jute.

In the area of health, there are three main topics:

(a) Botanical products - pesticides and herbicides, with concerns for human diseases, including toxicological studies (7 projects);

(b) Vaccines - development and testing of vaccines (hepatitis B, yellow fever and measles). Very advanced development of a contraceptive vaccine (12 projects);

(c) Diagnostics - pro-tests and dipsticks. Work on AIDS diagnosis, diagnosis of dengue fever and other epidemiological studies (11 projects).

In the area of agriculture and, more specifically, crop production, there are a wide range of research activities:

(a) Cell tissue culture of plant species, including trees (16 projects);

(b) Pest resistance and biological pesticides (3 projects);

(c) Biological nitrogen fixation (3 projects);

(d) Monoclonal antibodies for disease detection (1 project);

(e) Germplasm conservation (2 projects).

Access to technology and transfer

Information sources and systems

IDRC is interested in improvements in the flow of information from source to user in order to give researchers, policy makers and practitioners in developing countries access to scientific and technical information. IDRC has funded two reviews on biotechnology information sources, in 1985 and in 1989.

Collaboration

An in-depth review of Canadian biotechnology expertise in agriculture of relevance to developing countries has been completed. A similar study was conducted to assist IDRC in identifying Canadian capability and interest in developing country application of fisheries/aquaculture biotechnology.

Several laboratory-level projects include the collaborative mechanism where developing country and Canadian researchers, using their local resources at their home base, work together on solving a problem. This shows considerable promise for adaptation of biotechnology to developing country problems and opportunities.

Transfer

Almost all current R&D in biotechnology is conducted in the industrial world and aimed almost solely at markets in these countries. It is important that the developing countries have access to biotechnology applications, including proprietary products, so that they can decide for themselves whether and how to make use of them.

IDRC is exploring its role in establishing linkages to facilitate biotechnology access and acquisition as a co-sponsor for an organization recently established to act as a broker for biotechnology transfer, the International Service for Acquisition of Agri-Biotech Applications (ISAAA). ISAAA has a very specific action-oriented pragmatic mandate specifically designed to deliver near-term proprietary applications that can be tested in specific agricultural project activities.

Intellectual property rights

Support has been given to examine the implications of plant breeders' and patent rights and evaluate their impact on research in Canada and developing countries and on farmers. IDRC has also collaborated with the Keystone International Dialogue Series on Plant Genetic Resources and hosted a "mini-dialogue" on intellectual property rights (IPR) with the participation of representatives from industry, the research community, non-governmental organizations and developing countries. The recommendations from this dialogue series will be presented at the 1992 United Nations Conference on Environment and Development.

IDRC partially sponsored the International Symposium and Workshop on Property Rights, Biotechnology and Genetic Resources: Creating Incentives for Innovation, Conservation and Development, held at Nairobi in June 1991. The aim of the meeting was to develop effective incentives for the developing world to conserve and utilize biological diversity in a sustainable way.

Utilization of research results, linkage with the productive sector

IDRC supported a series of six regional workshops on university-industry linkages in developing countries as strategies for the application of research results. Case studies presented included several biotechnology examples where university-local industry alliances were established to ensure research was designed to suit local industries' needs.

Cases related to food biotechnology, among others, were presented by the following:

(a) The University of the Philippines Los Baños, where policies and procedures to promote utilization include (i) joint-ventures with the private sector in mass producing marketable technologies/products; (ii) tie-up with government agencies in mass-producing non-marketable technologies; and (iii) direct extension to small and medium entrepreneurs;

(b) Chula Unisearch, an autonomous organization of Chulalongkorn University in Thailand, promotes the utilization of knowledge and technology generated by the University to solve problems in commerce and industry. Chula Unisearch develops contacts and contracts with industry, government agencies and communities, acting as a promoter and facilitator, and acts as coordinator when a project is being executed to ensure high quality and timely delivery of products;

(c) University of Zimbabwe;

(d) Centre for Industrial Innovation, Autonomous University of Mexico.

Another interesting case is that at BAIF, an Indian NGO which contracts with universities and other institutions in order to develop new enterprises operated by them, e.g. in mycorrhizae, and cheaper, more productive fermentation technology for the production of vaccines.

A related project studies communication strategies between users and producers of innovations in applied and technical fields for bioindustries in Thailand. It aims to develop a system for evaluating the potential of indigenous research and analyzing industrial innovation potential.

Socio-economic impact/biosafety

Biotechnology is viewed as a promising area with potential to positively affect several areas, as listed above. Concerns about the potential negative impact of biotechnology on developing countries also exist:

(a) Product substitution and increased danger of dependence on imports;

(b) Genetic erosion caused by the introduction of improved and uniform plant varieties;

(c) Loss of control over genetic resources to the advantage of developed countries;

(d) Control by transnationals and loss of indigenous capability to develop adapted technologies;

(e) Restriction in the flow of technical research information through intellectual property rights;

(f) Absence of regulations for biosafety and concern about the testing of new products under lax guidelines.

IDRC has participated and sponsored activities and meetings to deal with some of these issues.

A study gathered information on the current status of agricultural biotechnology research in different developing regions to assist in the development and application of a policy in biotechnology commensurate with IDRC objectives.

This suggested a focus on benefit/risk assessments for evaluating procedures and laws for the responsible testing and release and introduction of recombinant DNA technology and for dealing with environmental considerations related to the sustainable production of food with, for example, decreased dependency on pesticides.

IDRC is funding studies on one of these aspects related to the control of biotechnology by transnationals and loss of indigenous capability to develop adapted technologies. Specifically, it examines the impact of patenting of new improved seeds by multinational companies on small-scale farmers.

LDC participation at relevant international

IDRC in all its divisions supports the participation of developing country researchers at meetings, conferences, workshops and symposia where biotechnology issues of relevance to developing countries are being discussed. The African Biosciences Network and UNSCTD collaborative workshop entitled "Biotechnology for food production in dry areas, a regional assessment", at Dakar, Senegal, in October 1990 aimed at outlining concrete policy options and strategies available to African countries in the utilization of biotechnology to increase food production in dry areas of the continent.

The International Institute for Tropical Agriculture (IITA) (Nigeria) conference entitled "Application of biotechnology for the improvement of African crops" discussed appropriate biotechnologies for use in the African context, in order to enable IITA, national programmes and interested donors such as IDRC to set priorities for support to research using these tools.

It should be noted that the areas currently supported are independently handled by the different divisions and programmes. IDRC is in the process of establishing the basis for effective coordination of projects with a biotechnology component between its different divisions.

Opportunities for experimentation in the food-processing sector

To take advantage of immediate opportunities for food biotechnology, donors should promote the development of systematic and integrated experiences in selected developing countries. IDRC would be interested to consider collaborating with researchers, institutions, companies, countries and donors in these endeavours.

Specifically in the food-biotechnology sector, applied research projects should build on the experience already accumulated in technological innovation, particularly that related to agro-industry development, already highlighted above, i.e. with the following characteristics:

Ex ante analysis of opportunities, markets and competitiveness

Researchers should be required to justify their choice of biotechnology research topics with a thorough systems analysis on all options for the particular process or product; assessment of the economic and market competitiveness of the proposed new technology in comparison with the existing or competitive products or processes; evaluation of the opportunities and constraints for commercialization of the technology in the food industry of the country; and the positive and negative impacts the proposed changes would have on the economy, social progress and equity. This will identify the most attractive opportunities together with the constraints and problems to be overcome. Little capability at the research level in developing countries exists to conceptualize and carry out such complex exercises, let alone operationalize the acquisition of proprietary technology from abroad and negotiate its transfer and adaptation to local industry if this is identified as necessary. Biotechnology researchers cannot be expected to handle this alone. Teams of analysts, together with scientists and industry representatives and appropriate government departments, can be encouraged in exploratory projects to work through these components and develop appropriate methodology, which can simplify and accelerate the exercise for future occasions and for other sectors or countries. Such experiences would contribute to methodology development for decision-making and research design, as well as the building of capacity across a range of institutions and actors to work together in the innovation process.

Emphasis may here be in identifying niche markets at home and abroad which are unlikely to be economically or strategically of interest to multinational corporations, e.g. production of unique enzymes, natural colourants and flavours from tropical plants, custom-designing of plants through recombinant DNA technology applied to key crops such as cocoa, coffee, spices etc. to improve productivity of desirable functional characteristics, to reduce production costs and increase value in order to compete with cell-culture approaches of developed countries.

Technological research

With the market and industrial opportunity identified, together with the constraints and requirements for commercialization, projects on product and process development research can be justified for support. Emphasis here will be in adaptive research using known or acquired technology applied to the local resources or products.

Specific attention must be given to bioengineering and pilot [illegible] research, for producing reduced cost processes and equipment for f[illegible]on, cell culture, separations, purification and preservation. Lack of knowledge and hence research in bioprocessing is said to be limiting commercialization in developed countries and hence this component is becoming increasingly protected by corporations in developed countries. Projects will need to comprehensively evaluate results, not only in terms of scientific rigour, but also on impacts to production costs, consistency and levels of quality, process and quality control needs, market acceptability, feasibility (including that

for the fabrication of new equipment) in order to ensure that the technology being designed will fit the context and constraints identified.

The contribution here will be in making available technologies and equipment for biotechnology applications in food processing and enhancing the capability in engineering schools and industry for process, product and equipment design research for biological industries.

Pilot enterprises

Projects must also explore the linking together of all components of process and product technology designed in an enterprise structure. This enterprise may already exist or it may need to be created, in order to test how the whole innovation performs as an enterprise in the market-place and to make the necessary adjustments so it is economically viable, technically feasible and socially acceptable. Complementary activities related to the evaluation of appropriate policies and incentives to promote the implementation of the technology, establishment of enterprises and commercialization of the products will be required at this stage.

These activities will encourage the setting-up of alliances between government policy makers, private industry, consultants, university and public sector researchers, engineers and enterprise development specialists, many of whom will have worked together in the ex ante analysis. This will contribute further to capacity building for teamwork at the national level, but will also provide hands-on experience of enterprise development issues in the application of food biotechnology under commercial conditions.

Biosafety and regulatory issues

Since developing countries have minimal, if any, regulations and experience with biosafety and food biotechnology, it will be important to ensure that they are able to access appropriate information and advice on these issues, specifically on the food biotechnology applications identified as priorities for their country. Therefore projects should include provision for collaboration with international agencies working on these topics and access to Codex Alimentarius discussions and recommendations as they evolve. Under this topic, early assessment of consumer attitudes to food biotechnology products in target markets should be undertaken, either through access to published studies or the commissioning of specific studies. This component will require considerable attention to the development of appropriate information systems accessible by developing country teams.

In addition, projects may be supported on the development or adaptation of biotechnology-based diagnostics for improvement of food quality analytical procedures for safety assessment.

Collaboration and networking

Since it is essential that working experience be gained rapidly and with success, project teams in the developing countries can take advantage of the opportunity to collaborate with Canadian scientists, government departments and the private sector working in biotechnology, if warranted. This will permit access to Canadian experience, facilities and technology as required to complement the developing country's team capabilities in the project. Since Canada has built up considerable infrastructure and experience in all aspects

of biotechnology, this resource could be most effective in contributing to developing countries' efforts. Collaboration amongst donors and countries will also be possible, particularly as related to technology acquisition.

Another possibility for strengthening projects, which has been effective in other research areas, is the association of a number of projects of similar nature in different countries in a network. Thus teams have the opportunity to communicate with each other and interact at regular meetings so that methodological experiences, problems and information can be shared. Stronger teams can assist weaker ones and new projects can accelerate their activities by taking advantage of the experience of earlier teams. The networks may be coordinated by one of the principal workers or lead institutions in order to make the interaction regular and effective. This approach will be particularly useful for food biotechnology projects in order to rapidly accumulate experience across a number of projects, which should lead to more effective work as experiences evolve.

Human resource development

A characteristic of all projects in this new field should undoubtedly be a major component related to individual and group training to improve institutional capacity across all the fields necessary. Support for formal scientific training should be limited, with the exception of the field of bioengineering. Group training in workshops on integration of all the topics for decision-making and innovation management must be the priority. This task could be effectively be handled through networks.

Conclusions

Currently opportunities exist for commercialization of biotechnology in the food processing sector. What is needed are creative, practical, efficient, multidisciplinary and multi-institutional programmes for innovation in developing countries to take advantage of these opportunities in the short term.

Applied research programmes across all of the issues involved in such innovations could contribute to the accumulation of experience and capacity-building in a number of countries, which could be shared through networks.

Collaborative mechanisms with Canadians and other nationals in public and private sectors could be employed to complement developing countries' resources.

Donors could collaborate in such programmes, with complementary funding to ensure that all the relevant issues are effectively covered but specifically to ensure implementation (promotion of venture capital, credit, technical assistance) at the national level as well as dissemination and application of the results, nationally and internationally, in order to promote rapid adoption of innovation in the South within a short time-frame.

XII. AGRICULTURE AND BIOTECHNOLOGY

Murray McLaughlin*

The business world

The agricultural business world has dramatically changed in the last ten years, which is reflected in the decreased number of businesses, joint ventures, acquisitions and so on. In the 1980s there were no fewer than 404 acquisitions (table 1). The 1990s appear to be a continuation of this trend, as reflected in tables 2 and 3, which show the pesticide and seed industry acquisitions in 1990.

Table 1. Acquisitions in agriculture, 1980-1989

Type	Per cent
Animal health	39
Agricultural chemicals	28
Plant breeding/seeds	18
Biotechnology	7
Laboratories (analytical	3
Animal breeding	2
Other	1

Table 2. Some agrochemical acquisitions, 1990

Purchaser	Acquisition	Comment
Ciba-Geigy (Switzerland)	Maag Group (Switzerland)	Major
Cyanamid (United States)	IGB Products (United States)	Biopesticides
Ishihara Sangyo (Japan)	SDS Enterprises	Major
W. R. Grace	Agrecetus	Biotechnolcgy
Rhone-Poulenc (France)	35% of Roussel Uclaf (France)	Major
Sumitomo Corp. (Japan)	Pan Britannica Industries (UK)	
ESSO AgChemical	Allelix Microbial	

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Table 3. Some seed industry acquisitions, 1990

Purchaser	Acquisition
Calgene (United States)	Bioseed International (United States)
Garst (ICI subsidiary)	Edward J. Funk & Sons (United States)
Limagrain (France)	Nickerson International Seed Company
Pioneer Hi-Bred (United States)	Allelix Crop Technologies (Canada)
Sanofi (France)	Schreurs (Netherlands)
Kemira (Finland)	Scanflower Fortuna (Sweden)
Unilever (United Kingdom)	AMI (Italy)

Over the last 10 years, there appear to have been some definite trends, some of which are as follows:

(a) Large companies are getting larger;

(b) Companies that have not diversified are being bought or divested;

(c) Japanese companies are penetrating Western markets more directly;

(d) Agrochemical companies are seeking to diversify into new, related fields such as home and garden care;

(e) Also, they are building on their present interest in formulation technology, biotechnology and seeds;

(f) In seeds, the biotechnology scene continues to change;

(g) All companies are active in Europe, due to planning for 1992.

What this really means is that the move is towards a true global economy and global market. Two things are taking place: global companies and niche market companies.

The changing Canadian agriculture

In western Canada, agriculture has been an area of continuous change ever since it began. It has moved from horse power to mechanization to chemicals, and it is now ready to move to biotechnology over the next 10 years (table 4).

Table 4. The changing face of agriculture in western Canada

Prior to 1900	1900-1940	1940-1960	1960-1980	1980-1990
Farming grain	Grain farming	Grain farming	Grain farms Speciality crops Oilseeds	Farming became a true business Grains Oilseeds Specialty crops
Horses	Horses/tractors	Mechanization Tractors/thrashers	Mechanization: Combines Bigger equipment	Mechanization: No significant change Computerization
Large number of farms	Large number of farms	Farm numbers Decreasing	Farm numbers decreasing	Farm numbers decreasing
	Research: Summer fallow	Research: Crop improvements	Research: Crop improvements Crop management	Research: Biologicals Biotechnology Crop improvement
		Fertilizers 2,4-D	Fertilizer application methods Herbicides Pesticides	Custom application Crop management programs High interest in diversification Consumer/environmentalists

If farming is to be maintained as a business into the next century, biotechnology will be needed for increased yields, improved quality, new crops, value-added niches, biologicals for crop management and so on. Biotechnology is expected to play an important role in this transition in Canada.

Biotechnology defined

Now that industry has been looked at, as well as the direction of Canadian agriculture, it is the turn of biotechnology and how it may impact agriculture.

Biotechnology has been so broadly used that it is often necessary to keep coming back to a definition to ensure that it means the same thing to many people. In the United States, the Office of Technology Assessment of the United States Congress defined biotechnology as follows:

> "Any technique that uses living organisms or substances from those organisms, to make or modify a product, to improve plants or animals, or to develop microorganisms for specific uses."

The reason this definition is included is that in the literature over 40 definitions of biotechnology can be found. So a definition is needed that properly encompasses the technology but does not isolate some important breakthrough.

A key point to remember is that biotechnology is not a new science but a tool to work with established sciences: biology, microbiology, biophysics etc. It has actually brought scientists together from various disciplines to solve problems of biotechnology.

The demystifying of biotechnology

We have all heard the stories about the mysterious new technology called biotechnology, that it is going to produce animals of all shapes and sizes, microbes that will cause mass destruction and plants that will grow out of control, but there are two things to remember: firstly, that biotechnology is not new; and secondly, that biotechnology is not a science. Rather, biotechnology is the application of technology tools and techniques to living organisms to get them to do something we want them to do ("bio" stands for biology, the science of living things).

There is "old" biotechnology and "new" biotechnology. New biotechnology is the use of the tools of recombinant DNA technology, i.e. gene manipulation. Old biotechnology is what provides much of the first products to be seen in agriculture. Some examples are:

(a) M-One, a Bacillus thuringiensis for Colorado potato beetle;

(b) BIOMAL, a bioherbicide;

(c) PB-50, for phosphate solubilization;

(d) Rhizobiums (N-Prove, N-Fix and Self-Stick).

The benefits of new science here are in the efficiency of fermentation and also in the capabilities of isolating and identifying soil bacteria and other micro-organisms (consider that one teaspoon of soil contains 2.5 billion bacteria, 400,000 fungi, 50,000 algae and 30,000 protozoa). The role of biotechnology in this area will be as a "revealer of knowledge", permitting science to work at the molecular level of microbes. In progressing through the 1990s and into the next century, we will see this shift to a combination of new and old biotechnology.

The first significant agricultural impact of new biotechnology that can be expected in North America and elsewhere will be in the area of transgenic plants, with genetically engineered biologicals becoming more commonplace by the turn of the century. During 1992 a number of applications to regulatory agencies for approval of genetically engineered living material to be used as food for human consumption are expected, involving plants, micro-organisms and higher animals. In Canada, canola (rape seed) will be the first crop to be approved for human consumption.

Transgenic tomatoes have been produced by ICI and transgenic canola by Hoechst and Monsanto; genetically engineered yeast that reduces the rising time in dough and transgenic fish that better withstand cold and disease have also been produced. Marker genes have also been used, i.e. luciferase, the gene that causes fireflies to light up, has been put into bacteria as a means of identification in their micro world.

This technology of genetic engineering is providing a green industry of major worldwide economic importance. Genetic engineering promises more rapid and focused improvements in the age-old and economically vital processes of fermentation, cereal production, fruits and vegetables and animal husbandry.

As far as diversification is concerned, interest has focused and needs to continue to focus on alternative outlets for cereals, for the simple reason that cereal is the most widespread of crops, which is not likely to change in the foreseeable future. Research into non-food uses is ongoing, but will not create overnight successes.

Specialized oils from canola and other oilseed crops will also help diversification. The areas of use for such products is in the manufacture of pharmaceuticals, detergents, adhesives, agro-chemicals, lubricants and plasticizers. Canada has the climate and knowledge to grow these crops as they come on stream.

Essentially, genetically engineered new crops will act as cheap solar-powered, non-polluting chemical refineries, i.e. plants and animals might become the drug factories of the future.

Switching from growing food to the more exotic uses for crops will not happen quickly. It will take a lot of development, as well as dealing with the conflicting reaction of consumers. Knowledge reduces anxiety, therefore consumers need to be provided with sufficient knowledge to allay their anxiety about biotechnology.

All responsible scientists and regulators alike have a duty to explain what they are doing, to demystify the science and provide the reassurance that will certainly be demanded. Mankind is not controlling, subjecting or perverting life, but has the power to make genetic changes in micro-organisms, plants and animals of great potential benefit. This power must be used wisely.

Concepts of biotechnology being researched

In agriculture, biotechnology is seen as something that will cut across all aspects of agriculture and actively pull scientists of different disciplines together. Table 5 provides a list of some major areas where biotechnology will impact agriculture. The areas are crop agriculture, animal husbandry and food processing.

Table 5. Concepts of biotechnology being researched

Crop agriculture	Animal husbandry	Food processing/ brewing industries
Diagnostics	Vaccines	Enzymes
Improved crops	Therapeutics	Diagnostics
Genetic engineering	Diagnostics	Flavours and fragrances
Pest/disease resistance	Feed additives	Sweeteners
Stress resistance	Growth hormones	Process-oriented improvements
Biological herbicide and pest control	Other hormones	
Nitrogen-fixation and other soil enhancements		

The major contributions of biotechnology to agriculture

The major impacts of biotechnology in agriculture are expected to be in plants, several of them coming in the next 10 years:

(a) Increased yields by making plants resistant to insects and diseases;

(b) Plants will be designed to withstand physical and chemical stresses such as salty soils, drought and cold, thereby enabling crops to be grown in divergent climates;

(c) Plant nutrition value will be improved, leading to increasing market value;

(d) Production costs will be reduced due to decreased chemical pesticides, herbicides and fertilizer requirements;

(e) New hybrids will be developed that are hardier and more productive;

(f) New, inexpensive, easy-to-use and highly accurate monoclonal diagnostic tests will spot diseases, soil residues etc. at an early stage;

(g) Efficient photosynthesis will be increased;

(h) Modified plant growth to gain higher ratios of edible to non-edible parts, improved structural strength etc.;

(i) Plant growth will be regulated to allow harvesting of fruit and vegetables of uniform ripeness;

(j) New foods will be developed from either unexploited plant species or by new products, reducing mankind's dependence on 18 basic crops (5 of which provide 60 per cent of our total caloric intake).

Regulations and biotechnology

Regulations are in general becoming more strict throughout the world. In Canada it is the biggest hurdle to the commercialization of biotechnology. The regulations are restrictive, but as the country moves toward its first commercial products, an improved regulatory situation may be anticipated. There are many unknowns to be dealt with at present, in order to gain a better comfort level with biotechnology, which is likely to happen as products appear on the market.

The harmonization of regulations is being scrutinized by several countries, particularly the trilateral discussions of the European Community, the United States and Japan.

In Canada several regulatory acts are undergoing revision. Some of these are:

- Pesticide Act (changing) (pentachlorophenol)
- Fertilizer Act (becoming stricter)
- Plant Breeders Rights
- Patent Act (changing)
- Canadian Environmental Protection Act
- Crop residues (stricter)
- Good Manufacturing Practices and Good Laboratory Practices
- Veterinary drugs
- Various provincial acts

Regulation is a sensitive area, necessitating the knowledge to understand the technology so that it is properly, but not overly, regulated. If properly managed, it will provide an agricultural future that will meet the needs of a growing world population.

What does biotechnology mean to your business?

Biotechnology means a lot, but not necessarily more than past technologies that created change. The difference is in the time-frame.

The following quotation on change is rather appropriate and may be applied to any country, province, business, farm or technology. It says, in essence, be prepared to change, adjust and innovate, or be overtaken. The world is rapidly becoming a more global market-place that will need agriculture. We therefore need to continue to improve and innovate to meet the needs.

> "Competitors will eventually and inevitably overtake any [nation] that stops improving and innovating."

Conclusion

Lead times in biotechnology will continue to be lengthy as new drugs and other biotechnology products undergo extensive testing prior to widespread use. It is still an industry with more hope than earnings, and commercializing research presents a major challenge.

Canada has a limited commercialization today. It will be another four or five years before much impact of biotechnology on agriculture is seen. However, it is going to be here and it will positively affect production.

There is no question that the biotechnology tools will create more products in the late 1990s and beyond, providing that an adequate knowledge base has been given to the public. The future of agriculture will depend on it.

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C. Case-studies: country-specific experiences

XIII. DEVELOPMENT OF THE BIOPHARMACEUTICAL MARKET IN ARGENTINA AND THE NEED FOR INNOVATIVE COMPANIES LIKE BIOSIDUS

Alberto Diaz*

Introduction

Biotechnology offers innumerable opportunities for the creation of new products and processes, and also for the improvement of existing ones, in almost every field of production. Nevertheless, it is in human health, especially in drugs and diagnosis, where its economic and technical results are more marked, e.g. 12 proteins elaborated through recombinant DNA techniques are on the international market, and there are about a hundred of them in different stages of development. The development of many monoclonal antibodies sold on the diagnosis market, the use of DNA probes, PCR etc., together with ingenious, practical and economical equipment designs, are proof of this. The present markets for these products amount to several billions of United States dollars, but it must be pointed out that biotechnology has particularly modified research into basic biology. It has also introduced a greater rationality for the design of new therapeutic drugs and their dosage and application to human beings.

The development of biotechnology in Argentina, and in Latin America in general, is as yet incipient. In South America there is only one enterprise that develops and produces biopharmaceuticals (BioSidus); one could say two if the development of human insulin by Biobras (Brazil) were included. Moreover, they are the only two enterprises developing this activity within FELAEB (Latin Federation of Biotechnological Enterprises), which is composed of national associations from nine Latin American countries: Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Peru and Uruguay. FELAEB was created on 22 August 1990 at Rio de Janeiro. Its aims are to coordinate, protect and support biotechnology enterprises development in the Latin American and Carribbean region. At present, the presidency and executive secretariat are held by the Argentine Forum.

Considering the enterprises that presently form part of the Argentine Forum of Biotechnology and that cater to the field of human health (see table 1), there is nevertheless only one modern biotechnology company. In relation with this, it is important to refer to the thorough analysis by Sercovich (1).

There are several reasons that account for this low development. Among these are (a) politico-economical instability, which during the last years has caused a big decrease in the industrial development process and (b) the minor importance given to the scientific and technical sector, in so far as investments in that sector and technological thrust are concerned.

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*BioSidus, Buenos Aires, Argentina.

Table 1. Argentine Forum of Biotechnology: member enterprises

No. of enterprises	Area of enterprise
6	Human health
3	Chemistry
2	Veterinary
8	Agro-foods
2	Finances
2	Universities

Pharmaceuticals: The Argentine situation

The development of a recombinant protein to be used in human medicine requires a long and difficult process. It begins with the identification and isolation of the corresponding gene, goes through its expression, production by cell cultures, purification, structural studies, chemical and biological controls, toxicologicals, pharmacological and clinical tests and, finally, packing in such a way as to be properly preserved and administered to the human body. To this we must add the regulations by health authorities, prices, marketing, public acceptance etc.

For the following analysis one should take into account that (a) one must refer to new macromolecules, which did not exist previously in the pharmaceutical market, and (b) at present the regulations in force in Argentina exclude patents for pharmaceutical products (towards the end of September 1991, the Executive Power sent a bill to the National Congress amending Act 111 on patents).

Three main characteristics differentiate Argentina from other Latin American countries in the health sector:

(a) The pharmaceutical industry developed in the 1920s through biological products (serum, vaccines and hormones) and continued expanding until the 1960s. A strong support to the industrial sector was given by the national institutes, such as the Carlos Malbran Microbiology Institute, with its highly qualified human resources and the capacity of producing biologicals. There were several companies which had fermentation plants for the production of antibiotics (Squibb, Pfizer, Bago etc.) which were favoured by the policy of import substitution; these plants were closed down in the late 1970s;

(b) An important aspect was the activity of our first Nobel Prize winner, Dr. Bernardo Houssay, who in the 1920s founded a school of biomedicine which was continued by his pupils. The Argentine University went through a brilliant period between 1956 and 1966 (especially the University of Buenos Aires). All of these determined the existence of highly qualified human resources in basic sciences, in clinical matters and medical research within Argentina as well as abroad (Argentina's intellectual patrimony). Although this cultural tradition still exists today, it is going through a severe crisis, which extends to the scientific and technological sector;

(c) The existence of a strong national pharmaceutical industry, which began to increase in importance during the last 40-50 years, has dominated 50-55 per cent of the Argentine market for the past 20 years. This market is today estimated at US$ 1.6 billion.

The pharmaceutical industry in Argentina formulates and produces practically the whole spectrum of pharmaceuticals and therapeutics for home consumption (table 2). Nevertheless the research, development and launching of new active principles are mainly accomplished in industrialized countries (1). Only 15 per cent of the active principles used to elaborate pharmaceutical products are manufactured in Argentina. Of the 255 existing laboratories (85 of which are subsidiary companies), only 15 have a vertical integration for the manufacture of active principles (1).

Table 2. Argentine pharmaceutical market, July 1991

Company a/		Sales rank	
		In terms of US$	In terms of units of final product
Roemmers	(N)	1	2
Bago	(N)	2	5
Roche		3	4
Sidus	(N)	4	8
Bayer		5	1
Hoechst		6	12
Beta	(N)	7	36
Montpellier	(N)	8	14
Ciba-Geigy		9	11
Boehringer		10	7
Temis	(N)	11	28
Lepetit		12	6
Parke Davis		13	10
Glaxo		14	16
Abbott		15	22
Essex		16	9
Phoenix	(N)	17	27
Syncro	(N)	18	25
Byk	(N)	19	19
Schering		20	17

a/ These 20 companies have 60 per cent of the market.

This important industrial framework enables many national companies to produce pharmaceutical products that meet all quality specifications and distribute them throughout the country.

Instituto Sidus S.A.

The company was founded in 1938 by Antonio and Miguel Arguelles, after taking over from Andromaco, a Spanish laboratory. In the late 1970s it began to expand rapidly, increasing its sales from US$ 8 million in 1978 to US$ 22 million in 1988 and going from place 35 in the 1978 rating to place 10-12 in 1988.

To its previous contracts and licence agreements with several European companies, it added a contract with Merck, Sharp & Dohme (United States) in 1988 to manufacture and sell its products in Argentina and also purchased that company's factory, one of the most modern plants in Latin America. In 1991 it will have made sales of about US$ 75-80 million and will rate third in the industrial rating. In the early 1980s there was a vertical integration process of its production, which resulted in the creation of two new and innovative companies: Lasifarma (pharmochemicals) and Biosidus (biotechnology).

BioSidus S.A.

The idea of organizing an innovative enterprise in biotechnology arose from the Instituto Sidus Board of Directors in early 1980. For that purpose it engaged a group of scientists and technologists, mostly from the academic sector. It started manufacturing human leukocyte interferon (Hu-IFN-alfa) from human leukocytes and simultaneously developed recombinant DNA techniques. Similar strategies have been followed in other parts of the world, particularly in Cuba. The difference was that Instituto Sidus was already marketing antiviral products containing Hu-IFN-alfa as one of its components. From then on, two strategies were followed, and due to the development of the company and of biotechnology throughout the world, a third strategy was then included (chart).

CHART 1

Biosidus strategy for production and development

Traditional biotechnology

Hu-IFN-a

Bovine SOD

anti RH-Ig G

Modern biotechnology: international development

r-Hu-IFN-a

r-Hu-IFN-

Modern biotechnology joint ventures

r-Hu-EPO

Interferon

Interferon was one of the first molecules chosen by the new biotechnology enterprises to be produced by genetic engineering. Unlike other molecules produced in that way (Hu-Insulin and human growth hormone), there was considerable uncertainty regarding its therapeutic application. Interferon is mainly used in cancer therapy (leukaemias, melanomas etc.) and in antiviral therapy (hepatitis B and C, hepatitis virus etc.). Its action as an immunomodulator, forming part of a system of communication between proteins and cells, is only now being understood, but it has potential and important future applications (2). Once again, biotechnology's main impact is on basic science.

Sale of traditional biotech products

Interferon-local (IL) applications

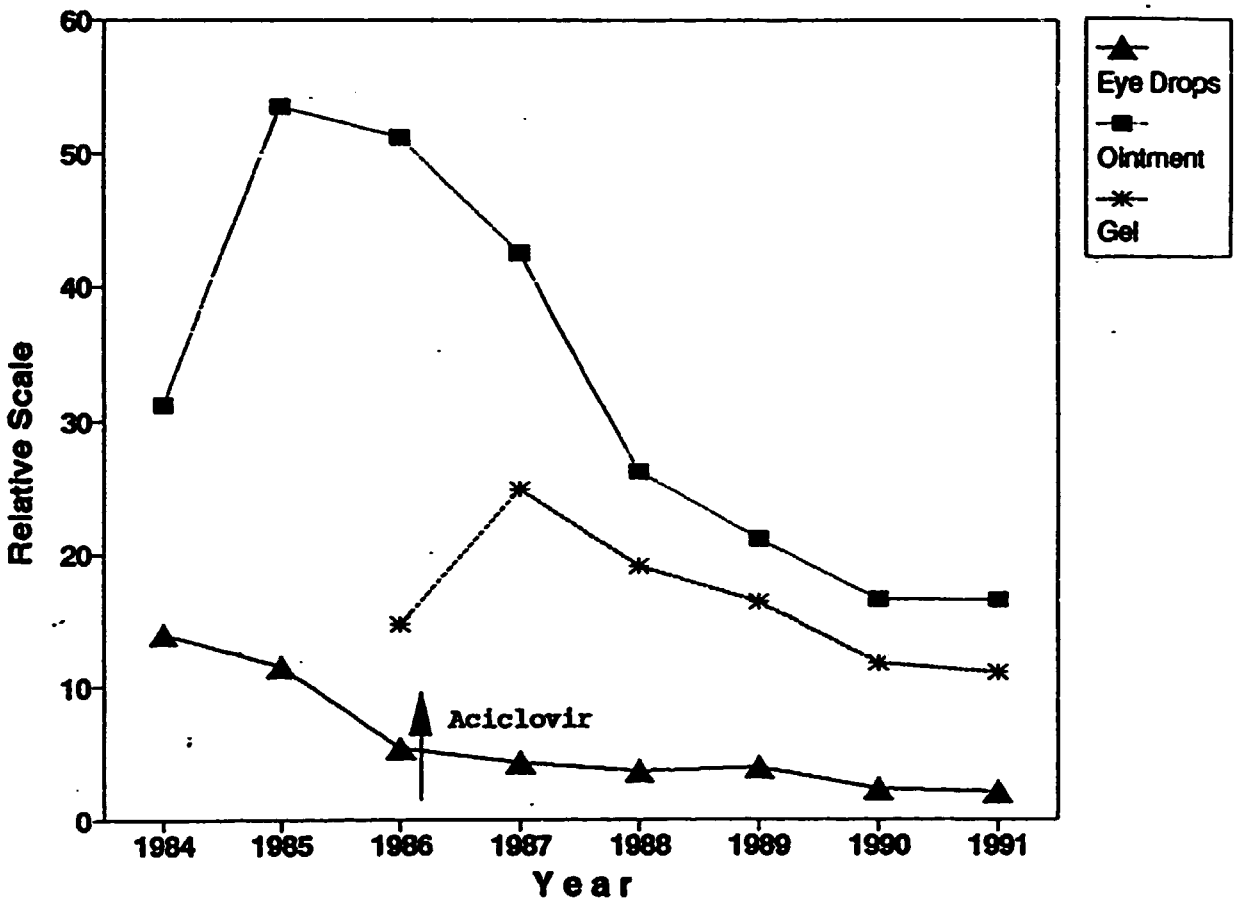
As a result of having achieved successful clinical trials in the fields of ophthalmology and dermatology (3) and taking into account the lower dosage of drug needed, the company chose to produce preparations for the above-mentioned fields. Furthermore, this also allowed it to avoid competing with large international IFN-producing companies. In this way, the IL line of products was introduced in the Argentine antiviral market, with a colirium and pomade for ophthalmology and an ointment for dermatology. They were mainly used for the treatment of infections by the herpes virus (HSV).

It was difficult to introduce these new products to the market due to the fact that IFN was a new molecule, and its use in HSV infections was not known. We were able to successfully launch the product because of the close relationship between the company's professional staff and the physicians specializing in these two fields. Clinical research, seminars, participation in congresses, publications etc. made it possible for the new product to be known among the medical staff, together with the commercial capacity of the pharmaceutical company Instituto Sidus.

In 1987 the antiviral market in Argentina was 0.1 per cent of the total pharmaceutical market. IL line sales amounted to 18 per cent in units and 24.5 per cent in terms of United States dollars. This meant the market increased, as it did not displace other products (1) (figure 1).

This shows that new molecules may increase the number of patients to be treated. The company also introduced the product Acicloferon (Hu-IFN plus Aciclovir) for the treatment of HSV in dermatology, as we believe that certain combinations of antiviral molecules offer more advantages than entities. Since June 1991 this product has been the first one to be sold by BioSidus to a company not belonging to the Sidus group, whose monthly sales duplicate those of Sidus.

Figure 1. Sales of Hu-IFN-alfa for local application



Gynaecological applications

Working together with dermatologists allowed both parties to have new projects and concepts. In this way a research line for diagnosis and treatment of skin warts was developed (4) which allowed us to have an early knowledge of human papilloma virus (HPV) and the use of DNA probes. Infection due to HPV proved to be more relevant in gynaecology as it is a sexually-transmitted disease and probably has connection with cervical sexually-transmitted disease and with cervical intraepithelial neoplasia (CIN).

The company developed a vaginal gel with Hu-IFN-alfa for the treatment of these diseases and after clinical trials with the injectable low doses (5), thus being in the vanguard as far as basic, diagnostic and therapeutical knowledge is concerned. Figure 1 shows sales of the gel since it appeared on the market.

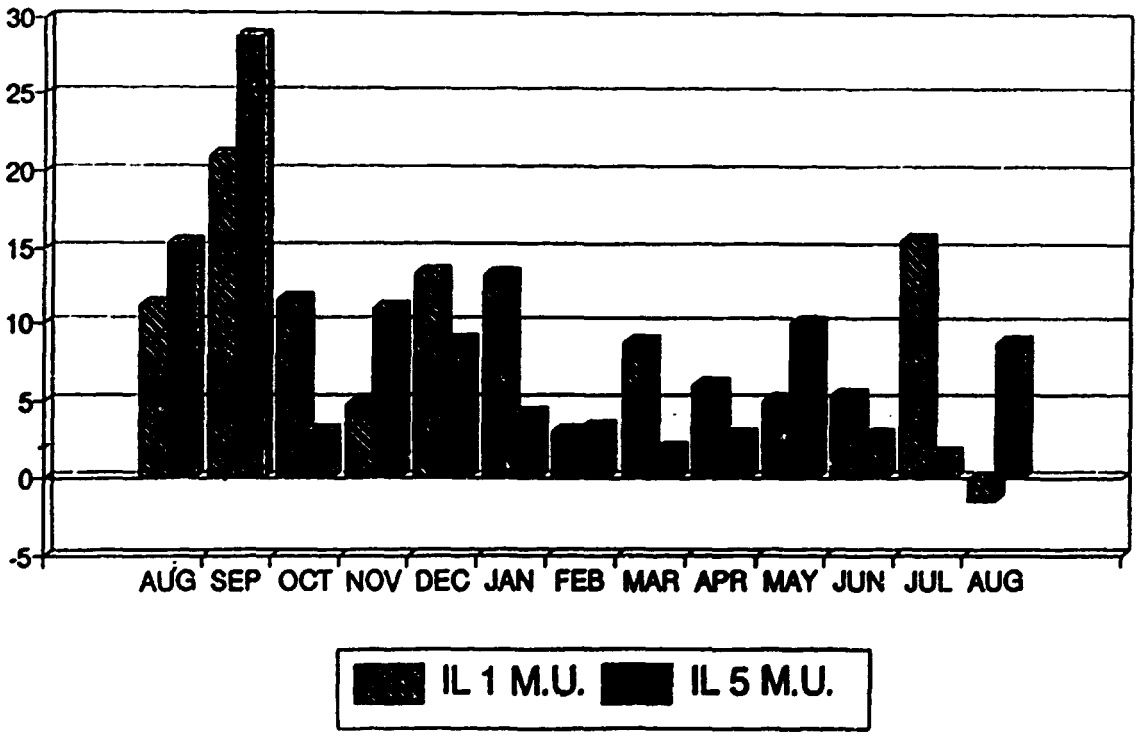
For a company in a developing country it is very risky to place a molecule for a new therapeutical application on the market. It must regulate its production capacity together with sales and R&D. It must also see that the efforts of the whole enterprise are homogenous, in relation to physicians and the national authorities.

Injectable interferon (Hu-IFN-alfa)

The line of injectable IL products for oncology and virology was released to the market after a certain delay due to economic and financial difficulties arising from the political and economic evolution within the country and because the health authorities were very slow at evaluating new medicines.

The product began to be commercialized in July 1990, whereas international companies had already been marketing the recombinant interferon since 1987. As one can see in figure 2, except for the first two months, sales were low, and perhaps one can say that the 1 million units dose interferon has a better market due to company specialization in gynaecological applications. Anyway, the present sales of the products are 1-2 per cent of the IFN market in Argentina, which is estimated to be approximately US$ 400,000-600,000 monthly. From the point of view of medicines with fewer side-effects, the Hu-IFN-alfa should remain on the oncological market as it allows an effective treatment for those few patients who showed resistance to treatment with recombinant interferons (6, 7).

Figure 2. Sales of IFN injectable ampoules by BioSidus, August 1990 to August 1991



Bovine superoxide dismutase (Bov-SOD):

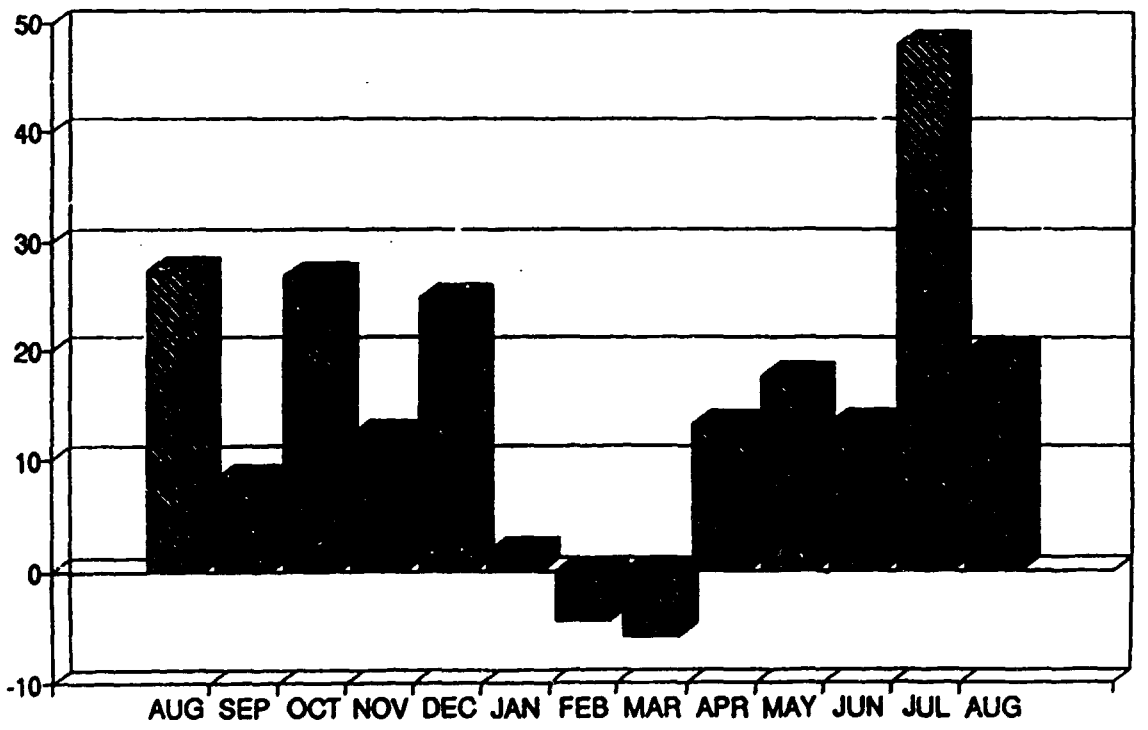
Established at the new industrial plant in Buenos Aires and having mastered the scaling-up of protein purification, the company decided to produce Bov-SOD. The product was till then being imported. This product is not heavily sold and met with some difficulties on the market (figure 3) due to supply problems. Its sales began to grow in April 1991 when its application in human and veterinary medicine was better defined.

Sales of products of new biotechnology

Human erythropoietin (rHuEPO)

Relating to its medium- and long-term strategies, BioSidus built its new 3,500 m^2 industrial plant in Buenos Aires, which began to operate in 1988 with up-to-date equipment and services. This strategy, together with its technical capacity, permitted the company to enter into a joint-venture (chart 1) with the Elanex Company from the United States for the production and marketing of recombinant human erythropoietin (rHuEPO) in Argentina and other Latin American countries. The product is a glycoprotein which acts as a growth factor, stimulating proliferation and differentiation of stem cells to mature erythrocytes.

Figure 3. BioSidus sales of SOD ampoules from August 1990 to August 1991



Chronic renal patients (CPR) do not produce EPO and show severe anaemia. Conventional therapy for this anaemia is blood transfusion, but it has the inconvenience of producing antibodies, which make transplants difficult and increase the possibility of infections. CRP are treated with extracorporeal dialysis twice a week. EPO availability has revolutionized the treatment of renal failure as it rapidly improves haematological indexes and the patient begins to lead a normal life. There are several medical specialists involved in the treatment of this disease: nephrologists, haematologists, psychologists, dialysis technicians etc.

BioSidus faced the project knowing that EPO was going to be one of the main molecules having high market value and that it would compete with strong international companies. To this aim, it centralized its know-how efforts as follows:

(a) Downstream process;

(b) Pharmaceutical form (lyophilized);

(c) Clinical trials;

(d) Marketing sustained by the above three items.

The clinical trials performed in several hospitals with the assistance of the Argentine Society of Nephrology gave a fuller understanding of the therapies and of the actual needs of the patient undergoing dialysis: iron supply, toxicity to aluminum, dose and correct posology etc. Also considered were the five erythropoiesis basic research groups formed during the 1960s in Argentina. The director of one of these groups is an advisor to the company supervises the biological dosage of EPO. Furthermore, under an agreement with UBATECH, a paid service was offered of EPO measurement in patients' serum (UBATECH is an enterprise associated with the University of Buenos Aires, the Argentine Industrial Union, the General Industry Confederation and the Town Hall of the City of Buenos Aires).

All the previous items, which are unusual in developed countries, are common in developing countries. The fact of having launched the product at the same time as international companies allowed Argentina to have approximately 70 per cent of EPO's market. The R&D of EPO was designed as the first step of its marketing. Figure 4 shows the evolution of sales during the first year. With these figures it is believed the coverage was only 50 per cent of renal patients under dialysis who need treatment. In table 3, the potential EPO market is projected.

Table 3. Potential anaemias to be treated with EPO

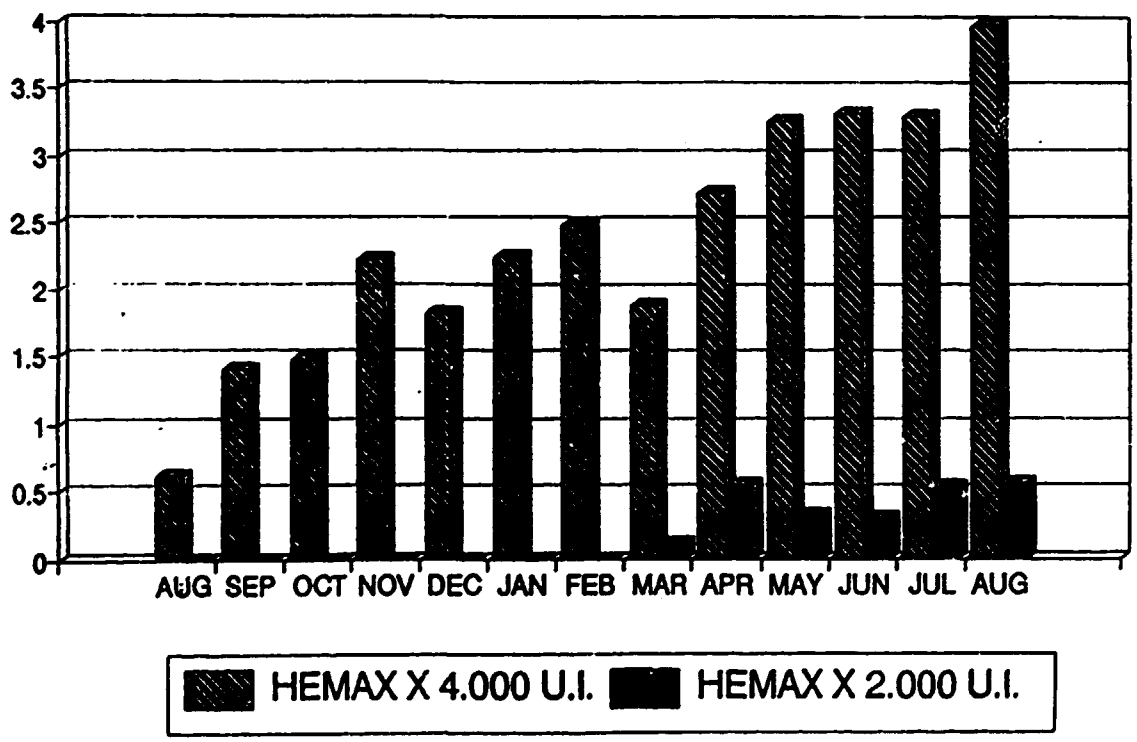
Type of patient	No. of patients
Chronic renal patients (dialysis)	1,800 (Over 6,000)
Chronic renal patients (pre-dialysis)	8,000-10,000
Acute tubular necrosis	?
Oncological (Esp. prostata and mama)	12,000-15,000
Oncohaematological	8,000-10,000
Prematures	?
AIDS	?

The average cost of treatment for a renal patient under dialysis during the first year of application is US$ 2,700-3,000/year. It is important that Governments must encourage the few industries investing in R&D in the health area. In the case of anaemic patients, it must be taken into account that a patient with a normal red cell level indulges in a productive economic activity and does not incur hospital expenses.

Recombinant human interferon (r-Hu-IFN-alfa)

This was the first molecule to be prepared in its entirety in Argentina and will be launched in the market in November 1991. Sales for oncology and virology in Argentina amount approximately to US$ 6-8 million/year. Although delayed in entry onto the market, it is believed the product will bring adequate returns to the company. The focus of the company, nevertheless, is to export products in areas of oncology and hepatitis B and C.

Figure 4. Sales of human recombinant EPO (Hemax) from August 1990 to August 1991 in Argentina



Difficulties for the commercialization of biopharmaceuticals

Some of the difficulties stated below are probably shared by developed countries, but Argentina has other characteristics in addition which make it difficult to achieve practical results:

(a) Biopharmaceuticals are in general new therapies: the country is on the learning curve in their use;

(b) They are "expensive" molecules (see comments on EPO);

(c) They involve chronic treatments;

(d) Health authorities have difficulties in controlling them;

(e, Future patent laws on medicines: uncertainty of including biotechnology products in patenting;

(f) Poor dialogue between State officers and company authorities;

In this report on sales of biological products by BioSidus, the following were not considered:

(a) The future potential market of its strong investments in R&D (approximately 50 per cent of its expenses);

(b) The SIDUS group's successful commercial performance during the last few years was due to the innovative activity of BioSidus, which allowed it to be identified with good science, technology and quality.

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XIV. R&D COMPANY'S CHANGING STRATEGY IN A DEVELOPING COUNTRY: FROM AN INDUSTRIAL CONGLOMERATE'S R&D CONSORTIUM TO AN AUTONOMOUS PUBLICLY OWNED COMPANY

Juan Carlos Castilla*

Before analyzing the particular experience of Peru, which is the subject of this presentation, it is important to take into account the characteristics of the biotechnology industry on a global scale.

Biotechnology industry in developed countries

The most important trends are clearly related to the efforts of the industrialized nations to commercialize biotechnology. From a developing country's point of view, there are four important negative trends characteristic of biotechnology developments in industrialized countries:

(a) Biotechnological research is becoming more and more proprietary and private. For developing countries, the restricted access to new developments could lead, in some cases, to the perpetuation of a technological dependency and to the transfer of inappropriate technological packages;

(b) As expected, the R&D priorities in biotechnology are focused on products whose consumer markets are based in these countries. For example, the high priority in developing countries for biomass conversion programmes is not shared by their industrialized counterparts because they are judged to be not economically attractive at present. The same applies to malaria vaccines, since even though the demand is considerable, the consumers cannot afford to pay enough;

(c) Developing countries have been experiencing considerable pressure from industrialized nations to accept the international conventions on intellectual property protection. This is of course, a two-sided issue. On the one hand, access to efficient natural resource utilization technologies can be secured through royalty payments or the like. On the other hand, the monopoly status of protected technologies in a developing country is, to say the least, inconvenient;

(d) Biotechnological developments in industrialized nations act, in some instances, to displace the primary product exports of developing countries (high fructose corn syrup for sugar-cane exports, for example).

Needs in developing countries

In general, in order to address these concerns adequately, a number of strategies must be implemented:

(a) We believe that it is of utmost importance to develop indigenous capabilities in priority areas for development, with the active and direct

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participation of the private sector. All too often, efforts carried out by public sector institutions are too ambitious, bureaucratic and unresponsive to the pragmatic needs of development. The rational exploitation of our natural resources oriented to developing unique markets of comparative advantages on a global scale is no doubt of primary concern to private corporations;

(b) In addition, the establishment of international networks, specializing in particular biotechnologies, in which partners participate with the goal of mutual benefit through the exchange of personnel, information and technologies, is of course very important indeed. In this context, the promotion of mutually important collaborative projects between R&D centres in industrialized countries and their counterparts in developing nations is critical;

(c) Finally and as an extension, gaining access to the relevant biotechnology industry and the associated venture capital sources in industrialized countries, through collaborative projects between private counterparts, is also ideal to promote the commercialization of indigenously developed technologies and products.

A number of different approaches in order to develop indigenous biotechnological capabilities are well known: through national programmes, through specialized government departments or through national biotechnology R&D centres. A policy survey carried out by the Council on International and Public Affairs concludes that not only is there a wide gap between plans on paper and real progress, but that also the majority of the policies lack, in many respects, enough focus to be effective. The authors also state that there is a tendency to follow research priorities that are fashionable in industrialized countries but of no direct relevance to natural resource utilization strategies in developing countries.

Peruvian experience

Having outlined the global patterns, limitations and possible strategies to counterbalance them, we now turn to the Peruvian case. To date, none of the approaches mentioned above have been implemented. This, of course, is not a reflection of the lack of interest in the matter, but mainly a lack of pragmatism from the public institutions in charge of formulating such programmes and policies. However, before we discuss an independent approach followed by a private biotechnology R&D company, let us discuss its context.

It is well known that Peru, Bolivia and Colombia are the world's suppliers of cocaine. Recent intergovernmental efforts have centered on coca plant eradication, the use of potent specific herbicides and stricter policing of coca-producing regions. However, these approaches have not had significant effects on diminishing world trade in the drug. A more intelligent approach, known as the Fujimori Initiative, gives crop substitution and alternative development the highest priority. The new concept rests upon a simple model of supply and demand economics whereby coca farmers opt, of their own free will, for alternative profitable cash crops that are legal, have national and international sponsorship, and are destined for large agro-industrial concerns that are capable of establishing commodity futures and suitable credit lines.

An analysis of the problem must, however, consider the problem on two levels: the level of the coca grower and Peru's foreign currency dilemma. An

estimated 180,000 hectares of coca plantations exist in Peru alone. From the peasant's point of view, the income derived from the dry leaves is estimated to be US$ 500-700 million per annum. From the Peruvian drug trafficker's viewpoint, an estimated US$ 1,900 million is grossed at the cocaine paste stage. One way or another, in an informal fashion, but on a massive scale nonetheless, a considerable portion of this income gets into Peru's formal economy, helping to fulfil its huge foreign currency requirements for food and other basic imports, wheat being amongst the most important (US$ 150-200 million per annum). To place this figure into context, it is noted that Peru's legal exports of US$ 3,700 million would be increased by more than 50 per cent if these illegal exports were taken into account and that the total coca revenue represents about 5 per cent of our gross national product (GNP).

It is precisely in the High Amazon Jungle, where coca is cultivated, that one of the richest reserves of plant species of commercial value has been identified. Many of the natural products from these species can be used as flavours, fragrances, pigments, pesticides and pharmaceutically active compounds such as anti-cancer agents, anti-AIDS compounds, hormones, steroids and growth regulators. In addition to their direct medicinal value, plant chemicals have also been useful models to the organic chemist in the production of new drugs. Since the plant chemical inventory currently available represents only a minor portion (5-10 per cent) of the plant species estimated to be existent on the planet, the potential for discovery of novel useful plant chemicals is enormous and offers exciting prospects for basic and applied research.

As one of the major centres of plant domestication in the world, according to the United States National Academy of Sciences, the Andean neotropical region contains an astonishing variety of higher plants. Many of these have been used for centuries by native peoples and are actively sought after as raw material by pharmaceutical companies. We believe that novel technologies for the utilization of this valuable genetic resource can be developed in countries of the Andean region. In this context, industrial biotechnology and natural product chemistry have a key role to play in order to reorient the massive natural resources in coca- producing regions to legal, high aggregate-value products. If successful, this will provide the basis for developing an Andean-based industry for plant-derived chemicals and in so doing, help to substitute the illegal coca-based economy.

It is in this context that Peru's severe economic and social crisis prompted a number of institutions to look for alternative models of development that prioritize agrarian-based rather than manufacturing industrialization, as a route to sustainable economic development. Exploiting agricultural resources in an environment-friendly way to generate value-added products that either replace imports or are destined for export is the working principle.

Bioingeniería Aplicada S.A.

In order to apply such a principle and develop the biotechnologies that will allow us to start implementing the proposed model, Bioingeniería Aplicada S.A. was founded in 1989. In such a model, a solid agrarian development policy would favour the establishment of internationally competitive agro-export markets of high aggregate value. As a research and development company, its principal aim is to use industrial biotechnology and natural product chemistry as tools for rational exploitation of our natural resources, converting renewable raw materials into export-oriented products.

In addition, its activities are directed to bridge the traditional gap between the basic science developed at research institutions and/or universities, and industrial implementation. By developing products and processes from the laboratory to the pilot scale, the company intends to transfer well-proven technologies of natural resource utilization to industrial end-users. The horizontal technology transfer bridge described is complemented with a vertical integration scheme, in which technologies developed at the most advanced R&D cen[illegible]s in the world are adapted for local conditions.

For the task at hand, a multidisciplinary team of highly trained professionals in the chemical, biological and engineering sciences has been set up. As for infrastructure, five dedicated R&D laboratories in microbiology, fermentation technology, analytical chemistry, natural product preparative chromatography and in plant organ/cell culture have been installed.

The modus operandi of the company's R&D division considers both the development of new technologies and the adaptation of external technologies to local conditions in an associative scheme in which the development costs are shared with our industrial and capitalist partners. At the level of industrial implementation, various alternatives of technology transfer capitalization are negotiated.

Finally, in order to focus on the central theme of this presentation and in the manner of a case-study, let us look at the barriers that, in one way or [illegible]nother, had to be surmounted with varying degrees of success for the founda[illegible]ion of an innovative R&D company. In the first instance, there is an evident [illegible]entality gap" in developing countries that manifests itself in the form of short-term investors who are really not interested in development at all. Such a class of investors would never "buy" the idea of backing R&D entrepreneurship through systems such as venture capital financing of promising projects which, as stated in the aide memoire of this meeting, constitutes the backbone of industrialization in developed countries. Additional barriers, such as the total lack of government support in the form of tax incentives and the like, added to the lack of experience of the general investor public in assigning a just value to technology, were also in our way. Worst of all, at the time of its foundation, the most severe economic and social crisis of Peruvian history was in the making. From our point of view, it was precisely in a scenario of crisis that renewed efforts based on the comparative advantages principle were most applicable. To our surprise, in early 1989, an industrial conglomerate "bought" the seed of what was to become Bioingeniería Aplicada S.A.

In the case of Bioingeniería Aplicada S.A. most of the capital requirements for infrastructure building and operational expenses were provided by a 100 per cent Peruvian-owned industrial conglomerate that was starting a diversification strategy based on the comparative advantages principle of natural resource utilization. As in the case of most transnational corporations, a percentage of the conglomerate's profits was destined to cover such capital demands. The complementary funds were raised through contract research agreements with the Andean Development Corporation, a regional development bank that has a very active interest in biotechnology and which no doubt has acted as an important catalyst for our activities from the conceptual stage onwards. The type of projects selected were mostly long-term innovative ones, and the basic philosophy was to establish an agro- industrial subconglomerate in which the R&D company would hold equity stakes in the newly created industrial firms, through technology capitalization schemes to be implemented. For a year and

a half, the company, under the scheme outlined above, consolidated its multi-disciplinary team of scientists and engineers and its infrastructure building under the auspices of a single shareholder. It is important to emphasize, at this point, that the company's strategic plan was based on the development and capitalization of technologies and not on the production and commercialization of specialty chemicals, as is typical of most traditional biotechnology R&D companies.

Due to the conglomerate's generalized financial crisis, we had to reformulate our strategic plan. The changing strategy referred to in the title of our presentation, rests on a simple principle of self-sufficiency, changing from an industrial conglomerate's R&D consortium to an autonomous publicly-owned company via three routes.

One route is to diversify our activities under two operating divisions: one dedicated exclusively to contract R&D activities and the other dedicated to supply both industry and trade with our technological evaluation services (through our Specialized Technical Services Division). The role of the latter is primarily to generate the "bread and butter" funds, whilst the role of the former is to implement a network of equity stakes in newly formed industrial concerns in which the company transfers a particular technology via capitalization.

The second route hinges on a strategy that seeks national and international corporate alliances on the one hand and national and international development agency/bank participation on the other, both by means of contract R&D activities and by going public through equity investment offerings of stock.

The third route is based on our firm commitment to form, together with local universities, a consortia-based research park environment. That would allow us to bridge the traditional university-industry gap referred to earlier in this presentation, and form a private corporation that benefits from both the research facilities available at the universities and from our pragmatic character.

With our changing strategy we hope to be in a better competitive position to materialize a model for a more sustainable economic development.

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XV. BRAZILIAN BIOTECHNOLOGY POLICIES AND PROGRAMMES

Guilherme Emrich*

A revie.. and evaluation of Brazilian biotechnology policies and programmes instituted in 1984 can only be made after understanding the political and economic environment that the country experienced during the whole decade. One can call it the lost decade. Some of the economic data are presented in table 1.

Table 1. National economic data for Brazil

Item	1980	1985	1990	1980–1990
Population (millions)	119	135	150	26% growth
GNP (billions of 1990 US$)	256	271	297	16% growth
Exchange rate on 31 December (Cr$/US$)	65.5	10 490	170 060 000	a/
Merchandise trade balance b/	(2.8)	12.5	11.1	97.0 (cumulative)
External debt b/	64.2	105	122	90.0% growth
Interest payment b/	7.5	10.5	3.8	102.0 (cumulative)
Principal payment b/	6.6	2.3	4.4	52.0 (cumulative)
Total b/	14.1	12.8	8.2	154.0 (cumulative)
Inflow of foreign loans b/	n.a.	2.8	3.6	23.3 (cumulative) c/

Sources: Central Bank of Brazil and Brazilian Geography and Statistics Institute (IBGE).

a/ Exchange rate 1990/exchange rate 1980 = 259,633,490% increase.

b/ US$ billion, current values.

c/ 1985-1996.

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The first civilian Brazilian president elect since 1964 took office in 1985; and in 1988 the new Constitution went into force. From 1980 to 1990, the population increased by 26 per cent while GNP only increased by about 16 per cent, with the result that the per capita income decreased. During this period the country experienced chronic, malignant and galloping inflation rates (an average yearly inflation rate of 375 per cent). With respect to Brazilian international trade and finance, the principal figures are as follows:

(a) The foreign debt jumped from US$ 64.2 billion in 1980 to US$ 105 billion in 1985 and then on to US$ 122 billion in 1990;

(b) The flow of new foreign loans reached US$ 23.3 billion from 1985 to 1990;

(c) Remittances abroad on account of interest and principal payments amounted to US$ 154 billion from 1980 to 1990;

(d) The balance-of-trade surplus totaled US$ 97 billion from 1980 to 1990.

During the 1980s, Brazil did not maintain the same performance as in the previous two decades, when intensive industrialization took place, based on an import substitution policy. In actual fact, the present population of 150 million means a consumer market of only about 30 million people.

In spite of this, the Brazilian pharmaceutical market ranks seventh in the world, and according to the Brazilian Association of Biotechnology Companies (ABRABI), the Brazilian market for biotechnology products will reach approximately US$ 1.5 billion by the year 2000.

In this almost chaotic setting, the appearance of biotechnology, as one of the most promising investment alternatives, induced the Brazilian Government to create a biotechnology programme to stimulate research projects in the sectors of agriculture, cattle raising, human and animal health and chemical specialties.

The programme started with the creation of the Biotechnology Secretariat within the Ministry of Science and Technology. The Biotechnology Secretariat has not been able to allocate government funds to the programme, has not succeeded in establishing rules and standards for biotechnology activities, whether research or production, and was not able to define and introduce an industrial policy for biotechnology.

The duplication of objectives of the Biotechnology Secretariat and other government agencies such as the Agriculture and Health Ministries, as well as the Social and Economic Development Bank (BNDES), the main financing agency for the industrial sector, together with the unstable macro-economic situation, were the basic reasons for the weakening of the Secretariat.

In spite of the limited impact of global policies, some specific sector initiatives have been implemented, some companies have started their own biotech projects and some objectives have been reached. The R&D investments in the field of biotechnology, in the public and private sector, for the period 1985-1988 are shown in table 2.

Table 2. Biotechnology R&D investments in Brazil, 1985-1990
(Millions of United States dollars)

Source/allocation	Amount
Public funds	176
Universities and research centres	167
Industry	9
Private funds	88.0
Universities and research centres	34.0
Industry	54
Others (international agencies)	5.3
Total	269.2

The programme for supporting scientific and technological development (PADCT) devoted a greater part of its budget to biotechnology research. Basically directed at universities and public research centres, with no obligation to become involved with private projects or interests, the major part of the projects has not contemplated applied research. Its main value has been the improvement of human resources capabilities.

The second phase of PADCT is starting now, and the new projects were approved under a requirement to tie private company interests to university and research centre capabilities. This means a possibility to optimize applied resources and eliminate previous deficiencies.

Traditional and intermediate biotechnology processes have a relatively high level of representation in the Brazilian economy and are especially important in the agro-business sector.

Several agro-industrial companies developed in-house-based research projects together with universities and public research centres.

The cellulose and paper industries are an example of success. They invested in the selection of new varieties of eucalyptus through in vitro culture techniques, increased their productivity, reduced their costs and are internationally highly competitive companies.

Other companies involved in vegetal biotechnology, such as Biomatrix and Bioplanta, did not experience success, basically due to market orientation and financing problems.

In the sector of cattle-raising, research projects were basically directed towards bovine artificial reproduction and embryo transfer techniques. Private companies, such Andrade Gutierrez, through their own efforts or in collaboration with universities and public research centres, such as Empresa Brasileira de Pesquisa Agropecuaria, are leaders in this area.

Concerning the human health sector, two basic questions must be raised:

(a) The research, development, production and commercialization of pharmaceutical products have undergone important changes in recent years. These changes have led to a significant increase in the cost of new drugs. At present, the necessary investment to launch a new pharmaceutical product in the world market is about US$ 250 million;

(b) The pharmaceutical industry in Brazil is controlled by transnational corporations, which hold a total market share of about 80 per cent. The Brazilian pharmaceutical companies have no tradition in the research of new chemical entities. International drug manufacturers carry out their R&D programmes essentially in their own R&D centres located at their headquarters. In spite of the scientific and technological update work undertaken under the sponsorship of the Brazilian government drugs distribution agency (CEME), the pharmaceutical industry in Brazil is very backward when compared to the pharmaceutical industry in other major countries.

However, some Brazilian private companies such as Cibran (antibiotics manufacturer by traditional processes), Biobras (insulin manufacturer, including the human semi-synthetic product) and Embrabio (immunoassay diagnostic products manufacturer) are providing funds to their R&D biotechnology projects. These local initiatives are directed at keeping up with the state-of-the art of biotechnology. It should be noted that BIOBRAS, through a joint research project with the University of Brasilia, developed the rDNA human insulin.

Public research centers, such as Fiocruz and Instituto Butanta, are also active in the development of vaccines and diagnostic products through biotechnology techniques.

In summary, it may be noted as follows:

(a) Very heterogeneous capabilities in the different biotechnology areas exist in Brazil;

(b) There is significant government involvement in the development of human resource capabilities;

(c) There is an increasing importance of joint collaboration between companies and universities and public research centres.

On a world basis it can be noted that biotechnology companies are establishing links with transnational corporations which are capable of introducing biotechnology products derived from their research projects into the world market.

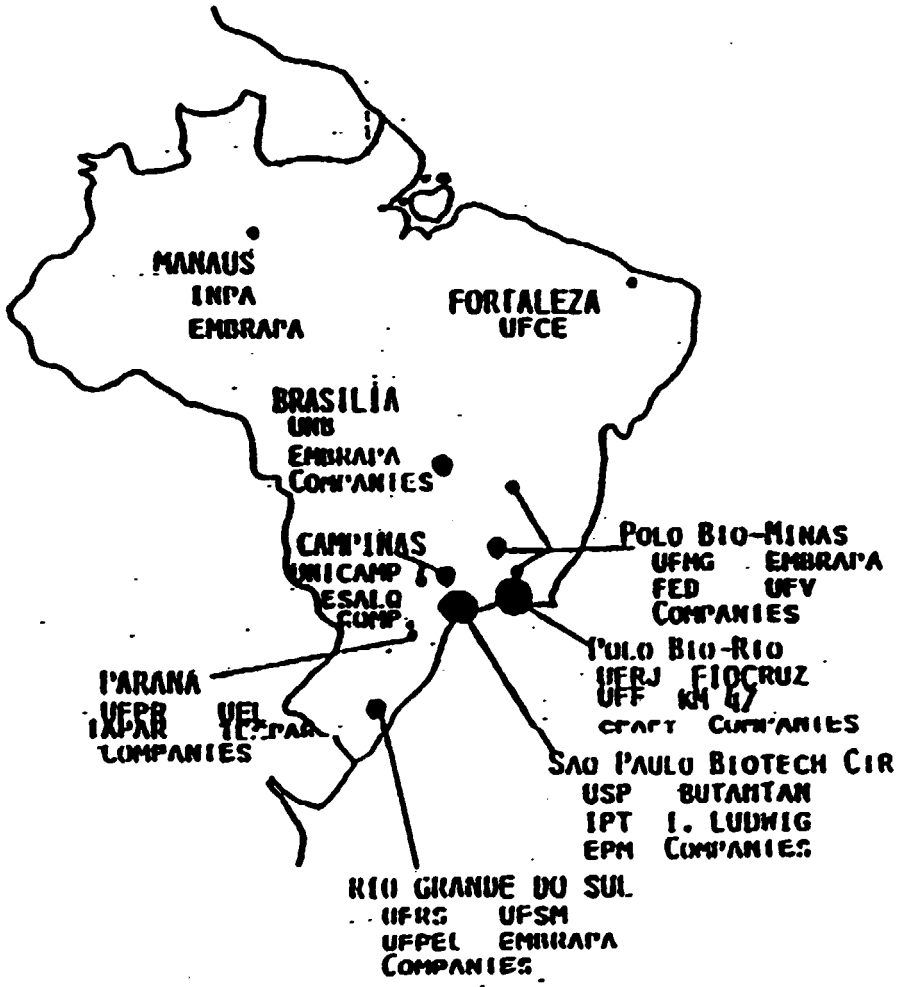
Several types of relationship are being established, such as licensing of products, acquisition, joint-ventures and joint marketing agreements.

Considering that the intellectual property rights issue in Brazil is being resolved, and considering the opening of the Brazilian market to imports and the present stage of Brazilian development, as well as the size of the Brazilian market, foreign biotechnology companies have an important role and advantage in collaborating with Brazilian companies. Brazilian companies have extensive and sound knowledge of their own market and business rules.

Collaboration, including research projects, clinical testing and licensing of products can be very attractive and advantageous for small and medium-sized foreign companies when compared to agreements with transnational corporations and will certainly have an impact on the development of biotechnology in Brazil.

Biotechnology activities are currently located in areas illustrated in figure 1. These Brazilian internal efforts at biotechnology development have to continue, and essential activities such as the optimization of the allocation of government financial resources have to be maintained and increased.

Figure 1. Biotechnology in Brazil



The aim has also been to encourage the development of biotechnology parks and incubator programmes.

The continuation of development of human resources capabilities is also essential for the success of biotechnology initiatives and the corresponding demand for qualified professionals is enormous (table 3).

Table 3. Human resource requirements

Professionals	Situation in 1990	Project needs in 2000
Ph.D. and M.S.	1 000	12 000
Graduated professionals	2 000	18 000
Technicians	500	15 000
Others	500	15 000
Total	4 000	60 000

Source: ABRABI.

Finally, stable and long-term conditions for collaboration between companies and universities has to be established, since such relationships mean the possibility of hastening the development of biotechnology products and processes, which will certainly return benefits to society.

XVI. DEVELOPMENT OF BIOTECHNOLOGY IN CUBA: MARKETING POLICY AND PRESENT OPPORTUNITIES

Manuel Limonta Vidal*

Introduction

How can a third world country obtain profits from first line technology? Never before has Cuban science faced a higher goal.

To design a strategy for the economic development of a country with no natural resources other than intellectual ability was no easy task. Scientific advances presented a solution. In the past 10 years (1981-1991), more than 200 new products have been developed in Cuba through the application of modern biotechnology (more than 25 recombinant proteins), comprising vaccines, drugs, monoclonal antibodies, restriction enzymes and industrial enzymes.

The key objective of this paper is to give some views on the conditions that led to this development and the present scientific and commercial policy and to reveal the successes of Cuba's biotechnology development.

Background

After a first decisive step in 1959, Cuba's social and economic conditions fundamentally began with the aim of obtaining a critical mass of interacting facts that would be capable of realizing a science explosion in the long term. It took 20 years to reach a higher educational level. Public health was the first priority, which resulted in health standards (figures 1 and 2) higher than many countries, including some developed countries (1, 2).

During the last decade conditions were created to exploit this achievement, supported by an intelligent policy of projection and the Cuban Government's support in promoting and developing biotechnology.

The future economy of the country is to be sustained by industries with immediate production incorporation, capable of producing competitive products with possibilities of accelerated acceptance by the specialized world market and increased demand. This industry is to be taken as a social and economic model to guarantee scientific and industrial development needs. An accessible and objective production system was required, capable of absorbing the most recent advances in science, thus reducing the effects in market variations of the traditional products in today's world economy scenario, with particular shades in the case of Cuba. In this vital and priority industry, a new necessity, as implied in facing the world market, is to establish an efficient commercial policy and management training.

Only a political decision in the establishment of priorities could support the huge investment needed to set up a scientific complex of institutions, with all modern facilities and possibilities and with the highest level of technology.

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Figure 1. Infant mortality until 1988

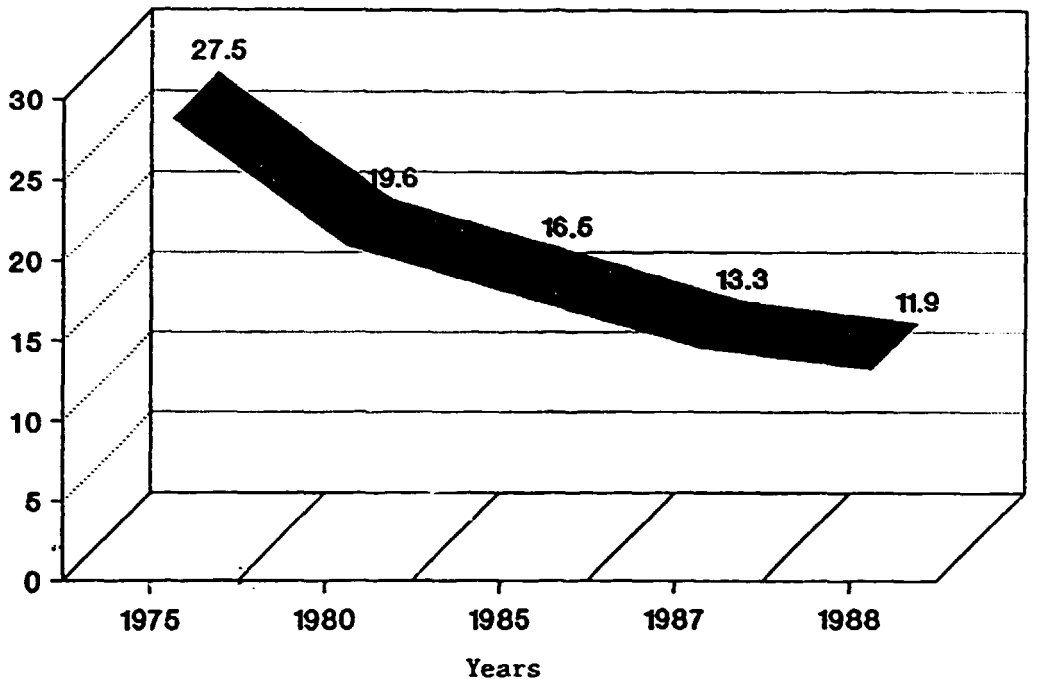
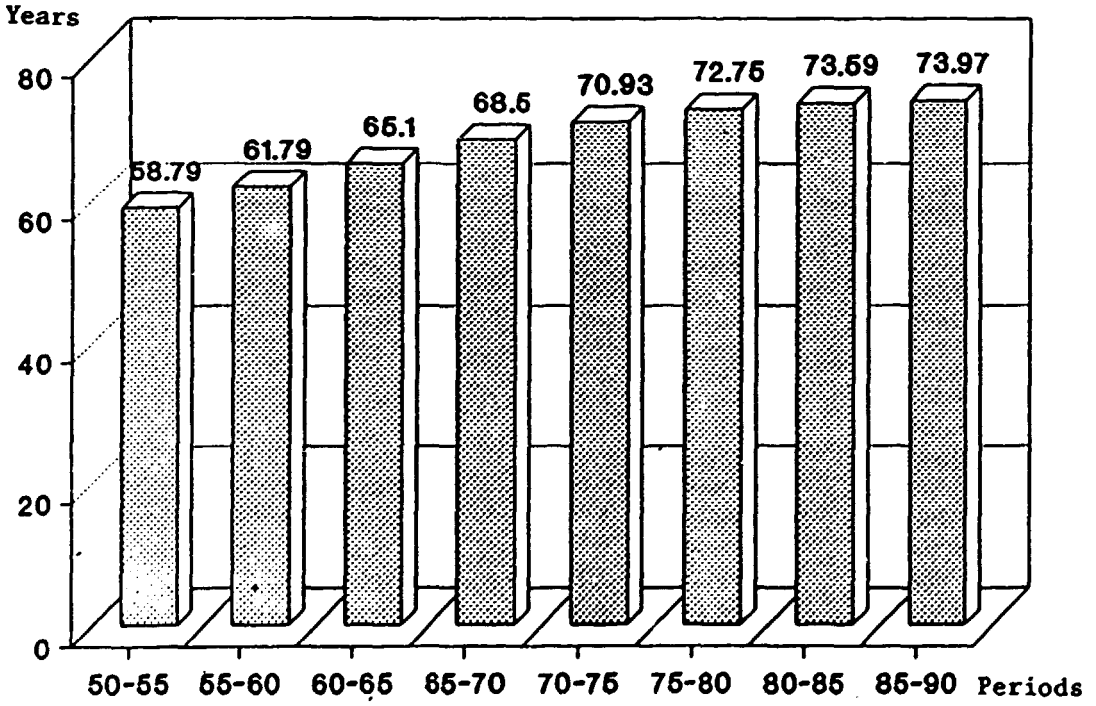


Figure 2. Life expectancy until 1990



This integrated technological potential could in the short term contribute to a large scale, profitable production of first line products with the initial purpose of meeting the country problems of the different branches of the new industry and set up the conditions for the development of a growing industry to assure highly competitive productions in a short period of time, with all the requirements of the world market.

All this integrated development generated the creation of new institutions in which more than 10 years of scientific research efforts are used (table 1), and the successes achieved by the Center of Genetic Engineering and Biotechnology (CIBG), Cuba's biotechnology flagship, acted as a stimulant.

Table 1. Centres of the scientific complex and their areas of function

Centre	Main field of action
Carlos J. Finlay Institute	Production of antimeningococcal vaccine
Biopreparados	Large-scale production
CNIC	Basic studies
Hemoderivados	Blood derived products
Immunoassay Centre	Automatized diagnostic systems
Tropical Medicine Centre	Diagnostic and treatment of tropical diseases
CIGB	Basic studies, development and production of substances for medicine, industry and laboratory

Center of Genetic Engineering and Biotechnology

Since its inception in 1986, from a small group of less than 10 researchers that had first assembled in 1981, CIGB has been expanding and specializing in molecular biology and genetic engineering techniques. The researchers established a constantly changing and flexibly organized system, according to the development needs.

The quick development of CIGB has a direct impact on the Cuban economy, mainly in the most developed sectors, such as the sugar-cane industry, agriculture and animal husbandry, but predominantly in the field of medicine. The transforming feature of the new technology, which until now was only accessible to highly developed countries, was associated to a new, efficient and inductive work style, with a constant generation of high technology results.

The CIGB complex comprises a 70,000 m^2 area, with an eight-story, air-conditioned building of modern functional design, where the following main research divisions are located:

(a) The Proteins and Hormones Division deals with the production, by recombinant methods, of proteins for use in human and veterinary medicine. The oligonucleotide and gene synthesis laboratory is included;

(b) The Vaccines and Diagnostics Division is involved in the production of vaccines against diseases by non-conventional methods, such as the cloning and expression of surface viral, bacterial or parasite proteins which cause disease; it includes the development and practical production of new diagnostic procedures;

(c) The Hybridoma and Animal Modelling Division concerns itself with the development and applications of murine, human and bifunctional monoclonal antibodies, as well as second-generation antibodies obtained by genetic engineering techniques, and helps in the development of transgenic animals, animal models for vaccines and toxicology tests, apart from the evaluation of recombinant and non-recombinant products.

(d) The Energy and Biomass Division works on the industrial application of biomass utilization, develops technological processes comprising the chemical and enzymatic transformation of substrates applied to industrial plants design, where the enzymes are used for the direct or indirect development of large productions;

(e) The Plants and Fertilizers Division uses genetic engineering techniques for species improvement, for studies on nitrogen fixation systems and to obtain more resistant species to different agents;

(f) The work of the Cell Genetics in Mammalian Cells Division is associated with the use of mammalian cells for the development of cloning and expression systems and the use of tissue culture laboratories dealing with the direction and execution of the work to obtain transgenic animals;

(g) The Restriction and Modification Enzymes Division manages the production of biological reagents required for the recombinant DNA methodology, such as restriction enzymes, modification enzymes etc.;

(h) The Analytical Unit engages in analysis and purification systems by high-pressure liquid chromotography, protein characterization by mass spectrometry, protein crystallography, electronic microscopy and immunomicroscopy, as well as the activity evaluation of specific biological peptides and proteins;

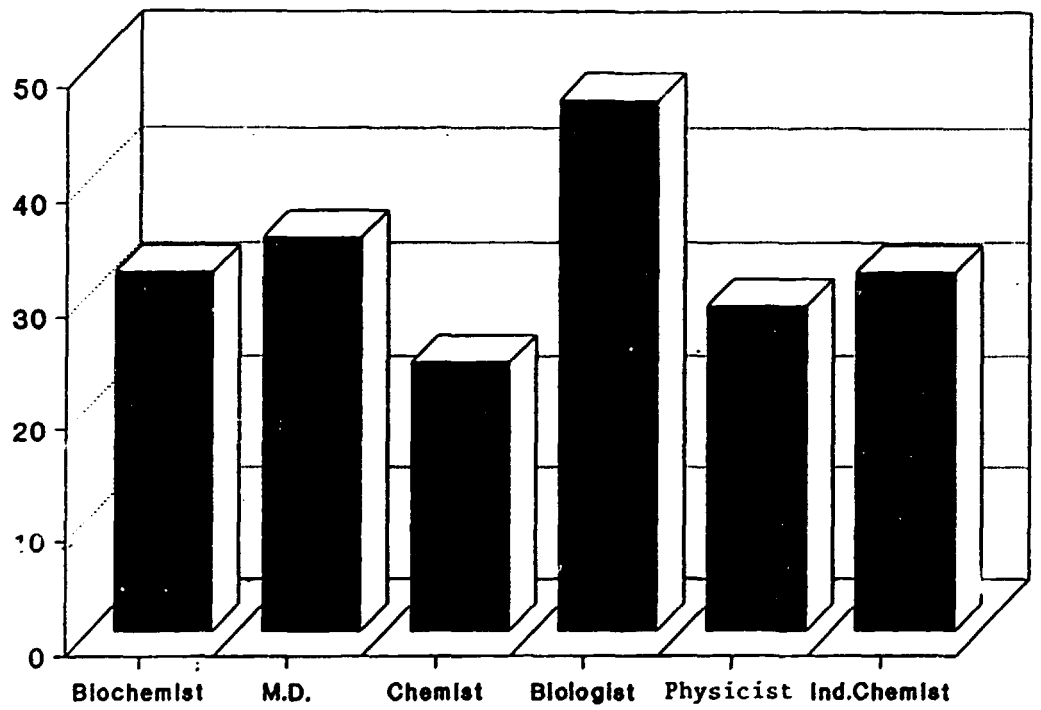
(i) The Quality Control Division reports directly to the Director General. It is formed by a strictly selected group that monitors purity, structural integrity, molecular composition, functions, clinical and pharmacological properties as well as immunological responses and side effects of all CIGB products.

P-3 and P-4 laboratories are available for the manipulation of high risk biological agents, which satisfy all international requirements for installations of this type. Also established is a theatre with a simultaneous translation system in four languages, where international scientific events take place every year with the aim of increasing a scientific exchange with foremost world international researchers in the different specialties.

CIGB avails itself of the most advanced equipment available in the biological industry, including the mass spectrometer, scanning and transmission electron microscopes, spectrophotometers, scintillation and gamma counters, electrophoresis facilities, DNA synthesizer and fermenters with downstream processing facilities.

The most valuable asset of CIGB is its staff. It has around 500 selected employees; 80 per cent of them are directly involved in research, while the rest are administrative and support personnel. More than 230 are university graduates and post-graduates with degrees from Finland, France, Germany, Sweden, Switzerland, the United Kingdom and the United States (figure 3).

Figure 3. CIGB staff by specialty



As a consequence of the intense work style directed towards expediting the incorporation of technology advances, the present structure has gone through different stages. The first was the development of interferon production as an anti-tumour and anti-viral drug in 1981. This was used as a scientific and methodological model. Nowadays, interferon is available to all health units, where diseases such as hepatitis B, AIDS, solid tumours, laryngeal papillomatosis and haematopoietic tissue malignant neoplasia are treated. This model was developed and today both alpha and gamma interferons are produced at CIGB by natural and recombinant techniques.

The direct effect of this policy is evidenced by the fast and constant incorporation of products into a catalogue. New products amount to 168 developed within five years, which belong to many developing lines, as seen in table 2.

Table 2. CIGB-Heber Biotec S.A. products list

Pharmaceutical products

Human leukocyte alpha interferon
Human recombinant alpha interferon
Human recombinant gamma interferon
Human transfer factor
Human recombinant epidermal growth factor
Hepatitis B surface antigen vaccine (recombinant)
Recombinant streptokinase

Industrial enzymes

Alpha-amylase
Sucrose invertase
Microbial cheese rennet

Diagnostic kits

Diagnostic system for the detection of anti HIV-1 and HIV-2 virus antibodies
Detection of antibodies (IgG) by golden/silver probes method

Monoclonal antibodies

CB-AC.1. For the detection of the alpha subunit of FSH
IA/CB-ApoA1.1. For the detection of human apolipoprotein A1
IA/CB-ApoA1.2. For the detection of human apolipoprotein A1
CB-CEA.13. For the detection of carcinoembryonic antigen
CB-CE.1. For the detection of Chlamydea trachomatis
CB-EGF1 and 2. For the quantification of hrEGF
CB-FSH.1. For the detection of human FSH
CB-HSV2.1 For the detection of herpes simplex 2 virus
CB-IFNG.10. For the detection of gamma IFN
CB-IFNA2.1. For the purification of alpha 2 IFN
CB-IFNA2.3. For the study of recombinant alpha 2 IFN
CB-IL2.1 and IL2.2. For the study and purification of IL-2
IA/CB-LDL.1 and 2. For the detection of apolipoproteins
CB-p24.1. For the detection of the p24 core protein of HIV-1
CB-PVX.1. For the detection of potato virus x
CB-tPA.1 and 2. For the detection of human tPA
CB-Hep.1. For the detection of hepatitis B surface antigen
CB-TSH. For the detection of human TSH
CB-R.1 and 2. For the detection of rotavirus
CB-RSV.1. For the detection of respiratory sincitial virus

Restriction and modification enzymes

Acc I	Cla I	Hird III	Nru I	Sfi I
Alu I	Eae I	Hinf I	Pst I	Sma I
Apa I	Eco RI	Hpa I	Pvu II	Sph I
BamH I	Eco RV	Hpa II	Sac I	Sty I
Ban I	Fok I	Kpn I	Sal I	Taq I

continued

Table 2 (continued)

Bcl I	Hae III	Mlu I	Sau 3A	Xba I
Bgl I	Hha I	Nci I	Sau 961	Xho I
Bgl II	Hinc II	Nco I	Sca I	Xho II

DNA polymerase I (E.coli)
T4 DNA ligase
DNA polymerase I large fragment (Klenow)
Exonuclease III
Polynucleotide kinase
AMV-reverse transcriptase
Thermus aquaticus DNA polymerase
Thermus thermophilus DNA polymerase

DNA molecular weight markers

Primers
Linkers
Oligonucleotide custom synthesis

The research advances permitted the production of first-line products by recombinant methods. A good example is epidermal growth factor (EGF), a 53 amino acid peptide that stimulates epithelial cells in vitro and fibroblast proliferation (3). With the property of improving wound healing in treatment, the EGF has important applications in skin burns, diabetic ulcers, cornea ulcers and skin grafts (4). It effects early stimulation and orientation of fibroblasts on the epithelial portion of the wound. A large-scale production of different formulations increases the availability of the product and its uses. The product is currently produced only in highly developed countries by companies with advanced technological backgrounds, such as Chiron in the United States. EGF is part of the growth factors market estimated in 1989 to be $2.8-4.8 billion in the United States alone (5).

The production and technological development nowadays make it possible to apply recombinant EGF in all burn treatment units in Cuba, where patient recovering time is diminished, thus reducing hospitalization.

Another product that demonstrates Cuba's technological advance is the hepatitis B vaccine, which is obtained by cloning and expressing a highly particulate surface viral antigen in yeast. The vaccine provides a high level protection against this serious worldwide disease. It is estimated that in the United States alone there are 200,000 cases annually with a growing incidence of 10 per cent and a mortality associated with the disease of 2 per cent, with sequels such as chronic active hepatitis, cirrhosis and hepatocellular carcinoma. The production of this vaccine facilitates the protection of the entire Cuban population, with sufficient surplus quantities to begin negotiations for export to the world market.

The fast research advances generated the need for a corresponding production process, involving the expansion of a suitable production capacity to sustain the nascent and potential industry's growing demands. The reinvestment

policy was directed to permanently guarantee the production process by balancing the increased use of the technology with management training. A main step of the reinvestment policy was the construction of the Centro de Biopreparados, which constitutes an expansive large-scale production facility for the products developed at the CIGB. This new complex includes flexible facilities for the incorporation of variable productions, which form the technological basis for the world market competitiveness.

To maintain industrial and stabilized production with all the constraints of competition is the permanent technological objective. Competitiveness is the outstanding attribute of products in today's market and is unlikely to be achieved without the following:

(a) Progressive technological support;

(b) Right investment policy;

(c) Permanent training of researchers;

(d) Commercial management training;

(e) Initial research policy;

(f) Industrial support development;

(g) Reinvestment policy;

(h) Objective commercial structure and functioning.

The best result of this work style is at present the possibility of offering highly competitive products derived from the unique availability in the world market. One of them is the meningococcal vaccine, a preparation that protects against infections of Neisseria meningitidis, which mainly afflicts children, produced by Finlay Laboratory in Cuba, a newly constructed production centre responsible for the production of this vaccine.

Recombinant streptokinase (SK) is one of the most outstanding and promising CIGB products marketed by Heber Biotec S.A., an enterprise created to commercialize CIGB products (6). The SK directed at the thrombolytics market is the best stabilized, less antigenic preparation having effects comparable to other similar naturally available products. The researchers developed the unique recombinant SK, which is mainly used as a fibrinolytic in vascular obstructions such as in myocardial infarction, the prime cause of death in the developed countries. Such products display the real beginning of biotechnology development in Cuba, the effect of the development programme changes and the opening of a great commercial prospect.

Marketing

The rapid advances in the research and production process bring about the exigency of creating a flexible commercial structure especially designed to market these products and result in the positive feedback process with the market to define new research and production needs.

The innovation and the industrial scaling-up support, once established, leaves a large technological gap to be filled: marketing technology.

Questions such as how to sell a product on the competitive world market, which elements comprise this technology and how this new enterprise can survive in the powerful business world need to be addressed.

Some elements in the economic structure generated the need for an awareness of this technology. The commercial strategy must be based on an analysis of a higher and variable market demand, the communications development, the technology impact on politics and economy, the high competitiveness and the generous capital movement directed during the last 10 years by the developed countries to the progress of this industry.

Only a critical analysis yields the correct approach towards obtaining biotechnology industry profits in the world market. The main problems for Cuba's products to be competitive were already considered at the start, in order to include solutions in the systems design. Heber Biotec S.A. was created and structured as a trading company to develop the marketing of products according to the experts' feasibility studies.

It is very difficult to introduce high technology products from non-traditional producers in the market without experienced business management, in order to obtain international credibility for the products. Heber Biotec S.A. follows a strategy based on the development of patentable products with an objective policy regarding intellectual property protection, an openness for high-level collaborative work and considerable interest in dealing with scientific and commercial exchange. These principles have generated a permanent scientific exchange and two-way healthy businesses with several companies in different countries which arose from an interest in the competitiveness of the products. Another important element relates to the carefully realized controlled evaluations following the procedures of the world's most prestigious institutions and a strong interaction with the partners.

The accelerated training of managers was a key factor for the organization of a flexible structure capable of generating permanently adjustable marketing strategies to the requirements of the present market and to face the fact that CIGB has the capability to produce and commercialize many recombinant products, while in no other Latin American country these products were produced. In short, only one word is suitable for the present strategy: competitiveness.

For a potentially strong newborn industry with a firm decision to develop, it is necessary to carefully consider several lines: the commercial associations, resulting from an analysis of the competitiveness, which includes many factors right from the design of the product; the incorporation of the quality control as a philosophy in all generation and productive phases; the distribution process; sales facilities; regional needs and post sales services, among other marketing elements. In order to achieve the highest competitiveness, more than investment and some results are required. It is necessary to build an integrated work philosophy.

Since the introduction of biotechnology products in the world market, the great commercial future for the new industry is already evident, even with only a few of these products being accepted. In 1984, the overall picture of competitiveness in biotechnology was studied, involving the evaluation of some facts identified as being potentially important in determining the future position of the United States and other countries in the commercialization of

biotechnology (7). Among these facts were the following: government funding of basic and applied research; personnel availability and training; regulations; intellectual property law; relations between industry and university; technology transfer; government policy and priorities; and public perception.

These and others facts are essential for the development of biotechnology companies. The importance of each one is defined in one phase or another. Some of them have relevance to the maturity phase of the technology and some others in the market establishment. Under Cuban conditions there are common facts affecting the competitiveness of our products. Only the objective and creative analysis of the present conditions will make it possible to generate really effective strategies for commercial purposes.

Conclusions

The achievement of the accelerated development of biotechnology in Cuba and the outcome of more competitive priority products are the result of a clear policy of perspective and strong support to solve national economic problems. This generated a research-production structure opened to the world market exigencies. The creation of a technological and productive centre, CIGB, resulted in the production of a growing list of biotechnological products (more than 168) in a very short time, readily available to the market and capable in this race to open, generate and materialize major commercial expectancies.

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XVII. PROBLEMS AND PERSPECTIVES OF BIOTECHNOLOGY IN THE USSR*

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Biotechnology in the Union of Soviet Socialist Republics is a rather new field, not more than 20 years old. The first considerable investments were made within the frame of a governmental act in 1975. A major part of the allocated finances was directed towards the development of genetic engineering and recombinant biotechnology. According to the act, a number of large biotechnological centres were set up, in Moscow, Leningrad, Novosibirsk, the Ukraine and in the Baltic region.

The projects were combined into the integral State programme involving both fundamental research and scientific developments aimed at practical realization. In particular, large-scale investigations were initiated to search for new enzymes of nucleic acid metabolism and cloning genes of restriction-modification, producing recombinant interferons, interleukins, insulin for therapeutic purposes and designing strains producing virus antigens to be used in diagnosis. At the same time, a network of biotechnological schools for qualified personnel training was set up. The main problem is that not every initiated programme could be finished due of bureaucratic, organizational and financial difficulties.

Nowadays a network of governmentally financed biotechnological laboratories exist that are well equipped and with a highly trained staff.

All biotechnological programmes in the USSR are funded through the State Committee on Science and Technology, which distributes the resources between various institutions and departments involved in these projects. The organizations running this work are the Ministry of Health, the Academy of Sciences, the Academy of Medical Science, the Ministry of Agriculture and the Ministry of Microbiology Industry.

A new financing system has recently been developed, for instance a grant system independent of State structures and the foundation of any project is to be decided by the Expert Council. Nevertheless the system does not work well due to of lack of opportunities to spend money properly. For example a manager can not conclude a contract with a potential recruit because the salary is governmentally restricted. Another problem is the absence of a free market and the non-convertibility of the rouble, which makes it impossible to fully provide the required materials and equipment for the planned research.

The last problem, but not the least, is that it is practically impossible to put into practice a project developed by a research centre not within the Ministry of Microbiological Industry as it is a rule interested only in the realization of its own projects. Thus one more obstacle in the way of a rapid development of biotechnology is the monopoly of ministries in the manufacturing area, which permits them to pursue a dictatorial policy with respect to

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*It should be noted that this paper was presented in November 1991. Therefore, the country designations Union of Soviet Socialist Republics and Soviet Union, which were in use at that time, have been retained.

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conditions of work and deprives the project leaders of the right to chose partners with whom to cooperate in producing biotechnological preparations.

The USSR is presently undergoing vast and profound economic reforms involving diverse aspects of research and production. Actually, the former system of links has been destroyed and new forms of business activity are fighting to emerge based on free enterprise. One of these is joint ventures.

The process of setting up joint ventures on USSR territory with the participation of foreign investors has evolved over four years. The analysis of this evolution allows us to distinguish the main tendencies in the development of joint entrepreneurship in the country, specify basic problems one encounters in the organization and management of Soviet-foreign business and suggest possible ways for their solution.

The analysed process is characterized by the stable rate of growth of the number of joint ventures set up in the USSR. Since 1987, when the first Soviet-Hungarian joint venture was set up, the record has been as follows: in 1987 we had only 23 joint ventures, 169 in 1988, but already 1989 was marked by registration in the Ministry of Finance of more than a thousand newly formed joint ventures. In view of a great number of proposals for setting up joint ventures now waiting for registration, it is expected that the registration of around 80-100 new joint ventures per month will be maintained in the near future.

Another distinct tendency is the reduction of investments contributed to the starting stock of newly formed joint ventures both by the Soviet and foreign partners. The average starting stock of joint ventures in the period from 1 January 1989 to 31 December 1989 decreased from 3.9 million roubles to 2.5 million roubles. The number of joint ventures having a starting stock above 10 million roubles diminished accordingly, from 14.5 to 6.9 per cent.

So, an ever-increasing number of joint ventures is being formed in those areas of activity that do not require substantial investments from cooperating partners. These are primarily various kinds of businesses in the service sector (information, consulting, intermediary services, staff training, advertising), as well as some types of activities in the field of medical service and care, and biotechnology.

One of the reasons for the growth of small-scale joint ventures is the very low activity of State institutions in setting up of joint enterprises with foreign partners. State institutions are so far insufficiently independent and self-sufficient in their economic activities, often lacking the means to make their own contribution towards the starting stock, and have a very weak interest in modernizing production technology and quality improvement of manufactured products. Therefore, a marked reduction in the number of State institutions and, vice versa, the corresponding increase in the per cent of cooperative societies among Soviet joint ventures partners were formed with the participation of cooperatives. This figure exceeded 30 per cent in the period from January to September 1989. At present Soviet cooperative societies act as partners in over 300 joint ventures.

Cooperatives have their own capital, albeit small with a free hand to use the money and actively strive for profitable investment. Cooperatives are not interfered with by any higher managing body to contribute part of their basic capital into the starting stock for joint ventures. In the meantime, State enterprises willing to contribute some part of their production capacities to

joint ventures need to obtain a corresponding reduction in their production plan, which often contradicts the requirements set by the ministries and creates problems when decisions should be taken about the setting up of joint ventures.

We can thus see that the development of joint ventures in the basic fields of the USSR national economy is closely connected to a wider and more profound democratization of economic management, with the promotion of self-sufficiency and economic independence of Soviet State enterprises.

Noteworthy are the distinctive features that characterize the structure of foreign joint venture partners on USSR territory. Joint ventures created in cooperation with companies from developed capitalist countries now account for over 80 per cent of the total number of registered enterprises of this type; this number is permanently increasing. By tradition, the leading role belongs to companies of German, Finnish, United States, Austrian, British or Italian origin. Joint ventures with companies from Germany, the United States and Italy have the largest amount of starting stock. The starting stocks of Soviet-Italian joint ventures is on the average 1.4 times larger than those with United States companies and 1.6 times larger than Soviet-German joint ventures.

Joint ventures as one of the elements of the market mechanism promote more rapid reorganization processes in this country and appear to be a positive factor in the strategy of Soviet economic development.

About 50,000 Soviet specialists are now working in joint ventures that, as a rule, have more sophisticated equipment and pay higher wages to their employees than analogous Soviet State enterprises.

Over 250 joint ventures are engaged in producing goods and providing various services for export and the home market. The overall costs of the production volume of joint ventures in the USSR in 1989 can be estimated as 0.9 to 1.0 billion roubles, including hard currency sales of 120-150 million roubles at home and 100-120 million roubles abroad. The nomenclature of manufactured goods and services provided by the joint ventures is fairly diverse and, apart from consumer goods, includes machinery and technological products (machine tools, elevating and transport machinery, communication systems, computers, light industry equipment etc.). There were more than 20 joint ventures set up and funded by the leading institutes and industrial centres, specialized in the field of molecular biology, medical and agricultural biotechnology and antibiotic manufacturing. This marks the beginning and gradual increase of the contribution of joint ventures to the USSR national economy.

In the meantime, the three-year period of joint entrepreneurship in this country has revealed rather acute problems arising both in the organization process of joint ventures and in their practical activities. These problems are caused by the current state of the Soviet economy and the characteristics of the internal economic mechanism, which is undergoing considerable overhaul.

The above problems not only decrease the efficiency of setting up new joint ventures and their activity, but occasionally lead to the secession of foreign or Soviet partners, or even the liquidation of some of these enterprises.

In our opinion, the most burning problems impeding progress in the development of joint ventures result from the slow and incomplete economic reforms within the USSR.

Thus, limitations to the economic independence of State enterprises make them disinclined to encourage the formation of effective variants of joint entrepreneurship. In their actions they are strongly dependent on the decisions taken by higher authorities; moreover, they are frequently defined as only formally participants in joint ventures, which causes difficulties at the enterprise formation stage. Since State enterprises have so far been obliged to transfer a major part of their produce to the centralized distribution system, joint ventures encounter serious problems as to the supply of necessary material and technological resources. Neither is it easy to command a ready market, due to the lack of freely accessed information on the needs for products of various Soviet enterprises, which is another inherent characteristic of the closed system of the centralized resources distribution.

The critical factor restraining the activity of joint ventures in the USSR today is the absence of both the developed wholesale market for industrial products and the market for securities and capital. Joint ventures, being outsiders not involved in the centralized regulated economy of the country, fail to find among State commodity producers partners who would be on a par with them on rights.

Many of the above difficulties can be essentially eliminated after the adoption in this country of fundamental laws concerning property, land and land-tenure, lease-holding relations, the single taxation system, such as are now being studied by the USSR Supreme Soviet or under public discussion.

In view of the complicated economic situation in the country in general, a significant reduction has been made in financing research institutions with a biotechnological trend, which has encouraged them to take the following steps: first, to search for independent means of financial support; second, to focus and accent commercial projects, and third, to start the mini-scale production of biotechnological preparations for implementation of original developments.

I will try to illustrate the tactics of a research institution that awaits a high scientific and intellectual potential but faces serious economic problems and financial pressure. As an example, I would like to take the All-Union Research Centre of Molecular Diagnostics and Therapy headed by Professor E. S. Severin, Academician of the Russian Academy of Sciences.

The Centre was founded in 1985 as a leader in developing advanced diagnostic approaches based on the latest achievements of biotechnology, molecular biology, biochemistry and immunology. Over the years, the Centre has succeeded in elaborating original methods for diagnosing hereditary diseases, viral and bacterial carriers and drugs monitoring. However, many of these developments encountered many obstacles on the way to their realization in practical medicine.

Under the country's new economic conditions, the Centre has the possibility of initiating a number of joint and small-scale enterprises, aimed at implementing novel developments and approaches. In particular, in 1989 the Soviet-United States joint venture Medtech was set up, which is run now on a self-supporting basis and fully pays its way. As its contribution to the initial stock of the enterprise, the Centre has transferred to the possession of the joint venture a number of technologies for the manufacture of biochemical kits. Research associates of the Centre participate by contract in the work of the joint venture on producing biochemical reagents, standardizing biochemical kits, enhancing the sensitivity of diagnostic test systems and

modernizing technological processes. The foreign partner provides equipment and reagents necessary for manufacturing the final products and that are absent on the Soviet market. The United States partner in Medtech has, for instance, supplied equipment for packing biochemical reagents.

The biochemical kits produced are today on sale on the home market and in 1992 are to be put on foreign markets as well. The profits from the sales are partly assigned to the Centre as wages for the researchers and for the promotion of fundamental investigations that lack financial support from the Government.

The second example I feel of interest is the creation of the immunoenzyme diagnostics base.

Within the Centre, several major laboratories are involved in raising monoclonal antibodies. A rich collection of hybridoma-producing antibodies to various viral and bacterial antigens, oncoproteins, low molecular weight drug substances etc. has been compiled. The modified economic policy prompted the organization of the production of immunoenzyme diagnostic kits, employing the available scientific potential of the Centre.

The preparations for starting the production of diagnostics for hepatitis B, herpes viruses I and II, cytomegalovirus, Epstein-Barr virus and HIV I are close to the final stage. Aided by a society with the limited responsibility constituted by the Centre, the scientists have begun producing peroxidase and alkaline phosphatase as well as developed the technology for chemical synthesis of chromogenic substrates for these enzymes.

In fact, the Centre has the necessary facilities and is actually capable of producing actually all components of the above-listed diagnostic kits. The only problem restraining the production level is the lack of plastic plates for immunoenzyme assay; we are trying to overcome this difficulty by enlisting the cooperation of a foreign partner.

Among the research projects of the Centre which, as we believe, may be of commercial interest, mention should be made of diagnostic test systems based on the polymerase chain reaction (PCR) and biosensors for detecting virus antigens and drug monitoring.

Within the frame of the former project, we have isolated and described new thermophilic DNA polymerase from Thermus thermophilus (Tth-polymerase) that is capable both of DNA segments amplification and DNA synthesis on the RNA template, i.e. possesses reverse transcriptase activity. This finding opens up wide prospects for diagnostics of RNA-containing viruses. Also, genes of Tq and Tth-DNA polymerases have been cloned and bacterial superproducers constructed which allows large-scale production of these enzymes. The project is being realized together with the Italian company Bioline. The Centre disposes of fairly good facilities for synthesis of oligonucleotides, and to date PCR tests have been developed for HIV I, herpes simplex, Epstein-Barr virus, chlamidis trachomatis, toxic strains of Staphylococcus aureus etc.

The key problem in designing biosensors and achieving progress in bioelectronics on the whole, is the elaboration of new approaches and methods of producing protein supports with high density of immobilized protein molecules.

At our Centre, we have developed the basic technology for producing antibodies and applying them to various surfaces of monomolecular supports,

as well as employing enzymes as special monomolecular polymer layers for protecting the support structure and conformation of protein molecules from destructive effects.

The technology of the support manufacture has been checked using the following models: monoclonal antibodies against hepatitis B, insulin, morphine, enzymes (glucose oxidase and tyrosine hydroxylase) the polypeptide fragments of specific proteins of HIV I. All these supports were utilized for constructing laboratory prototypes of biosensors.

As noted above, the Soviet Union is abundant in highly efficient and skilled research workers. There is a danger in the present-day economic situation that some of the well-trained and qualified specialists could face the problem of unemployment. Under these conditions, a new type of commercial activity is emerging, namely the establishment of educational centres on personnel training and familiarization with modern methods in biotechnology, molecular biology and diagnostics.

In particular, the All-Union Centre for Molecular Diagnostics and Therapy has got all facilities for organizing such educational processes. New buildings belonging to the Center that are now under construction, to be ready by early 1992, will be able to accommodate foreign students. By that time, the Centre will be fully prepared to organize a permanent international biotechnology school, providing both a theoretical course of lectures and practical training for students.

Briefly summarizing the above, the following aspects are emphasized:

(a) The economic situation in the USSR is really complicated by profound inflation processes, disorders in the Soviet market, disintegration and failure of former manufacturing systems and business links, as well as ways of financing forward enterprises and research institutions to seek new forms of economic activity;

(b) New business structures are created in the country, for example, joint ventures, limited liability companies and share holding companies. Their main aim is to promote the transformation of original scientific developments into high-quality biotechnology products and launch them on the world market.

(c) Most of the biotechnology projects being developed in the USSR need the following investments by foreign partners:

(i) Technology for quality control and standardization;

(ii) Equipment for the material packing;

(iii) Design and marketing of the product.

(d) The USSR possesses huge intellectual potential and highly qualified specialists in various areas of biotechnology.

There is a good base for setting up a network of international biotechnological educational centres.

XVIII. IMPACTS OF BIOTECHNOLOGY ON FOOD PRODUCTION AND PROCESSING IN VIET NAM

Nguyen Van Uyen*

Introduction

Self-sufficiency in food supply has been the prime target of the Vietnamese economic effort for the last 30 years.

Food shortage was compensated by an annual import of roughly 1 million tonnes. From 1989 however, there was a marked increase in food production. In 1990, Viet Nam became a rice exporting country, ranking third in the world rice export market.

As in other South-East Asian countries, the Vietnamese have a strong preference for rice as a staple food. Maize, cassava, yams, cocoyam, potatoes and sweet potatoes are mostly consumed by highland inhabitants or by low-income inhabitants of cities.

Considering the limited potential to further increasing rice production, enlarging the planting area and yields of maize and root crops and their appropriate processing, will occupy a crucial position in the long-term food strategy of Viet Nam.

Priorities in the development of biotechnology in Viet Nam should be given to agricultural biotechnology with definite goals, on a short-term basis, by putting emphasis on the transfer of appropriate technology to small-scale farmers.

The National Biotechnology Programme of Viet Nam, formulated every five year period since 1985, has been focusing on the following tasks:

(a) Improvement of seed quality and the availability of food crops, especially root crops (potato, sweet potato, cassava etc.) by plant tissue culture and related techniques;

(b) Production of bioinsecticides and biocontrol agents;

(c) Biotransformation of wastes by appropriate fermentation techniques;

(d) Production of biofertilizers;

(e) Small-scale food conservation and processing techniques.

Improvement of seed quality and availability of root crops: the case of the potato (Solanum tuberrosum L.)

One of the objectives of the Vietnamese national potato programme is increasing potato production to 1 million tonnes annually during the last decade of this century.

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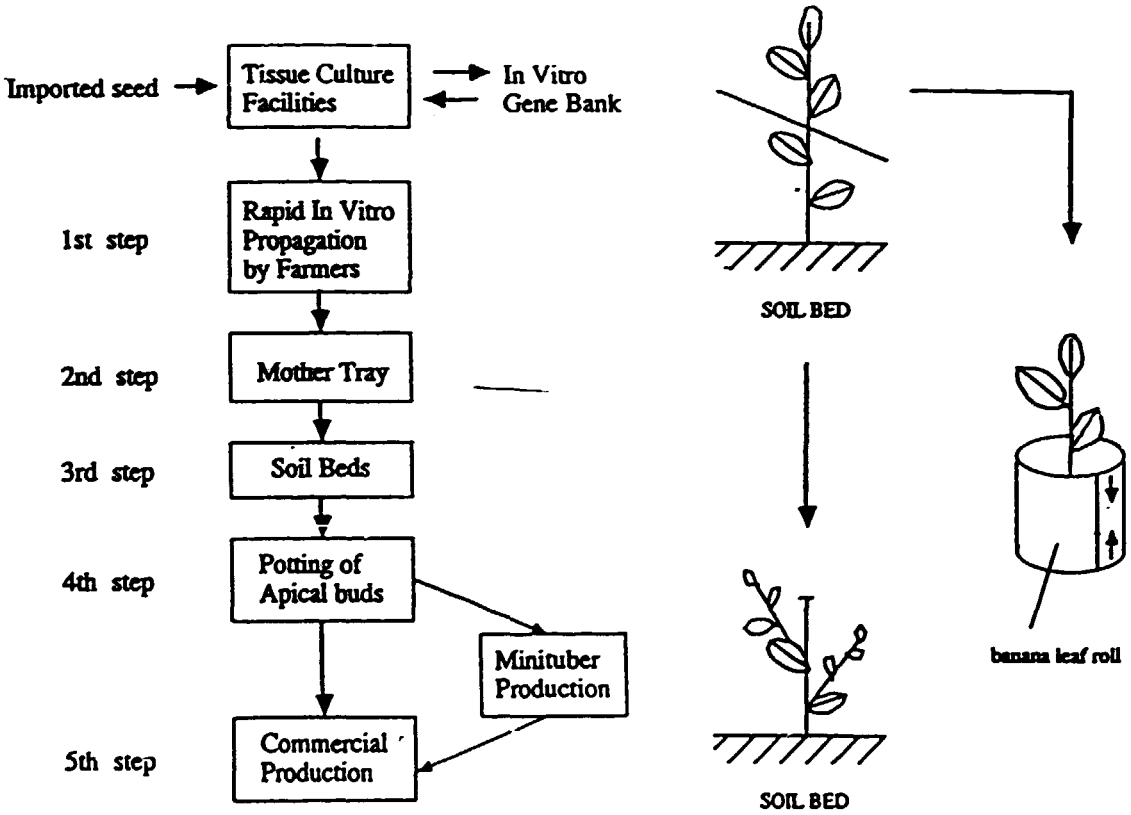
Availability of high quality seed tuber at low cost is the priority target of the programme.

The micropropagation of the potato began in Viet Nam from 1977, but this approach could not itself become an appropriate technology to solve the problem. Apart from the obvious advantage, even by using the simplest model the cost of in vitro plantlets is still higher than traditional seed tubers.

This is the main constraint to the utilization of a typical micropropagation system in developing countries. Furthermore, to reach a commercial scale, substantial capital investment is required to assure a continuous supply of glassware, chemicals and clean space. The potato plants taken directly from test-tubes require delicate care during hardening and perform poorly in the initial stage of growth. Test-tube plants give a slightly lower yield than plants from their tubers.

To avoid these difficulties, a rather simple yet effective system has been established, which resulted from the collaborative efforts of scientists and farmers in Viet Nam. Upon observation that the potato plants in test-tubes are physiologically as young as true seed-derived plantlets and have a high morphogenic capacity (rapid rooting, rapid axillary bud forming etc.), a flash-out system (FOS) for rapid propagation of the potato in a semi-sterile condition has been tested (figures 1 and 2).

Figure 1. Flash-out system for potatoes



500 vitro plants ⟶ 500 x 50 apical buds from mother plants ⟶
60 m^2 soil bed ⟶ 60 x 5,000 apical buds/year ⟶ 300,000 pots

(10 hectares)

Establishment of mother trays

Test-tube plantlets were grown at high density (5 x 5 cm) in a wooden tray on fine sand watered with dilute MS medium or a solution of mineral fertilizers. Care must be taken in the first few days to ensure high humidity by covering the tray with a thin plastic sheet. Growth resumes after one week. After three weeks, all apical buds are removed by using sharp razor-blades. This operation of destroying apical dominance starts the dormant buds to grow. The next harvest of apical buds is from one to two weeks after the first depending on nutrient availability. The harvesting operation can then be repeated every two weeks and can prolong up to six months or more until the plants begin to have compound leaves, a morphological indication that the juvenile stage is over.

Establishment of soil beds

The harvested apical buds are grown at the same density on a soil bed enriched with cow manure. The soil beds are preferably under shade from direct light and protected from heavy rain and strong evaporation by covering with plastic sheets. The beds are usually 80-100 cm wide and framed with bricks, wood, bamboo or other materials.

Apical buds of the same harvest are very homogenous in rooting and growth. The stems and leaves of these plantlets are much stronger and larger than those on sand trays and in test-tubes.

After two weeks, the first harvest of apical buds from the soil bed can be carried out. At Dalat, the farmers harvest apical buds once a week on the same bed, resulting in a large number of vigorous, homogenous individual potato apical cuttings for rooting at the next stage.

Rooting in pots

The rooting of such a vigorous juvenile apical bud often takes 304 days without any hormone treatment. Manure enriched soil is used as a substrate. The small pots (5 cm length and 2-3 cm in diameter) are made from any suitable, locally available materials: banana leaves, bamboo leaves, discarded journals etc.

With appropriate care, an apical bud from the soil bed usually requires two to three weeks to grow to a commercial size.

Field planting of these plants poses no special problem. At Dalat, farmers growing FOS potato are quite satisfied with the yield, even in the first generation. The highest yield is usually obtained in potato fields planted with small tubers from the first generation. There is some decline in yield with tuber seeds from the second and the third generation, so farmers returned again to purchase potato plantlets to begin a new cycle.

Production and commercialization of bioinsecticides and biocontrol agents

Chemical insecticides and fungicides have been an essential element in introducing the green revolution into Viet Nam. In 1990, the Vietnamese Plant Protection Agency imported US$ 1 million worth of active substances, which were formulated locally to commercial plant protection products. The danger of destroying the natural equilibrium became apparent, illustrated by several

outbreaks of rice leaf hoppers transmitting viruses, causing considerable loss in rice production.

In vegetable production, the control of Plutella requires an increasing dose of insecticides, so that the green belt surrounding big cities is becoming polluted with chemical insecticides to an alarming level.

In the case of cabbages, the imported hybrid FI seed from Taki Co. and pesticides from Sumitomo Co. (both Japanese) constitute two thirds of the production cost.

The Government had the possibility of using an integrated control system, including the use of bioinsecticides to improve the situation.

The production and commercialization of Bacillus thuringiensis (Bt)

A pilot-scale 2,000-litre capacity fermenter has been producing a quantity of Bt products in the last five years. B. thuringiensis var; kurstaki HD_3 was used after field trials of several strains. Powder and liquid forms are both accepted by farmers who are very sensitive about cost reduction.

The biggest constraint in Bt production and commercialization is the phage contamination. On an average, a quarter of the fermented batches have been discarded because of phage destruction. Using phage-resistant strains has had a very limited effect.

Production of Bt on a smaller scale (10 litre fermenters) at the farmer's level using less sophisticated technology, with the pure strain being provided by governmental institutions, could be an alternative. This procedure has been successful in the vegetable growing area of Dalat. Some of the more advanced farmers producing Bt in such locally made fermenters could sell the fermentation broth without any downstream processing to their neighbouring farmers. The medium consists of corn powder peanut meal or soybean meal and minerals, all locally available. The production could be programmed according to field survey, by spraying the fermented broth right at the third instar of the insects, which is the most effective time for treatment.

The production of other biopesticides and biocontrol agents

Entomophagous, filamentous fungi have been used to control insects damaging several agricultural and forest plants.

Beauveria bassiana, Metarhizum anisoplae and Trichoderma harzianum were produced by solid state fermentation on rice bran supplemented with minerals and other ingredients.

The production cost is low and the technology is much more simple than bacterial fermentation, which permits the production to be carried out at any scale. A clean plastic bag with an inlet and outlet of sterile air was filled with the steam-sterilized and inoculated substrate. The fermentation was then carried out at room temperature without shaking, cooling or mixing. Heat and mass transfer are not serious problems. The resulting fermented mass was dried in shade, powdered, sieved and packed in small plastic bags for use within two months.

Recently, we have tried to produce Paecylomyces liliacea, a nematicide fungus, by the same procedure.

The acceptance by different farmers of these simple products is quite different. Chemical insecticides impress them by their immediate effect, while the field effect of bacterial or fungal products is much more slower. Some farmers prefer to use chemicals due to their small working volume.

For the better commercialization of bioinsecticides, we believe that an appropriate governmental extension service, with a good pricing policy for agricultural commodities having lower pesticides residues, should be applied.

Solid state fermentation with its obvious advantage should be an important and appropriate technology for developing countries.

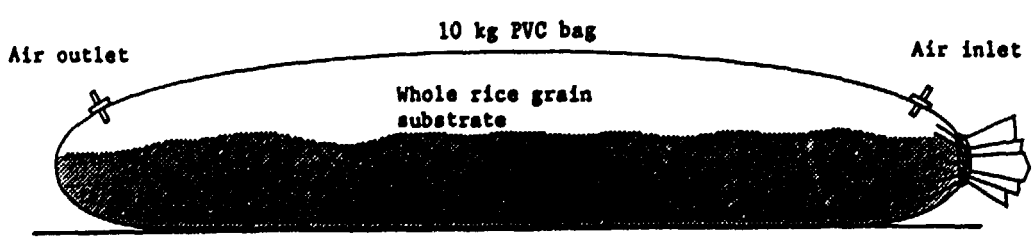
UNIDO and NGOs could accelerate the transfer of this technology by organizing several pilot-scale demonstration units at appropriate sites so that the farmers could visit them and become informed about the advantage of using bioinsecticides and biocontrol agents.

Production of cotton in Viet Nam has been a difficult target, although climatic conditions favour the growth of this important textile plant.

The cotton plants were seriously damaged by Spodoptera and Heliothis, which could not be prevented even with high doses by chemical insecticides. Recently, the researchers at a central province of Viet Nam have been successful in using Trichogamma to parasite the eggs of these dangerous insects. Simple mass rearing of this predator permits the use of this biocontrol method on a large scale.

A local gibberellin product was also produced and commercialized by the Biotechnology Research Centre, using solid state fermentation of Fusarium moniliforme on whole rice grains. The product, containing 2 g equivalent of gibberellic acid per kilogram, was sold for farmer use without isolation and crystallization (figure 2).

Figure 2. Simple solid state fermentation of fusarium moniliforme for production of Gibberelline and entomophagous fungi



Utilization of wastes

Agricultural waste represents a major source of material for biotechnological conversion. On 5 million hectares of rice harvested annually, the amount of rice straw that could be processed into useful products is considerable.

Viet Nam has around 200,000 hectares of sugar cane, the main by-product being cane-molasses, which is not being effectively used.

Other wastes are the refuse from fruit canning factories, the coffee processing industry, effluents from rubber processing units and municipal wastes.

Mushroom cultivation

Mushrooms (*Volvariella volvace, Pleurotus sp.*) are traditionally produced in several regions in Viet Nam, using rice straw and wood sawdust as substrates. The product is sold locally or exported.

Better spawn are required by farmers, who do not have access to sterile procedures for the isolation and maintenance of good strains.

Research on an effective way to protect mushroom farms from attack by mites and wild fungi is very important to boost production. Researchers are also trying to reduce manpower costs by improving the production techniques necessary for farmers who wish to organize large private mushroom farms.

Bioconversion of low-grade materials: citric acid fermentation

Viet Nam annually imports around 1,000 tonnes of citric acid and the same amount of acetic acid for use in food processing and the rubber industry.

A pilot-scale installation for the pilot production of citric acid by the solid state fermentation of tapioca processing residues has been operating as of 1991 in Ho Chi Minh City.

Thousands of tonnes of waste from the cassava starch industry could be used for this purpose.

The production of low concentration (7-8 per cent) acetic acid from low-grade alcohol (molasses-derived) is still not accepted by the rubber industry, due to transport cost. The distillation of acetic acid to higher concentration (90 per cent) requires energy and stainless steel distillators, and the product is at present not competitive with imported petrochemical acetic acid.

Municipal waste

Ho Chi Minh City is a big city of more than 4 million inhabitants. An efficient procedure for waste management has not been worked out, and some parts of the city are very polluted, mainly with organic waste.

Since 1990, the Biotechnology Research Centre has been working on a municipal waste integrated management programme, in which the organic wastes are first fermented anaerobically to produce biogas, while the effluent and

CO_2 is diluted and serve as nutrients for the large-scale cultivation of Spirulina platensis. This research project is being funded by the city authority and partly by CNRS, France.

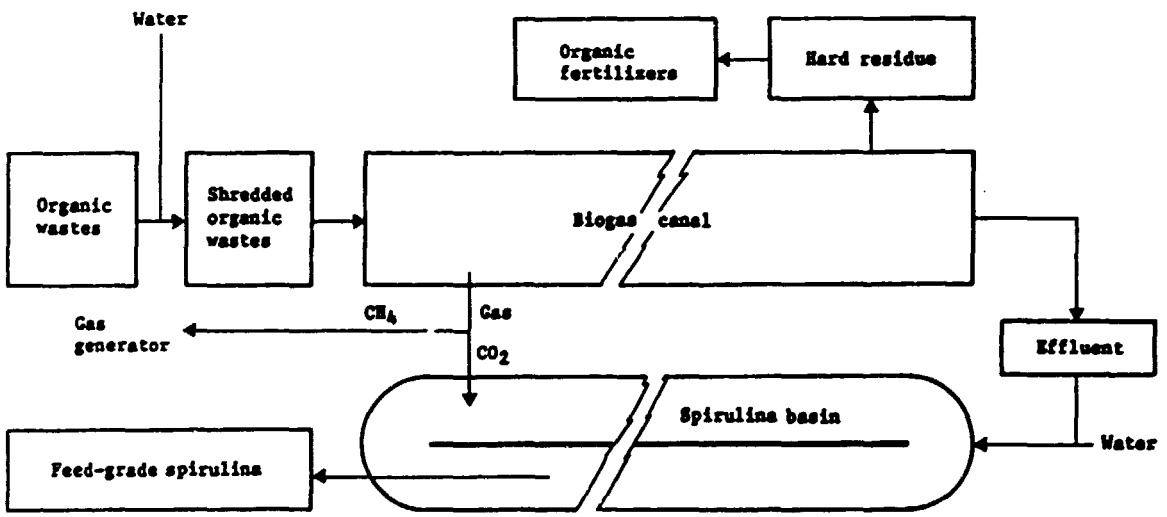
The main component of the project is the concept of a simplified large biogas unit harbouring the shredded organic waste. This unit consists of a long canal covered with several double plastic sheets to recover the gas. This simple biogas construction has been successfully used in the United Republic of Tanzania. The resulting gas is stripped of CO_2 by bubbling through an algal culture medium and pipelined to a gas engine to produce electricity.

The diluted effluent, enriched with CO_2 and sterilized at 80° C by solar energy heating devices, is discharged into algal basins (raceway type) for Spirulina cultivation. The harvested products containing 60-70 per cent protein, rich in vitamins and pigments, are spray-dried and used for various purposes.

The hard residue of the anaerobic fermentation is sun-dried and sold as organic manure.

A 100 m^2 pilot project has been successfully operating near Ho Chi Minh City this year. Its scale up, however, is waiting for an appropriate funding source (figure 3).

Figure 3. Schematic presentation of a simple waste treatment system



Biofertilizers

Viet Nam produces only a very small amount of its required 800,000 tonnes/year of urea. On average, US$ 100 million worth of urea is being imported each year to cover farming needs.

Biofertilizers are familiar in the northern provinces, whereas the southern provinces are heavily dependent on imported fertilizers.

Nitrogen-fixing Azolla pinuata is grown traditionally in the north on hundreds of thousands of hectares during the winter season, providing a large amount of nitrogenous compounds to rice plants. The major constraint of growing this floating fern is its difficult maintenance during the hot summers. Vegetative propagation is time- and manpower-consuming. The Institute of Biology at Hanoi is working on mass-producing viable spores of Azolla and on an efficient way to use these spores in rapid Azolla propagation. However, this important biotechnology is still not at a commercial level.

Nitrogen-fixing blue-green alga, especially Hapalosiphon Sp., was found in most rice fields at the Mekong River Delta. It is very important to transfer the appropriate algal technology obtained in India and Thailand to Vietnamese farmers, since algal inoculation could contribute more than 30 kg nitrogen to one hectare of rice field.

A group of researchers at Ho Chi Minh City is working on the nitrogen-fixing rhizosphere bacteria (Azospirillum, Pseudomonas etc.), in a cooperative project with CNRS, France. Inoculants have been tested on rice and maize with very promising results.

Two small factories producing Rhizobia inoculants for soy bean have been operating for a few years in Hanoi and Cantho provinces, providing enough inoculants for several thousands of hectares. The major constraint is the limited conservation period of the products.

Food conservation and processing

Loss due to poor food conservation in Viet Nam is a serious problem. Losses of between 15 and 20 per cent due to insects has been reported. More serious losses are reported for root crops (cassava, sweet potato etc.) due to lack of processing facilities, high temperature and high humidity.

The post-harvest biotechnology is therefore a field that needs to be developed in Viet Nam, as well as in most developing countries.

Several Asian food processing technologies originated from century-old traditions. Among these, the Indonesian tempe and ontjom and the Vietnamese nuoc mam (fish sauce) are traditional biotechnologies for food processing.

Viet Nam produces roughly 10 million litres of nuoc mam per year at the family level as well as at factories producing several millions of litres per year. The enzymes in fish intestines are released during processing and digest the fish protein in a high saline medium, which prevents the growth of unwanted groups of microorganisms. Digestion takes place several months in non-sterile conditions in wooden tanks at room temperature without mixing or aeration. Colours and tastes develop slowly. The resulting product is a brown clear liquid, containing 20-30 g amino acid N per litre.

We believe that nuoc mam has been and will be an important source of amino acid to balance the amino acid profile of the vegetable protein and rice protein in Viet Nam. Research has been carried out to accelerate the digestion process with external microbial proteases and/or pineapple bromelins and papains. The new process could produce high quality nuoc mam in two weeks instead of several months.

Enzyme biotechnology also plays an important role in the rapid processing of food crops, for instance the processing of cassava starch into maltose, glucose or high-fructose syrup.

These products have better keeping quality and can be marketed more easily. The Vietnamese Government has created advantageous conditions for companies dealing with indigenous processing of the root crops to prevent the large-scale export of raw, dried slices of cassava and sweet potato. These root crops are mostly planted in remote regions where transport is very difficult. Some of these regions even have no access to electricity, so the processing procedure must first of all be very simple.

Efforts have been made by governmental institutions to boost animal husbandry. Rice bran is the major source of feed for poultry, pigs and fresh water fish; cassava and sweet potato cannot be used as a sole source of feed raw material without mixing with fish meal and oil-seed meals.

One simple way of increasing the protein content of these low quality root crops is solid state fermentation with filamentous fungi.

According to our preliminary results, fermentation by a strain of Endomycopsis could increase the protein content of cassava from 3 to 10 per cent. The medium was enriched with 4-5 per cent urea as the mineral source of nitrogen. Drying of the products into a conservable state usually increases the production cost considerably. Solar dryers have been successful, but only in the dry season (November-May). The fermented products should compete favourably with other sources of protein, such as fish-meal or peanut meal on the protein content basis.

Conclusion

The impacts of biotechnology on food production and processing in developing countries will indisputably be very significant in the last decade of this century.

In this area, in our opinion, priorities should be given to the transfer of the following four appropriate technologies to the small-scale farmers' level:

(a) Micropropagation of plants;

(b) Production of biopesticides and biofertilizers;

(c) Solid state fermentation;

(d) Enzyme application at small-scale food processing units.

North-South scientific cooperation would help the developing countries to avoid the establishment of heavily funded, sophisticated biotechnology centres.

For instance, the genetic engineering of microorganisms, plants and animals should not be considered as a privilege of advanced laboratories of the developed world. The transformation itself is relatively simple and could be done at selected laboratories in developing countries.

However, tailoring the molecules into suitable shapes for genetic transformation work is rather complex. This justifies the need to strengthen North-South cooperation, which could permit the developing countries to enjoy most of the scientific biotechnology advancements of our era and on the other hand minimize the danger of complete dependence on multinational biotechnological monopolies.

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XIX. APPROACHES TO COMMERCIALIZATION OF BIOTECHNOLOGY IN A DEVELOPING ECONOMY

A. H. Zakri*

Introduction

In Malaysia, interest in biotechnology is still confined to the scientific community in universities and public research institutions except for some of the larger plantation houses, which also have their own R&D arms. Agricultural biotechnology is given a greater emphasis due to the importance of this sector in the national economy.

Agriculture is a major occupation in Malaysia, the country being among the world's largest exporters of rubber and palm oil and a major producer of cocoa. Biotechnology has the potential to improve the yield performance of the above crops, in addition to tailoring certain novel products so as to give them more value-added. This is not to say that other sectors of biotechnology have been neglected. Environmental and industrial biotechnology, health care and food processing are also seen as areas of potential. However, most of these activities are still in their preliminary stages. This paper discusses the current status of biotechnology in food processing and health care only, but the appraisal of national biotechnology capabilities and the approaches to commercialization may apply to other sectors of biotechnology as well.

Biotechnology in food processing and health care

Biotechnology in the broad sense, which includes traditional technologies, has been around in this country for quite a while, mainly in the food and beverage industry. Some of them are even multi-million dollar commercial ventures involving the business of transnational corporations (table 1). However, none of these activities are the direct results of technologies developed through endogenous R&D efforts.

Table 1. Current biotechnology-based food and beverage industries in Malaysia

Activities and products	Companies
Alcoholic beverages	Carlsberg, Guinness, Malayan Breweries
Food additives and seasonings	
Monosodium glutamate; soy sauce and soy-related products	Ajinomoto, Nestlé, small local companies

continued

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Table 1 (continued)

Activities and products	Companies
Fermented dairy products	
Cultured milk drinks	Sunglow Natural Foods, Malaysian Dairy Industry
Yeast	
Food Animal feed	Mauri Fermentations, Carlsberg, Guinness, Malayan Breweries
Sweeteners	
High-fructose corn syrup Cereal enzyme by hydrolyzed extract/sugar substitutes	Jamanis, Nestlé

Traditional food fermentation is still a major research interest. Various aspects of this work include identification of the specific micro-organisms involved, fermentation parameters and packing procedures. There is some interest in mushroom cultivation.

To date the activities in biotechnology for health care in Malaysia are still minimal but some progress has been made. Researchers at the Faculty of Medicine, Universiti Kebangsaan Malaysia, have successfully produced ELISA and RIA kits to measure thyroid, steroid and pituitary hormones. Work is now in progress to produce and evaluate primary monoclonal antisera and to produce RIA and ELISA with these antisera. Eventually the aim is to manufacture diagnostic cheap and easily available assay kits for distribution at the hospitals.

A researcher at the Universiti Sains Malaysia at Penang has successfully developed a biodiagnostic kit for the diagnosis and surveillance of dengue virus infections in human populations. Wellcome Diagnostics, whose funding arm, Wellcome Trust provided the initial research allocation, was not interested in diagnostics without a worldwide implication. The university then made contact with the Penang Development Corporation to set up Venture Technologies Ltd. with the aim of financing and developing the product. Due to their lack of marketing capabilities and restrictions imposed by the Malaysian health authorities for distribution of the product in the country, Diagnostic Biotechnology Ltd. in neighbouring Singapore was brought in as a partner. The product is packaged in Penang and distributed out of Singapore.

Government policies on biotechnology

Malaysia regards biotechnology as an important thrust area for research and development, together with advanced materials, electronics, automated manufacturing technology and information technology, which would propel the country into being an industrialized nation by the year 2020. The National

Biotechnology Committee was established in 1987 under the Chairmanship of the Science Adviser to the Prime Minister's Department. Earlier this year, following the restructuring of the National Council for Scientific Research and Development (MPKSN), the National Biotechnology Committee became a National Working Group of the permanent committee on the development and management of science and technology under MPKSN.

The terms of reference of the National Working Group remain the same and are as follows:

(a) To advise the Government on matters pertaining to policy in research, funding and incentives to industries in the area of biotechnology;

(b) To monitor and assess worldwide development in biotechnology, especially on the current state-of-the-art of biotechnology and to relate it to national needs;

(c) To evaluate the economic and trade implications of the technology;

(d) To facilitate and promote cooperation in R&D between research; institutions and the industry;

(e) To establish a mechanism for funding of research activities;

(f) To prepare annual reports on the status and advancement of biotechnology in the country;

(g) To establish guidelines on a code of ethics and safety in all aspects of biotechnology development.

Budget allocation for biotechnology research

It is the intention of the Malaysian Government to increase R&D expenditure to 2 per cent of the GNP by the year 2000. Biotechnology is seen as an important and key technology of the present and future because of its potential for economic development that can lead to the process of industrialization.

The R&D component of the National Working Group on Biotechnology has proposed 25 projects at a cost of M$ 12.5 million for the Sixth Malaysia Plan (1991-1995). This represents more than a 100 per cent increase in the proposed budget as compared to the Fifth Malaysia Plan (1985-1990) of M$ 5.45 million. At the same time, there is also a substantial increase from M$ 8.3 million in the fifth Plan to M$ 28.2 million in the sixth Plan under the Intensified Research in Priority (IRPA) mechanism for biotechnological research where 24 programmes are supported by the IRPA panel with the participation of 15 agencies.

To alleviate the lack of technical manpower, especially in the field of molecular biology, a separate annual budget of M$ 250,000 has been proposed by the Ministry of Science, Technology and the Environment for manpower development in selected fields of training.

Appraisal of national biotechnology capabilities

A SWOT analysis is carried out to appraise the national biotechnology capabilities (table 2).

Table 2. SWOT analysis of national biotechnology capabilities

Strengths	Weaknesses
Human resources	
Scientific literacy basic sciences & engineering	Insufficient critical mass Lack of expertise in biotechnology *per se*, molecular biology and process engineering Unattractive emoluments for scientists and technicians
Natural Resources	
Availability of agro-based products and agro-waste Forest products Underexploited species Non-seasonality of growth duration	Local lack of know-how to tap biotech inputs of existing crops/under-exploited species Lack of input from industries
Research	
Adequate organizational set-up	Facilities: Lack of hi-tech labs Lack of pilot plants Absence of safeguards/codes for biotechnology R&D products Absence of patent laws Lack of focus in programme priorities (current disbursement of funds not based on prioritized national needs but on existing capabilities) Lack of funding (presently only from governmental sources and none from industrial sector) TNCs R&D done in parental labs abroad Costly research: High capital outlay High maintenance cost Inaccessiblity to crucial information Low sustenance to "see through" product development from R&D to safety and approval tests and to marketing Unrealistic time-frame (brief) of expected research results

continued

Table 2 (continued)

Strengths	Weaknesses
Commercialization	
Excellent facilties, attractive industrial and investment climate Political and economic stability Fairly high standard of living Experience in traditional (food) biotechnology	Small home market Short life cycle of biotechnology products High investment in biotechnology but uncertain returns Limited global marketing network Absence of patented products Small number of companies with resources to commercialize products
Opportunities	**Threats**
Human resources	
Advanced training in developed countries In-house training in developed countries Availability of foreign experts	Better biotechnology opportunities in neighbouring countries, e.g. Singapore and Thailand Zero input in technology transfer by TNCs
Natural resources	
Cocoa butter substitute from palm oil Joint ventures with TNCs Import substitutions Pharmaceuticals Antibiotics, vaccines, diagnostics	Substitutes: Rubber (guayule) Palm oil (soybean, corn, sunflower, rapeseed) Coca (cocoa butter from tissue culture) Improved facilities in neigbouring countries Inaccessibility to foreign markets Competition from non-biotechnology processes
Research	
Adequate literature and information flow Development of basic technology, e.g. recombinant DNA techniques, monoclonal antibodies, tissue culture technology and fermentation technology	Costly capital investment Competition from TNCs Lack of research collaboration with industries Health, environmental and safety issues in biotechnology products

continued

Table 2 (continued)

Opportunities	Threats
Future applications, e.g. Human and animal health care products, custom-design of raw agricultural commodities, engineered enzymes and proteins, natural ingredients and chemicals by fermentation or cell culture and DNA probe and monoclonal antibody-based detection systems	
Amicable relationship with industrialized countries	
Reasonable liaison and support from international bodies concerned with biotechnology, e.g. UNIDO, UNESCO, FAO and WHO	
Commercialization	
Endemic diseases and pests	Alternative products (e.g. synthetics)
Novel indigenous products	Products from TNCs
Enzymes for bio-industries	
Halal products, e.g. gelatin, insulin, rennin, pharmaceuticals, cosmetics	
Availability of funds for industrialization (sourcing from raw materials)	

Approaches to commercialization

In January 1991, the National Working Group on Biotechnology convened a three-day round-table meeting entitled "Commercialization of biotechnology in a developing economy", at Kuala Lumpur. The meeting was attended by scientists, entrepreneurs, bankers and businessmen. The objectives were to review current developments and trends in biotechnology with an emphasis on commercialization; assess the prospects and implications of biotechnology industries with special reference to a developing country such as Malaysia; identify areas of biotechnology having potentials for commercialization; create awareness of the potentials of biotechnology industries in Malaysia among policy makers, entrepreneurs, investors and financiers.

From the round-table deliberations, it was found that the commercialization of biotechnology in developing countries is hampered by the lack of products ready to be commercialized. It is imperative that research in biotechnology be strengthened. Only in this way can one be assured of a sustainable and steady growth of biotechnology products for commercialization. It is recommended that the infrastructure involved in biotechnology be strengthened, namely in manpower development and research funding.

It is further recommended that within each research institution, centres of competence in biotechnology be upgraded. In view of its pivotal role and the government emphasis in these emerging high-technology areas, on-going research on the scientific basis of these technologies should be strengthened and intensified. The Government is also urged to support the establishment of centres of competence in molecular biology at universities. These centres should also serve as a platform to link the universities to industry.

To encourage the development of commercialization of products and processes of biotechnology, the following elements have been identified as being crucial:

(a) Educating industry and investors;

(b) Encouraging industry participation;

(c) Industry-investor-scientific linkages;

(d) Incentives for R&D personnel.

Educating the industry and investors

Despite some investors having suffered substantial losses worldwide, investments in biotechnology over the years have produced encouraging rates of return. Optimism in the industry can be seen from the ever-dramatic expansion of venture-capital industry in the United States and Europe to evaluate and support biotechnology-based investment proposals. At the end of August 1990, the portfolio of Biotechnology Investment Limited, United Kingdom, contained 24 quoted biotechnology companies with a market value of US$ 60 million and 36 unquoted companies valued at US$ 63 million. The majority of these companies are located in the United States. The local industry has yet to appreciate the opportunities in biotechnology and its importance to their long-term growth.

Industries in developing countries need to be aware of the implication and potential of biotechnology in improving their existing business as well as creating new ones. In the Malaysian scenario, biotechnology is going to have a tremendous impact on agro-based industries in the country's effort to maintain competitive positions in the world market. Malaysia's position as a market leader in the export of palm oil and rubber is increasingly under threat as the agricultural sector is becoming less and less competitive, e.g. due to labour shortage and the emergence of competition from neighbouring countries. In this context, biotechnology would help in the improvement of the country's traditional practices. The two most important influences that can establish a commitment and nurture the right attitudes towards biotechnology among existing industries are as follows:

(a) To provide opportunities for the better interaction of the scientific community with industry and financiers;

(b) To set an achievable goal by selecting projects that are pragmatic and most likely to generate marketable products.

Such deliberate efforts in the educating process will help give the investors confidence in biotechnology and in the scientific personnel involved. Likewise, the scientific personnel of such projects would be more aware that

the translation of research results to commercial application is only possible if the technology is profitable.

Investors and existing industries need to be made aware of the practical realities in the commercialization of biotechnology. They ought to be informed of the short-term market opportunities and the long-term possibilities when dealing with commercialization of any research finding. Investment in what seems a brilliant and worthwhile project may fail because of several shortcomings, including an unacceptable risk-benefit ratio in the start-up R&D phase, poor cost-benefit ratio to the consumer or a naive view of the market or biological complexities.

Encouraging industry participation

Research and development

Malaysia's current research and development expenditure is estimated at 1 per cent of its GNP, in comparison to 4-5 per cent spent by developed countries.

The country's private sector contribution to R&D is only 10 per cent, compared to 45 and 70 per cent in the case of the Republic of Korea and Japan, respectively. The R&D expenditure of Malaysia's private sector is concentrated mainly on problem-solving, and it is not surprising that basic research in biotechnology is confined to universities and research institutions. Encouragement of more vigorous industry participation in research will involve the following approaches:

(a) Aggressive encouragement to existing companies with in-house R&D facilities to set up subsidiaries solely to handle research. In this context, established foreign biotechnology companies should be encouraged to set up service facilities offering new technologies at the doorstep of local scientists;

(b) Corporatization and privatization of certain existing public biotechnology centres. This endeavour will facilitate increased funding into biotechnology activities and thereby give a further boost to the development of the technology;

(c) The establishment of research centres at universities and research institutions to facilitate mobilization of scientific personnel from industry to these centres in joint research projects. In Thailand, the establishment of the National Center for Genetic Engineering and Biotechnology in 1983 helped significantly in strengthening biotechnology in that country. A similar centre in Singapore formulates policy and plans on biotechnology, provides support for R&D activities and serves to link public institutions with the private sector. Similarly, the secondment of academics and scientists to industry should be encouraged to enable rapid transfer of valuable scientific information from research laboratories to industry.

An effective means to help nurture awareness pertaining to biotechnology among existing industries is to co-locate industrial R&D groups within, or adjacent to, major academic and research institutes. This will help in bringing together the critical mass who are sensitive and knowledgeable on current biotechnological trends. Longer term relationships between scientific personnel and existing industries will be established, linkages which are so essential for the rapid transfer of research and technology.

Commercialization

For a start, it is considered particularly advantageous to involve those companies that have been engaged in traditional biological industries such as agriculture, brewing, food processing and pharmaceuticals. Their participation can normally reduce the conventional difficulties and problems often encountered in the process of commercializing new research findings, namely:

(a) Facilities required for industrial or scale-up production;

(b) Knowledge about the product market, its opportunities and limitations;

(c) Availability of a strong cash-flow and capital base to underwrite high research expenditure, especially during the start-up phase.

The Government should reinforce its commitment in designating biotechnology as one of the strategic technology areas. Biotechnology business should be entitled to various incentive programmes to further promote the technology. The current promotional policy by the Government may well contribute to the development of biotechnology. To ensure Malaysia's ability to attract foreign investors and the best-brains in this field, this policy must at least match those offered by other countries and regions like Singapore, Thailand and Taiwan Province. For example, Singapore allocated a sum of S$ 20 million for its Biotechnology Investment Fund to stimulate and generate biotechnology business activities.

Industry-investor-scientific linkages

Development of biotechnology in Malaysia should not be limited to commercialization of local results per se but should also encompass utilization of established foreign technology. This is especially relevant as Malaysia is a newcomer as far as biotechnology research is concerned. Japanese companies, realizing that basic research is still the weakest link towards their advancement in biotechnology, have aggressively sought strategic alliances with United States biotechnology companies (particularly the start- ups) in order to gain access to new technologies. Licensing and marketing agreements are the most common forms of business alliances. In addition, Malaysia is also lacking in the industrial management and confidence in raising capital for innovative projects and in the formulation of a global strategy. For example, the financial institutions in this country have yet to appreciate the potential rewards that can be obtained from medium- and long-term investment in biotechnology.

The current research programmes in Malaysia will soon reap its harvest from local laboratories doing research in biotechnology. It is thus imperative that a national biotechnology coordinating bureau be established to facilitate the transformation of such findings from laboratories to the pilot scale in conjunction with the participation of investors. This National Biotechnology Investment Bureau must be able to:

(a) Disseminate and collate information on potential business investment in biotechnology;

(b) Critically evaluate investment opportunities in biotechnology;

(c) Monitor global trends and regional trends in biotechnology investments;

(d) Formulate global strategies and identify market niches suitable to Malaysia's capability;

(e) Promote financial linkages between investors, entrepreneurs and technologists;

(f) Establish the biotechnology industry through strategic alliances with established multinationals.

The establishment of such a bureau will help maintain the spirit of partnership between the investors, management and the scientific team.

This bureau can be part of an existing government structure, preferably within the ambit of the Malaysian Industrial Development Authority. Research programmes under the Intensified Research in Priority (IRPA) and National Biotechnology Working Group should utilize the services offered by the bureau in evaluating these projects for commercialization.

It is viewed that free-standing organizational structures guided and monitored, but not tightly controlled, by boards of world-calibre scientists and appropriate commercial representatives will be much more likely to succeed, because of their ability to respond quickly and effectively to commercial opportunities than traditionally administered institutes, which could well continue to be crippled by time-consuming, ineffective and inappropriate administrative procedures, and would thus be unable to function well in the commercial sphere.

Incentives for R&D personnel

Intellectual property rights have been a central issue in the overall development of biotechnology, especially in the protection of intellectual property as a means of providing incentives to R&D personnel. Two mechanisms for the protection of intellectual property exist: patents are used to protect the basic research findings and prototypes; commercial confidentiality is used to protect all of the more minor, but equally important, aspects of product development. In biotechnology, patents can be filed which describe new genera or strains of plants, animals or microorganisms and their practical applications, provided that there has been some degree of genetic engineering involved. It is, however, unclear what effect the current law has on protecting intellectual property rights in Malaysia. Direct equity participation of R&D scientists in the investment of biotechnology-related products or processes can also act as an effective incentive to the researchers. Profit-sharing is normally negotiated in the form of a royalty on sales, which may vary from 1 to 20 per cent, depending on circumstances. As a source of further support for good research, constant ploughing back of revenue to the originating research development, laboratory and staff must be considered.

From the perspective of universities or public-funded research institutions, partnership in commercialization of biotechnology can be beneficially accomplished through contract research. Among the benefits of contract research is the provision of direct research funding by private sectors and better salaries and equipment for researchers.

It is important that the performance of the commercial partner be established over a specified period and that this be clearly stated in the contractual agreement. This will enable the scientific partner to pursue an alternative route if the project is being unsatisfactorily prosecuted.

Conclusion

The imminent impact of biotechnology on various industries is well recognised by many Governments of developed and developing countries. The outlined foregoing recommendations should form an integral component in formulating a national biotechnology master plan. It is envisaged that this plan could enhance the level of biotechnology in the country, thereby enabling it to assist the country's industrial growth and its ability to compete regionally, if not globally. The plan should map out strategies to cover at least five main areas: technology, manpower, industry and infrastructure development and the promotion of public awareness of and interest in biotechnology.

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XX. THE ROLE OF BIOTECH CONSORTIUM IN COMMERCIALIZATION OF BIOTECHNOLOGY

S. Chandrasekhar*

There is an increasingly accepted belief that waves of innovation have occurred more or less regularly over the past 250 years in roughly 50-year cycles. The first few years in a cycle see a build-up of new technological potential, followed by a period during which new and far-reaching innovations burst on the scene. Then, things gradually slow down during the period of commercialization. This idea was first proposed by a Russian economist - Nikolai Kondratiev. A German economist, Joseph Schumpeter, picked up the idea in the 1930s and showed that the first wave lasted from 1790 to 1840 and was largely based on new technologies in the textile industry, which exploited the potential of coal and steam power. The second wave took place between 1840 and 1890 and drew directly on the development of railways and the mechanization of production. The third wave (1890-1940) was based on electric power, advances in chemistry and the internal combustion engine. The fourth wave (1940-1990) was based on electronics, but the pace of innovations may not pause the way it did between the previous cycles. Christopher Freeman of Sussex University in England thinks that biotechnology could at least be part of the basis for a fifth Kondratiev wave, which may have already started. Advances in physics and mathematics, which underlie computer science, would add another key element to the fifth wave.

Biotechnology would have an impact on many sectors of the economy. It is likely, for example, to rejuvenate several agro-based industries through the application of tissue culture and the use of hybrid seeds, the use of biofertilizers and biocontrol agents, and also in medicine and health care. It would also have a significant role to play in the treatment of effluents.

The real problem for many developing countries is not a race to catch up with the industrialized countries but the need to master science and technology and build up a strong base, which would allow the production of goods and services essential for the well-being of the whole population in a sustainable manner. This calls for a decisive role for science in developing countries within the process of absorption and development of new technologies "as an intangible precondition for catching-up". A proper mix of the use of traditional labour-intensive technologies, highly skilled science-intensive technologies, and some of the modern capital-intensive technologies would be needed to ensure sustainable development, to the extent possible. Science can help to make traditional technologies more efficient. For example, in fermentation or biomass conversion, or in combating tropical diseases.

Major research efforts in biotechnology are currently focussed on the areas of agriculture, health care, aquaculture and more recently on the environment. In agriculture, the major thrust areas have been biofertilizers, biopesticides, tissue culture and hybrid seeds, while in the medical field the focus has been on the development of new diagnostic tools which use monoclonal antibodies, or the production of new vaccines, hormones, enzymes and proteins using recombinant DNA and cell-fusion.

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The strategy for assigning priorities for technology development should be selective in nature to make optimal use of the available limited resources in developing countries like India. The need for selectivity implies the right choice of priorities. The priority choices for R&D are made at different levels: at the national level first, but have to be chosen within each of the areas of application of the R&D results. In the case of biotechnology, the mapping of the strategy calls not only for cooperation between Government, industry and scientists, but also for interaction between such diverse areas of application as the chemical industry, pharmaceuticals, the agro-food industry, health, agriculture and the environment. Apart from the efficient management of limited resources, one would need to add the critical mass of complementary investments and skills needed in priority areas of biotechnology development.

About BCIL

In India, a public limited company, Biotech Consortium India Limited (BCIL), has been formed by the All-India Financial Institutions, with the Industrial Development Bank of India playing the lead role and others like the Industrial Finance Corporation of India, the Industrial Credit and Investment Corporation of India, the Unit Trust of India, the Risk Capital and Technology Finance Corporation and industry also subscribing to its share capital. BCIL was conceived and most actively promoted by the Department of Biotechnology of the Government of India.

The objectives of BCIL are to catalyze the interaction between the industry and the institutes of R&D, including the universities, so as to convert such interactions, concepts and ideas in biotechnology, into products and processes, and to take such goods and services to the market, through industry. The objectives would include the funding of short- and long-term adaptive research, with one-to-one tie-ups with industries, leasing and renting of R&D facilities, development of entrepreneurs, taking up specific projects on a jobbing basis, initiating product development and furthering process improvements in the field of biotechnology. The main components of this interactive chain are the relationships between the consortium and universities/R&D institutes/entrepreneurs/industry and financial institutions. BCIL was inaugurated by the then Prime Minister of India on 20 December 1990.

Initial thrust areas of BCIL

The thrust areas for the BCIL would initially be those identified by the Department of Biotechnology. The following selected areas would be taken up during the first few years of BCIL operations.

Agriculture

Plant biotechnology

With the advent of commercial tissue culture practices, ventures in plant biotechnology have become more efficient, more predictable and more profitable. Indigenous technology, based on tissue culture for various crops identified below, is available for commercialization, which BCIL would encourage and support. It has also identified two other areas which have recently assumed importance, particularly in international trade, namely the use of diagnostic kits for the early diagnosis of plant diseases and quality control of planting material as well as packaging aspects.

Horticulture

There is immense export potential for horticulture products, particularly processed fruits and vegetables. The crops that have been identified are mango, citrus, papaya, banana, grape, guava, apple, pineapple, tomato and onion.

There are three areas of thrust:

(a) Standardization of rapid clonal multiplication with minimum variability and detection of *in vitro* variation;

(b) Post-harvest support, including pulp processing, packaging and marketing strategy;

(c) Biotechnology approaches for disease and pest control.

Floriculture and ornamental plants

These account for more than 75 per cent of global production of tissue-cultured plantlets. However India (5 million plantlets) has yet to make an impact at the international level (500 million plantlets). Each medium-sized tissue culture unit can earn foreign exchange worth Rs 20-30 million (about US$ 1 million), and there is potential for at least 100 such units. Time taken to set up a tissue culture plant is around 6-12 months. So far, 10 export-oriented units have been licensed. The industry has a tremendous growth potential, with present projections placed at 15 million plantlets per year.

Colombia is second only to the Netherlands in flower exports, with some 8 per cent of the world market. Colombia has benefitted from cuts in import tariffs, but its limitation is reported to be in freight capacity. India also has similar problems in infrastructure, which need to be tackled through innovative and cost-effective means.

A new development in transport, the Freshtainer, which has total atmospheric control of temperature, humidity and gases, may provide the answer to the freight problem. Freshtainers can be packed with eight tonnes of carnations and the Bogota-Hamburg journey, by truck and sea, takes 24 to 26 days. The system is reported to be a little cheaper than the cost of air freight to Europe.

Climate conditions on the Sabana-de-Bogota are ideal. It has plenty of light, few frosts and barely any seasonal change in temperature. Kenya has even better conditions, with clear skies and well-drained soils. The airport is good, with adequate facilities for storage and handling, and is only eight hours to Europe. Flowers can be produced all year round without much heating or cooling costs. Many cities in India have a similar advantage. The crops that have been identified are orchid, rose, gerbera, carnation, gladiolus and chrysanthemum (indicative list).

There are two areas of thrust:

(a) Standardization of micropropagation techniques;

(b) Development of greenhouse, post-harvest support.

Quality seed

The seed market, which was Rs 6 billion (US$ 200 million) in 1986, is estimated to touch Rs 24 billion (US$ 800 million) in 1990-1991 and thus holds enormous potential to earn foreign exchange. Eight joint ventures with leading overseas firms for quality seeds, including PHI Biogene Pvt. Ltd. with Pioneer Overseas Corporation and Hindustan Lever with Unilever Group, have been signed. Most vegetables would be suitable.

Plantation crops

These account for three-fourths of the total agricultural export earning and thus play a vital role in the country's export trade. Biotechnology approaches have achieved significant increases in the production and productivity of plantation crops, as is evident from the recent success in the production of an export variety of small cardamom. Total indigenous technology promoted through the Tissue Culture Cardamom Product Plan has increased the productivity three- to sixfold. By virtue of its excellent yield and rate of return, the corporate sector is entering it in a big way. The crops identified are rubber, coffee, tea, cashews and spices.

There are five areas of thrust:

(a) Widening the genetic base;

(b) Bioprocessing for quality improvement;

(c) Micropropagation of high-yielding clones;

(d) Biotechnological approaches for disease and pest control;

(e) Quality and cost-effective packaging.

Agricultural crops

Biotechnology approaches have achieved remarkable success in the productivity improvement of agriculture crops, one of the important ones being oilseeds. Greater emphasis is laid on oil palm, which boasts the highest productivity (4-6 tonnes/ha) and returns (Rs 40,000/ha/yr) among edible oil-yielding crops. The Government of India, through the Department of Biotechnology (DBT), has undertaken several oil palm demonstration projects in various states to show its feasibility and has offered several incentives for ventures in this field. The crops identified are sugar cane, cotton, oilseeds (oil palm, rice bran), pulses and potato.

There are three areas of thrust:

(a) Micropropogation of high-yielding varieties;

(b) Development of disease- and pest-resistant varieties;

(c) Technology and infrastructure development for harvest and post-harvest processing for oil recovery from fresh fruit buds of oil palm.

Biopesticides

Biopesticides form an important component of the integrated pest management strategies being encouraged by the Government of India to reduce the damage caused by the indiscriminate use of chemicl pesticides. As compared to chemical pesticides, biocontrol agents are environment-friendly, highly cost-effective, have lower import intensity and are amenable to decentralized operations.

DBT has established a network programme on biological control with 10 R&D projects in seven centres throughout the country for the control of serious insects, pests and diseases of crops such as sugar cane, cotton, chick-pea, pigeon pea, oilseeds and vegetables. The main objective of this network is to lay greater emphasis on developing biological control product formulation and pilot-scale production technologiesfor large-scale field demonstration for their efficacy and end-use by farmers and cultivators.

There is a need for a large-scale production plan for continuously culturing the biocontrol agents for supply to farmers. It is proposed to develop a process of continuous culture of host/prey insects, synthetic-semisynthetic diet and cheap food for the production of biocontrol agents. This is one of the first projects taken up by BCIL for funding.

To promote the use of biocontrol agents among farmers, large-scale efficacy demonstrations have to be taken up, which requires the development of pilot-scale production techniques. In these pilot plants, work can also be taken up to develop suitable product formulation to reduce the overall cost of production. Entrepreneurs would be provided with training and financial assistance, with the aim of decentralizing the manufacturing programme and spreading it countrywide.

Biofertilizers

The demand for chemical fertilizers is likely to shoot up from 11.6 million tonnes at present to 20.6 million tonnes by the end of this decade. Domestic production will lag behind consumption by an estimated 5.5 million tonnes, which have to be met substantially through imports and other means. In the light of this and the constantly rising fertilizer subsidy, cost-effective and pollution-free biofertilizers seem to offer much hope.

The biofertilizers, or bioinnoculants, as they are sometimes also called, are preparations containing microorganisms which are beneficial to agricultural production in terms of nutrient supply, particularly nitrogen and phosphorus.

Among the nitrogen-fixing biofertilizers, blue-green algae for rice and Rhizobium for legumes have special potential as technology for their production is readily available. However, the availability of scientific manpower in adequate numbers is a serious constraint to the adoption of biofertilizers on a large scale. There is also a need to create awareness among the farmers of the economic and ecological benefits to soil health and fertility. Realizing the importance of biofertilizers, the Government of India has set up one national and six regional centres for their development and use.

Special efforts have to be taken in the following areas for enhanced use of biofertilizers in the country:

(a) Intensive education and training programmes;

(b) Development of better strains, improved methods of inoculation, cheap and readily available carriers etc.;

(c) Strict quality control measures and proper storage and packing facilities.

BCIL will provide assistance in the above areas to encourage the large-scale use of biofertilizers.

Sericulture

Sericulture is an important and rapidly growing agro- and forestry-based cottage industry, earning foreign exchange worth Rs 350 crores per annum (one crore = 10 million). The National Sericulture Project, started by DBT in 1989 to enhance rural employment, has recorded a significant increase in silk production (11,799 tonnes in 1989-1990 against 7,900 tonnes in 1985-1986) through biotechnology approaches, with projections placed at 15,000 tonnes by 1994-1995. Studies carried out in Maharashtra and Gujarat have indicated it to be more remunerative than even sugar cane, the best cash crop of the region. The crops identified are mulberry, eri, muga, tropical tasar, oak tasar.

There are four areas of thrust:

(a) Database on silkworm races and strains;

(b) Development of better races of silkworm;

(c) Control measures for major diseases/pests of silkworms;

(d) Micropropogation of elite strains of non-mulberry plants.

Aquaculture

India is one of the few countries in the world with rich natural resources in the form of brackish water estuaries for shrimp and fish aquaculture. At present, India produces 3.4 million tonnes of fish per annum and by the year 2000 it is reported that India would need about 13.0 million tonnes of fish to meet the minimum protein needs of 1 billion people. The developments in hi-tech aquaculture have been spectacular and have opened up tremendous investment opportunities.

Shrimp and carp culture

Scientific and technical improvements have paved the way to increase carp and shrimp production. The adoption of extensive, semi-intensive and industrial systems of shrimp farming will be encouraged. Here again, DBT has done considerable work and laid the foundation for the growth of this industry. For prawns and fish, proposals for the manufacture of feed will also be supported. Economically viable packages of carp polyculture for commercial exploitation and higher production using hi-tech approaches (genetically improved varieties, hormones for inducing breeding etc.) could be taken up for implementation.

Fish seed

Seed is a major input in aquaculture, and most of the farmers still depend on wild seed stock. Projects aimed at quality shrimp and carp seed production will be promoted.

Fish feed

Nutritionally balanced high-quality compounded prawn/fish feed production with a good food conversion ratio and water stability will also be supported to replace imported feed. Economically viable packages for intensive culture of zooplankton such as Artemia sp. Moina sp. Brachionus sp. Daphnia sp. Euchlanis sp. etc. would be supported for implementation.

Demonstration projects

Demonstration of commercially viable semi-intensive prawn farming with the application of biotechnology has been undertaken by DBT. The project aims to achieve 10 tonnes of marketable-sized prawns per hectare per annum in two successive crops by the end of 1992-1993, both at Nellore (Andhra Pradesh) and Paradip (Orissa) in a waterspread area of 9.45 ha. In an initial demonstration, the technique has been standardized to achieve more than 9.76 tonnes of prawn per hectare per year with better biotechnological inputs. The project would undertake R&D work on the development of indigenous feed for adults, farm management and post-harvest processing. The success of this programme would help in taking a decision on the development of more brackish water aquaculture to bring under the semi-intensive prawn farming.

A significant breakthrough has been achieved by DBT by a successful demonstration of more than 10 tonnes of carp per hectare per annum at the Central Institute of Freshwater Aquaculture at Bhubaneswar. Under this project, it is expected to develop different packages of crops, i.e. production of 10, 15 and 25 tonnes/ha/annum for field propagation of carp at the farmers' level by 1992-1993. The research component includes fish hybridization; fish feed formulation; disease diagnosis and control; and pond water management.

Technology transfer

BCIL's first attempt at technology transfer is from one of the distilleries in South India, which started to find a solution to its industrial waste problem and ended up making money on selling fish that thrive on the waste. The distillery, which had a BOD of about 50,000 ppm in the early 1980s, was issued a notice by the State Pollution Control Board that it would have to shut down if the effluent problem was not sorted out. There are generally two ways of getting rid of distillery wastes. The first involves incineration, which is costly. The alternative is to install digesters, in which micro-organisms act on the effluents to produce biogas. The bacterial biomass is treated to render it edible by fish. Finding the right fish for the job took the distillery time. The choice of fish finally narrowed down to a hybrid called Golden Fish, which is a cross between the golden-coloured and the dark-brown-coloured strains of Tilapia. The fish are fed with the nutrient-rich biomass from the bioconversion/anaerobic digestion step. Since the effluent in this case consists of organic matter and not chemicals, there is no fear of the fish containing toxic substances. BCIL has signed a memorandum of understanding with the distillery with a view to passing on know-how to as many distilleries in the country as possible.

Accelerated product development

All nations now face one inescapable rule: "the survival of the fastest", as Alvin Toffler, best-known for his books Future Shock and The Third Wave, puts it. So demanding is time compression becoming, not just in the development of new products and services but also in factory throughput, market response times and almost every other aspect of business, that consultants are turning time-based competition into big business. George Stalk and Tom Hout of the Boston Consulting Group go so far as to claim that, after two decades of industry obsession with cost and then quality, time is now the key performance variable to be managed to attain competitive improvements in all aspects of a business. BCIL hopes to focus its attention on this area on the coming years.

Research-industry links

Smith Kline Beecham United Kingdom and Oxford University have a legal agreement which requires scientists at the Oxford Centre to give six weeks to review any research results before submitting them for publication. This is a normal feature of academic/industrial collaboration to give the company time to patent any discovery that may be commercially valuable. From Smith Kline Beecham's point of view one reason for setting up a direct link with Oxford University is to help recruit well-trained and committed scientists to its own R&D laboratories. And the company benefits from privileged access to the Centre's research, which may lead to developing new drugs even though it is not driven by product development considerations.

In India, the set-up of the ASTRA-IDL laboratories at Bangalore, near the campus of the Indian Institute of Science, and the campus of the National Institute of Immunology, which currently houses the ICGEB, provide the environment for strengthening research-industry links. Such research-industry linkages could also be established in other cities, like Lucknow, Chandigarh, Madras, Bombay and Calcutta, to start with.

Information services

Information technology and services are a vital link to commercialization efforts. Information available in patent literature, for instance, is very valuable, and it is surprising that very few researchers, let alone progressive industrialists, realize its immense value. It was by the Director of the United Kingdom Patent Office Information, Ted Blake, in a recent symposium on intellectual property rights, that £20 billion a year is being wasted by European countries on unnecessary research "reinventing what has been done before". As Blake says, "Anyone not looking at patents, automatically cuts himself off from at least 80 per cent of the available information". Patent literature is quite simply the single most important source of technical information in the world. With over 80 per cent of the information on patents being unavailable elsewhere, no European country in any industry can catch up with Hitachi, the Japanese electronics giant, which, according to Blake, has fielded 150 people to search the world's patent literature. Many are put off by the mere size of the database. There are now 32 million patent documents worldwide, increasing by 1 million a year. The relevant information can now be reached relatively easily by a computerized search.

Another area of immense potential with respect to commercialization efforts would be through financing of computerization, in both information technology and computer-aided design (CAD). CAD makes it easier for consultancy organizations to liaise with international clients and collaborators. There are now networks of designers working simultaneously on the same projects in different countries.

A survey of 80 companies and 90 academic institutions, conducted by the management consultants McKinsey for Partners in Innovation, the initiative by the Prince of Wales to improve links between educational institutes and industry, suggested that factors other than links between academies and industry are more important. The survey found that 73 per cent of the companies would be using higher education institutes as a source of innovation in the future. Links between companies and educational institutes may be undervalued because companies are failing to fully exploit the ideas available in universities and the academics are usually bad at selling their work. The corollary is that once academics and industrialists start to work together more effectively, they will realize the potential of collaboration. Both executives and academics rate personal contacts as the most important factor facilitating collaboration.

Involvement in information exchange and the development of databases with facilities for online access would be one of the major thrust areas of BCIL. BCIL is also in the process of bringing out a joint newsletter with an institution called Research & Information System for the Non-Aligned and Other Developing Countries, to disseminate information on developments in the field of biotechnology and issues and constraints that are likely to confront future developments in this area, particularly for developing countries like India. The Bioinformatics Division of DBT has done considerable work in keeping track of the latest information on advances and developments in biotechnology. DBT has established a national network on biotechnology information interlinking several information centres at prime locations in universities and R&D institutes in India.

The new industrial policy and its impact on biotechnology development

A new and more open industrial policy has been announced by the Government of India. This policy recognizes the need for necessary policy measures to encourage increased applications of biotechnological tools and techniques for the improvement of agricultural productivity. The role that biotechnology could play in improving the country's export potential has also been recognized in the Government's export/import policy. An indicative list of the industries eligible for automatic approval of foreign technology agreements and for 51 per cent foreign equity participation is shown in table 1.

The objective of the policy is also to encourage a free flow of technologies and investments. Foreign investment approvals, which were roughly about US$ 250 million a year up to 1989, dropped to about US$ 70 million in 1990. The World Bank forecasts US$ 180 million of foreign investments in 1991. The World Bank is also likely to fund several projects in which biotechnology has a role to play (table 2).

Table 1. List of industries for automatic approval of foreign technology and for 51 per cent foreign equity participation

Bioinsecticides
Genetically modified free-living symbiotic nitrogen fixers
Photosynthesis improvers
Pheromones
Certified high-yielding hybrid and synthetic seeds
Certified high-yielding plantlets developed through tissue culture
Drugs and pharmaceuticals (according to the Drugs Policy)
Soya products:
(a) Soya protein concentrates
(b) Winterized and deodorized refined soybean oil
All items of food packaging industries excluding items reserved for the small-scale sector

Table 2. Five development projects proposed for funding by the World Bank

1. Industrial pollution control projects to set up a toxic and hazardous industrial reduction programme.

2. A Maharashtra state forestry project to initiate a comprehensive approach to forestry resource management.

3. A West Bengal forestry project to initiate a comprehensive approach to forest resource management.

4. A shrimp and pisciculture project to provide support services, training and technical assistance for the development of brackish water shrimp ponds, fresh water fish ponds and reservoirs in West Bengal, Orissa and Andhra Pradesh.

5. A Bombay sewage disposal project.

The present strategy of agrochemical inputs, particularly fertilizers, would also have a significant bearing on biotechnology product developments, particularly biofertilizers and bioinsecticides. In the recent budget of the Government of India, an attempt was made to reduce the subsidies on chemical fertilizers and a dual pricing policy on nitrogen fertilizers, accompanied by the decontrol of some fertilizers like ammonium chloride. Considering the high prices of chemical fertilizer in the country, and taking into account the subsidy element, the role of biofertilizers and pesticides in our economy cannot be overemphasized.

During the last couple of years, significant investments in biotechnology have been made by some of the large Indian companies (table 3).

Table 3. Recent investments in biotechnology

Company	Investment (Crores of rupees)	Area of specialization
Indo American Hybrid Seeds (IAHS), Bangalore	7	To develop better varieties of seeds
Southern Petrochemicals Industries Corporation (SPIC), Madras	5-10	Tissue culture
ITC Agro Tech, Hyderabad (a division of ITC Limited)	5	Increase the yield of sunflower seeds to raise production of edible oil
Harrisons Malayalam Ltd (a member of RPG group of companies)	20 (proposed)	The company is planning to develop a biotechnology division in Bangalore
Hindustan Lever Ltd.	N.A.	The company has a research centre in Bombay and is working on virus-free strains of sugar cane and cotton to resist bollworm
The UB group (through the Vittal Mallaya Scientific Research Foundation)	2	Development of yeast-based drugs, e.g. insulin

To sustain this momentum, a lot of effective coordination will be required between industry, government bodies, research and academic institutions by making maximum use of the existing infrastructure in terms of human resources, laboratory facilities etc. BCIL has a well-defined programme and looks forward to gaining from this interaction with UNIDO as well as companies and institutions from various parts of the world.

XXI. DEVELOPMENT OF BIOTECHNOLOGY RESEARCH AND INDUSTRY IN INDIA

Habil F. Khorakiwala*

It is no longer science fiction. The dreams of scientists are coming true. We have our sights set at applications from therapeutics development to the human genome project. But the end of the tunnel is still dark. The expectations from biotechnology by industry and the public in general are ever increasing. It is a second technological revolution of the century, after the success of computers. The first computer was the size of a football field. Through constant research and innovation we have reached minis, micros and laptop computers. The future will tell us where biotechnology will take the world.

For the United States and other developed countries, the end of the 1980s marked the end of the biotechnology industry's adolescence, when Wall Street believed it was the equivalent of someone discovering perpetual motion. The part about the discoveries was true, but the timing for these products was not by an order of magnitude. The payoff for these products is beginning and will come 10 years from now. For those in India, the decade of efforts in biotechnology is now beginning, yet the time to enjoy its fruits is much further away, although for various reasons the phase between efforts and results could be much shorter. The prospects for biotechnology as the last major industrial technology of the twentieth century are sufficiently exciting to attract the attention of investors, industries, Governments and the public.

For India, biotechnology offers both threats and opportunities. The threats are posed by the possible substitution of new products for traditional ones that so far have been a major source of income. A typical example is the potential threat to the sugar industry by new sweeteners created by biotechnology. Social and political factors will play a major role in determining the success of this technology.

While several new opportunities may also arise for India and other developing countries, their ability to reap the benefits will be determined by their technological capability. In other words, the commercial application of biotechnology depends on the national level of development of science and technology and the kind of interactive process between research and industry.

In India, future projects indicate a strong growth in human therapeutics, human diagnostics, veterinary medicine and the rate of market penetration of the new products. The rate of entry into the agriculture and veterinary medicine markets is likely to be more rapid than into the human health care market, due to regulatory requirements and clinical trials, and also due to the fact that more than 70 per cent of the population is employed in the agricultural and veterinary sectors. Pharmaceuticals offer great opportunities to tackle many developing countries' problems, especially in the areas of preventive treatment, such as vaccines for AIDS, hepatitis, malaria etc.

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Research-industry collaboration

The development of biotechnology has been driven by advances in basic biomedical and biological research. University-industry collaborations have mushroomed, particularly in the United States, where several corporations have established long-term research programmes with universities and virtually all companies involved in biotechnology research have forged strong links with academic researchers.

Other countries are emulating this trend, and many Governments actively support programmes and encourage links between science and industry. In the third world countries, these relationships are few and still in their infancy.

In India, we have seen a number of such joint ventures, some of which are as follows:

(a) Wockhardt Limited has undertaken a unique industry-research collaboration with the International Centre for Genetic Engineering and Biotechnology (ICGEB) of UNIDO to jointly develop several genetically engineered pharmaceutical products. Wockhardt would provide a research grant to ICGEB over the next five years to develop genetically engineered pharmaceutical products such as human insulin, tissue plasminogen activator, hepatitis vaccine, erythropoietin etc.;

(b) A consortium has been formed with the support of the Government of India between the Industrial Development Bank of India and many other industrial houses to fund and support biotechnology research and its commercialization. Venture capital and research institutes have come together to produce commercially viable genetically engineered products;

(c) ITC Limited has entered into research collaboration with a number of organizations such as the University of North Dakota in the United States, the Cereal Research Institute in Hungary and an Australian company, Pacific Seeds, for a hybrid sunflower variety;

(d) Harrison Malyalam has collaborated with two German companies, Agri Saaten and Semundo Saatzucht, and will focus on research of sorghum, maize and sunflower.

The various advantages of these relationships are as follows:

(a) Industry does not have to reinvent the wheel by going into basic science research;

(b) It saves time and expenses by not investing in equipment and entering into large-scale manufacturing quickly;

(c) Researchers have the chance to obtain the views of industry and end-users, thus knowing the needs of the country;

(d) The country saves foreign exchange by avoiding duplication in investment in equipment and consumables;

(e) It gives immense satisfaction to the researchers by providing the fruits of success through their work;

(f) Industry personnel can use the resources to refresh their knowledge by interacting with scientists.

In India, there are more than 30 companies working on the development and commercialization of biotechnology. Some of the major ones are Cadila Laboratories, Ranbaxy Laboratories and Wockhardt Limited. Similarly, there are more than 40 research institutes working in a wide range of biotechnology fields. Some of these institutes are ICGEB, the National Institute of Immunology, the Jawaharlal Nehru University and the Centre for Cellular and Molecular Biology. The Department of Biotechnology of the Government of India has done a stupendous job in guiding these institutes to meet international standards.

Strategy

The Indian medical therapeutic biotechnology industry has not reached the commercialization level but has learnt many lessons from the industry in other countries, especially the United States.

It is not possible for biotechnology companies to exist on their own, so they coexist with large pharmaceutical companies as peers. This is due to the diverse fields of biological sciences that are involved in the success of genetic engineering and biotechnology.

The Ernst & Young High Technology Group reported that there were more than 1,095 biotechnology firms in the United States as of mid-1989, more than 250 of them involved in human therapeutics. On the other hand, the average cost of developing a drug in the United States is over US$ 130 million. Clearly, few of the biotechnology companies have the financial resources to develop even a single product all the way to the market. The majority of the biotechnology pharmaceutical companies are small to medium-sized companies, on the average with less than 100 employees. Their average R&D burn rate (monthly R&D spending) is US$ 0.75 million; the average technology burn rate (monthly R&D spending and expenditures on property, plant and equipment) is US$ 1.15 million. As a result of the high cost for drug development, the most important business issue facing the biotechnology industry is financing.

The lesson companies and investors have learned is that although biotechnology creates protein molecules, such as interferon, already found in the human body, they must undergo a lengthy approval process when made into medicines. So investors do not get the fast return they had hoped for. The reason it costs so much and takes so long is that these products cannot be produced in a garage. It took these companies about eight years to do the research, carry out the clinical trials and get the product made. In addition, companies found they had to defend their product patents in court. The investor certainly would not like to play with so much of uncertainty.

On the finance side, biotechnology is now considered to have a history on which to base investment decisions, but the payoff can still be years away. On the regulatory side, laws are likely to get tougher in response to general public concern about health and the environment. Whatever happens, it will be interesting. The 1990s will certainly witness a biotechnology boom.

Can biotechnology companies in India and the third world afford such investments? The answer is "no" if we have to follow the same approach when developing biotechnology products. Hence, there is a need to apply a more

innovative and creative approach to developing and commercializing biotechnology products. It is possible to develop and evolve a strategy based on an appreciation of the following issues:

(a) There is a fund of knowledge available in literature and universities in the West. Therefore any new commercialization effort must begin more with the application of this knowledge rather than focusing on fundamental research;

(b) Specific identification of products required should be focused upon for future development, manufacturing and commercialization;

(c) To arrive at a strategic alliance with various research laboratories in biotechnology and industries and fund a joint project for development to commercialization;

(d) In the United States and other countries there is a large number of research-based biotechnology companies. A strategic alliance between these research companies and pharmaceutical and agricultural industrial business can also give more fruitful results at relatively low cost.

Existing companies and industrial houses in pharmaceutics and agriculture will take a long-term view on investing in the research and development of biotechnology products. They have a motivation to develop a vision of focusing and investing in this area for the future and are also in a better position relatively to identify products which have a significant potential in their own countries and in developing countries.

Issues in the commercialization of biotechnology

Although pharmaceutical and agricultural applications of biotechnology have significant potential and hence are widely undertaken in the developed world, their application in India is still impeded by certain problems. Some of these are as follows:

(a) India can claim to have several well-established, well-equipped and well-manned genetic engineering and molecular biology research facilities. These laboratories have been involved more in fundamental work and appear to have lost their way, in terms of aligning themselves to bringing out useful biotechnology products, as there is a lack of industry interaction;

(b) There seems to be an urgent need for these institutes to re-orient the direction of biotechnology research and develop a more intensive consultation and interaction with the industry. The assessment of the work of the institutes must also be judged in terms of their ability to successfully commercialize their products;

(c) The regulatory and bureaucratic procedures impede the work of research, especially in respect of customs and import regulations. This delay slows down the pace of research enormously. The incentive for high class scientists to remain in the country is negligible and this leads to a significant "brain drain". One finds brilliant Indian scientists working in world renowned research centres outside their native country;

(d) Tariff barriers for the import of consumables and equipment for privately funded research and manufacturing organizations are enormous, with a

customs duty of as high as 150 per cent. Biotechnology research is extremely expensive worldwide, but in India it becomes prohibitively expensive. This has acted as a major negative factor for the absence of a major thrust in biotechnology research in the private sector. The Government may consider addressing this issue urgently to give a thrust to biotechnology research and manufacturing facilities.

Intellectual property rights

Currently the Indian Patent Act 1970 provides a positive environment for the development and commercialization of biotechnology products in India for the benefit of a very large section of the population. The fruits of biotechnology research, especially in the area of agriculture, biopesticides and pharmaceuticals, must reach a large population of the developing world in order to ameliorate their economic dependence on food and medicines and make them available at a reasonably low cost. Biotechnology offers a breakthrough approach in the field of preventive medicines through the development of vaccines. It also provides an opportunity by the development of seeds for various crops and other related agricultural fields, such as high-yielding varieties. The Indian Patent Act provides for automatic and compulsory licensing, which will ensure the creation of a competitive environment with a reasonable return of royalty to the innovator. However, there has been enormous pressure from the developed world, and especially from the United States, to change the Patent Act and give a far stronger protection to the innovator.

Today India remains one of the last countries to have evolved intellectual property rights, which they believe best serves their national interest. It therefore also provides a unique opportunity for applied research by using the fund of knowledge available the world over. In the current regime of patent protection, it is very unlikely that companies will get into very expensive litigation in India, as is happening in the West.

With the scientific base already existing in India, especially in terms of research facilities, scientific manpower and a very advanced pharmaceutical industry base, India can provide a window, given the right internal environment, for a major breakthrough in the commercialization of biotechnology products in years to come.

Conclusion

Today India produces nearly all its requirement for food grains and agricultural products on the one hand, and is a significant world producer of pharmaceuticals, on the other. In value terms, the production of pharmaceuticals in India is 1.3 per cent. However, it is estimated that in terms of volume of production it is as high as 10-12 per cent, considering the significantly lower price of pharmaceuticals in India. This base provides optimism for the growth of the country's biotechnology industry. Currently a significant number of private initiatives are under way to commercialize biotechnology products in various fields, from human diagnostics to human therapeutics, biopesticides and agricultural products. Already various human diagnostic products are being manufactured in India. In the next three to five years, commercial manufacturing of human therapeutics may also be expected.

A number of issues will develop the base of biotechnology commercialization in India: the stand it ultimately takes vis-à-vis the Intellectual Property Act; creating a more supportive infrastructure for biotechnology research and manufacturing; removing significant tariff barriers for consumables and equipment imports; and developing a significantly closer interaction between the publicly funded research institutes and commercial organizations.

XXII. EUROPEAN EXPERIENCE IN THE DEVELOPMENT OF INDUSTRIAL BIOTECHNOLOGY: POLICIES, ISSUES AND CONSTRAINTS

Philippe De Taxis du Poet*

The importance of biotechnology

Biotechnology is a key technology for the future competitive development of the Commission of the European Communities and it will determine the extent to which a large number of industrial activities located within the Community will be leaders in the development of innovatory products and processes. The recent communication from the Commission on industrial policy stressed that only those industries in the forefront of technological process can maintain and improve competitiveness in the European economic system as a whole (1). The capacity of the industries that use biotechnology as a tool of production to play a leading role in research and to master industrial applications will be crucially affected by the economic environment within which these industries work. The main responsibility for industrial competitiveness rests with the firms themselves. It is therefore crucial that public authorities, both at the European Community and member State level, provide clear and predictable conditions for the activities of industry. This strategic dimension is important if the Community is to be in a position where it can offer a combination of factors and/or preconditions essential to the full industrial diffusion of biotechnology.

An indication of the potential size of this sector can be ascertained from an estimate according to industry sources. The world sales of biotechnology-derived products (excluding fermented foods and drinks) were approximately 7.5 billion ECU in 1985, representing three times the volume of investment in the field made between 1980 and 1985. Industry estimates for the year 2000 vary widely, between 26 billion ECU and 41 billion ECU. Even the conservative estimate yields a threefold increase in sales.

The recent increase in biotechnology products is only a beginning. It is clear that biotechnology will have strategic significance in dealing with some of the major challenges facing the developed and developing world, i.e. food, health, environment and population growth. Biotechnology will play a significant role in protecting and improving our environment. New vaccines, developed through biotechnological techniques, have already saved many lives and improved the quality of life for both humans and animals. Efforts are being directed towards the development of drought-resistant plants (of great interest to many developing countries) and making certain plants unattractive to their traditional predators, thus reducing the need for excessive use of pesticides. The application of biotechnology to increasing food production will be of great importance to developing countries while at the same time having a profound impact on agriculture in the Community with major implications for the Community's agricultural policy.

At the same time, biotechnology suffers from a bad image amongst policy makers and the general public. Concerns have been expressed about the potential impact on human and animal health and the environment resulting from the

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incorrect use of new biotechnology. Each strategy to improve the economic framework for biotechnological techniques must be aware of these dimensions, not only as a constraint but as a challenge to balance the different aspects. Although some of the expressed fears seem exaggerated, they are, nonetheless, of great political influence. It is imperative therefore that problems of public acceptability and ethical questions be recognized and dealt with. It is suggested that there should be advice available to the Commission in the area of ethics in biotechnology.

The biotechnology revolution will ultimately have an impact on our everyday lives as profound as that of information technology, but the time-dependence of industrial applications must be recognized. While scientific progress is as rapid in many areas of biology as it is in informatics, for many of the applications, especially those where added value is greater, such as in the pharmaceutical industry, the time required for innovations to reach the market is much greater, largely due to the time required for registration. This cost, in terms of time as well as money, makes prenormative research in such sectors particularly important.

It is of paramount importance that the industries using biotechnology develop competitively. This need to create favourable conditions for the biotechnology industries, which are crucial to the development of the Community as a whole and which will affect competitiveness across a broad spectrum of the Community's industries, including the agricultural sector, must be combined with the protection of human, animal and plant health, safety and the environment. In fact, the need to achieve higher standards of health, safety and environmental protection does not act as a limiting factor but as a major opportunity for industry to develop through biotechnology more precise, effective and non-polluting products and services which will contribute to these aims. It is therefore the role of Government to ensure that the framework provided for such activities is comprehensive enough to satisfy public concerns while at the same time encouraging the industrial development of biotechnology. The Commission considers that the Community should be attractive to both Community and non-Community investors so that it may reap the accrued benefits from the industrial application of biotechnology. The purpose of this communication, therefore, is to examine the future perspectives for competitive biotechnology in the Community.

The Commission has been active, through communications to the Council in 1983 and 1986, in defining a comprehensive framework for biotechnology and in identifying policies across a broad spectrum of Community activities which aim at encouraging the conditions necessary for competitiveness while ensuring the protection of health, safety and the environment (2, 3). These Community activities have encouraged biotechnology firms in the Community.

The general approach to the Community's industrial policy was laid down in the aforementioned industrial policy communication. The Commission considers that a separate paper on biotechnology is needed due to the growing importance of biotechnology in the Community. Biotechnology is confronted with differing expectations and strategies, and this paper shows the necessity of having a coherent industrial approach for competitive biotechnology in the Community.

Conclusions and recommendations

The Community will continue to promote the beneficial application of biotechnology while ensuring safety for man and the environment. In doing so it will avoid creating undue burdens for industry.

The legislative framework

Within the overall goals of ensuring adequate protection of health and the environment, environmental and health legislation has been adopted at the Community level. This should be implemented as a matter of urgency.

The Commission will continue to ensure a coherent regulatory approach and an efficient and simplified interaction between sectoral and horizontal legislation.

New biotechnology products involving gene manipulation may need to be considered and assessed. The Commission foresees, therefore, that in the future a number of biotechnology products will have to be regulated under the Community's existing sectoral legislation. The Commission will only do so where a thorough case-by-case examination in the light of characteristics inherent to specific biotechnological products or processes indicates that this is necessary.

Sectoral legislation may require adaptation to technical progress and the progress of scientific knowledge in order to deal with advances in biotechnology. Review of existing legislation will be ensured to reflect rapid developments and technical progress. In the exceptional cases where legislation does not provide for adaptation to technical progress, the Commission will keep this legislation under review.

Where a biotechnological product is assessed, the three traditional criteria based on scientific evaluation apply. By their nature, socio-economic aspects need to be considered in a different way. It is not the intention to have another systematic assessment in addition to the three criteria. The Commission will normally follow scientific advice. However the Commission reserves the right take a different view in the light of its general obligation to take into account other Community policies and objectives.

Duplication of testing and authorization procedures will be avoided. In this regard the Commission will ensure that testing and authorization procedures are streamlined and that one integrated assessment and notification procedure covers all that is required for product authorization.

Adopted Community legislation in the field of public health and the environment will continue to provide adequate protection in cases not covered by sectoral legislation.

Measures to enhance competitiveness and public acceptability

The Commission proposed that priority be given to the following:

(a) The Community's contribution to research and development in the area of biotechnology should be reinforced. This will be undertaken in the review of the R&D framework programme;

(b) The Community will, through its research programmes, information market policy and international collaboration, contribute to the development of a biotechnology information infrastructure within the Community and world-wide (including data banks, software and electronic networks and services);

(c) In order that work in the field of standards may fully complement the Community's legislative work, a clear and precise mandate shall be prepared by the Commission's services, in consultation with CEN;

(d) Community legislation currently under discussion in the area of intellectual property should be adopted, and Community legislation already adopted should be transposed into the legislation of the member States as a matter of urgency in order that the Community will have a coordinated approach that will strengthen its position in international negotiations;

(e) Statistics specific to biotechnology should be compiled in order that statistical monitoring of developments in the industrial application of biotechnology may take place;

(f) Bilateral and multilateral international contacts must be further strengthened. In addition to this, the Community should pursue, within the context of international bilateral working groups, the General Agreement on Tariffs and Trade, the Organisation for Economic Co-operation and Development (OECD), the European Free Trade Association (EFTA) and, where appropriate, other international bodies, the establishment of environmental and health objectives and should ensure that these are integrated into economic and other policy decisions;

(g) To enable ethical issues to be clearly identified and discussed, the appropriate advisory structure at the Community level should be established;

(h) The Commission will regularly evaluate the progress and competitiveness of the biotechnology industries in Europe in order to make sure that the agreed framework remains appropriate. Success in this regard will essentially depend on the strategies adopted by the industries concerned.

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XXIII. INDUSTRIAL BIOTECHNOLOGY POLICY: GUIDELINES FOR SEMI-INDUSTRIAL COUNTRIES

F. C. Sercovich*

Introduction

Entry into biotechnology manufacturing does not follow entry into biotechnology research as naturally as is sometimes assumed. The transition is not an easy one, even for firms engaged in commercial production of biotechnology-based R&D services. Entry into biotechnology production, marketing and distribution means having to cope with things such as the paucity of off-the-shelve technological and manufacturing solutions and fierce competition from established firms trying to retain their market shares.

Save for a few exceptions, like that of *in vitro* diagnostic kits, the customary reference to low barriers to entry into biotechnology in the literature should be taken with a grain of salt since it applies to pre-competitive entry only. The passage from the laboratory to the industrial arena is less trivial than many enthusiasts admit.

Furthermore, entry into biotechnology as an industrial activity cannot be dealt with as a purely firm-specific phenomenon. For an emerging, generic technology-based industry, it also refers to a whole set of interacting agents, which calls for the often-neglected systemic aspects of entry.

Particularly in developing countries, the accumulation of basic biotechnology knowledge does not trickle down easily into the economic sphere. This diminishes its potential for wealth creation. The passage from the realm of the scientifically possible through that of the technically feasible on to that of the economically profitable is much smoother in the industrialized countries, where for this reason bio-policy often entails industrial policy, although it may not be called so.

For a workable transition from scientific effort to the market to occur, a wide variety of capabilities and institutions have to be in place, such as a reasonably well articulated risk capital market; an enterprise sector permeable to the scientific culture; a scientific sector permeable to the enterprise culture; and corresponding sets of institutions and legal codes.

Although policy interventions are justified on grounds of indivisible investments in R&D, uncertainties and non- appropriabilities, clearly they cannot substitute for an efficient interface between the scientific and the industrial systems, the availability of entrepreneurial and management skills or the necessary interactions among the agents of innovation. In developing countries, external dis-economies lead to misallocation of resources, e.g. by deterring out-sourcing, thus detracting from the effectiveness of the innovative process.

Actually, not even in the industrialized countries is the trickle-down effect taken for granted. Market failures (and national rivalries) lead to active government promotional and stimulatory involvement. Although market

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failure is nowhere as pervasive as in developing countries, in most of them the industrial policy content of biotechnology policies is not very readily identifiable, to say the least.

Developing countries have a lot at stake on the issue of what standards are set to define entry into biotechnology. After so many short-lived incursions into industrialization, they cannot afford taking false steps into such a critical cluster of generic technologies by adhering to loose guidelines. This refers not just to scientific quality. It concerns especially industrial, engineering, organizational and entrepreneurial standards. These can in no way be satisfied if due attention is not paid to a set of key dimensions such as gaps in technological mastery, polyvalent engineering skills and scale-up-related issues. Perhaps too much voluntarism has been one of the most outstanding features of advocations for biotechnology in developing countries. Meanwhile, precious time is being wasted.

In principle, there is nothing wrong with a science-push entry, particularly in a science-driven industry like biotechnology, provided that the incentives, markets, capabilities and institutions are in place and work effectively so as to meet social needs and reach consumers competitively. However, the existence of externalities, indivisibilities and like market failures involve the need for industrial policy. But industrial policy cannot do without the necessary capabilities and conducive institutions.

The main global trends in biotechnology are discussed in the first section. Entry into biotechnology is dealt with in the section section. The third section is devoted to various specific industrial policy issues focusing on the case of semi-industrial countries. The last section offers some closing remarks.

The global setting

Some of the most relevant global trends and factors affecting biotechnology industrial policies in developing countries will now be reviewed. They are (a) scientific and technological uncertainties; (b) relative competitiveness; (c) timing of introduction and rate of diffusion; (d) routinization of basic techniques; (e) threshold barriers and the shifting manufacturing frontier; (f) company strategy; (g) national policies; (h) trade reversals; (i) scope/scale trade-offs; (j) privatization of scientific knowledge; (k) industrial property regime; and (l) need focusing.

Scientific and technological uncertainties

Biotechnology's future is highly uncertain. Because the knowledge base is growing at a faster rate than the use of such knowledge in practical applications, the technological and industrial trajectory of biotechnology is not yet quite clear, even within the not too distant future.

In the scientific sphere not enough is known yet about things such as the relationships between protein structure and functions, the mechanisms of pathogenicity in plants and drug delivery methods. However, if feasible technical solutions and profitable economic outlets are found, an ever-increasing number of radical technological and commercial breakthroughs will certainly take place. This may lead, among other things, to a shift away from anti-cancer

chemotherapies and agrochemicals, thus bringing about major shifts in market structure. But this is highly unlikely to happen before the turn of the century.

Relative competitiveness

Examples of biotechnology's superiority abound. For instance, biotechnology methods for protein manufacturing are far superior to those relying on extraction from vast amounts of animal tissue or the random screening of organic compounds. However, the relative competitiveness of the products and processes remains to be demonstrated, except in the few cases where it has given birth to entirely new products (like monoclonal antibodies) or has overcome absolute physical and/or cost limits to input availability (to produce insulin, for instance). High costs related to research, stringent process and quality assurance requirements, handling, delivery systems etc. so far offset biotechnology's inherent advantages. Sharp changes in relative prices may improve the competitiveness of biotechnology in some applications and encourage efforts in areas such as energy and commodity chemicals. Technological mastery plus the diminishing quasi-monopoly power in established pharmaceuticals and agrochemicals will gradually offset the initial handicap of biotechnology products.

Timing of introduction and rate of diffusion

These variables differ widely across sectors. The diffusion rate is the highest in drugs, followed by chemical and agricultural applications, with the rest far behind. Within drugs, the diagnostics sector is more advanced than therapeutics and therapeutics, in turn is more advanced than preventive applications. These contrasts follow a complex and uncertain interplay among the state and evolution of the knowledge base, policy priorities, the role of the regulatory environment and public opinion, the relative competitiveness of biotechnology processes and products, the interplay of competitive forces and the status of industrial property rights.

Cross-industry diffusion rates depend much on industry-specific variables such as unit product value, R&D thresholds and payback periods. Drugs, a highly R&D-intensive industry, will keep a headstart in biotechnology as long as the efforts required for scientific breakthroughs and engineering constraints are not made trivial by technical progress. As for the rest of the potential biotechnology user industries, the key largely lies with technological mastery. The building up of savoir faire is going to take long in most biotechnology user industries while the basic techniques are routinized and intermediate supplier networks developed.

The timing of introduction and the pace of diffusion are also influenced by the policy environment. Thus, for instance, in 1989 over US$ 245 billion were poured by OECD countries into import quotas, acreage set-asides, export subsidies and other policies, making agriculture the most manipulated industry of all (1). This affects the timing of introduction and pace of diffusion of biotechnology innovations (like bovine growth hormone), since these would deprive cozy subsidies of justification. United States subsidies that encourage more research into sugar or petroleum substitutes than warranted by market prices work in the opposite direction (2).

Routinization of basic techniques

The routinization of the basic scientific techniques, coupled with the growing application-specificity of biotechnology engineering and manufacturing know-how, cause biotechnology to be absorbed into the various user sectors rather than evolve as a readily identifiable industry, except for the intermediate input and instrument segments. The acquisition of core in-house R&D biotechnology capabilities by large firms in many industries strengthens this trend (Toyota being the latest reported entrant) (3). As biotechnology matures, so does the growing differentiation of entry barriers relating to sector-specific engineering, manufacturing, marketing, regulatory standards, routines and practices. As a result of this, the current science-led stage will give room to a more market-driven stage.

Over what remains of this century, the structure of the biotechnology "industry" will probably become well defined. In the United States, it is likely to take a multiple, application-sector-focused and hub-like shape, centered around a rather limited number of large firms playing nexus among hosts of research boutiques, research institutions and dedicated biotechnology firms serving niche markets, through a complicated network of financial and technological arrangements. In the European Community and Japan, the structure will be less diversified.

Threshold barriers and shifting manufacturing frontier

Because of competition from conventional products, scientific uncertainties, intense R&D rivalry and evolving manufacturing practices, reaching the market with a specific product does not guarantee the recovery of the substantial sunk R&D investments involved. This is why risk-sharing through subcontracting, partnerships or subsidies has become inescapable even for the largest players. Although it is true that biotechnology has brought about a compression between the different stages that go from basic scientific discoveries to actual applications, exaggerating the existence of short-cuts and quick fixes pays lip-service to the interests of developing countries contemplating their entry into the industry.

Company strategy

Strategic partnering with large multinationals appears so far to be the only way new entrants can hope to get into mainstream biotechnology markets. In mutual partnerships, both start-up companies and multinationals have valuable assets to offer. The former provide their ability to leverage knowledge from universities, hire university faculty on a part-time basis and motivate contributions by scientists and entrepreneurs through stock ownership and other economic incentives. The latter contribute with their R&D financing muscle; regulation-related experience and resources; scale-up capacity; established marketing networks; and diversity of product lines that make it possible to reap economies of scope. Often, start-ups have a high price to pay which they cannot afford, but to get into this kind of arrangement, they are often obliged to relinquish control on their scientific and technological developments. Except in niche and highly specialized market segments, alternatives to this are becoming less and less feasible.

Although multinationals can strongly affect the timing of introduction and pace of diffusion, they cannot suppress them; nor are they likely to try to do so in order to protect their markets for conventional agrochemical and

pharmaceutical products. For one thing, many of their patents protecting these products are expiring so that profit margins are diminishing. For another, public opinion and pressure groups are creating an atmosphere hardly conducive to keep relying on conventional products. Thus, although the intrinsic potential superiority of the biotechnology route remains to be expressed in the economic arena, multinationals are definitely open to the prospect of using it to recreate their weakening quasi-monopoly power.

National policies

Industrialized countries are explicitly applying infant industry policies in biotechnology. For instance, the European Community has recently lifted its opposition to proposed Belgian government subsidies to commercial R&D on recombinant products on the grounds of the innovative nature of genetic engineering and its associated risks. This is in addition to things such as the Third European Community Framework Programme (1990/1994) recently approved by the Council of Ministers that will provide US$ 200 million for biotechnology R&D. The United States provides subsidies to (tax exempted) schemes such as Research and Development Limited Partnerships and tax preferences to patent royalty income.

Industrialized countries are also targeting support of scale-up efforts. The so-called "downstream processing club" in the United Kingdom involves two research institutes and various firms in search of improved separation and purification of products from bioreactors. Direct support to scale-up is considered one of the most relevant policy issues in the United States. Japan paid attention to scale-up-related problems very early in the development of its own biotechnology industry.

Trade reversals

Cases such as those of sugar and vanilla substitutes show that biotechnology is aggravating the impact of trade reversals originating from the automation of labour-intensive processes. A further example: the plant shikonin (grown in China and the Republic of Korea), which, thanks to its medical properties, sells at US$ 4,500 per kilo, is now being produced in bulk through tissue culture techniques by Mitsui in Japan. The case is similar with products such as pyrethin, codeine and quinine. However, industrial use of the knowledge base is often kept on a tight hold due to economic and social uncertainties. This cushions the actual impact on developing countries.

Scope/scale trade-offs

Biotechnology poses the need to master skills such as the ability to manage multidisciplinary R&D teams and to take prompt advantage of synergies and cross-fertilization in scientific and technical knowledge in order to exploit spin-off potentials. Particularly when the time c[illegible]ale-up biotechnology processes, trade-offs arise between reapin[illegible]of scope in R&D and exploiting economies of scale in specialized m[illegible]ing. Few firms can have it both ways. In developing countries lack of markets and interactions induce the first route at the cost of delaying actual entry into the market. But this undermines the economic prospects of the ventures by preventing the timely recovery of R&D investments (see examples further below).

Privatization of scientific knowledge

Basic scientific knowledge is no longer flowing as freely as it used to. Nowadays, when scientists are on the verge of a breakthrough, the first thing they are advised to do is not to publish or disclose it in any way, but to reserve property rights through patenting. Their activity affects stock market quotations directly, which indicates the extreme sensitivity of the biotechnology business to shifts in the scientific frontier.

Industrial property regime

The strengthening of industrial property rights is intended to offset diminishing imitation time-lags. There is a conflict of interest between industrialized country-based enterprises that want to maximize global returns accruing to their R&D investments and developing country firms trying to gain a breathing space for their imitative activities. To make things worse, only very few hold indisputable or undisputed rights on biotechnology patents. But the key to entry into biotechnology resides ever less in getting access to basic knowledge and ever more in knowing how to apply it industrially. Herein lies the main challenge ahead for developing countries.

Need focusing

The trajectory of the biotechnology has so far been focused on the needs of OECD country populations and within this, on the highest value-added products. Two thirds of drug R&D in the United States go to applications catering to the needs of the oldest segment of the population, while less than 3 per cent goes to tropical disease prevention or cure. Meanwhile, the rate of infant mortality in developing countries is assessed at 20 per cent, while hundreds of millions of people are infected by parasitic organisms.

Developing countries' market entry

In discussing the entry of developing countries into biotechnology and related policy issues, the first thing that comes to mind is market failure. Acute imperfections in the markets for factors and information prevent biotechnology developments from reaching those market segments where they are needed most. This poses formidable challenges to policy makers.

To date, most biotechnology developments are sharply at odds with views that suggest that biotechnology is particularly suitable to developing countries, because of what it promises, its allegedly low entry barriers and its assumed appropriateness or amenability to be used for leap-frogging. However, while the birth of biotechnology is still being laboured, basic techniques are being routinized, the technological trajectory is becoming increasingly user-specific and imitation costs and time lags are being shortened. All this may facilitate the market entry of developing countries, provided that scaling-up and downstream processing problems are addressed appropriately. The genetic endowment of developing countries is a purely static advantage. It will be irremediably lost unless its value is enhanced through science and technology efforts. Not even the shrewdest protective legal devices will do in their place.

Although the entry of most developing countries (like industrialized countries) into biotechnology are supply-led, there are variations. Sometimes

the push from science is stronger than the pull coming from industry, or vice versa, while strong market-driven elements can be identified in some cases.

Cuba is a good example of a science-driven entry into (largely health-oriented) biotechnology, mainly at the R&D stage. Although some production capacity was developed, it cannot reach world markets because of allegedly deficient quality assurance guarantees (so far Cuba is only serving some third world markets based on concessionary assistance and science and technology co-operation deals). Its cost competitiveness is unknown. The Centre for Biological Research, set up in 1982, produces its own restriction enzymes and does research on the synthesis of oligonucleotides, the cloning and expression of a number of other genes and the production of Mabs for diagnostic purposes.

Cuba's entry into biotechnology pursued social ends, i.e. the interest in interferon was prompted by the outbreak of dengue haemorrhagic fever affecting some 300,000 people in the late 1980s. But there also was a science-push drive: first-rate bioscientists were available, and it was thought that biotechnology suits Cuba because of its research-intensive nature (which applies to entry into research rather than into manufacturing). If Cuba is to take steps to get closer to the world market, substantive efforts will have to be made to set up a cost-efficient and world quality process, product and production engineering standards as well as marketing and distribution channels.

Argentina's entry into biotechnology shows strong industry-push elements. It is based on a small, though rather dynamic, industrial biotechnology establishment, drawing on the remainders of a world class biology science base. There are a few biotechnology firms working in the field of diagnostics, vaccines and micropropagation, led by two small pioneer firms mainly active in human health. The predicament facing one of these firms is typical of a developing country milieu (i.e. external dis-economies and the need for expensive in-house efforts).

In order to enter the r-DNA route, a series of related techniques such as cell culture, protein purification, Mab production and fermentation, had to be learned. But their mastery would not have made sense in order to produce just one product: a steady drive towards exploiting scope economies plus a lack of out-sourcing networks led to a steady growth in the size of an initially modest project. Size escalations and start-up delays followed. What first looked like short-cuts drawing on imitation and extensive use of freely available information, later turned into unexpected bottlenecks and difficulties requiring a good deal of unforeseen experimental work and innovative efforts to learn a wide range of basic techniques and to apply them effectively. The start-up of the laboratory, isolation of the gene, its expression and optimization, added up to six years prior to commercial production. The initial budget grew ten times (4). Little time was saved compared to what it takes a dedicated biotechnology firm in an industrialized country, although the investment was significantly lower because it relied on reproducing a process already known. Although the project was technically feasible, its economic rationale remains to be demonstrated. No industrial policy framework was available to support this effort.

Much stronger and effective demand-pull elements are found in Brazil. The elements behind the rationale for the Alcohol Programme were energy dependency, a very high level of photosynthetic efficiency and an expected

price of a barrel of petroleum over $40. Brazil's head start in the field of ethanol from sugar cane relied on natural advantages and upon the mastery of all skills and capabilities needed to turn out complete package deals, including project design, execution and start-up, process know-how, machinery construction, training, technical assistance and planning of integrated agro-industrial operations. The programme sought to control natural processes rather than to engineer them. Hence, it relied largely on known fermentation-related process control engineering, scaling-up and mass production rather than on the manipulation of genetic information. However, the programme, which is now re-entering a more favourable phase, along with the exploitation of a variety of biomass sources, created a large and avid market for biotechnology breakthroughs (5).

Brazil's head start in traditional biotechnology has spun-off what has now become an incipient and dynamic development of frontier biotechnology. These efforts are being led largely by academic research scientists and by increasing numbers of innovative start-ups. University-industry links are being forged through initiatives like Bio-Rio, a science park that will offer an incubator facility, central labs for sequencing and synthesis of nucleotides, rDNA experiments and scale-up, administrative support and technical services.

While in Latin American the weak link is usually industry, in developing South-East Asian countries it is the domestic science base. The Republic of Korea, Singapore, Taiwan Province of China and Thailand show comparatively stronger market-driven orientations. They also have more explicit and focused industrial policies towards biotechnology, including supply of credits, grants, risk capital and support for skill formation and process and product development. Thailand pays relatively more attention to agricultural and the other countries to health-related applications. In Singapore, Taiwan Province and Thailand, start-ups play an important role. The Republic of Korea relies much on chaebols, large conglomerates that devote substantial resources to biotechnology R&D. South-East Asian countries offset the relative weakness of their science base by drawing directly on the scientific establishment of industrialized countries through their expatriates and by setting up biotechnology research firms there - the Republic of Korea's Samsung and Lucky-Goldstar have done so in the United States (6). And the circuit goes both ways. Glaxo is setting up a US$ 50 million research joint-venture with Singapore's Institute of Molecular and Cellular Biology. Not accidentally, all three senior scientists involved in the IMCB are, or have been, associated with major research institutions in the United States and Europe (7).

In conclusion, demand-driven elements appear to have a stronger presence in South-East Asia than in Latin America, where supply-led elements tend to prevail; (b) within the supply-led experiences, science-push forces are particularly strong, most of the action taking place at university research centres or in research-oriented firms, and (c) there is a pervasive lack of skills and capabilities to bring scientific output into industrial use. The scope for LDC firms to continue to take advantage of shortening imitation time and cost lags is at stake in bilateral and multilateral TRIP (GATT)-related negotiations currently underway. A weak industrial policy content is particularly noticeable in the Latin American experience.

Industrial policy issues

Biotechnology poses plenty of room for controversy and doubts, for it challenges a good deal of the conventional wisdom regarding issues such as the

role of basic science in industrial progress, the economics and management of R&D efforts, the locus and focus of technical change, industrial property rights and biosafety-related issues. However, all this ought not to delay industrial policy action anymore.

The science-push drive fails to work in some cases, like in vaccines, where price competition allegedly discourages leading firms from engaging in development and manufacturing. This case dramatically illustrates the critical importance of threshold barriers to developing countries entry. Plainly, as long as technological and manufacturing barriers are not overcome, a number of vaccines that can be produced today on the basis of existing scientific knowledge will just not reach those who need them. Because industrialized country markets do not justify their commercial development, they remain expensive and because they are expensive they are beyond the reach of those who need them most.

The progressive routinization of the basic techniques makes it easier for user industries to appropriate the know-how concerned. Developing countries have the possibility to undertake such appropriation directly in connection with applications most relevant to them, be it in agriculture, food, health care, mining, waste disposal or whatever.

This prospect is not favoured at all by the increasing privatization of scientific knowledge in industrialized countries. However, this problem particularly concerns the very cutting edge of the scientific frontier. Short of it, developing countries have a lot of room to take advantage of the already routinized breakthroughs, like gene splicing engineering.

One of the main promises biotechnology brings with it is that of letting developing countries wean themselves from economic dependence on commodity prices. Australia has focused on this problem as the main target of its policy in biotechnology. From this angle, Australia's approach is relevant to most developing countries (8). However, such a promise must be looked at with a great deal of caution. The route to it may be hazardous.

Developing countries remain relatively backward, despite all their potential for catching up, because they lack many or all of the ingredients that concur in forming the social capability required to realize such potential. There should be no illusions as to biotechnology being an exception in this regard. Many developing countries can put together a group of first-rate scientists and even endow them, at the cost of great sacrifices, with the resources necessary to undertake high quality research. But to expect to be able to reach the world market on this basis is an illusion. As Japan, and then the Republic of Korea, Hong Kong, Singapore and Taiwan Province have shown, the key to effectively exploiting the leap-frogging potential does not just lie in the mastery of the scientific underpinnings of a technology, but rather in the mastery of the engineering, industrial and commercial skills and capabilities that make it possible to reach the market competitively. Although less successful, Brazil and Mexico have been trying to apply the same lesson. Science-intensiveness does not make matters any easier; rather, the opposite is true.

The case of idiosyncratic, developing countries-specific needs for which biotechnology applications may be sought, as well as all those instances where the market fails to operate efficiently (as in vaccines or in bGH), merits a special consideration of the scope for government intervention.

But no matter how much or how little the Government intervenes, the fact still remains that entry into biotechnology cannot be seriously considered if enough attention is not paid to things such as skills to be mastered, resources to be commanded, products to be manufactured, organizational modes and manufacturing standards to be adopted and markets to be served right from the laboratory throughout all stages up to the distribution to the final consumer.

The above does not mean - particularly after allowing for differences among countries - that developing countries should focus on low-end applications, most of which are still to be developed. It simply indicates the need for paying enough attention to bottlenecks and constraints to the high-end applications which are sometimes recommended.

Entry into high level biotechnology research can render extremely valuable services because, among other things, it makes it possible to keep an eye on what is going on in the scientific frontier and eventually take advantage of it as a possible quick follower. However, entry into the research stage without having much chance to proceed forward along the innovative chain entails the risk of having the results industrialized elsewhere and, what is even worse, of subsidizing the research endeavours of industrialized countries.

Over and above the need to bridge the gaps between scientific breakthroughs and technological design, between technological design and engineering development and between engineering development and manufacturing practice, there are also requisites regarding the necessary interaction among the diverse agents of the innovative process. The Brazilian experience in ethanol is a good illustration of the role of the systemic and synergistic aspects in biotechnology development. But only a few developing countries can afford engaging in an effort on such a comprehensive scale.

Some 20 to 30 years will elapse before biotechnology becomes a widely utilized technology affecting many industrial sectors. How can developing countries take better advantage of it over this period?

The intensity of current international competitive rivalry and the fact that the United States, the leading country in the field, is on the defensive and trying to offset its eroding competitive power, is a rather unfortunate coincidence for developing countries endeavouring to enter biotechnology. Conditions for access to technological know-how are now harder than they used to be when a lot of knowledge and information regarding manufacturing processes was transferred on a commercial basis. Today this kind of transfer to developing countries has become rare. The rapidly shifting scientific, technological and industrial frontiers in biotechnology accentuate the risks and uncertainties linked to developing country moves.

For instance, initial price quotations for biotechnology products are very high since the firms concerned intend to recover R&D costs as quickly as possible. But prices may go down substantially any time. This makes it rather tricky for developing country firms considering whether to get into the biotechnology business to undertake a realistic assessment of future returns, even though their own R&D costs may be substantially lower thanks to imitator's advantages. Another difficulty lies in the sparsity of engineering cost estimates, since most relevant equipment for advanced biotechnology applications is currently being made to order.

The potential success of attempts at entering biotechnology depends, among other things, on the previous experience profile at the firm and country levels; interorganizational synergies within the private sector and between it and the public sector; availability of risk capital; innovation financing; linkages between industry and the scientific and technological system; and application-sector-specific scale-up skills and capabilities.

Although developing countries may have little chance of entering directly into high value-added product lines involving heavy R&D expenses, they do have certain indirect strategic routes for taking effective economic and social advantage of advanced biotechnology and building up the experience necessary to enter increasingly higher value-added products. Such routes include applications regarding (a) plagues and idiosyncratic diseases; (b) improvement in the competitiveness of traditional industrial sectors (agriculture, biomass, food and drinks, forestry, textiles, mining etc.) by enhancing existing product quality and process efficiency; and (c) developing new products based on traditional industrial sectors aimed at niche markets.

But it would be absolutely illusory to attempt entering commercial biotechnology without paying enough attention to the mastery of effective downstream processing technologies through joint work between chemical engineers and biochemists. The lack of bioprocess engineering skills may effectively block scale-up efforts, particularly at the purification stage (the major cost item). The ability to undertake effective scale-up is a major barrier to entry into most commercial biotechnology segments. Substantial lead-times are involved. Genetic engineering has permitted mass production of proteins and lower fermentation costs for products such as enzymes and amino acids. But it does not substitute for more traditional engineering disciplines. The choice of techniques (e.g. regarding the optimum expression medium) is still another important challenge to engineering developments involved in scale-up efforts.

The rich variety of agents of biotechnology change in the world market provides plenty of room for identifying and resorting to sources of international scientific and technical co-operation. Many industrialized country-based biotechnology start-ups are eager to engage in technology transfer agreements with developing country-based firms. However, it is necessary to proceed with caution, since in most cases their technologies are still at an experimental stage. On the other hand, examples of developing countries' excellence in biotechnology research abound. There are also many instances of successful applications of the outputs of such research (like Zimbabwe's DNA probes for salmonella, Argentina's diagnostic test for Chagas disease and Colombia's malaria vaccines) (9).

As pointed out, Singapore, along with other South Asian countries and Spain, pursued a shrewd strategy that consists of taking advantage of expatriate scientists and engaging in joint-research ventures in industrialized countries. Zimbabwe, for instance, takes advantage of expatriate scientists working in France in the area of DNA probes for salmonella. This work is of global interest as the disease causes 3.5 million deaths each year in children with diarrhoea (10).

But joint-research ventures do not necessarily work to the advantage of developing countries. Some agreements may allow industrialized countries-based corporations to use developing countries research skills and capabilities as a source of cheap inventive labour whose output is subsequently

processed industrially and commercially back in the industrialized country (11, 12). The Chinese are involved in this kind of joint research venture while at the same time acquiring turnkey, prefabricated biotechnology facilities from a major multinational to manufacture recombinant hepatitis B vaccines. This black box type transfer includes highly sophisticated hardware items, such as ultracentrifugation process equipment that brings into play forces hundreds of thousands of times as powerful as gravity.

Concluding remarks

One of the basic dilemmas developing countries face in biotechnology is how to enter it at the right time and how to avoid pursuing wrong leads and dead ends. Getting into biotechnology at a point too far removed from the market or too dependent on price-sensitive products in highly competitive and risky markets may not be a sensible approach.

Developing countries need to understand the dynamics of biotechnology change in developing countries in order to identify technology and market trends and valid interlocutors (universities, research boutiques, dedicated biotechnology firms or multinational corporations) according to specific needs. This, in turn, requires a clear assessment of the nature of these different actors, their relationship to each other and their respective strategies and likely trajectories.

It is also essential for developing countries to understand the nature of the most important factors that affect the timing of introduction and rate of diffusion of biotechnology, such as company strategies, scientific, technological and engineering bottlenecks and uncertainties, barriers to entry and threshold factors and the relative competitiveness of biotechnology products and processes.

To bridge the gap between the rapid development of the scientific frontier and the lagging evolution of the technological and manufacturing frontiers will take a great deal of time and resources. An increasing number of entrants at the R&D stage can be anticipated. But it is not so certain that the state of the art in manufacturing will catch up any time soon with the acquisition of applied scientific skills at the enterprise level. Herein lies a vital breathing space for developing countries.

However, the inability to supply products and services at competitive prices (net of infant industry learning-related costs and external diseconomies) downgrades the capacity to generate wealth. No matter how creative the efforts involved might be, this kind of situation is likely to lead to a dead end. High value added products make it possible to pass on high costs of research, but for now they do not appear to be the solution for developing countries attempting to enter biotechnology commercially.

The 1970s have witnessed the birth of biotechnology industrial applications. During the 1980s MNCs cautiously followed events, becoming more and more involved and thus getting ready to fully enter it. During the 1990s they are likely to impress their particular mark upon future developments.

Once the basic biotechnology techniques become routinized, one of the main questions to be addressed is what to do with them (new proteins or life forms can be created without a clear purpose). The answer to this question

cannot be prefabricated. It can only result from a learning process whereby the accumulation of scientific, technological and manufacturing skills and capabilities interacts with social needs and market realities.

This process entails, on the one hand, the carrying out of basic and applied research on a continuous basis and, on the other, setting up the engineering capability that is needed to translate the resulting insights into competitive products. This process will be more and more influenced by the increasing absorption of biotechnology by user industries, whereby its trajectory will be progressively assimilated by that of those industries.

The above is precisely what, once again, the Japanese appear to have understood very early. In their two-tier strategy, the first stage (1981-1988) consisted of achieving mastery of the scientific underpinnings and practical use of the basic techniques of biotechnology. For this, they have taken full advantage of research links with the best centres of excellence in the world. The second stage (1988 onwards), which started while the first was still in progress, consists of acquiring the necessary manufacturing experience through licences and then starting to enter the real game as innovators, forging ahead both at the scientific, technological and commercial levels (13).

International technical cooperation has an important catalytic role to play. This includes, first, supporting the setting up of information networks. In the second place, it concerns the building up and strengthening of domestic scientific and technological capabilities. This comprises areas such as bio-process engineering skill formation, experimental development and scale-up efforts, setting up and upgrading standards of manufacturing, quality and process and product safety and working out of industrial policy guidelines. Thirdly, it concerns assisting in the transfer and adaptation of technology. And fourthly, it concerns supporting the development of new products and process.

Initiatives such as Programme of Policy Research and Technical Assistance in Biotechnology (PRATAB) (14) would help tackling an urgent need to avoid duplications, create synergies and improve the use of resources.

PRATAB is intended to perform as a scanning and early warning system for the benefit of developing countries through the execution and support of technical assistance and policy research in biotechnology, based on the articulation of the so far scattered efforts made by Governments and international organizations. A network of data banks would be set up and consulting services to developing country Governments and organizations would be provided. PRATAB sponsorship is to come from Governments and international sponsoring agencies. It would establish a network of researchers and policy makers from both developing countries and industrialized countries so as to facilitate their reciprocal consultations on a periodical basis. Its financing would result from sums granted by the different sponsoring agencies to specific research, consultant and technical assistance tasks in the context of their on-going activities so that overheads would be kept to a bare minimum.

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XXIV. THE CREATING PROCESS OF NEW INDUSTRIAL ACTIVITIES TO MEET THE CHALLENGE OF A NEW WORLD

Ulf Andersson*

Realization and commercialization of biotechnology, like any other process, is to make technology real in relation to market and society. It is best comprehended by looking into the general process of the realization of an innovation or any knowledge-based idea.

The process of innovation from a macro perspective

In Europe, quite a different situation will have to manoeuvre in industry when the integration of the Common Market becomes a reality. An integrated market and the potentials to create new markets will give a much stronger position for the commercialization of new industrial products and new industrial concepts. The really big step ahead is the integration of all European economies. There is a new map to consider when Europe reaches the year 2000 and beyond. In the Far East there are several very fast growing economies, and Europe will also have to strengthen its position in relation to northern America. On the other hand, Europe will be in a stronger position when major international business and industrial groups form their strategies as to where new industrial plants should be located and even which new developments to concentrate on in relation to market potential.

New infrastructures and planning for modern urban societies with its associations and economic interactions are taking place in different regions, and the fast-growing information technology and telecommunication networks can open up many new possibilities for industrial and business networks. The process of evaluating new ideas and the creation of possibilities for their realization on a joint-venture basis throughout Europe will clear the way for new industrial opportunities.

Historically, European traditions and culture have always had the great ability of creating new structures and centre. An example of this phenomenon is the sunbelt of growing economies near the Mediterranean coastal regions of Spain. Classical centres such as the institution of the Viennese coffee-houses and the Sacre Coeur in Paris were cultural meeting-places with the critical mass for the spawning of new ideas. As a Scandinavian visiting Hungary, I am very aware of this. Hungary is another country which has the potential to play an important and active entrepreneurial role within Europe.

The process of innovation from a micro perspective

Finance and capital are very often focused as central problems by politicians, economists, industrialists and scientists in the discussions on how to support development in a region or country. Questions relating to the realization of new technologies and industries focus on the creation of new jobs and social welfare structures. The problem, one often assumes, is how to raise risk capital. The inventor in his efforts to realize his invention, frequently projects the lack of an appropriate body to support his invention with risk

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capital, while others in the process also conclude that the whole problem in realizing a new technology is an absence of risk capital. This is not the right impression to act and operate from. The process of creating and realizing new ideas and technologies is complex, consisting of an integration of a whole cluster of parameters in order to make it succeed. The basic parameter is, however, the availability of the right know-how at the right moment. The process itself can be defined as knowledge just in time. Knowledge is needed to evaluate ideas and to carry them out. Therefore, of prime importance is human capital.

The gateway to the Baltic Sea: the Bay of Hamlet (Öresund)

Our extensive experience in the development of staff at the University of Lund and the Ideon Science Park may be illustrative of conducting project management and entrepreneurship. The University of Lund, south of Malmö, Sweden, is the biggest university in Scandinavia, integrating the Swedish Institute of Technology. The university has some 25,000 students and a budget of over US$ 350 million. Malmö is the third largest city and is the commercial and industrial centre of southern Sweden. The Ideon Science Park is situated both at Lund and Malmö and is run in close cooperation with the university, with Malmö Ideon Science Park also having close links with the Symbion Science Park at the University of Copenhagen in Denmark. More than 65 per cent of the Scandinavian pharmaceutical industry is located within a radius of roughly 50 km of Malmö, with some 15,000 scientists working at the university and other institutions.

In the year 2000 Malmö and thus Sweden will even be more closely linked to the European continent by the bridge to be built connecting Denmark and Sweden. Universities are important centres for development opportunities, infrastructure and communication. With the establishment of transport links between Malmö and Copenhagen the urban region around Öresund will become a very important economic region of Scandinavia and northern Europe.

Universities as important partners for innovations and know-how

In its simplest sense, the academy has two main goals. The first and exclusive one is the generation of knowledge through science. The second is to communicate and disseminate the knowledge to society. This is done through the academic courses and education. Other actors then come into play for the application of the knowledge generated by the university into industrial output. Qualified industrial and social development must be strongly knowledge-based and competitive.

As an example of the role a university has in relation to the surrounding society and how important it could be to a region for its progress, prosperity and social welfare, let us look into a historical case as an example. In the United States in the year 1858, the state of Minnesota had to establish three main legal organs and institutions. The first, at the time considered as the most important by the federal Government, was the possibility of having a state prison. Second in priority was the location of the local state government and its parliament. Third, the possibility of having a university located at one of the cities in the state of Minnesota. At that time, three cities, namely Still Water, St. Paul and Minneapolis, were the candidates. It turned out that Still Water and St. Paul were chosen as sites for the state prison and local state government, respectively, and Minneapolis was given the university, which at that time was considered least important.

The impact of these locations on the three cities can be seen today. Minneapolis has evolved as the most progressive city, largely because of its university. Good educational and training institutions, together with efficient transport and communication facilities, contribute to the economic and industrial development of a region. Indeed, universities are central for the development of any region of the world.

There is, however, another dimension to be kept in mind. This relates to the science park, technology park, research park or innovation park concept. Let us imagine that the cooperation between a university and the established mature industry in a university region is in a theoretical sense optimal and the industry is putting up new products. In order to disseminate the information to the public and achieve consumer acceptability, science parks have a role. The science park will be looked upon as a technology window between the established industry and society.

The idea of a development park strategy to support the developing countries

In the realization and commercialization of new technologies, especially biotechnology, science parks and industrial incubator centres are of strategic importance as technology windows. In the industrialized countries, the trend of creating different kinds of technology centres is therefore very strong. In Japan for example, science parks and technology parks are put together into patterns of multiple functions that are integrated networks to create new opportunities for the realization and commercialization of new technologies. At a recent conference of the United Nations Educational, Scientific and Cultural Organization (UNESCO), the concept of evolving science parks was advocated to the participants, particularly those from developing economies.

The phenomenon of the science park, as a strategy to realize and commercialize knowledge and technology, has been defined from situations in the industrialized world. In this motion, there exist leading universities and research centres, good engineering education, supporting infrastructure, knowledge-based big industries and operating market economies with strong international integration. The situation in a developing country, being altogether different, requires that another concept has to be thought of. The suggestion is to have development parks on similar lines to science parks situated near universities, research centres or educational institutions. It will be important that a development park receives official recognition by the Government and the established business organizations. International recognition from organizations such as UNIDO and UNESCO is important. These development parks, as technology windows, should project important local needs to industry and vice versa, and apprise the public of the products brought out by industry to meet their needs. A network of development parks can be linked to the science parks of developed countries so that entrepreneurs may promote the building up of bridges of technology and educational transfer. A strategy like this will be successful and will go a long way towards contributing to industrial development.

In any technology, it is vital to have human resources which contribute to project development. Once a good project shows promise, financing it is not usually a limiting factor. Of course, there are many aspects of this strategy, but technology transfer from an industrialized country can be facilitated through the development park concept. Similarly, when an idea in a

developing country seeks international support for realization and commercialization, the development park will promote the competence, identity and good international links in this perspective.

Experience with Ideon

The University of Lund, founded in 1666, and the Institute of Technology, established in the middle of the 1960s and integrated into the University of Lund, could be looked upon as the parents of Ideon. To have regional support in the creation of the Ideon Science Park concept, a special foundation, the SUN Foundation (in Swedish that denotes cooperation between university and industry) was established by an initiative from the university and the regional governor. The SUN Foundation was established in 1982 by the University of Lund, the regional government, the regional chamber of commerce and the regional development fund. As an associate member, the agricultural university was linked to it. From a regional perspective the initiative of the idea of the Ideon was to form this technology window and link between the university and industry in the area.

There are three different parks established under the SUN Foundation. The first park started in Lund near the Institute of Technology in 1983 and can be defined as a research or technology park. Here one can find new industrial technology in many start-up companies or big companies like the Ericsson Radic Systems, Mobile telephone company, in development operations. About 140 companies are established in this park and most of them are new start-up high-tech companies which have a benefit or support in being close to the Institute of Technology. The cooperation links are also strong in relation to other R&D companies in the park.

The second park started in 1985, also in Lund, and is designated as the Ideon Industrial Park. Here the companies are somewhat advanced in industrialization and commercialization and they are allowed to operate small-scale or pilot-scale production. About 40 companies are established in this park.

The third park started as a project in 1985, but was identified as the Ideon Science Park in 1986. This one is established in the city of Malmö near the university and general hospital. Ideon is operating new industrial concepts for new products or designs. Because of its closeness to the medical and the odontology faculty, the activities lean towards medicine, medical technology, pharmaceuticals and technology for the disabled. Today it is also operating industrial automation and different types of computers and electronic industrial development and other information technology. Almost 40 R&D companies are established in Ideon Science Park.

From the start, and because the SUN Foundation is non-profit-making, capital was obtained from the biggest building constructor in Scandinavia, the Skanska Company. Skanska has played a very important role, not only as a building constructor for all the buildings; it was also the developer, in cooperation with the SUN Foundation. Altogether, all three parks in the Ideon concept invested capital (without subsidies from the Government) of more than US$ 200 million for housing, laboratories and offices.

Today, the structure is such that two real-estate companies have been formed in Lund to operate the housing for the first Ideon near the Institute of Technology. Together they have a common service company to operate

different kinds of service facilities and marketing of this first Ideon park. There is a separate real-estate company to operate the Ideon Industrial Park. In Malmö there is a fourth real-estate company to operate the Ideon Science Park. Altogether in the Ideon parks there are about 220 R&D-oriented companies and about 1,500 employees.

In a separate network organization we also operate links, projects and seminars together with the agricultural university in an identity named Ideon-Agro. This deals with matters relating to farmers and the food industry, but could have other connections, even to the development of new pharmaceuticals.

Conclusions

In order for an entrepreneur to initiate and operate innovative industrial research and development, it is desirable to create the science park concept, which ideally should be situated near a university. To capitalize on the ideas coming from a university, three factors must be considered for successful industrialization.

Management is the first. To start a company is always a risk. Entrepreneurship means risk. A possible strategy would be to have the incubator network organization evaluate and even support the basic invention idea with the right know-how. This is the initial phase of the realization process. After that it is a question of management and financing. It is in fact better to talk about risk management than risk capital. Secondly, to start a company one needs production competence and facilities. A company must have the possibility of delivering products and services. One way would be to build up subcontractors; another could be to create one's own production plant or maybe organize it on a joint-venture basis in a separate production company. Thirdly, one should have competence in marketing.

Management, production and market competence are not to be found in a university. This triangle to support the realization of a new industrial idea is found in industry and industrial business life. So if this triangle of the three competences can be integrated, then even a science park concept could become successful. For developing countries, the concept of establishing development parks has been proposed on similar lines to science parks.

D. Safety issues and education and training

XXV. THE COMMERCIALIZATION OF BIOTECHNOLOGY: THE SHIFTING FRONTIER*

Marion Leopold**

Introduction

During the 1980s, as advanced biotechnology moved out of its infancy, science push optimism gave way to a more realistic appraisal of what could be expected from the technology. Not that anyone questioned biotechnology's potential for becoming a driving economic force in the twenty-first century, but it became progressively evident that putting the new scientific knowledge to industrial use was a considerably more formidable task than had initially been surmised; the path from laboratory to market-place was strewn with obstacles of all sorts.

As this awareness has increased, so have attempts by both government and industry in the advanced economies to tackle the obstacles. These efforts, which are all borne of the same basic interest, i.e. to enhance country and/or company competitiveness in commercial biotechnology, are being undertaken on many fronts at once. For instance, several countries are applying specific measures to overcome specific barriers to innovation while simultaneously confronting larger questions of public policy and industry structure and organization as these facilitate or hinder progress in biotechnology (and other knowledge-intensive industries). Innovative steps are also being taken by the biotechnology industry itself. Thus, in a recent precompetitive move, the major industrial biotechnology associations of the United States, Japan, the European Community and Canada have undertaken to develop a common approach in policy areas deemed critical to the industry's overall success; significantly, the first such area to have been targeted is biosafety regulation.***

In fact, country differences in areas such as industrial policy and corporate culture notwithstanding, a salient feature of the increasingly international environment in which biotechnology is evolving is the growing de facto consensus among national Governments and industries as to the requirements for and obstacles to a growth-oriented and globally competitive biotechnology industry.
This is spelled out in the recent policy statements

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*The central arguments of the first three sections draw on Sercovich and Leopold (1).

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***Established in 1988 as a bilateral group under the auspices of the United States-Japan Business Council and the Japan-United States Business Council, the Forum on Biotechnology decided in 1990 integrate the European Senior Advisory Group on Biotechnology. In 1991 the Industrial Biotechnology Association of Canada also joined the Forum, the United States and Japanese memberships of which have been passed on to the respective industrial biotechnology associations. In 1990 the original Forum issued a report on the "harmonization of the scientific principles and procedures underlying the regulations related to biotechnology".

of the various Governments and in private sector reports. It is also evidenced by the actual steps being taken by industry. For instance, while the United States has begun to work on strengthening its downstream scale-up skills and capabilities, Japan has been moving upstream into basic research.

The fact that countries and companies are increasingly aggressive in attempting to identify and overcome barriers to competitive market entry, is a clear indication of the dynamism of the industry. But it is also an indication of the importance of those barriers. The translation of scientific discoveries into useful and competitive products is simply not a small matter. In fact, since the breakthroughs of the early 1970s that laid the foundations for the new biotechnology, relatively few products have actually been commercially marketed, while literally hundreds are being held up at various phases of the innovative chain. It would thus appear that factors that are slowing up product development, approval and commercialization are presently more than offsetting factors that are propelling the process forward.

In the following pages we identify some of the main impediments to the timely introduction and diffusion of the products of biotechnology as well as various measures that are being taken to counter them. Developing countries seeking competitive entry into biotechnology have everything to gain by selectively drawing on these experiences.

Obstacles to commercialization in biotechnology are quite variable, in that they often differ in importance according to country, application sector and user-industry, company size, learning-curve and other time-related considerations and changes in the macro-economic climate. Furthermore, factors that hamper innovation under certain conditions may actually accelerate it under others. Since the limits of the present paper make it impossible to take full account of these and other variables and the complex interplay among variables, our approach should be considered indicative.

We have drawn heavily on the United States experience, which is the most important to date, and for which there is the greatest amount of readily available information. Furthermore, most examples relate to therapeutic and agricultural applications of biotechnology, where entry barriers are considerably higher than in the diagnostic and supplier sectors of the industry. For reasons related, among others, to the state of basic knowledge, competitive potential, entrenched corporate interests and policy priorities, other application sectors such as chemical production and bioremediation presently lag far behind and will not be dealt with.

Although most of the bottlenecks, scale factors and entry barriers discussed here should decrease in importance as commercial biotechnology moves up the learning-curve, considerable time will elapse before timely market introduction becomes the rule rather than the exception.

Scientific, technological and engineering bottlenecks

Ultimately, if the products and processes of biotechnology are to be commercially successful, they must hold a competitive advantage over existing products and process or, should they be entirely new, they must correspond to market demand/social need. Even in the case of engineered drugs such as human insulin, human growth hormone, alpha interferon, t-PA and erythropoietin, high relative prices and technical difficulties are impacting market size.

Some of the factors interfering with competitive market entry have to do with as yet unresolved scientific, technological and engineering problems. A sample of such bottlenecks serves to illustrate this point.

Despite unprecedented scientific and technological advances over the past decade, major bottlenecks in basic and applied knowledge continue to affect research aimed at the development of human therapeutics. Knowledge gaps in the field of protein drugs concern the structure, function and engineering of proteins, the effect of metabolism on gene expression, and drug delivery methods (1, 2).

One of the major challenges to the development of protein and peptide drugs has been that of finding appropriate delivery systems. The large and delicate molecules of drugs such as human and animal growth hormones, human insulin, and interferon cannot be delivered orally, because they are degraded by stomach enzymes. With injection as the only method of administration, market size is limited. In the cutting-edge field of antisense therapeutics, delivery is turning out to be an even more formidable obstacle: in addition to resisting enzymic degradation at target sites, effective, yet not toxic, doses of compounds will have to accomplish the difficult task of penetrating cells. It is thus possible that commercial application of the antisense approach will be put on hold until the advent of drugs that either cause genes to produce antisense substances within the cell or use lipid coatings capable of fusing with the cell (3).

Equally important unresolved questions in the field of protein drugs involve the structure, function and engineering of proteins. Since protein engineering - a critical step at the biotechnology frontier - requires understanding the protein's function, which in turn depends upon its shape, considerable and costly efforts have been undertaken to unravel protein structure, including attempts at protein crystallization in space (1). In this context, significant interest was aroused in April 1991, when researchers at the rational drug design company Agouron published the crystal structure of an enzyme the HIV virus needs in order to replicate (4). But other scientists were quick to question the importance of the discovery. In particular, it was noted that because the crystal structure described is that of an inactive protein, its usefulness in designing a drug to inhibit the virus remains to be proven. This and other uncertainties linked to the rational drug design process, which includes protein purification and crystallization, X-ray crystallography and computer modeling, are slowing innovation in protein engineering (5, 6).

Curiously, these caveats do not seem to dampen investors' spirits. In fact, on the day following the publication of the enzyme structure, Agouron's stock shot up a spectacular 85 per cent (7). In the same vein, commenting on the above-mentioned bottlenecks linked to antisense drug-delivery, one biotechnology financial analyst observed: "There are loads of unresolved technical questions that [investors] don't seem to care about" (Berler, cited in (3)).

Important deficiencies in the stock of basic scientific knowledge have been recognized as seriously delaying developments in agricultural biotechnology. An insufficient understanding of key traits in plants has hampered the use of genetic engineering to produce certain types of transgenic plants, particularly when this involves multiple gene transplants. Although major efforts to overcome these obstacles are in the works - including, in the

United States, a 10-year research project aimed at mapping the plant genome and a proposed reallocation of government basic research funds from medicine to agriculture and other areas - it will be well into the next century before agricultural biotechnology can be expected to fully reap the benefits of these efforts.

Furthermore, advances in agricultural biotechnology will also depend upon progress in related areas. Thus, for instance, plants programmed to express insect-resistance, as well as biopesticides themselves, face a potential problem that has long plagued the chemical pesticide industry, i.e. the emergence of insensitive strains of pests (8). Failure to understand and master insect resistance to biocontrol agents can wipe out a potential competitive advantage of these agents.

Threshold factors

Research and development

As mentioned above, barriers to commercialization are largely user-industry specific. In the R&D-intensive pharmaceutical industry, which is heavily involved in biotechnology, both soaring R&D costs and declining productivity have been affecting innovation rates. During the 1980s, R&D expenditures by the world's main drug companies increased fourfold, while applications to the United States Food and Drug Administration (FDA) to market new drugs dropped some 60 per cent and the actual introduction of new products has been falling since 1960 (9, 6).*

In the case of dedicated biopharmaceutical companies, most of which are still in a precommercial phase, an average of 63 per cent of product sales is spent on R&D, compared with 16 per cent for traditional pharmaceutical companies (10). Thus the relative burden of R&D costs is even greater.

These threshold factors, among others, are causing major industrial restructuring, including mergers, acquisitions and, prominently in the biopharmaceutical sector, strategic alliances (1). Since 1988 no fewer than 15 major drug firms have consolidated, and the search for opportunities is becoming increasingly aggressive as companies seek to strengthen their R&D capabilities and underwrite the growing costs of doing so (9). Meanwhile, dedicated biotechnology companies, which remain the driving force in the innovative process (and thus offer the possibility of partially offsetting declining productivity), continue to be the target of takeovers, with more than 30 United States start-ups being acquired between mid-1989 and mid-1990 (12).**

Strategic alliances, which usually bring together a dedicated biotechnology firm and a large established corporation, are also an important

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*Declining productivity has been linked to stringent regulation and a decrease in returns to trial and error screening techniques used in traditional drug development. Safety and efficacy testing is said to account for some 60 per cent of the cost of developing new drugs (1).

**In many instances acquisition is actively sought by start-ups and some of the latter are actually founded with the objective of being sold.

means of overcoming R&D-related obstacles, insofar as they provide the smaller partner with financial resources and the larger partner with human or technological assets or with products.* In the USA, such alliances presently represent the second most important source of capital for startups, after the public markets.

Another strategic move by industry to overcome R&D cost thresholds is in the area of pricing. The premium prices charged for new drugs in the United States** are explained by industry as necessary in order to generate the profits that finance major research.*** In the case of biopharmaceuticals, whether they be produced by established corporations or start-ups, pricing policy is particularly draconian; given the uncertain climate in which products are introduced, companies seek to recoup sunk R&D investments as quickly as possible (1). A case where the speed of investment recovery has been of the essence is that of Genentech's recombinant blood clot dissolver t-PA; priced at $2,200 per dose, the drug recently took a serious blow when it was shown to be no more effective than streptokinase, a synthetic heart attack drug marketed at $186 a dose.

These high relative prices have been facilitated by the so-called Orphan Drug Act of 1983, which grants seven-year monopoly conditions to companies developing new drugs for diseases affecting fewer than 200,000 people. Companies have, furthermore, drawn scope-economies from the Act through a loophole

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*R&D threshold factors are not the only barriers that strategic alliances help to overcome, particularly in the case of biotechnology start-ups; in addition to being a major source of capital, these partnerships can offer support in the areas of production and marketing/distribution capabilities and regulatory expertise. Dedicated biotechnology firms that are engaged in several partnerships (as most are) gain the additional advantage of tying up their assets in such a way as to make them less vulnerable to takeovers.

**Average drugs prices are much higher in the United States, where they are fixed by industry, than in Europe, where Governments usually negotiate prices. American consumers are thus subsidizing worldwide R&D (35). Market size notwithstanding, pricing flexibility is an important reason for non-United States firms to seek a strong United States presence and for United States firms to offset relatively lower overseas returns. This situation can be expected to change somewhat as cost-containment issues begin to be addressed (see section on competitiveness).

***This explanation has recently been stood on its head in a draft Office of Technology Assessment (OTA) report to Congress, which holds that the industry's $US 221 million estimate cost of developing a new drug is an arbitrary figure aimed at justifying exhorbitant prices (36). With returns on sales of over 20 per cent and profit margins three times those of most other major United States corporations in 1990, pharmaceuticals are indisputably the most profitable United States industry. In fact, profitability is often cited as one of the major reasons why the biotechnology start-ups choose to go into pharmaceuticals rather than other application sectors. Industry sources also link high relative prices to the fact that United States law allows for quick release of inexpensive generics when patents lapse - as will be the case for many major products in the coming years - with no new drugs to pick up the slack.

in FDA regulatory policy that allows doctors to prescribe a drug for off-label uses. By targeting the narrowest indications for regulatory approval, companies thus qualify for orphan status designation, while at the same time positioning themselves to cash in on the benefits of broader off-label indications (for which, to boot, costly clinical trials have been avoided). Human growth hormone, for instance, was originally approved for treating growth hormone deficiency, but has obtained orphan status for 11 indications involving four drug companies and commands a large market for the treatment of burns and ageing. Orphan status has allowed some $200 million in annual sales of both hGH and EPO (12).

A still embryonic approach to actually bringing down the costs of R&D and to increasing productivity involves targeting the techniques of drug research itself. As mentioned, the time-consuming and inefficient random screening of chemicals used in conventional drug research has a lot to do with increasing costs and declining productivity. A small number of new start-ups are in the process of rationalizing drug development by integrating the research techniques of genetic engineering with the chemical synthesis process: biotechnology is a research tool to produce chemical molecules in a less expensive way.*

Production

Production-related threshold factors have not received as much attention as those linked to R&D. Low production volumes and high returns, as well as the science-driven nature of biotechnology, all contribute to explain a situation whereby, until recently, efficient production processes were not a priority issue.

This is not to say that companies were unaware of the complexities involved in bioprocessing scale-up; clinical trials in pharmaceuticals already require scale-up capabilities, and companies seeking to be first to market in competitive situations have had to confront manufacturing-related technical and engineering problems early on (1). In fact, in the case of dedicated biotechnology firms, accessing production skills and capabilities has been an increasingly important reason for strategic alliances. But generally speaking, the efficiency of scale-up *per se* has not been given due consideration.

This is beginning to change: with competition and production volumes on the rise and profit margins bound to fall, scale-up cost-cutting is becoming increasingly critical to success in the market place. This is particularly so in the area of downstream processing (purification and protein recovery),

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*Established pharmaceutical companies are keeping a close watch on developments at rational drug design start-ups, with some already engaging themselves financially. Such cases include Japan's Chugai Pharmaceutical Co.'s buying heavily into Vertex, a cutting-edge drug-design company, as well as a recently concluded strategic alliance between Schering-Plough and Agouron Pharmaceutical, whereby the former is investing US$ 6.5 million in the latter in exchange for non-exclusive rights to Agouron's technology and expertise in determining the molecular structures of proteins. Together the companies will attempt to design anti-cancer drugs targeting the RAS protein (6, 37).

which, in the case of biopharmaceuticals, represents upward of 50 per cent of total production costs and as much as five times the cost of purifying traditional drugs (13).

This bottleneck has given rise to innovations in downstream-processing technologies, where new approaches to cost reduction include perfusion chromatography, membrane affinity separations, protein refolding improvement and the engineering of recombinant proteins to include properties that improve purification.

More efficient technologies are a necessary but insufficient condition for downstream cost-reductions. For one thing, companies must be prepared to adopt the technologies, which, in the United States anyway, is not necessarily as easy as it appears. Because present analytical techniques cannot fully define recombinant proteins, the FDA takes into account production processes when characterizing the proteins; this means that a change in process requires a new product license, which in turn increases lead-times and costs.

Improvements in upstream processes are also still called for. Of note is the fact that, contrary to early expectations, bioreactors have not succeeded in replacing fermenters, despite the technology's greatly superior productivity on non-commercial scales. Scaling up has proven to be a major obstacle, as has the cell line specificity of the reactors. Other problems are related to the costs of building bioreactor plants as opposed to converting fermenters, and to the fact that companies racing to bring products to market are reluctant to use production techniques less familiar to federal regulators. This situation may change in the 1990s, as bioreactors are being used in the production of many pharmaceuticals presently in clinical trial, and improved bioreactors are coming to market; meanwhile a potential competitive advantage, related not only to productivity levels, but to operating and purification costs, is being lost (14).

The overall importance of scale-up as a barrier to commercial entry is corroborated by the fact that the Governments of the leading economies have manifested an interest in supporting industry efforts in this area. In the United States a recent expression of this interest is found in the Report on National Biotechnology Policy, which states that "research focused on generic principles and procedures common to scale-up processes could generate large spill over benefits that could not be captured by any one firm and hence would be an appropriate area for Federal support" (15). Japan addressed scale-up problems early on.

Agricultural biotechnology presents its own set of production-related threshold barriers, which tend to be linked to agronomic rather than engineering problems. Although, as in pharmaceuticals, scale-up capabilities are required early on (i.e. for small-scale field trials), the difficulties encountered, not only in seed scale-up but in all phases of the growth cycle, relate to issues such as reproducing in the field results that have been obtained in growth chamber conditions, dealing with the seasonality factor and so forth. As in pharmaceuticals, maximizing yields, assuring a high degree of purity and reducing the waste stream are major preoccupations, but most of these problems are confronted upstream, with process biologists working in the laboratory to design appropriate traits into host vectors.

Market creation

Given the science-push nature of biotechnology, market demand, indeed social need, sometimes has to be created more or less ex nihilo. A case in point is that of Genentech's recombinant human growth hormone, Protropin, which was developed essentially because researchers discovered how to produce it. The natural United States target population of the drug, pituitary dwarfs, of whom there were only some 20,000 when the drug was approved (1985), would not have allowed the company to rapidly recoup its R&D expenses, even at an annual treatment cost of some $15,000 and under quasi-monopoly conditions afforded by the Orphan Drug Act. Genentech moved to solve this problem by making the drug available for children who, unlike pituitary dwarfs, are not hGH deficient but are below the third percentile in height.

This strategy was possible thanks to a number of ingenious marketing moves made by Genentech,* and to the above-mentioned regulatory loophole, whereby doctors were not confined to prescribing Protropin for dwarfism. By creating the perception that normal shortness is a disease,** Genentech has tapped into a potentially major market of 90,000 children born in the USA annually who will fall under the third percentile for height, and rapid sales growth has helped the company not only to recover R&D expenses, but to offset a stagnating market for t-PA, the cost-effectiveness of which, we have seen, has been seriously challenged (16).***

Not all biotechnology companies have been able to create and service their own markets. In fact, even when demand exists, accessing markets is a compelling reason for most dedicated biotechnology firms to either license their technology to, or market through, large established corporations with appropriate sales forces and far-reaching distribution channels (Genentech itself had to enlist the help of Eli Lilly to market its hGH overseas).

Regulation

It has been said and repeated over the years that biosafety regulation is one of the most important obstacles to the timely market introduction of the products of biotechnology. Any doubts about the truth of this observation should be dispelled by measures recently taken at both industry and government levels. As mentioned earlier, biosafety regulation has been targeted as the first area for precompetitive collaboration among the major industrial

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*These include the exploitation of inaccuracies in the diagnosis of hGH deficiencies, heavy financing of the Human Growth Foundation, funding and courting researchers in pediatric endocrinology.

**The President's Council on Competitiveness Report (cf. supra) has discretely admonished such practices by recommending that the FDA "develop administrative proposals to address concerns about the definition of disease used in the program to avoid overextension of the program to treatments that are not orphan" (15).

***This marketing success story may yet meet an unhappy ending: long-term efficacy of the drug (i.e. increased adult height) has not been clinically proven in the case of non-hGH-deficient children, nor have potential long-term health risks to this population been excluded.

biotechnology associations of the United States, Japan, the European Community and Canada, the objective being to put pressure on the various national Governments to harmonize regulatory principles, policies and practices. This attempt to reduce the effects of regulatory externalities on an increasingly global biotechnology industry concurs with the fact that companies regularly evoke experience with foreign regulatory systems as a reason for seeking alliances with foreign partners.

Also underscoring the importance of regulatory barriers is the fact that earlier this year both the United States and the European Community came out with policy statements that focus largely on the effects of regulation on competitiveness (15, 17). Although in both cases a streamlining of the regulatory framework is sought, the respective approaches are markedly different, with the United States administration pushing towards greater laissez-faire - a position not shared by those concerned with market failures - while the European Community puts the accent on standardization, by creating a Community-wide body of regulatory legislation (the likely effect of which will be to relax rules in countries like Germany and Denmark, to tighten them in others, and to create a framework for oversight where little or none exists - Greece, Italy, Portugal and Spain).

But neither Government nor industry can will away the long lead-times, costs and uncertainties linked to biosafety regulation, although certain policy measures could help to alleviate the situation. These entry barriers stem from a complex interplay of factors, including bottlenecks related to risk assessment, uncertainties and overlaps as to regulatory jurisdiction, debates over product- versus process-based rules, a lack of qualified regulators and adequate infrastructure and, in the case of certain bio-applications, pressures from public interest groups. Most of these problems concern the United States and/or European Community member States, while in Japan, where regulatory directives are much less detailed, much is left to discretionary decision-making and informal mechanisms.

Risk assessment

In the early years of the new biotechnology, there was concern among scientists and public interest groups about the accidental dissemination of genetically engineered microorganism (GEMs) designed for application in the contained environment of laboratories and industrial fermentation processes. The concerns subsided over time, as strict standards for physical and biological containment were adopted; furthermore, successive risk assessment experiments led to the conclusion that the rDNA techniques were not inherently dangerous and that most GEMs designated for large-scale industrial applications were of low risk. These conclusions in turn made it possible to apply traditional criteria for assessing biotherapeutics: safety, quality and efficacy.

As biotechnology moved into non-medical applications such as agriculture, bioremediation and leaching, different kinds of questions were raised: in these cases, the engineered organism or microorganism was not a means of production to be used within the confines of laboratories and bioreactors, but rather an end product designed to be applied in the environment. Thus misgivings shifted from potential risks linked to accidental discharge to health and safety risks associated with intentional environmental release.

At this point in time, environmental release remains a sensitive and widely debated issue, particularly between molecular biologists and ecologists. According to a National Academy of Sciences report (18), intergeneric organisms do not present unique hazards and most engineered organisms will not be as fit as their parent organisms. A contrasting view identifies the following ecology-related information gaps with regard to the release of GEMs: detection and monitoring; horizontal transfer of the genetic information of the GEMs; fate of the GEMs after release into the environment, e.g. survival and dispersion; effects of GEMs on the environment (19). One thing upon which scientists seem to agree is that GEMs present greater potential risks than other transgenic organisms, such as plants and animals.

Regulatory policies and politics

Making matters more difficult is the fact that biosafety regulation is not a purely technical process, founded in science and risk assessment. Regulating biotechnology is also a complex political process, aimed at fostering, or at least not undermining, economic objectives. In fact, the fundamental challenge posed to policy makers is precisely that of establishing a regulatory regime that strikes an acceptable balance between safeguarding the public and the environment on the one hand and, on the other, avoiding unnecessary impediments to the innovative process.

To date there is considerable disagreement among Governments, within Governments and between Government and industry as to the terms of that balance, the definition of which, moreover, appears to be shifting over time, as biotechnology becomes an increasingly high stakes international game. In any event, it can be safely said that to some extent all biosafety policies and the political processes in which they are enmeshed, are slowing market entry.

In the United States, the entire question of regulating commercial biotechnology coincided with the Reagan Administration's move to deregulate the economy, and as early as 1981, an executive task force set forth principles aimed at alleviating regulatory burdens on the private sector. This position was a determining force in shaping the so-called "Coordinated Framework for Regulation of Biotechnology", a series of proposed policy guidelines issued in 1986, the essence of which was to affirm the principle of product-based (as opposed to process-based) oversight. Scientific considerations notwithstanding, assessing bioproducts on their inherent characteristics and intended use had the advantage of rendering superfluous the need for biotechnology-specific legislation; regulation could be carried out by existing agencies under existing (if sometimes modified) statutes, with product-use determining agency jurisdiction. Avoiding the legislative route would, it was believed, afford flexibility to the regime, which, in turn, would facilitate keeping pace with the rapidly advancing scientific and technological frontiers.

This approach has worked well enough in the case of biopharmaceuticals. With the risk assessment process more advanced for industrial than for environmental applications of biotechnology and the health and safety stakes lower, FDA has been able to regulate along more or less conventional lines, although bioproducts are evaluated on a case-by-case basis, a practice that has increased both time-lags and the demand for capital and human resources on industry and FDA itself.

In the area of environmental release, United States policy has met with considerably less success; with critical scientific questions remaining unanswered and quantitative risk assessment still very uncertain, the inadequacies of existing legislation have been blatant, particularly under the Toxic Substances Control Act, which authorizes the Environmental Protection Agency to oversee recombinant microorganisms, but which was designed with chemical substances in mind. Caught between legitimate scientific concerns and pressures from the administration and industry, both the EPA and the USDA have been hard put to come up with rules on deliberate release (indeed, in the case of the EPA, to determine the scope of such rules). Moreover, since agency jurisdiction is determined by intended product use, many products fall under the regulatory responsibility of more than one agency; for companies, this means multiplying filings and meeting differing sets of requirements. Regulation presently proceeds on an ad hoc basis and within the confines of small-scale tests. Meanwhile the advantages of flexibility have been more than offset by obstacles linked to regulatory unpredictability and lack of clarity, and to overlapping bureaucracies, with the agricultural biotechnology industry paying dearly in time and resources.

European Community regulatory policy stands in rather stark contrast to that of the United States. Deeming it necessary to oversee not only the products of biotechnology but the processes by which they are produced, the Community has combined a vertical (application-specific) and a horizontal (technology-specific) approach to regulation. Moreover this approach has been embodied in Community-wide legislation, whereby once the European Community Council adopts biotechnology directives (of which four have been approved to date, with many more in the pipeline), member States must enact them into national law.

By opting for umbrella, Community-wide legislation, the European Community has given priority to inter-agency consistency and cross-country standardization as ways of optimizing the regulatory process and, specifically, of levelling the competitive playing field among European Community member States and avoiding intra-community trade barriers. Thus, for instance, although regulation of environmental release is clearly more stringent than in the United States, the European directive provides a uniform and binding set of rules covering everything from notification preparation through small-scale field trials to the marketing of recombinant products (20).

This having been said, there are signs that, in its preoccupation with international competitiveness, the European Community is also sensitive to elements of the United States regulatory philosophy. Thus, for instance, in its document "Promoting the Competitive Environment for the Industrial Activities Based on Biotechnology Within the Community" (17), the European Commission simultaneously reiterates the necessity for member State enactment of directives approved by the European Council and speaks of "constant assessment of the appropriateness of existing and proposed legislation", a clear step in the direction of regulatory flexibility. It is furthermore believed by some that stringent directives on the contained use and deliberate release of genetically engineered organisms may undergo just such a reassessment (21).

The political process in which biosafety regulation is immersed is also affecting both the shape of regulatory regimes and the rate of biotechnology innovation. Above and beyond the conflict and bargaining process that is part of rule-making and that involves lobbying by interested parties, regulatory

politics brings into play inter-agency jurisdictional turf wars, with industry often caught in the middle.* But more disturbing still are the high-level power politics that are plaguing the regulatory system, particularly in the United States, where accusations of secrecy, high-handedness and interference have repeatedly been levelled against executive appointed committees charged with coordinating regulatory activities. As recently as July 1991, it was reported that members of Congress were debating whether to request a Government Accounting Office investigation into alleged "White House interference with science advice to the Agencies". As a congressional staffer put it, it is "a matter of who's in charge of developing scientifically based regulations - political appointees or scientists" (22). Externalities of this sort cannot but increase regulatory inefficiencies, even when they are generated by those who invoke the "invisible hand".

Human, material and budgetary resources

In the United States and probably a number of other countries, a lack of qualified regulatory personnel, particularly top-level and entry-level scientists and physicians, is linked to competition for human resources from the private sector and even academia, which offer more attractive salaries and working conditions. In the United States, deep cuts in agency funding that have accompanied laissez-faire policies since the early 1980s have fed into this problem. Budgetary restrictions are also related to lags in up-to-date laboratories and equipment and to the inability to computerize the review process. As the number of product applications continues to increase, regulatory delays stemming from personnel and infrastructural shortages may well offset gains in lead-times, due among other things, to the standardization and routinization of regulatory procedures.

Public acceptance

There is a growing consensus within both Government and industry that a key element in determining the ultimate success of commercial biotechnology is the capacity to create a climate of public trust. With respect to this problem, an OECD report puts responsibility squarely in the lap of Government, noting that "in cases where the public has shown concern about a technology, scientific acceptability is a necessary, but not sufficient condition of acceptance. When a gap between acceptability and acceptance appears, it will be a goal of public policies to attempt to close it" (23).

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*In the United States jurisdictional disputes concern not only the agencies themselves, but the various congressional committees mandated to oversee them and to interpret statutory reach. In the case of the European Community, interbureaucracy conflicts may involve up to a dozen directorates potentially involved in regulating the work of biotechnology companies, and the above-mentioned directives on the contained use and deliberate release of genetically modified organisms are seen in many quarters as an attempt by the Environmental Directorate - author of the directives - to force other Directorates to either adopt its rules or to forfeit any control over regulation in these areas.

Regulatory bodies obviously play a critical role in securing, or failing to secure, public trust, and risk assessment is indissolubly linked to questions of public policy. This is particularly so in the sensitive area of environmental release. Agencies mandated to oversee the environmental applications of biotechnology already bear the legacy of radioactive waste linked to technological innovations in the nuclear industry and toxic waste generated by the chemic l industry. This legacy undoubtedly contributes to the fact that environmental agencies in many countries tend to view anything associated with biotechnology with extreme caution.

But environmental release is not the only area in which regulators must bear in mind both earlier failings and the credibility problem those failings have helped to create. As recombinant products such as engineered tomatoes begin to enter the food chain, new concerns will become the focus of public scrutiny and debate, partially because of past difficulties. The latter include the banning of the hormone diethylstilbestrol after 25 years, because of carcinogenic chemical residues discovered in treated meat, and more recent public outcries involving pesticides. As late as 1990, EPA recognized that "legal limits on chemical residues for most pesticides in use before 1985 are based on inadequate information" (24). Public confidence in the FDA will certainly not be boosted by ongoing investigations into its alleged role in covering up concerns about animal health and possibly human safety, in an attempt to accelerate the approval of recombinant bovine growth hormone (bGH).

As regards trust building, undoubtedly the most important thorn in the side of regulatory bodies (and industry) has been the highly visible environmental and other public interest groups whose use of the media has been effective in arousing public biosafety concerns. Among the tactics used by such groups are the sabotaging of agricultural biotechnology field tests, as well as petitioning and even suing Government and industry. In the United States, litigation is a particularly effective means of creating regulatory delays, even when cases are lost, and the sole issue of liability coverage presents a potentially serious threat to small, cash-poor biotechnology companies.

Another public policy issue that has generated considerable public reaction is that of socio-economic impact, particularly when agricultural productivity enhancers are involved. In the by now notorious case of genetically engineered bGH, concern that inexpensive, hormone-induced milk would drive small farmers out of business, as well as skepticism about the effect of bGH on dairy cows and the milk's safety for human consumption, has provoked strong reactions on both sides of the Atlantic, with public interest groups exerting considerable pressure on Government and industry. With regulatory agencies traditionally mandated to assess drugs on the basis of three scientific criteria (safety, quality and efficacy), the de facto introduction of a needs criterion, the so-called "fourth hurdle", into the product approval process, has contributed to keeping bGH off the commercial market. In the European Community, furthermore, implicit regulation by public interest groups and farmer lobbies have undoubtedly played a role in the drafting by the Agricultural Directorate of legislation that, if adopted, would make socio-economic needs assessment part of the approval process.

As biotechnology gets more deeply involved in areas such as human gene therapy and the engineering of farm animals, sensitive bioethical questions are certain to provoke yet further public reaction, creating new regulatory externalities.

The preceding observations well illustrate the more general problem of making ends and means meet in regulatory policy-making and implementation. Stated goals of fostering the innovative process, commercial interests and national competitiveness are undermined by a host of regulation-related rate-limiting barriers.

With the exception of fast-track and/or parallel-track review for biotherapeutics aimed at life-threatening diseases, long lead-times and the associated costs and uncertainties created by regulatory externalities are plaguing the United States biopharmaceutical industry. Following years of regulated clinical tests, FDA approval of genetically engineered drugs still takes an average of 34 months, with the result that only 13 drugs have been approved, while over 100 are caught up in the final pipeline, not to speak of some 800 other bioproducts, including diagnostic tests and drug delivery systems. This in turn has many companies planning initial clinical trials abroad (25).

Agricultural biotechnology firms face even greater regulatory delays. As of 15 May 1991, applications for the environmental release of some 156 genetically engineered plants and 28 genetically engineered microorganisms had been approved or were under review by USDA and EPA (26), but almost all these applications concern small-scale field trials and permits continue to be issued on a case-by-case basis. In the absence of overall rules for large-scale testing, and given the pressures exerted by public interest groups, it is likely that most engineered bioproducts, particularly living microorganisms, designed for release to the environment will remain in the regulatory pipeline for some years to come. Under the circumstances it would not be surprising that, as many believe, some companies will seek to accelerate the testing process by conducting early trials in countries that do not regulate deliberate release, although this does not solve the problem of meeting home country criteria and involves the risk of potential public image fallout.

In both the pharmaceutical and agricultural application sectors, regulatory barriers give a competitive advantage to large established corporations, which have greater financial staying power and regulatory experience than dedicated biotechnology companies. However, even the most powerful corporations can experience financial strain when the approval of heavily funded products becomes a protracted and precarious affair. For instance, Monsanto has sunk an estimated US$ 250 million into recombinant bGH and is spending some US$ 58 million annually to keep prepared for the launching of bovine growth hormone (27). Meanwhile, FDA approval of bGH does not appear to be imminent.

Finally, it should be noted that regulatory barriers play a critical role in determining not only the timing but also the direction of innovation in biotechnology; this is true both across and within application sectors. One of the reasons that commercial agricultural biotechnology lags behind biopharmaceuticals is that the scientific basis for risk assessment is less advanced. Similarly, within agricultural biotechnology, controversy over deliberate release, especially of GEMs, and recombinant products entering the food chain has many companies, both small and large, redirecting R&D towards more readily acceptable products, while some existing projects have been put on the back burner or simply dropped.

Intellectual property rights

Since patent approval does not pay off until the sale of a product has also been authorized, lengthy patent delays are considerably less damaging to industry than regulation-related time lags. Nonetheless long patent-issuance lead-times do constitute an entry deterrent barrier. Among other things, they expose unprotected technologies, impact the competitive position of companies and products and increase costs (11).

Between April and December 1988, United States patent pendency periods for biotechnology averaged 29.4 months, as opposed to 21.0 months for all patent issuances/rejections. By application sector, periods were the shortest and issuances the most numerous for equipment (26.0 months/401 patents) and the longest for genetic engineering (39.2 months/36 patents). During the same period, the backlog of biotechnology patent applications grew at a 19 per cent rate (5,200 to 6,200) (28).

The reasons for patent issuance time-lags are in several ways strikingly similar to those causing long regulatory time-frames. In both instances, the complexities, newness and rapidly advancing frontiers that characterize biotechnology create learning-curve-related delays and shortages of senior examiners qualified to train junior staff. As in the regulatory arena, the best human resources are siphoned off by the private sector, although in the United States, the Government has recently undertaken to redress this situation by granting the Patent and Trademark Office special engineering salary rates. Furthermore, industry itself has shown interest in addressing staff shortages, with the Industrial Biotechnology Association setting up its own institute for training biotechnology examiners.

But patent issuance is not the only problem linked to intellectual property externalities. Loopholes, ambiguities and unanswered questions about patent scope, leave plenty of room for legal challenges, particularly in the United States, where, for instance, it is possible to hold a product patent without having rights over the processes involved in making the product. Similarly, different patents can cover different aspects of a given product or process or, conversely, a single patent can in some cases cover the application of an idea to different species. One of the unanswered and controversial issues concerning patent scope is, Should a patent's claims ever encompass progeny? (29, 11).

When the threat of costly and time-consuming litigation is added to patent-issuance delays, it becomes understandable that many pharmaceutical companies seek the advantages of orphan drug status, which offers seven-year exclusive marketing rights, costs nothing beyond the preparation of the submission and can be granted within as little as 30 days after filing. Furthermore, an orphan designation can be established for just about every bioproduct derived from the mammalian or human genome, i.e. the area where patenting has proven the most problematic (12). Companies are also increasingly turning to cross-licensing as a less expensive, less uncertain and less-drawn-out alternative for maintaining market position.

Cross-country patenting differences, both procedural and substantive, also impact the timing of market entry and decisions as to which markets to enter. In Japan, patent approval time-lags are even greater than in the United States, with foreign applications for biopharmaceuticals sometimes held up in the Japanese Patent Office for years before first actions are made and

during which time these same products are being sold by Japanese firms. Similarly, many countries use a "first to file" criterion for awarding patents, while in the United States patents are granted on a "first to invent" basis. This makes it more difficult to protect rights in the United States and in cross-border filings.

Substantive limitations on the patenting of bioproducts also vary. For instance the Japanese patent is so narrow in scope as to be easily circumvented; this contrasts with United States and European practices of offering broad coverage. Likewise, many countries do not offer protection for recombinant microorganisms, plants and animals and/or limit the ability to exercise patent rights, as through extremely broad compulsory licensing schemes (30). All of these considerations obviously play an important role in the international strategies of companies.

Competitiveness

In the last analysis, the commercial success of biotechnology depends not only upon its inherent advantages, of which there are now many examples, but also upon the relative competitiveness of its products and processes. A notable exception to this rule concerns instances where the technology has generated totally new products or has overcome absolute limits to the availability of inputs (31). This latter situation applies, among others, to the production of insulin and human growth hormone, which until recently involved the costly and time-consuming tasks of drawing and then processing minute quantities of extracts from large amounts of animal tissue or, in the case of hGH, from human cadavers.

Some of the more important bottlenecks, scale factors and barriers interfering with competitive market entry have been identified in the preceding pages. These include gaps in basic and applied scientific knowledge, heavy research-related costs, scale-up inefficiencies, expensive and protracted regulatory procedures, patent litigation, skill shortages and a sometimes unreceptive public.

Additional factors that negatively impact relative competitiveness and the overall timing of introduction and rate of diffusion in biotechnology are rooted in organizational, institutional and managerial inefficiencies, as in the case of the United States health-care system (1). With medical costs now accounting for 12 per cent of the country's gross national product, pharmaceuticals are under increasing pricing pressure from the public and private health insurance system, and reimbursement issues are rapidly becoming a major new hurdle for the industry. Although biopharmaceuticals tend to be treated with more latitude than traditional drugs, their coverage by the insurance industry, which is crucial to their success, will be increasingly linked to cost-effectiveness criteria. Cost/benefit analysis will probably raise questions about many products on the market and in the pipeline: tPA and EPO are already under scrutiny, and companies that do not or cannot afford to factor such analysis into their clinical trial strategies will be at increased risk. Furthermore, in those instances where cost-effectiveness does afford a competitive advantage to biopharmaceuticals, the question remains as to how the United States economy is going to absorb the costs of large-scale marketing.

The rate of product development is also affected by difficult and inconsistent access to capital. This is particularly clear in the case

of biopharmaceutical and agricultural biotechnology applications, which have the longest development lead-times and are submitted to the full rigours of biosafety regulation, and with regard to small and medium-sized firms, which have the same up-front investment needs as larger companies but neither the revenues to support them nor, it follows, the capacity to wait out lengthy payback periods.

Company strategy also influences biotechnology's relative competitiveness and the timing of product introduction. Generally speaking, established pharmaceutical and agrichemical corporations do not seek to block the new technology. On the contrary, it is these companies that tend to take control of biotechnology products as they approach the market and that are usually in the forefront in the race to reach the market-place (32). But in those instances where bioproducts are actually competing with profitable and established markets, corporations may use biotechnology to extend the life cycle of existing products, as in the case of pesticide-resistant plants being developed to work with new generation pesticides. Such strategies can slow advances in cerain areas of biotechnology, but they cannot actually bring progress to a halt. Nor is it in the long term interest of corporations to do so, given the erosion of their market positions. This is why, for instance, the same companies that are developing pesticide-resistant plants to accompany their new generation pesticides are also working on pest-resistant plants and biopesticides.

As long as, and to the extent that, biotechnology does not secure a clear competitive advantage over conventional products and processes, its future trajectory remains uncertain. Gaining this advantage is likely to be an uneven process, since the weight of entry deterrent barriers varies across application sectors and user industries, and according to company size, country, learning curve and other time-related factors. Unanticipated events such as radical scientific and technological breakthroughs or significant shifts in relative prices can dramatically enhance the relative competitiveness of biotechnology, but here again, changes will not impact all sectors at the same time and/or to the same degree.

The competitive potential and diffusion rate of specific applications is not easy to predict, and there have been several surprises to date. In the case of chemicals, particularly commodity chemicals, the impact of biotechnology has fallen far short of initial forecasts, partly because of major technical limitations on the technology's use for chemical production and partly because of underestimations as to the relative competitiveness of organic chemistry and highly optimized chemical manufacturing processes (33). However, with major biotechnological inroads presently being made in the area of specialty chemicals - including the highly productive "farming" of biopolymers, a field in which growing manufacturing efficiencies will allow increased competitiveness vis à vis oil-based plastics (34) - it is difficult to anticipate the future overall impact of biotechnology on chemical processing. Similarly, in the area of pollution prevention, several biotechnology-based projects are presently being developed, but it is too early to determine how the new techniques and products will fare in the regulatory arena and in terms of relative costs, etc.

Competitive dynamics can also be redefined by the introduction of rival technologies or by synergistic approaches to product development. A previously-cited example of this latter case is that of rational drug design,

whereby genetic engineering is used to improve conventional pharmaceutical R&D. Whether this industry-driven approach in turn proves competitive depends in part on newly created challenges. Among other things, the synergistic use of biotechnology, protein crystallography, computer modelling and chemical synthesis requires a highly coordinated and successful effort at scientific sharing and the associated interdisciplinary managerial skills.

Although many factors are still preventing biotechnology from fully realizing its competitive potential and although present time-lags may in and of themselves open the door to an altered competitive dynamics, rapid advances at the scientific and technological frontiers, a steady stream of secondary innovations and the inevitable shortening of lead-times keep alive expectations that biotechnology will indeed become a major social and economic force in the coming century. One recent example of such promises involves a double milestone in the attempt to find a substitute for blood: the production of human haemoglobin in transgenic pigs and a breakthrough technique for purifying the haemoglobin. If proven safe for human transfusions and if it is cost-competitive, this blood substitute, which has several inherent advantages over donated blood, could meet an important need of society.

LDCs: lessons to be learned

In developing countries, as in the advanced industrial economies, the real-world difficulties of entering biotechnology are in the process of superseding early hype. The shedding of illusions is undoubtedly requiring that much greater an effort that much has been made of biotechnology's potential for solving economic and social ills of LDCs and that the technology was heralded by many as being particularly appropriate for leap-frogging (Sercovich and Leopold, 1991).

This is not to say that LDCs cannot or should not enter biotechnology - in fact a considerable number of them already have - but the scale, scope, timing and success of the undertaking, as well as the actual entry scenarios and application sectors, will depend in good part upon the capacity of the various countries to deal with the sorts of oostacles to commercialization identified in the preceding pages.

These obstacles are, to be sure, not the only factors that will determine the future of biotechnology in LDCs. Indeed, that future will result from the interplay of a large number of variables, including, on the country level, threshold factors such as market size, industrial infrastructure, availability of financing, scientific, technological and manufacturing skills and capabilities, as well as national science and industrial policy and linkages between the public and private sectors. Furthermore, much will hinge upon developments in the industrialized countries, where the new biotechnology came into existence and where its trajectory is being defined. Thus, for instance, the rate at which multinational corporations seek to export biotechnology products, technology or activities to LDCs will depend, among other things, on various aspects of company strategy and on conditions that prevail in home markets and in other industrialized economies.

These and other considerations notwithstanding, it is imperative that LDCs pay due attention to the question of gaps, bottlenecks, scale factors and entry barriers. The countries that are presently leading the way in biotechnology have understood that successful market entry is closely linked to correctly identifying and overcoming these obstacles and they are acting correspondingly; it is incumbent upon LDCs that seek to compete to do as much.

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XXVI. CONSIDERATION OF ASPECTS OF SAFETY OF BIOTECHNOLOGY-DERIVED PRODUCTS

John S. L. Fowler*

Introduction

Although currently a cause of concern to the public, media and regulatory authorities, biotechnology is new only in name. Fermentation to make wine and beer, use of yeasts to raise bread, marinading meat to improve texture and the basis of all the technological processes using biosubstrates and living organisms were in existence before man learned to write.

It is hard to envisage why the great current concern of the public, media and even some regulatory authorities should focus onto products of biotechnical processes: after all, what nature makes she can also destroy. On balance it seems that the most likely cause for this over-reaction is the belief that there is a hitherto unknown potential of genetically modified organisms to prove hazardous to product users or to the environment. "Genetic engineering", "genetic manipulation" and "genetic modification" are the words that seem to capture the public's eye and to constitute the hazard of biotechnology.

There is perhaps a more insidious and worrying belief or point of view that also seems to be popular in para-scientific circles. Stemming perhaps from centuries of safe use of micro-organisms in traditional biotechnical processes such as brewing, bread-making and cheese-making, there has developed a view that natural products are bound to be safe. This is, of course, by no means true.

Natural products are not safe: be alert to the unexpected

Dangerous substances that have been generated as weapons in the war raging between plants and animals since evolution began include natural products from plants such as curare, tubocurarine, botulinum toxin, aflatoxin and ricin, some of the world's most toxic entities. Even within animals, and quite apart from the venoms, there are vital endogenous chemicals whose actions, whilst essential and beneficial *in situ*, can also lead to violent reactions. The violence and outcome of some of these reactions can be comparable in intensity to those caused by the more potent exogenous toxins: they will arise if endogenous chemicals are allowed to accumulate to excessive concentration, reach inappropriate locations or persist for too long. Examples of such powerful chemicals are in all our bodies - we could not manage without them. For example, they are involved in extracellular or intracellular digestion, as hydrochloric acid, bile, proteases or lysosomal enzymes; as receptor agonists and antagonists exemplified by acetylcholine, noradrenaline and adrenaline and as chemical mediators such as prostaglandins, steroids, releasing factors and hormones.

Natural processes are not necessarily safe either

Nature's processes are not necessarily entirely safe either. Genetic change, which is constantly occurring in nature and leads to the diversity of

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species, sub-species and varieties, is one example. Natural genetic modification occurs spontaneously, in response to natural selective forces and other forces, some of which are clearly attributable to the actions of man. Genetic changes are most visible in those species which have short generation intervals, such as bacteria. It is well known that such organisms can, and do, constantly adapt to the stresses imposed by their environment, as occurs, for example, in the phenomenon of antibiotic resistance.

The doomsday effects of engineered organisms, which have often been predicted, whether in laboratory, environmental or agricultural scenarios, have not as yet come to light. Laboratory genetic manipulation, the so-called genetic engineering of organisms, vegetables or food animals may be seen as merely a means of speeding up the natural process. Nature imposes her own limits to what can be achieved, even in the laboratory. Excessive genetic change leads to lack of fitness and extinction of the organism.

What must be done

The media and public concern

There is no doubt that, during the next decade, the safe exploitation of biotechnology will ensure the availability of a vast and diverse range of products suitable as end products for the user or as processing agents for manufacturers. Although we believe that fears of large-scale calamities arising through the commercialization of biotechnology are largely false, toxicologists and regulators must ensure that this is indeed the case.

Experts, training and public relations

One way to counter the undue media attention and thereby reduce public concern is to emphasise that well-designed systematic risk-assessment programmes run by well-trained and experienced scientists are in place to safeguard the public and the environment from undue hazard. Toxicologists and regulators are well used to, and indeed are motivated by, the pressures that arise out of public concern and from the sharp focus that can be induced by the more sensational of our media colleagues. Toxicologists and risk assessors, being conservative by nature, are unlikely to sanction premature release of risky products. Indeed there are times when they will be seen as an unnecessary overhead cost and even a hindrance to the project.

In reality, the availability of sound advice and knowledge of precedents will improve the rate of commercialization of a much-needed biotechnological project. Advice from toxicologically qualified advisors should be sought at least at two key points in the project, that is, at the initial specification stage and prior to the decision to scale up production and distribute the product.

Investment of the necessary expertise, whether scientific or public relations, should prove well worthwhile in the long run.

Concepts of risk, hazard and exposure

Advice from safety experts will include suggestions for training of supervisors and operatives, if necessary by secondment to establishments that are up and running. The public and media will have been informed of the aims and

objectives of the new project - their fears will have been allayed - and the scientists can get on with what they have been trained to do, i.e. identify the real risk, not the imagined hazard.

The ability to separate risk, a day-to-day problem, from hazard, the worst case scenario, is the hallmark of the safety-evaluation toxicologist. "Hazard" and "risk" are two of the most commonly used words in the toxicologist's vocabulary. In real life, calculation of the risk which may arise from a particular hazard is based on knowledge of a third factor: exposure.

To be at risk from a hazard there must have been some access or exposure to it. For example, flying at an altitude of 10,000 m and a speed of 800 km/hr sounds quite hazardous, yet we know from surveys that the risk run by an individual who undertakes such travel is low, a lot less than that of being a pedestrian in a busy city.

So undoubted hazards do not necessarily translate into real risks. Even so, the risks from flying are not so slight that they cannot be reduced still further!

Containment and testing

Establishment of safe working practices is the first priority. The people directly involved in research and production need to be sufficiently protected, and to ensure this, effective containment procedures must be designed and implemented.

To succeed in this, it must be remembered that extremely potent molecules may be encountered. It can turn out that major expenditure will be required for the development of appropriate and effective handling techniques and for sufficient training of operatives. Only if substantial resources are committed can the risks inherent in the research and development of very potent molecules be managed without tragedy or jeopardy to the future.

Aside from the establishment of safe working practices, the requirements to test, assess and regulate the safety of biotechnology processes and products do not differ from the requirements to determine the safety of other relevant new products.

At the start-up of a project which is intended to be commercialized, the toxicologist will advise which tests should be applied to the intended product and process, bearing in mind the safety of the product, the safety of the process, the control of any catalyst and process organism, the control of all products of the process organisms and the eventual disposal of all by-products and spent organisms.

At a later stage of the project and prior to the onset of marketing or distribution, the advice of the toxicologist should be sought regarding aspects of the safe release and use of the product. These considerations will vary according to the nature of the product, whether it be biomass, gene-modified vegetable, animal food, pharmaceutical, diagnostic aid etc.

Methods

The need to identify intrinsic hazard(s) attributable to a new substance is no different whether the substance is biogenetically formed or chemically prepared, i.e. the same standards of safety testing. For example, the determination of mutagenic potential, determination of product composition and identification of impurities, will apply.

Although theoretically and potentially a different spectrum of harmful effects can arise from biotechnologically derived products, the actual testing procedures which are applicable are no different than for a new chemical made by a non-biological synthesis.

Given that anything new is a little scary, after the first rush of concern it was realized that the needs of the biogenetically-based technology industry were not so very different from those of the more familiar chemical synthetic industry. The safety evaluation process in either case is usually sequential and consists of an early phase whose purpose is to delineate the worst-case scenario, or the intrinsic hazards of the material and later phases, the purpose of which is to address the extent of exposure to the material under various controlled circumstances. These contained and controlled trials allow accumulation of a database from which to extrapolate to the user situation.

Assuming that the extrapolated case is optimistic, and after peer review of the data, premarketing trials of new product under the less controllable user conditions can commence.

Delineation of hazards

Calculation of real as opposed to imagined risks is based on data from the toxicologist regarding the possible hazards and probable exposure using already existing tools. Whilst there is no need to envisage new methodologies, it is important to commit sufficiently experienced, enquiring and well resourced teams of scientists to the development programme.

The spectrum of types of hazard envisaged as possibly being attributable to the biotechnical approach will be biased by the fact that the product is frequently a protein or is glycosylated and will therefore be potentially antigenic; often the new entities are also very potent, are agonists and in their marketed form may require the addition of specialized vehicles.

The properties of the final marketed form, including vehicle, must be investigated. The types of problem most often encountered may be summarized into main categories as follows:

(a) Indirect toxicity that is immunologically mediated, leading to sensitization conditions. Usually these are seen in workers who are involved in the manufacturing process and are attributable to contact with antigenic or haptenic substances. Typical conditions include bronchial asthma, extrinsic allergic alveolitis, contact dermatitis and oculo-rhinitis;

(b) Direct toxic reactions. These are attributable to materials and vehicles which have intrinsic pharmacological activity. Detection of offending substances may be difficult if they have very high potency, since their

levels may be extremely low. Examples of directly toxic agents having high potency include certain antibiotics, mycotoxins, hormones and endotoxins.

(c) Afflictions and infections. Contamination can arise from inadequate control of, or unexpected, effluents from production processes. This may lead to impurities in the final product or to environmental contamination due to failure to contain solid or liquid by-products. Such problems may arise through utilization of contaminated seed-stocks, by inadequate control of organisms or their products, or due to inadequate disposal of mother liquors, solvents or inadequate decontamination of plant.

Types of risk

Risks may be regarded as being of two types, those important to individuals and those relating to communities.

Testing approaches can be regarded as being well-developed where they relate to individuals but are less effective and rather empirical when it comes to communities and larger scale problems. The most usual and accepted approaches employ laboratory animals and model systems as surrogates for man and are performed in approved testing establishments that have current certificates of compliance to so-called good laboratory practices.

Data generated by such laboratories are likely to be verified and should provide a reliable basis from which extrapolation can be made to the target species.

This approach is undoubtedly sound and has proved acceptable for the development of new pharmaceutical entities intended for use in man and for agrochemicals with strictly circumscribed applications. There are, however, shortfalls and limitations when it becomes necessary to attempt risk calculation in the wider environmental context. New laboratory tests, bio-markers of ecotoxicological change and post-marketing surveillance programmes will need to be devised.

The surrogate-based approach requires that for heterologous protein entities, having chosen a responsive species, close attention must be paid to (a) quantification of exposure to the test substance and (b) appearance of antibodies to that substance.

The appearance of antibodies to the test substance may signify the onset of a species-specific hypersensitivity. Since this may be a reaction peculiar to and limited to the chosen species, it may have no relevance to the target species and may well confound results from the study in the surrogate.

Regulations, guidelines and guidance

Although we already have sufficient experience to know that the hazards arising out of the biotechnological synthesis area are by no means unmanageable using existing safety evaluation techniques, it is true to say that biotechnology has forced toxicologists and regulators to stop and think.

As little as six months ago, the safety assessment process for biotechnological products was regarded as rather variable, quite exceptional and unique in that it was virtually unregulated: the experts, almost to a man, deemed it

a special case. Fortunately this view has not only persisted, it has also ramified. Today it is recommended that a case-by-case approach to be adopted whose object must be to identify direct and indirect toxicity attributable to the synthesized entity and delineate hazard arising out of the manufacturing process.

Recently, the weight of opinion has seemed to shift so that the case-by-case approach has become regarded as preferable for all substances, regardless of synthetic origin. This makes very good sense and could constitute a remarkable breakthrough. However, it remains to be seen whether the idea will survive the process of international harmonisation, which is also gathering pace at present.

An absence of definitive regulatory requirements is not necessarily helpful to the inexperienced developer. At the moment there are few, if any, regulations that govern the development of biotechnology entities, and this situation seems likely to continue. To help in the absence of regulation, guidelines and guidance from experts should be sought. International efforts should be devoted to summarizing and promulgating current principles on which successful biotechnological developments are being based.

The absence of regulations or licensing arrangements should not be allowed to reduce the impetus behind the development of generic forms of needed materials. Every encouragement must be given to commercialization of biotechnological projects, provided that the appropriate quality and socio-economic criteria are met.

Thus, it may be envisaged that the so-called "fourth hurdle", which has caused such consternation in the West recently, could become a springboard which works to the advantage of the less developed countries. Presumably a patent-holder should not be allowed to restrict development of a useful product if sufficient need can be demonstrated for it. The opportunities offered by biotechnological processes to the less developed countries must not be limited by patent laws, over-regulation or inexperience.

Lack of experience can now be overcome by proper deployment of consultants from the fields of toxicology, ecotoxicology, safety assessment and regulatory toxicology to projects as and when their advice is needed.

XXVII. CONSTRAINTS FOR THE COMMERCIALIZATION OF BIOTECHNOLOGIES: PROCESS ENGINEERING AND ECOLOGICAL SUSTAINABILITY

Anton Moser*

Summary

Two constraints have been proposed for the commercialization of biotechnologies. One which is quite often neglected is the discipline of process engineering, also called bioprocess technology. This includes the scientific areas of upstream and downstream processing as well as bioreactor performance and measurement and control techniques. Process engineering is responsible for the optimal transfer (scale-up) of bioprocesses from the laboratory to the technical/industrial scale. The general methodology of process engineering is summarized. It is of general validity in all fields of application of biotechnologies involving health care, food and agriculture, industry and environment.

Another constraint is seen in the pre-commercialization stage where a new science and technology policy is under development. In contrast to the existing concept of environmental management, which is an end-of-pipe approach, a completely new concept is presented here, called "ecologically sustainable technology". This innovative approach follows the philosophy of pollution prevention and is able to work as the new science and technology paradigm in the vision of ecologically sustainable global economy system. All technical activities of men will obey a number of given bioprinciples, which can be extracted from ecosystems. A new generation of environmentally clean production processes will be developed, replacing long-term existing processes/products which are producing pollution on earth.

Introduction

Commercialization of bioprocesses includes a series of areas and problems such as human resources, public acceptance, industrial policy, regulations and property rights and, finally, infrastructure. From a process engineering standpoint, knowledge has generally to be transferred from the laboratory to the industrial scale before commercialization can be envisaged.

Thereby, two main questions are to be identified:

(a) How should a bioprocess be transferred (know-how)?

(b) What types of bioprocesses are to be transferred (know-what)?

In this paper both questions are considered to represent a bottleneck in commercialization.

Know-how: process engineering methodology

The scale-up of bioprocessing needs not only an appropriate infrastructure, i.e. laboratory and pilot-scale equipment, but adequate knowledge on process engineering methodology at the same time.

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Bioprocess engineering is understood as being the engineering discipline within the multi- and interdisciplinary field of biotechnologies. It includes four main scientific areas:

(a) Upstream processing (media preparation etc.);

(b) Bioreactor performance (bioconversion);

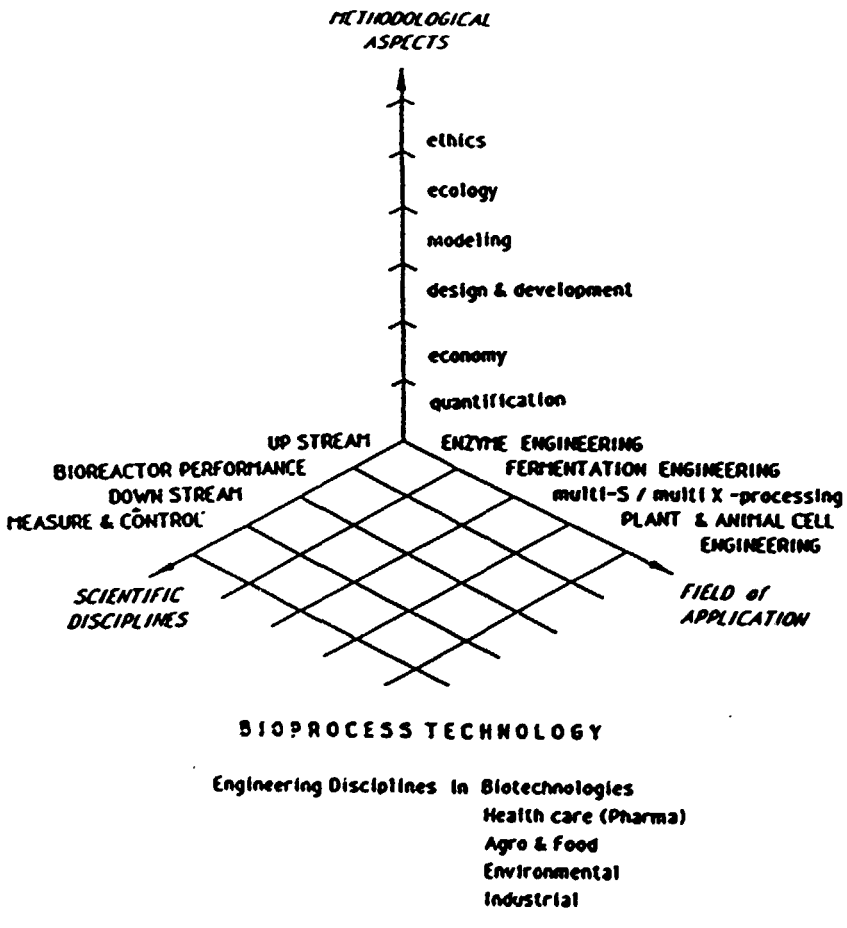
(c) Measurement and control techniques;

(d) Downstream processing (product recovery).

All of them should be integrated for optimal realization in practice.

At this point it should be added that R&D cannot be successful at only the laboratory scale. The significant interactions taking place in bio-processing must be identified at the pilot scale; therefore work at this stage is essential with bioreactors, as well as with downstream processing. R&D work often suffers from this kind of deficiency. It is sometimes thought that process engineering can be neglected as the scale often remains small as in the case of some pharmaceuticals. Nevertheless, the importance is in the holistic approach, which is needed as a mode of thinking not only in the longer scale bioprocesses. Figure 1 shows a three-dimensional pattern defining the discipline of bioprocess engineering, its applicability and the intrinsic aspects of the methodological level on the third axis (see section on know-what).

Figure 1. Bioprocess engineering (technology): its definition, applicability and methodology



Methodology in bioprocess engineering can be basically regarded as being analogous to chemical process engineering. However, due to the higher sensitivity of living systems in relation to environmental changes, an adequate methodology has to based on the interactions between the physiology (metabolism) of the biological system and the physical transport phenomena (mass-, heat-impulse-transfer) of the bioreactor system, including the physical/chemical properties of the media in the reactor volume. Details are to be taken from the literature. Application of this systematic methodology includes the use of regime analysis for the detection of process bottlenecks at the industrial scale and its experimental simulation in the laboratory, and the use of mathematical modeling as a general tool for optimization and extrapolation. Finally it should be added that two main strategies exist when developing a bioprocess to industrial maturity.

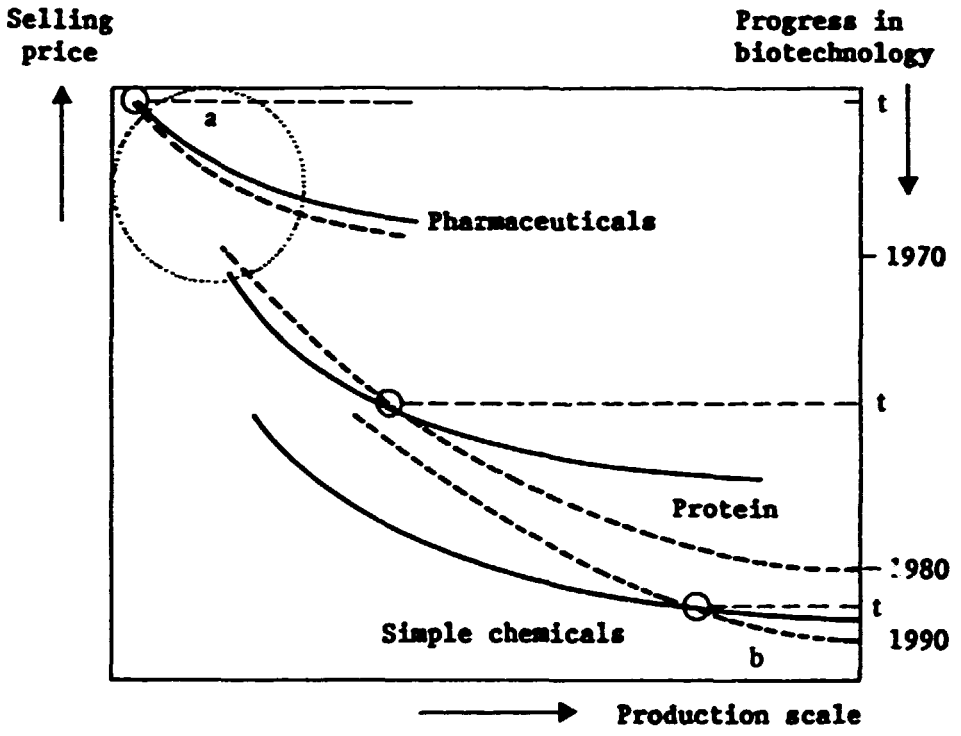
(a) The pragmatic, purely empirical approach, which in practice still dominates at present, as in the past. This approach is based on trial and error and with experience gained from single cases;

(b) The systematic/empiric approach, which in future will play an increasing role in order to save time and money. This approach, which was recently developed to quite an advanced state by leading researchers, is based on the aforementioned interactions and deals with mathematical models that allow for generalizations and extrapolations.

Generally, a holistic approach is the only suitable one: a living organism should be regarded as an integral entirety, i.e. a dynamic network of coordinated activities, with the cells non-linearly interacting with the environment within and outside the reactor, and not as a sum made up of separate parts consisting of genes, chromosomes, metabolism, cell tissues and populations, physical transports in the reactor and the environment.

In summary, it becomes clear that process engineering will be a linchpin in the commercialization of biotechnologies in general. In the case of commercializing a typical pharmaceutical product, the entire costs for R&D consist of three parts, where the costs for process engineering is about 25 per cent of the total, while genetic work is a minor part (1 per cent) and the largest part goes for product formulation (75 per cent). The significance of bioprocess engineering can finally be illustrated with the aid of figure 2, which shows the selling price of bioproducts in relation to the production scale as a measure of applied process engineering methodology. From this graph the competitiveness of bio-versus chemo-processing can also be concluded.

Figure 2. Predicted development of biotechnical processes (——) compared with development of chemical processes (___) for three classes of products (pharmaceuticals, single-cell protein, simple chemicals) as examples of products with different molecular complexity. The date (t) shows when it is predicted that the bioprocess will be more economical than the chemical process. Region (a): small-scale, high-price processes. Region (b): large-scale, low-price processes. (After Hines. 1980. With permission of Butterworth Scientific Ltd.)



Know-what: ecologically sustainable technology concept

Commercialization of biotechnologies is at present concentrated in the industrial fields of human and animal health care (pharmaceuticals), food and agriculture, where the contribution by recombinant DNA products is seen as the strongest input. Biotechnology is also playing an increasing role in the environment. In reality this situation can be generally characterized by the fact that industrial development clearly has to follow the existing laws of economics, leading to the fact that profit is the driving force.

However, some drastic and global challenges/crises exist:

(a) Environmental global pollution (air, water, soil, living bodies);

(b) The socio-cultural conflicts (first versus third world, South versus North, East versus West, especially in Europe);

(c) The economic crisis.

Particularly for the countries in the developing world these facts create a series of problems and heavy economic burden as well as economic dependency. The payback of these debts can only be managed when raw materials are exported relatively cheaply, hindering the development and restoration of indigenous, well tried technologies. These trends lead to undesirable developments such as carrying out R&D mainly for export products and crops rather than for local needs; the promotion of intensive farming similar to that carried out in the developed world, leading to the destruction of the environment (green revolution/Food and Agriculture Organization of the United Nations (FAO) programme) without regard to local needs and methods, which are socially and ecologically accepted.

The background for all these problems can be seen in the dominating materialistic/mechanistic/reductionistic point of view, where people treat nature as an infinite resource. Frontiers in science are projecting that our society is at a turning point, where we switch from the old point of view to a new paradigm called "an ecologically sustainable global economy system", realizing that all natural phenomena are fundamentally interdependent and all societies and individuals with their attendant activities are embedded in the cyclic processes of nature. Thus, from this ecological standpoint, progress must be regarded as anti-evolutionary, with our civilization and the technosphere in dangerous opposition to the biosphere.

This change of pattern in society as well as science and technology can be briefly characterized by the following four points derived from the structure/function relationship, which is of central importance and which also obeys the bioprinciples.

(a) From structure to function. Function is fundamental while structure is only a manifestation of the function, which possesses the intrinsic capability of self-organization leading to creativity with order, harmony and symmetry as the final aim;

(b) From the parts to the whole. Structure is not an inert clockwork but a dynamic network of coordinated activities;

(c) From an objective to an epistemic view. Everything interacts, nothing is independent. Thus the observer is also part of the system;

(d) From certainty to approximations. Due to dynamic network interactions, a mechanism can never be proven to be accurate. Only under given preconditions can a model be set up using formal analogies as an approximation, mainly based on a macroscopic pattern. It is expected that a new macroscopic simplicity will be discovered, e.g. the formal macro-approach.

A number of essential actions have recently been taken, indicating that frontier people in all fields are increasing their ecological awareness (figure 3). For example:

(a) The United Nations will elaborate a new criterion called "ecologic national product" and edit a book (C. Stahmer, 1992) entitled Integration of Environmental and Economic Accounting, which will then replace the "blue book" (1968) containing the old criterion of gross national product, which is far from being able to measure the usefulness of mainly short-term activities;

(b) The OECD has stated the need for environmental as well as socially and politically acceptable technology;

(c) The European Commission coined tne term "bio-society", expressing the need for a large-scale agro-based industry;

(d) The European Federation of Biotechnology (EFB) added a preamble to its definition of biotechnology, stating that biotechnology "is directed towards the benefit of humankind by obeying biological principles";

(e) The EFB also installed a European task force called Ecologic Bioprocessing, which will develop the concept of ecologically sustainable technology to a fully matured concept for industrial application;

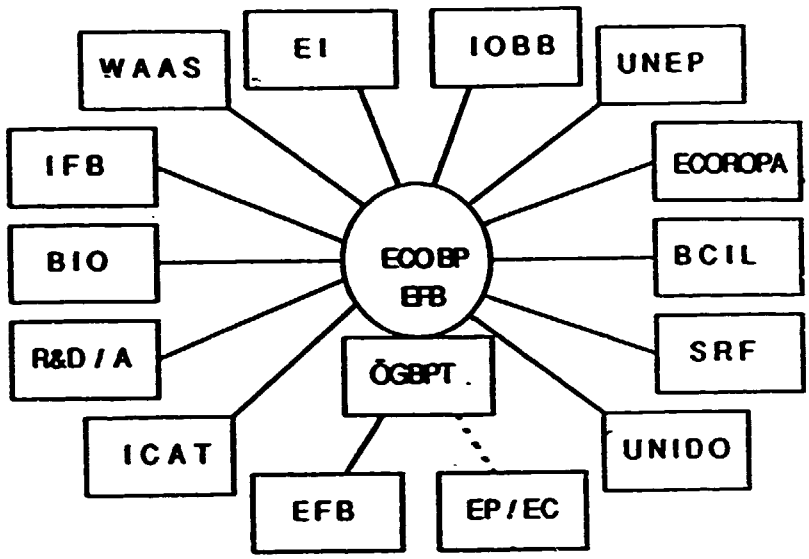
(f) The United Nations Environment Programme (UNEP) Working Group on Biotechnology for Cleaner Production.

However, ecology may be regarded as being based on either the old or new model on different levels, "shallow" or "deep". "Shallow" ecology supposes a better technology and a better social management, having a prime expectation in science and planning. This is the function of environmental management and of quick fixes in technological and political actions, where everything can be "made" (manipulated), because capacities and resources are commonly regarded as being infinite. This approach comes fairly close to the technocratic approach of the Marxist system. Environmental biotechnology belongs to this "shallow" type. The technical question is how to reduce, re-use or recycle existing products and polluting substances. This is a short-term activity, even though presently needed, it represents a defensive and expensive approach with a low capacity for problem solution according to the holistic view, as it is mainly the result of end-of-the-pipe technologies.

Clearly a long-term strategy is needed to supplement the existing approach described earlier. As a more profound search for technical solutions at the end of the pipe has to be made, people have to change their behaviour, values and tools drastically and thoroughly. Wisdom leads to skillfulness and know-what to know-how. A transformation of society as we know it is needed to (ultimately) lead to a homogeneity of all our activities. "Bio-centric equality" for all beings in nature has to replace anthropocentrism: mankind and nature at every level are equal; nature is an asset that needs re-investment, i.e. protection and defense. It should be added that equality does not mean complete homogeneity and ecological justice. Ecologic balance requires a thorough understanding of the intrinsic hierarchy and diversity of the biospheric network with its ability for self-organization.

Manipulations, for example in the field of genetic modification, are not completely excluded. But it has to be said that the sustainable promise of genetic engineering, i.e., increased productivity, herbicide-tolerant crops, pest resistance and low risks for genetically modified organisms (GMOs), seems to flow as a purely technocratic approach. The full range of ecological impacts of GMOs is unknown at present; additional and more thorough ecological research is needed. The problems of conventional agriculture will be further exacerbated, ecological methods of farming will be undermined and the release of GMOs without caution will erode genetic diversity and distort the natural ecological processes in the biosphere.

Figure 3. International network of EFB task group on ecologic bioprocessing



EFB European Federation of Biotechnology

ÖGBPT Austrian Association of Bioprocess Technology (secretariat), Graz, Austria (A. Moser and M. Narodoslawsky)

EC/EP European Commission/European Parliament, Brussels/Strasbourg

UNIDO Vienna (Venkataraman, Subrahmanyam)

UNEP Group on Biotechnology for Cleaner Production (Luyben, Kothuis)

IFB International Forum on Biophilosophy, Louvain, Belgium (K. Simpson)

BIO Biopolitics International Organisation, Athens, Greece (A. Vlavianos-Arvan)

EI Elmwood Institute, Berkeley, California (F. Capra)

IOBB International Organization Biotechnology & Bioengineering, Guatemala (C. Rolz)

R&D/A Research project in Austria "sustainable economy" (F. Moser)

WAAS World Academy Art & Sciences, Stockholm (C-G. Heden)

BCIL Biotech Consortium India Ltd., New Delhi (S. Chandrasekar)

SRF Swaminathan Research Foundation, Madras (Swaminathan)

IACT International Association for Clean Technology, Vienna

ECOROPA European Group for Ecological Action (F. Meissner-Blau)

ECO BP EFB Task Group on Ecologic Bioprocessing (A. Moser)

Ecologic process engineering: the new technology parallel to effect ecological sustainability

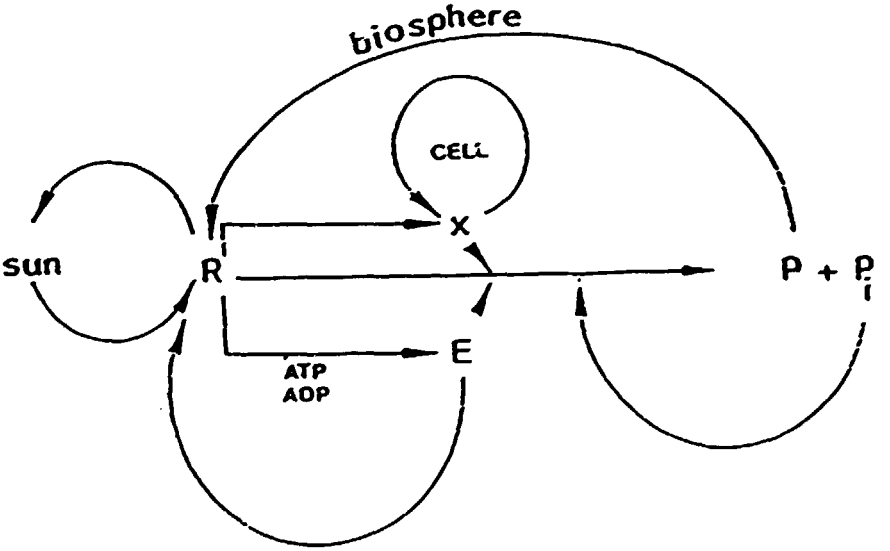
Sustainability is understood as being the capacity to satisfy the current natural needs of mankind, without jeopardizing the prospects of future generations. Herein, the finiteness of nature and its resources are considered together with the equality of human rights and obligations of all human beings. The technosphere must be integrated into the biosphere: this is the future challenge for process engineering. This is the deep and holistic approach leading to the new model for science and technology, also called "hyper-tech" instead of "high-tech", as it represents a new dimension of mankind's technological activities.

Biological principles are manifested in the set-up of such clean and appropriate technologies and show their ability to serve as a general guideline for all cases of restructuring. The essence thereby is pollution prevention. Environmental costs are not regarded as being external, the principle of causer/consumer pays will be followed, with the result that the quality of life can be installed at an appropriate level, effecting a supply of natural goods together with a clean environment at the same time. This long-term strategy requires the development of new technologies, where environmental protection is directly integrated into the production process.

Unclean, unsustainable chemo-technologies should be replaced as soon as possible, especially in the area of large-scale industrial products. This is an essential point for the future competitive advantage of biotechnologies over chemical processes (figure 2). Renewable raw materials will form the basis of bulk production, which will lead to biodegradable products being manufactured with the aid of biocompatible biocatalysts/bioprocessing, as shown in figure 4. Thereby, an adequate process engineering methodology is of utmost importance, as the price still depends on the scale of operation.

The needed restructuring will come about with an increased awareness and an installed ecologically oriented tax system, where levies are no longer raised on work and profit, but on raw materials and energy.

Figure 4. Graphical representation of bioprocessing following the concept of closed cycle production using raw materials (R) renewed by the sun, biocompatible catalysts (X), energy partly resulting from substrate degradation in the form of adenosene triphosphate and products (P), which are biodegradable in the natural circles of biosphere



Restructuring: the bio-principles

As already mentioned, a series of bio-principles will be very helpful in this restructuring. They can be relatively easily extracted from ecosystems in the biosphere following the approach of learning by listening to nature. However, they should not emulate nature, but serve as guidelines without contesting to evolution nor prescribing technologies. The basis is given by describing the function and structure of a system, i.e. function, with the intrinsic property of self-organization and structure, as a dynamic network of small, open and asymmetric sub-units interacting in a closed cycle with feedback control.

Bio-principle 1: Use the potential of biosphere in biocentric equality

Take advantage of the rich genetic information of existing plants, animals and cells; physiological work goes for genetic modifications; ecological research needed for the full understanding of technospheric effects on the biosphere; integrate technologies into the biospheric cycles with its environmental assimilation capacity; integrate human resources.

Bio-principle 2: Protect existing high biodiversity according to evolution

Take advantage of the assets, especially of plants for bio-drugs etc.; establish ecologically sustainable technology and replace unclean technologies; technologies thus have to be prophylactic and friendly; follow ecological path by using the intelligence of living systems with their abilities compared to chemical processes and the general learning capability.

Bio-principle 3: "Think and act in the long-term"

Benefit is long-term profit; ecology is long-term economy; replace gross national product by "Eco national product" as the new criterion for accounting; quantify living quality; enhance restructuring by installing new tax systems (e.g. on raw materials); include ecological research in product and process development and also in the case of genetic modifications of organisms.

Bio-principle 4: Close material cycles in shortest way possible

Use mainly solar energy in all future variants; use renewable raw materials (biomass from agriculture and forestry) for industrial scale productions to replace fossil non-renewable materials; use renewable (bio)catalysts in place of toxic heavy metals; produce (bio)degradable products; recycle undegradable materials such as minerals; close the cycle early.

Bio-principle 5: Think globally, but act locally by maintaining and/or creating high diversification in the technosphere

Adapt activities to local/social boundaries (local niches); "small is beautiful"; develop decentralized knowledge; satisfy local needs first before entering the world market; realize "technology mix" (e.g. solar energy) resulting in higher local stability, i.e. independence from import and export and therefore global stability, as in ecosystems.

Bio-principle 6: Minimize (save) mass and energy instability by optimizing efficiency

Apply known methodology, e.g. in process engineering for its sake; do what is needed and not all that is possible; look for sense and holism; intensify processes for better competitiveness, e.g. bioprocesses versus chemical processes; research in process integration at all levels inclusive the environment. Work with formal analogies.

Disadvantages of biotechnologies are given by their biological nature: at present low efficiency and economics based on profit; low concentrations; high water content; strain instability and metabolic flexibility; greater need for education and equipment due to higher complexity; weak public acceptance especially by its fear of genetic manipulations; biotechnologies are not clean a priori (water and air pollution, GMO).

How realistic is the vision and how far are we?

The concept of an ecologically sustainable economy is quite well developed in its fundamentals, but still suffers from a lack of realization. However, it should be borne in mind that the old paradigm, which in its economic consequences stems from Adam Smith creating the capitalistic system around 1750. The fact that a vision is realizable is no argument for or against it. According to Einstein, it should however be clear, "that nothing is more realistic than a good vision".

The management of the transition to an ecologically sustainable world - the trajectory - can be based on several factors:

(a) Increasing public awareness of ecology (green movement);

(b) Pressure from the existing trinity of crises;

(c) Engaged frontiers and personalities;

(d) Potential economic advantages given by ecologically sustainable technologies. For a better understanding of this, a list of environmentally clean technologies according to the concept of ecologic bio-processing is to be found in the annex.

Annex

ECOLOGICAL BIOPROCESSES

A series of bioprocesses can be mentioned here, falling in five categories according to figure 3 depending on the type of replacement: raw materials (1), catalyst (2), products (3), by-products (4), energy (5):

Biopolymers, e.g. polyhydroxybuturic acid

Biocontrol agents (pesticides), e.g. biotoxins from Bacillus thuringiesis

Biofertilizers, e.g. algae, rhyzobium, azotobacter for N_2-fixation

Bioleaching of ores, e.g. Cu, U, Au, ..

Biosorption of heavy metals from waste waters, e.g. Ag, Zn, Sn, Cr.

Enzymetechnology as a whole is a clean technology, e.g. paper industry, starch as raw material for bulk products

Biodegradation/depolymerization of wastes and cellulosic materials, with enzymes (trichoderma, cellulose, lignin and hemicelluiose as raw materials, with bacteria (e.g. aerobic thermophilic sludge)

Biodesulfurization, e.g. coal

Biodenitrification, e.g. of drinking and ground water

Biodepestification, e.g. ground and/or drinking water

Biofuel (biogas), e.g. esters from plant oil ("bio-energy")

Biodegreasing with biosurfactants, e.g. in electroplating and metal-working industry, cleansing agents

Biodehairing, e.g. leather industry

Biodefatting, e.g. recycling of Cr

Bioremediation, in general for the detoxification of water and soil

Biodrugs, e.g. from the high diversity of exotic plants

Biocosmetics, in general as high quality products

Bioflavours/bio-odors in general

Bioenrichment of soil by minerals in order to increase food quality

Eco-sustainable farming and pest control according to locally adapted old technologies in developing countries

Biomaterials, e.g. for housing in third world

Biomembranes

Biosensors

Bionics

Ecological bioreactor operation based on multiple criteria

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XXVIII. THE ICGEB-UNIDO PARTICIPATION IN BIOTECHNOLOGY TRAINING

Oscar Burrone*

Biotechnology is multidisciplinary. It is the result of the development of many areas that can be grouped into the so-called biosciences. Although all of these areas have in practice contributed to modern biotechnology, molecular biology is the area which has had a major impact on its development.

This fact stresses the importance of centering a biotechnology training programme not only on teaching but also on implementing research projects based on high standard molecular biology.

Although biotechnology has a certain degree of complexity, it represents a technology that is feasible for implementation by developing countries. It requires modest installations and equipment facilities compared to other modern sophisticated technologies.

But above all, biotechnology is time-consuming and brain-intensive. Its development depends on the availability of human resources and on their appropriate training. Many developing countries have a varied number of technicians and professionals in various biology-related areas, who could participate in the development of biotechnology. They need to have the opportunity to follow the continuous changes observed in a fast-growing field.

It is essential that those countries interested in having good biotechnology take the decision to implement a reasonable and sustained financing in order to run research programmes and to retain the best scientists. It takes many years to train scientists but only a few days to discourage them and oblige them to move. All these decisions can only be the consequence of considering science and technology as the key elements for progress.

Different approaches can be followed to run a biotechnology programme. These can range from support-only total basic research to support-only applied research. However, product-oriented research would probably be more suitable if it takes place within an institution which is also running basic science. It is hard to contemplate successful development of biotechnology in its different areas without the support of basic research. Sooner or later it will become essential, not only to produce new products and ideas, but also to train people to have scientific approaches in solving practical problems and to have the capacity to adapt and merge new techniques. Those countries with well-established universities and strong research projects are those likely to profit from biotechnology.

The International Centre for Genetic Engineering and Biotechnology (ICGEB) is an institution aimed at providing a centre of international interaction for all its member countries through its affiliated centres. ICGEB, with its two components, at New Delhi and Trieste, is based on strong research programmes in different fields of basic and applied biotechnology, from plants to human genetics, virology, molecular biology, protein structures, immunology, microbiology etc. In its laboratories, many young scientists from several

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different countries find the opportunity to be trained whilst participating in various research projects. In this way, they are able to acquire a broad general knowledge as well as a specialization in specific matters.

Two other main activities of the ICGEB are directly related to training in biotechnology. One concerns the ICGEB short-term training programme involving the organization, sponsoring and financing of courses (both theoretical and practical), colloquia, symposia, workshops etc. (tables 1-3 and figures 1-3). These are held either at Trieste or New Delhi and also in the various laboratories of the member countries. In general, financing accommodates the participation of prestigious scientists from all over the world who hold intensive and high level practical courses attended by young scientists.

Table 1. ICGEB Short-Term Training Programme: theoretical and practical courses

Type of programme	Title	Location	Dates
1988			
Practical Course	Eukaryotic Expression Vectors	La Plata, Argentina	10/07/88-30/07/88
Practical Course	Genetic Engineering	Enugu, Nigeria	01/09/88-10/09/88
1989			
Theoretical Course	Molecular Genetics of Yeast	Trieste, Italy	29/03/89-31/03/89
Practical Course	Genetic Manipulation of Streptomyces	Wuhan, China	09/04/89-24/04/89
Practical Course	Computer Applications in Molecular Biology	Trieste, Italy	03/07/89-13/07/89
Practical Course	Methods in Eukaryotic Gene Expression	Szeged, Hungary	01/10/89-14/10/89
Theoretical Course	Genetic Pathologies and the Human Genome	Trieste, Italy	06/10/89-10/10/89
Practical Course	Molecular Virology	New Delhi, India	01/11/89-10/12/89
Practical Course	Molecular Biology of Chloroplasts	New Delhi, India	03/07/89-10/08/89
1990			
Theoretical Course	Bacterial Genetics	Trieste, Italy	23/03/90-29/03/90
Theoretical Course	Modern Techniques in Nucleic Acid and Protein Synthesis and Analysis	New Delhi, India	26/03/90-14/04/90
Theoretical Course	Molecular Genetics of Yeast	Trieste, Italy	09/04/90-13/04/90
Practical Course	Techniques in Human Genome Research	Santiago, Chile	18/06/90-06/07/90
Colloquium	Lignin Biodegradation and Practical Utilization	Trieste, Italy	27/06/90-30/06/90
Practical Course	Computer Applications in Molecular Biology	Trieste, Italy	16/07/90-27/07/90
Theoretical Course	Molecular Virology	Trieste, Italy	04/11/90-09/11/90

continued

Table 1 (continued)

Type of programme	Title	Location	Dates
Practical Course	Molecular Basis of Protozoan Parasitism	New Delhi, India	05/11/90-30/11/90
Theoretical and Practical Course	New Tools for the Study and Diagnosis of Parasitic Diseases	Caracas, Venezuela	26/11/90-14/12/90

Table 2. ICGEB Short-Term Training Programme: major conferences and research colloquia

Type of programme	Title	Location	Dates
1989			
Colloquium	European Affiliated Centres	Trieste, Italy	09/04/89-12/04/89
1990			
Symposium	Molecular and Genetic Approaches to Plant Stress	New Delhi, India	14/02/90-17/02/90
Colloquium	Eukaryotic Gene Regulation and Expression	Heraklion, Greece	22/05/90-24/05/90
International Symposium	Molecular Genetics and the Human Genome Programme: Perspectives for Latin America	Santiago, Chile	28/06/90-29/06/90
Colloquium	Lignin Biodegradation and Practical Utilization	Trieste, Italy	27/06/90-30/06/90
Colloquium	Diagnostic Approaches to Schistosomiasis	Beijing, China	15/11/90-18/11/90

Up to the present, the ICGEB courses have had the participation of a total number of 250 trainees from 30 different developing countries. Although most courses have taken place in Trieste and New Delhi there have been events in other countries such as Argentina, Chile, China, Cuba, Greece, Hungary, Mexico, Tunisia and Venezuela.

The second main activity is the ICGEB fellowship programme, which grants fellowships to applicants from member countries at the post-doctoral level. These are intended to be a means of allowing scientists to directly participate in the development of the various projects of the two ICGEB components as well as in selected Italian laboratories with programmes related to those of the Centre. This programme grants fellowships for a period of one year, which can be extended to two years. In 1989, 22 fellowships were granted and 26 in 1990, from a total of 21 different countries (figure 4). In 1991, there were 25 grants to the individuals listed in table 4.

In addition, a pre-doctoral training programme is currently being organized. This will include agreements with university institutions of international character in Trieste and New Delhi in order to offer a three to five-year Ph.D. programme to member-country candidates having at least a B.Sc. degree. The students will be working in the various scientific programmes of the ICGEB.

Table 3. ICGEB Short-Term Training Programme, 1988-1991

Year and Type of Programme	Title	Location	Dates	Total No. Working Days	No. ICGEB Member Countries	Total No. Students	Total Cost (US$)
1988							
Workshop	Biotechnology for Latin America and Caribbean Countries (UNIDO with ICGEB participation)	Havana, Cuba	08/02/88-12/02/88				
Workshop/ Symposium	From Protein Structure to Protein Engineering	Trieste, Italy	21/03/88-25/03/88				
Forum	Forum of Scientists	Trieste, Italy	27/03/88-30/03/88				
Workshop	Lignin Biodegradation	Urbana, USA	18/04/88-19/04/88				
Practical Course	Eukaryotic Expression Vectors	La Plata, Argentina	10/07/88-30/07/88	18	6	14	20,000
Practical Course	Genetic Engineering	Enugu, Nigeria	01/09/88-10/09/88	10	3	49	29,000
1989							
Mini Colloquium	Progress in Molecular Biology (Part of 8th Panel of Scientific Advisors)	New Delhi, India	02/03/89	1	.	.	
Theoretical Course	Molecular Genetics of Yeast	Trieste, Italy	29/03/89-31/03/89	3	4	18	6,975
Colloquium	European Affiliated Centres	Trieste, Italy	09/04/89-12/04/89	3	.	.	24,926
Practical Course	Genetic Manipulation of Streptomyces	Wuhan, China	09/04/89-24/04/89	11.5	4	18	25,000
Practical Course	Computer Applications in Molecular Biology	Trieste, Italy	03/07/89-13/07/89	9	11	28	18,064
Practical Course	Methods in Eukaryotic Gene Expression	Szeged, Hungary	01/10/89-14/10/89	11	8	16	25,000
Theoretical Course	Genetic Pathologies and the Human Genome	Trieste, Italy	08/10/89-10/10/89	5	9	24	9,160
Practical Course	Molecular Virology	New Delhi, India	01/11/89-10/12/89	25	8	14	24,433
Practical Course	Molecular Biology of Chloroplasts	New Delhi, India	03/07/89-10/08/89	28	6	15	19,294
1990							
Symposium	Molecular and Genetic Approaches to Plant Stress	New Delhi, India	14/02/90-17/02/90	3.5	.	.	
Theoretical Course	Bacterial Genetics	Trieste, Italy	23/03/90-29/03/90	6.5	14	34	17,503

(continued)

Table 3 (continued)

Year and Type of Programme	Title	Location	Dates	Total No. Working Days	No. ICGEB Member Countries	Total No. Students	Total Cost (US$)
Theoretical Course	Modern Techniques in Nucleic Acid and Protein Synthesis and Analysis	New Delhi, India	26/03/90-14/04/90	15	7	11	9,814
Theoretical Course	Molecular Genetics of Yeast	Trieste, Italy	09/04/90-13/04/90	4	9	24	9,066
Colloquium	Eukaryotic Gene Regulation and Expression	Heraklion, Greece	22/05/90-24/05/90	2	-	-	25,000
Practical Course	Techniques in Human Genome Research	Santiago, Chile	18/06/90-06/07/90	15	8	19	26,000
International Symposium	Molecular Genetics and the Human Genome Programme: Perspectives for Latin America	Santiago, Chile	28/06/90-29/06/90	2	-	-	
Colloquium	Lignin Biodegradation and Practical Utilization	Trieste, Italy	27/06/90-30/06/90	3.5	-	-	9,461
Practical Course	Computer Applications in Molecular Biology	Trieste, Italy	16/07/90-27/07/90	10	14	29	23,220
Theoretical Course	Molecular Virology	Trieste, Italy	04/11/90-09/11/90	5	7	24	18,670
Practical Course	Molecular Basis of Protozoan Parasitism	New Delhi, India	05/11/90-30/11/90	20	5	11	21,597
Colloquium	Diagnostic Approaches to Schistosomiasis	Beijing, China	15/11/90-16/11/90	3	-	-	25,000
Theoretical and Practical Course	New Tools for the Study and Diagnosis of Parasitic Diseases	Caracas, Venezuela	26/11/90-14/12/90	15	8	16	25,000
1991							
Practical Course	Molecular Biology and Diagnosis of Human Papilloma Virus	Havana, Cuba	01/02/91-23/02/91	15	3	12	25,000
Practical Course	RFLP's in Plant Breeding (co-sponsored by the Rockefeller Foundation)	New Delhi, India	04/02/91-22/02/91	15	9	15	
Practical Course	Protein and Peptide Purification, Microsequencing, Biotechnological Applications	Buenos Aires, Argentina	11/03/91-27/03/91	13	7	15	25,000
Theoretical Course	Bacterial Genetics	Trieste, Italy	18/03/91-22/03/91	4.5	9	35	17,347
Theoretical Course	Human Genetics	Trieste, Italy	21/04/91-27/04/91	7	12	26	15,331
Theoretical Course	Yeast Molecular Genetics	Trieste, Italy	08/05/91-11/05/91	4.5	10	18	18,970
Practical Course	Yeast Molecular Genetics	Trieste, Italy	13/05/91-24/05/91	10	10	18	(included in above total)
International Symposium	Pseudomonas Biology and Biotechnology	Trieste, Italy	16/06/91-20/06/91	4.5	7	11	21,161
Theoretical Course	Genetically Manipulated Organisms: Safety in the Laboratory and the Environment (co-sponsored by UNEP)	Trieste, Italy	01/07/91-03/07/91	2.5	7	11	4,483

(continued)

Table 3 (continued)

Year and Type of Programme	Title	Location	Dates	Total No. Working Days	No. ICGEB Member Countries	Total No. Students	Total Cost (US$)
Conference	Genetically Manipulated Organisms for the 1990's	Trieste, Italy	03/07/91-05/07/91	2.5	11	16	(included in above total)
Practical Course	Plant Transformation	New Delhi, India	15/07/91-05/08/91	15.5	10	13	
Practical Course	Computer Applications in Molecular Biology	Trieste, Italy	22/07/91-02/08/91	10	14	28	21,526
Practical Course	Genetic Pathologies and the Human Genome	Trieste, Italy	22/09/91-27/09/91	5.5	11	16	13,518
Practical Course	Nucleic Acid Synthesis and Gene Assembly	New Delhi, India	04/11/91-22/11/91	15			
Theoretical Course	Marine Microbiology and Biochemistry (joint with UNEP)	Trieste, Italy	16/12/91-20/12/91	5			
1992							*Estimate Only*
Practical Course	Gene Isolation and Analysis for Crop Improvement (co-sponsored by the Rockefeller Foundation)	New Delhi, India	03/02/92-21/02/92	15			*29,480 Loc: 25,800*
Practical Course	Environmental Biotechnology	Morelos, Mexico	17/02/92-28/02/92	10			*25,000*
Practical Course	Methods in Disease Diagnosis (co-sponsored by the World Health Organization)	New Delhi, India	02/03/92-20/03/92				*37,700 Loc: 11,700*
Practical Course	Bacterial Genetics	Trieste, Italy	16/03/92-03/04/92	15			*20,000* Loc: 30,000
Theoretical Course	RNA Structure and Function	Trieste, Italy	08/12/92-10/04/92	3			*18,000 Loc: 15,000*
Theoretical Course	Yeast Molecular Genetics	Trieste, Italy	12/04/92-15/04/92	4			*18,000* Loc:15,000
Theoretical Course	Sound Environmental Applications of Genetically Modified Organisms	Trieste, Italy	?	?			*20,000 Loc:?*
Practical Course	Computers	Trieste, Italy	?	?			*25,000* Loc: 22,000
Workshop	Protein Structure: Theory and Principles of Computation Approaches	Trieste, Italy	02/09/92-06/09/92	5			*20,000 Loc: 25:000*
Theoretical and Practical Course	Enzyme Engineering	Sfax, Tunisia	16/09/92-26/09/92	9			*25,000*
Practical Course	Recombinant DNA Immunology	Trieste, Italy	21/09/92-26/09/92	6			*15,000 Loc: 15,000*
International Symposium	Trends in Vaccine Research	New Delhi, India	08/12/92-10/12/92	3			*? Loc: ?*
Conference	Science Policy for Development: Biotechnology *R&D* Trends	Trieste, Italy	December	?			*? Loc: ?*

(continued)

Table 3 (continued)

ICGEB SHORT-TERM TRAINING PROGRAMME

Year and Type of Programme	Title	Location	Dates	Total No. Working Days	No. ICGEB Member Countries	Total No. Students	Total Cost (US$)
International Symposium	Trends in Vaccine Research	New Delhi, India	08/12/92-10/12/92	3			? *Lec: ?*
Conference	Science Policy for Development: Biotechnology *R&D* Trends	Trieste, Italy	December	?			? *Lec: ?*

Figure 1. ICGEB Short-Term Training Programme: number of trainees by country

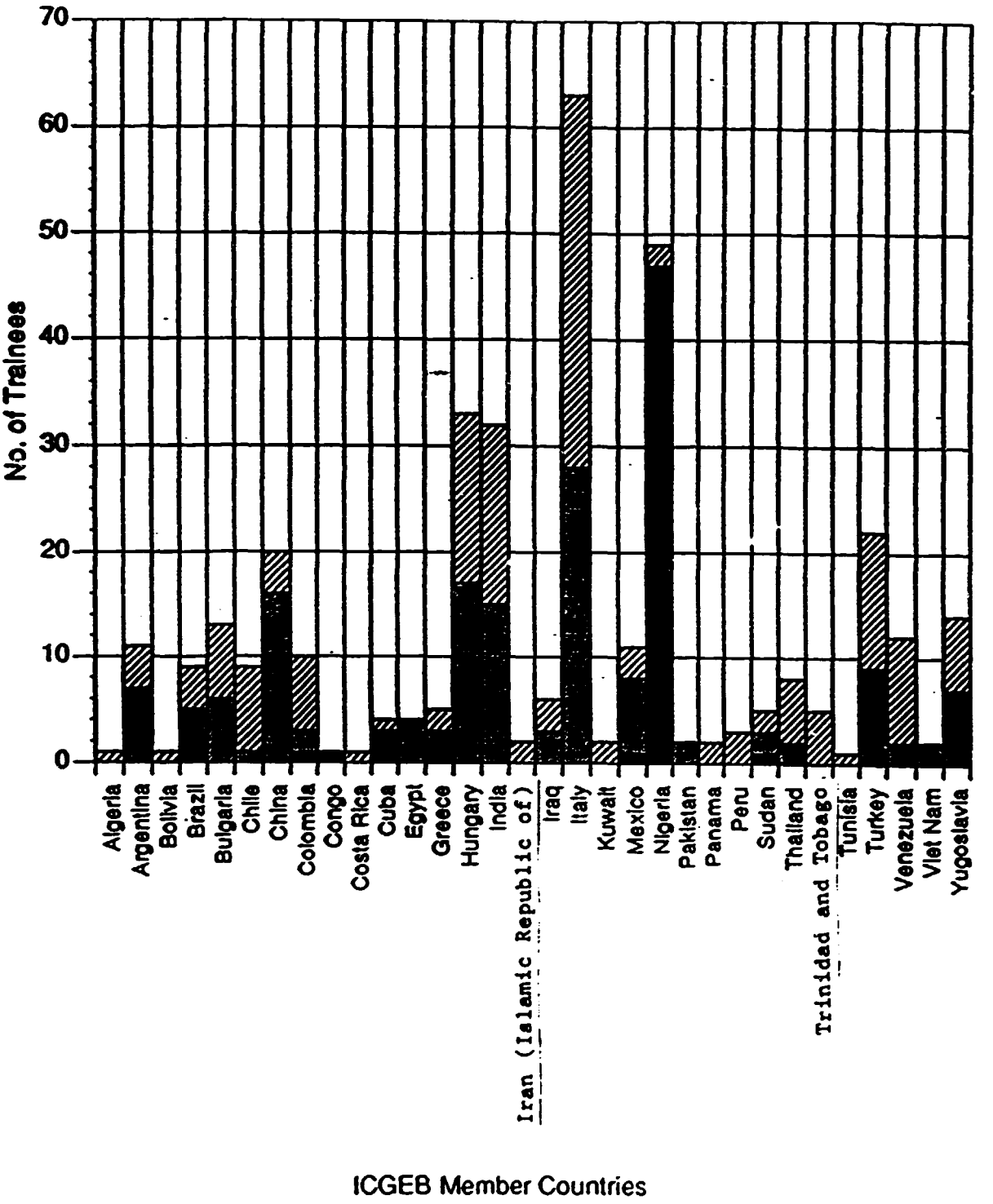

Figure 2. ICGEB Short-Term Training Programme: number of trainees by year

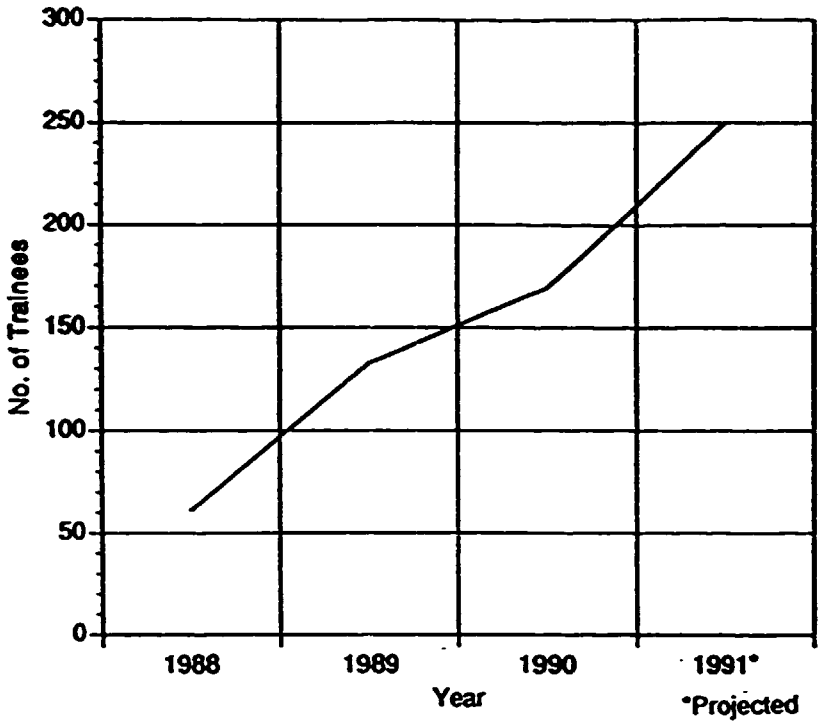

Figure 3. ICGEB Short-Term Training Programme: financing

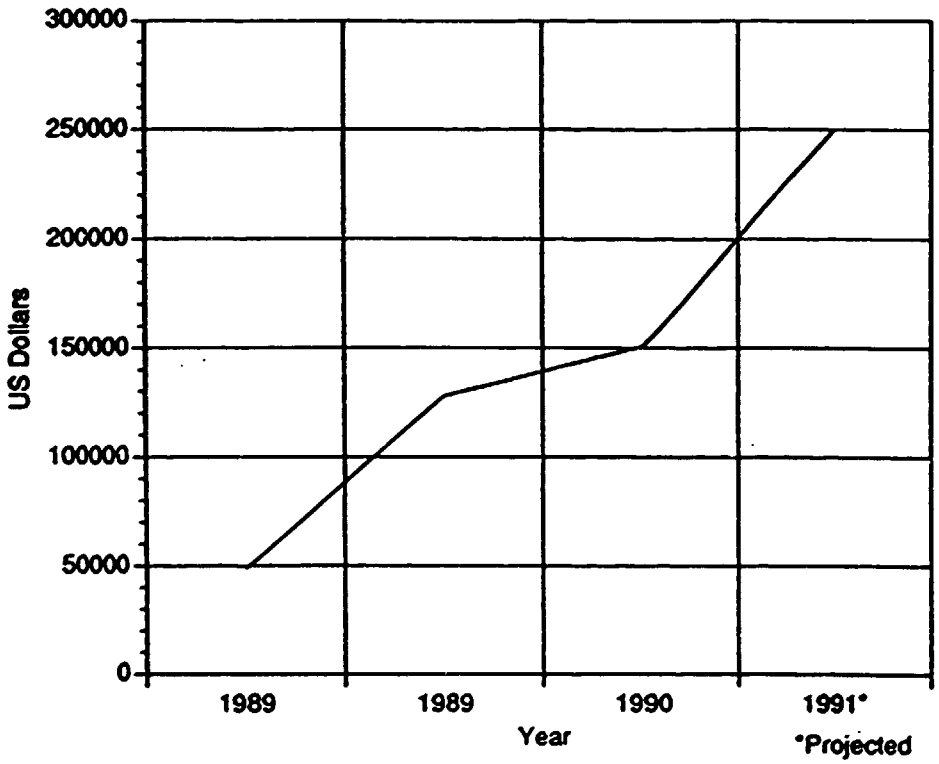

Figure 4. ICGEB Fellowship Programme grants awarded, 1989-1991

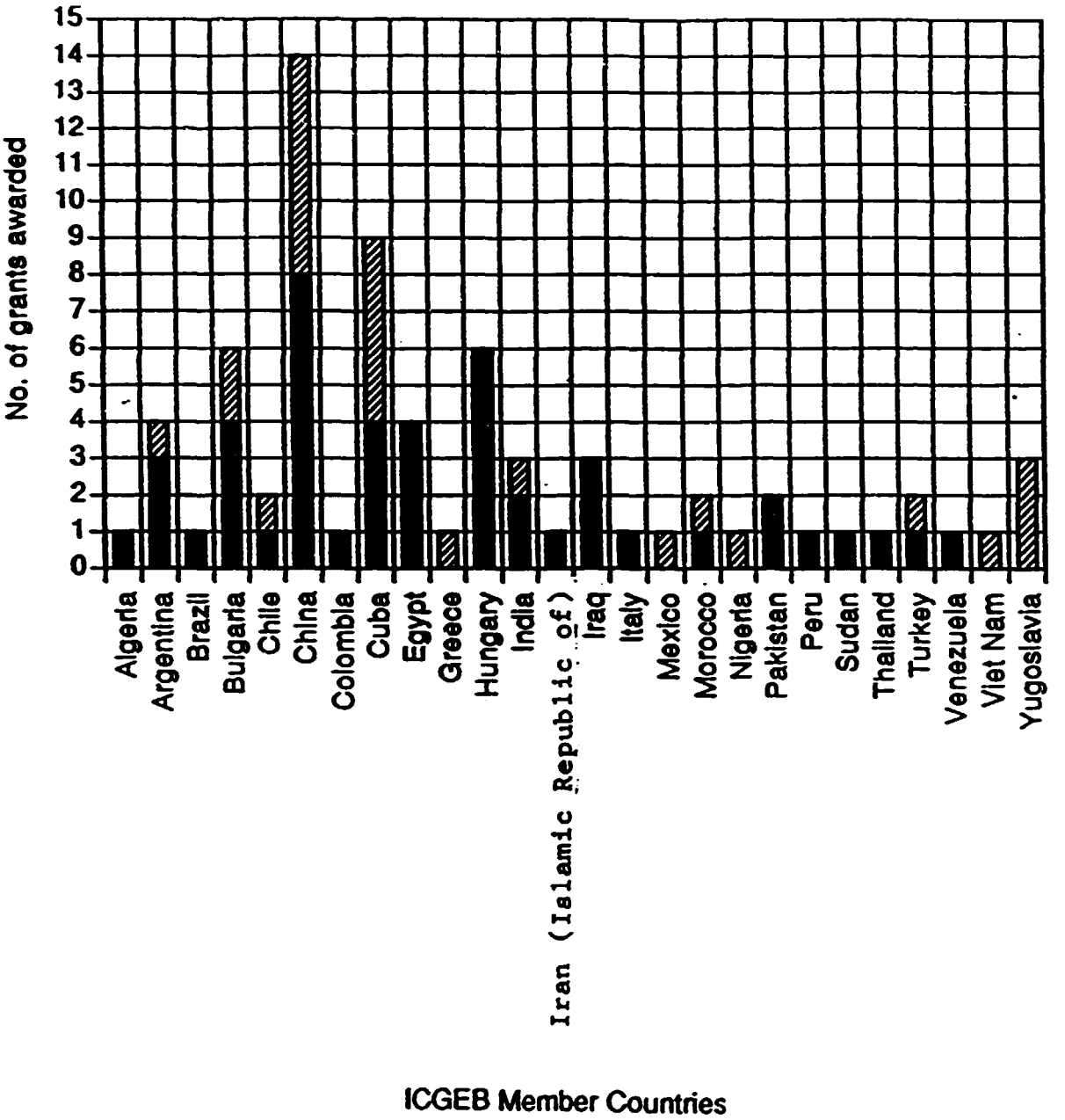

Table 4. ICGEB Fellowship Programme 1991: details of the 25 grants awarded

Name	Country	Host Laboratory
Arturo ROMANO	Argentina	UNIV.Rome, Italy
Sotir ZAKHARIEV	Bulgaria	ICGEB, Trieste, Italy
Violeta STOYANOVA	Bulgaria	ICGEB, Trieste, Italy
Raul AGUIRRE	Chile	ICGEB, Trieste, Italy
Erqui Li	China	ICGEB, Trieste, Italy
Yuo LIN	China	LGM/Gaslini Genoa
Ningwu HUANG	China	ICGEB, Trieste, Italy
Yuanding CHEN	China	ICGEB, Trieste, Italy
Rengang WU	China	ICGEB, Trieste, Italy
Mao Sheng SUN	China	ICGEB, Trieste, Italy
Pedro MOLINA GUEVARA	Cuba	ICGEB, New Delhi, India
José BRITO	Cuba	IGBE/CNR Pavia
Roger RUBIERA	Cuba	UNIV.Rome, Italy
Nelson SANTIAGO VISPO	Cuba	UNIV.Rome 'Tor Vergata' Italy
Isabel APEZTEGUIA	Cuba	UNIV.Torin, Italy
Paraskevi TAVLADORAKI	Greece	ENEA, Rome, Italy
Anil Kumar TRIPATHI	India	UNIV.Florence, Italy
Alicia CHAGOLLA LOPEZ	Mexico	ICGEB, Trieste, Italy
Mohamed AMAR	Morocco	IIGB/CNR Naples, Italy
John AGUIYI	Nigeria	ICGEB, Trieste, Italy
Ali Fazil YENIDUNYA	Turkey	ICGEB, Trieste, Italy
Phan Huy BAO	Viet Nam	IGBE/CNR Pavia, Italy
Aleksandra COMINO	Yugoslavia	ICGEB, Trieste, Italy
Dimitar EFREMOV	Yugoslavia	ICGEB, Trieste, Italy
Vesna SKERL	Yugoslavia	ICGEB, Trieste, Italy

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