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CANADA EUROPE

BIOTECHNOLOGY

SPAIN - CANADA

1992

External Affairs and International Trade Canada

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Canada

BIOTECHNOLOGY

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FROM THE GOVERNMENT OF CANADA

External Affairs and International Trade Canada (EAITC) is pleased to offer the Canadian biotechnology community, as part of the Going Global trade strategy, this analysis of the Spain - Canada biotechnology industry. This project was undertaken by the Canadian Embassy in Madrid under the Going Global European Initiative Fund, an initiative of the European Community Division of EAITC. This fund is part of the Europe 1992 Awareness Campaign.

Europe 1992 is happening now. The European Community's ambitious Single Market program has already dramatically changed the way Europeans are doing business. The process is irreversible; the pace is rapid and accelerating. If Canadian businesses are to profit from the opportunities that this enormous market will bring, they must be well-informed.

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He is the president of the Spanish-Canadian consulting group Ecotechnos, and Director of the Business and Economics Division with the Board of Directors of the Canadian Society for Chemical Engineering.

PREFACE

During the preparation of this report, informal exchanges with professionals and business people of Spain and Canada have made me aware of the considerable lack of familiarity with each other country's economic, social and political status. Although this document was initially conceived as a report on the status of biotechnology in Spain and Canada, some pertinent questions were raised to us by some business people from both sides of the Atlantic. These could be condensed into two questions; Why Spain and Canada? Why biotechnology? To answer convincingly those questions we have incorporated a selected amount of socio-economic information. That information makes this document a more valuable point of departure for business professionals of either country. Indeed, both economies are of comparable size, and both countries have in common an important number of features. The document is not a collection of profiles of Spanish and Canadian companies. That is not its objective. Nor is a "me too" report based on the conclusions reached by previous studies. In fact, there are no previous comparative analyses on biotech opportunities between Spain and Canada.

Biotechnology is neither a technology nor an industry or sector. To cover its present status and potential is an enormous task well beyond the scope of this document. Nevertheless, we have endeavoured to present an updated view of the most relevant industries affected by that set of technologies called biotechnology. In that regard, the statistical data presented in here have been taken from the most recently available official publications. A brief review of the business aspects of biotechnology have been included and should be specially useful to non-technical business professionals. Indeed **BIOTECHNOLOGY SPAIN - CANADA** should be seen as a point of departure to facilitate the exploration of opportunities in both countries.

M. Alvarez Cuenca

Toronto, May 1992

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The preparation of **BIOTECHNOLOGY SPAIN-CANADA** within the given time constraints has involved an important effort in the collection, synthesis, and presentation of information. A number of individuals and organizations from Spain and Canada have assisted us either with their views or providing pertinent information. Among them deserve special mention Mr. Bob Mac Arthur of the Council of Toronto Biotechnology Initiative, Dr. Graham Strachan of Allelix (Toronto), and Mr. Richard V. Laughton of Pollutech.

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

Two of the ten world's largest industrial economies, Canada and Spain, have an insignificant trade and investment level. Their membership in the two largest trading blocks in the world, the European Community and the North American Free Trade Zone make a major upsurge in their commercial relations inevitable.

Biotechnology, called to transform the economy and quality of life of the incoming century, is considered of strategic importance by the governments of both countries. Because of the impact biotechnology has in all aspects of human activity, the choice to promote Spanish-Canadian investment and trade could not be better. The current status of biotechnology, its potential, economic impact, and research trends in major industries are described.

To have a business perspective of biotechnology in Spain and Canada, we give comparative view of both countries main economic and social indicators. Strengths and weaknesses are pinpointed as business opportunities between both countries. This comparative evaluation is followed by Section IV and V where the variables affecting a "typical" biotechnology company are discussed.

Biotechnology in Spain is commented in Section VI. Government policies, areas of priority in R & D and industrial applications of biotechnology are presented. Spanish human resources, major biotech research centres, R & D funding mechanisms, and Spain's access to the industrial research programs of the European Community are discussed. Finally, it is reviewed Spain's biotech industrial sector, and intellectual property.

Biotechnology in Canada is commented, in a parallel fashion to that for Spain, in Section VII. The section is addressed to Spanish entrepreneurs, investors, and government officials, although it might be useful to their Canadian counterparts. The Canadian government policies on biotechnology and areas of priority, as well as funding agencies, major research centres, and the biotechnological industrial sectors are commented. A brief reference to Canadian intellectual property laws closes this section.

Areas of business opportunities for both countries are shown in Section VIII. The section is divided into three areas: 1) Opportunities for Canadian manufacturers and firms interested in the transfer of technology, or training to Spain; 2) Opportunities for Spanish manufacturing firms and firms interested in technology transfer to Canada; and 3) Areas where collaboration and balanced partnership are the preferred formula. This section leads to the

Conclusions (Section IX) and the **Recommendations** (Section X). Based on the biotechnology development trends, national priorities, economic potential, strength of their R & D policies, and the applications of biotechnology in their industrial sector we make the following recommendations:

1. **To identify and select by sectors, Spanish companies and their Canadian matching counterparts in the following industries and services:**

   A) **Human and Animal Health Care**
   B) **Agrifood Industries**
   C) **Environmental Applications**
   D) **Forestry**
   E) **Training and Education**

This selection should produce a well focused document on Spanish and Canadian firms interested in strategic alliances in manufacturing, services, investment, and technology transfer.

2. **Simultaneously and in conjunction with recommendation 1., we propose the immediate preparation of two biotechnology seminars on selected industries, one to be held in Madrid and the second one in Ottawa. The document prepared in 1. should be made available to the participants of these seminars. To facilitate exploratory meetings among the companies participating should be one of the major objectives of these seminars**

3. **In parallel with recommendation 1., we propose the immediate initiation of exploratory conversations between the following Canadian and Spanish organizations:**

   A) **Centro Nacional de Biotecnología (Madrid) and the Biotechnology Research Institute (Montreal)**

   B) **The National Research Council of Canada, and the Consejo Superior de Investigaciones Científicas of Spain**

   C) **The Spanish and Canadian R & D funding agencies (NSERC, CDTI, and CICYT) should explore formulas that allow the participation of firms and researchers from both countries in Canadian, Spanish, and European biotech programs.**

4. **To develop the necessary instruments which permit to facilitate, follow up, and evaluate of the previous initiatives**

I. INTRODUCTION

Canada and Spain are among the world's ten largest economies, with gross domestic products (GDP) in the $600 billion* range. Even so, they rank only 29th. and 19th. respectively as each other's trading partner.

Historical and cultural links between countries naturally contribute to trade relations. Common language and culture, geographic proximity, or a large immigrant population, are factors which tend to stimulate international commerce. Lacking the benefit of these factors, Spanish-Canadian trade relations have not developed to their full potential.

As early as 1774, four years earlier than Captain Cook and 18 years earlier than Captain Vancouver, Spaniards explored the West Coast of North America. Spanish navigators established settlements and mapped the area. Hence the abundance of names like Juan de Fuca, Galiano, Quadra Island, Valdes, Texada, etc.

In more recent times, we are reminded of another Spaniard, Leonardo Torres Quevedo, an engineer and inventor of the first electro-mechanical chess player, and the first automatic computational machine. In 1916, Leonardo Torres Quevedo constructed the *Spanish Aerocar* which today conveys Americans and Canadians across the Niagara River at Niagara Falls, Ontario, making an important contribution to tourism between the USA and Canada.

The Canadian physician Dr. Norman Bethune will always be linked to Spain's 1936 Civil War, not only for his idealistic collaboration with the Republican side, but also for his introduction of the first mobile blood transfusion unit to be used in Madrid.

The historical and cultural links between Spain and Canada have not been overly abundant. The number of Spanish immigrants in Canada is relatively insignificant at 0.1 % of the Canadian population in 1986[1]. This is a small figure compared to immigration from other European countries, even those with much smaller populations than Spain.

Another factor which has detracted from trade activity between Spain and Canada has been each countries' tendency to focus on their respective powerful neighbours, the other members of the European Community and the U.S.A. In 1990, 68% of Spanish exports went to the European Community, and the USA received 75% of Canada's exports.

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* The dollar currency unit used in this report refers to the United States dollar, unless otherwise noted; for example, the Canadian dollar is written Cdn. $.

For historical reasons, many Canadians tend to look at Europe only from British or French perspectives. This has eclipsed a deeper Canadian understanding of the cultures and commerce of other European countries. Europe is not a homogeneous economic, political, and cultural entity. References to European culture or to European business styles are restrictive and misleading. Even between the Latin European countries, these characteristics vary considerably.

Similar misconceptions prevail among Spaniards, who often perceive North America as simply the USA. Sheer habit and inertia induce Spaniards to view Canadian culture, business practises and laws as USA off-shoots. In fact, Canadian business styles are noticeably different from those considered typically American, being in some respects closer to the Europeans.

In spite of the above obstacles, recent statistics (Figure 1) do indicate a steady growth in Spanish-Canadian trade activity since 1985. This increase in business ventures between both countries has two additional major reasons to experience an expansion in the near future.

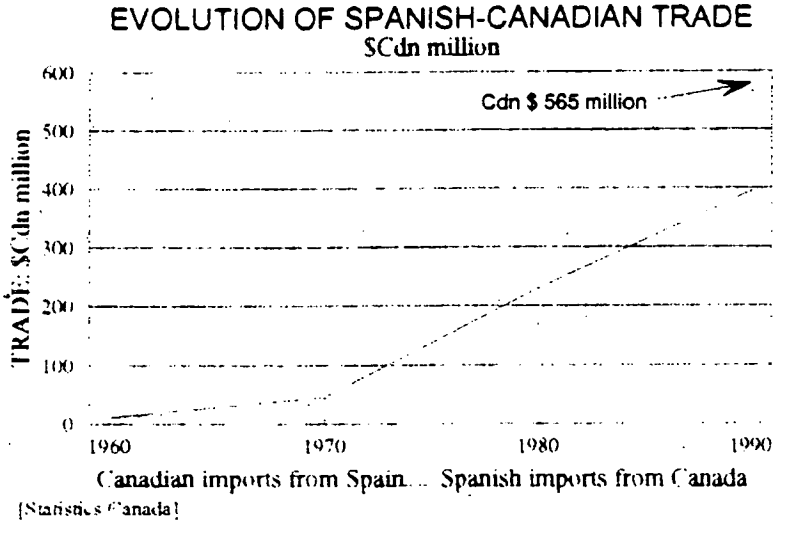


Figure 1

Canada's integration in the North American Free Trade Zone and Spain's membership in the European Community, facilitate the access to US and European markets, R&D funding, and investment institutions. The eventual incorporation of Mexico to the North American Free Trade Zone, and the enormous possibilities for Spanish-Canadian firms in the Hispanic American market with more than 350 million consumers, are real arguments to give major strategic importance to business ventures between both countries.

Few technological endeavours can provide the exciting business prospects associated with recent developments in biotechnology. Biotechnology's

potential to impact upon social, ethical and economic values, has earned it the status of the third technological revolution of this century.

Two similar observations can be made about Spanish and Canadian trade:

1) Full potential has not yet been realized,
2) Important business opportunities are now beginning to emerge as a critical mass of know-how and economic interest is established.

Before reviewing areas of biotechnology where definable business opportunities are appearing in Canada and Spain, an overview of the major biotechnological industries will precede a comparative analysis of Spanish and Canadian markets.

II. BIOTECHNOLOGY: A Current Perspective

The perspectives and the terminology used in this report recognize the increasing involvement in biotechnology of professionals who do not necessarily have a life-sciences or engineering background. Biotechnology is not an industry or a sector[b]. Nor it is new. Indeed some of the biotechnology products (wine, cheese, bread, etc.) are several thousand years old. Biotechnology is a set of multidisciplinary technologies whose application affect a vast number of industries. There are many official definitions of biotechnology according to international institutions or national origins. For example, Australia, Canada, Germany, France, Japan, Holland, the OECD, the European Federation of Biotechnology, the International Union of Pure and Applied Chemistry, etc., all have their own definition of biotechnology. It appears however, that a number of countries have adopted the following definition: "Biotechnology is the synthesis of multiple disciplines including Genetic Engineering, Chemical Engineering, and Industrial Microbiology with the market forces to create products and services".

The biotechnological revolution taking place in the last decade of the 20th Century is being reported in newspapers and financial publications. Molecular biology first suggested revolutionary cures and enormous markets in the mid-1970s. But not until the late 1980s did the right combination of circumstances occur to put this new knowledge into commercial ventures. The relentless pace brought about by the application of new biotechnological methods into such sectors as pharmaceuticals, wastewater treatment, food processing and agri-culture, makes it difficult to portray definitively the present status of biotechnology.

[b] The above is not a superficial observation. It is surprising the number of documents and publications, particularly those arising from financial and market analysts who use the term "biotechnology industry" (sic). This confusion leads to poor business data and predictions as industrial sectors and production volumes are indiscriminately lumped together.

A revealing indicator of the extraordinary performance of biotechnological applications is health-care. As the GDP of a country increases so does the proportion of the national budget allocated to health-care. Furthermore, these new products tend to be classified as advanced medical technology. An area where traditionally European and North American firms have made a good return.

Brisk biotechnological development is by no means confined to the medical and pharmaceutical sectors. Biofuels, specifically biodiesels are being tested in European and North American commercial bus and taxi fleets[2]. These fuels are derived from esterified vegetable oils extracted from rapeseed and sunflower seed in Europe, and from soybeans in North America. Since they do not contain sulphur, they are less toxic and therefore environmentally preferable to petroleum-based diesel fuels. Large scale production of biodiesels could have major economic, political and strategic implications. The current world trading patterns for petroleum fuels could be altered; relieving some countries of their crippling dependence on oil imports, at the same time bolstering agricultural economies. Government incentives and tax breaks are needed to off-set the currently high cost of biofuels. Another commercial application of biotechnology is the utilization of microbes to break down the cancer-causing industrial solvent methylene chloride. This process is being implemented by General Electric in the USA. Also, in the USA, rot-resistant tomatoes, with a market potential of over $150 million, is expected to be approved sometime in 1992[3].

Commercial successes have been associated to an unprecedented funding of Research & Development by both Government and the private sector. On January 31, 1992, the United States government announced a plan to increase annual federal support for basic biotechnology development by 7% to $4.03 billion.

We have noted that the application of the term "biotechnology" is often imprecise. One reason for this is the frequent overlap of product sector classifications between conventional chemical and biochemical processes, and (recently defined) *biotechnological* processes. Inevitably, many reported trade figures are quoted with insufficient identification of what is being measured.In 1984, eleven different institutes[4] involved in biotechnology, made global market forecasts offering an extremely wide range of predictions for the year 1990. Also predictions made in 1991 for the year 2 000 on worldwide markets for biotech products have been reported as $ 70 billion by M.D. Dibner of North Carolina Biotechnology Centre, $ 50 billion by Business Week magazine, Cdn $ 100 billion by Ernst & Young, and Cdn $ 60 billion by R. Miller [c]. A 100 % discrepancy in forecasts is hardly favourable to astute business decision making.

[c] Business Week, March 2, 1992, P 67. Bio/Technology Vol. 9, Dec. 1991, P. 1337, Canadian Biotech '89: On the Treshold, NRC, 1989

According to recent statistics[5] annual sales worldwide for biotechnology-related drugs, excluding antibiotics but including vaccines and diagnostics, grew to $4 billion in 1991. For agricultural-related biotechnology products, worldwide sales exceeded $200 million.

The following is a review of current biotechnological activity, and commercial implications.

A. MEDICAL RESEARCH and HEALTH CARE

Biotechnology is recognized as a driving force in medical technology. In the period from 1991 to January 1992, public offerings for biopharmaceutical ventures in the USA had reached $4.5 billion; more than the industry raised in the ten year period 1980-1990[6].

In 1987 more than 100 new products were under development, but only few reached the market. Currently, biotechnology-related drugs, vaccines, and diagnostics are yielding more than $4 billion annual sales world wide. A number of significant products have emerged. Many more are being evaluated currently, involving diagnostic and drug-delivery methods, genetic and protein engineering and gene-based immunology.

A recent illustration of the advances in medical biotechnology is provided by Tracy, the super-sheep. Tracy is behind a multimillion dollar deal between Bayer, the German chemical giant and Pharmaceutical Proteins, a venture capital start-up organization based in Edinburgh[7]. This contract could mark the first step in the commercial use of genetically engineered animals as "biological factories". Genetically modified, Tracy synthesizes the protein AAT (alpha-1-antitrypsin) at a cost of $100 per gram. The substance, extracted from the milk of a super-sheep like Tracy, will not only ease the shortage of ATT but eventually will replace the traditional method of producing ATT in human blood. Human deficiencies of this protein cause liver failure or emphysema. The development of this alternative source of ATT will significantly ease the cost burden of current treatment, which can reach $20,000 per year. What began in the mid-1970s as a dream has become one of the commercial milestones of biotechnology in early 1992.

Concurrently, a team of Canadian scientists from the Hospital for Sick Children in Toronto announced on February 28th., 1992, the successful transplant into mice of stem cells. These are human bone-marrow cells involved in the production of blood. In allowing human conditions to be more extensively replicated in animals, breakthroughs of this significance may well facilitate the development of new gene-altering treatments for hereditary diseases, leukemia, AIDS, etc. As well, this experiment should have major implications in speeding up the development of new therapies in

which humans cannot be subjected to clinical tests.

B. AGRICULTURE and FORESTRY

Agriculture is said to be the only truly indispensable industry. Globally, it represents one of the largest economic sectors; where the stakes for biotechnological investment are immense. Although agrobiotechnology has a robust market of over $1 trillion in the USA alone, commercially it lags behind biopharmaceuticals. The reasons are not hard to understand:

- Plant culture is complex
- The cellular physiology of plants is less well understood than that of animal species
- Since the growth of plants is seasonally dependant, so are many of the experimental procedures

Agricultural sectors which are seeing encouraging development include:

- Pesticides and fungicides
- Insect-herbicide resistant crops, (farmers annually spend over $20 billion on crop protection)
- Agricultural chemicals for growth enhancement (hormones)
- Rot-resistant species
- Vaccines and animal health products
- Transgenic animals

C. FOOD and FEEDS

Progress in molecular biology and enzymology has provided additional dimensions to traditional plant breeding and fermentation technology, providing new ingredients, and economical, healthier, and tastier products.

Fermentation processes, known and applied throughout the world for thousands of years, are being constantly improved in the name of modern biotechnology. The incentive to exploit biotechnological innovation in the food industry has been increasing due to consumer rejection of processed food and artificial additives in favour of natural and more wholesome foods.

Areas of major activity include:

- Handling and preservation control of primary food sources;
- Modification of basic foodstuffs to improve nutritional and other

characteristics (oils, fats, polysaccharides);
- Production of novel ingredients and flavours

D. SPECIALTY and COMMODITY CHEMICALS

World wide sales of chemical products were $1,230 billion in 1991[8]. The chemical industry represents 10 % of the GNP of the OECD countries. Together with pharmaceuticals, specialty chemicals will dominate the scene for the next two years. Only a handful of specialty fine chemicals are currently produced using biotechnology processes. These include acrylamide, amino acids, ethylene oxide, pantothenic acid and adenosine triphosphate.

The chemical industry has been somewhat slow in accepting biotechnology as a viable production alternative. In the near term, the replacement of existing capital equipment is expected to be difficult, and biotechnological impact in the petrochemical industry for example is expected to be minor. Nevertheless, the potential for biotechnology innovation in chemicals manufacturing and extraction, is considerable.

It is likely that conventional manufacturing processes for commodity chemicals like sucrose, methanol, starch, paraffins, and lignocellulose will be replaced by biotechnological processes. In any event, biotechnology will focus preferentially on chemicals with large added values[9].

E. ENVIRONMENT and MINING

In volumetric terms, the treatment of municipal waste water, sewage and toxic waste, is by far the largest biotechnological industry. The introduction of increasingly stringent environmental regulations is driving the search for effective and economic solutions. However, while much has been written about the applications of biotechnology to environmental problems these applications will mature more slowly than those industries discussed earlier. The reasons for this slower realization of possibilities is the processing costs of conventional technologies, the economics of raw materials, and full stop capital costs. Attention has focused on aspects of biotechnology involved in the microbial break-down of contaminated landfill, and the treatment of wastes and wastewater biofilters.

F. FLAVOUR and PERFUMERY

In 1986, the world market for flavours and fragrances was estimated to be $6 million, with about 5% annual growth rate. The annual world market for food

flavours is about $2 billion per year, representing nearly 12% by weight and 25% by value, of the world food additives market. Europe's cosmetics market is estimated at about $21 billion per year[10].

About 50 % of the total business is carried out by the 15 largest companies. Economies of scale of production and bulk buying are not significant. Of the 3,000 aroma chemicals currently produced, only 400 are made in quantities greater than 1 ton per year.

The number of naturally occurring compounds known to be important for aromas is at present about 5,000 and may ultimately rise to as many as 10,000. Most traditional agricultural resources cannot meet the current demand for naturally-derived fragrance and flavour materials. Important developments are taking place which will significantly improve production techniques within the decade. These include plant culture, synthetic biocatalysts, gas-phase reaction, multiphase reactor development, and the integration of product formation and recovery[11].

G. OTHER AREAS OF RESEARCH & TECHNOLOGY DEVELOPMENT

The development of new processes in the above areas will require major advances in ancillary fields. Process improvements in the biotechnological industries will ensure a higher product yield and purity per unit investment. Some additional research areas are discussed below:

1. BIOREACTORS

Bioreactor design, is an area of research whose results affect in a major way the economics and competitivity of a product or operation. These devices are invariably at the heart of production, and profitability is closely linked to efficient and cost-effective production processes. Continuous bioreactors achieve greater productivity and lower operating costs than batch operations. They are employed in the food, pharmaceutical, and waste water treatment industries, and to a limited extent in the chemical industry.

Bioreactor success is measured by productivity, reliability and operating costs, and are compared with batch reactors (fermenters). These are preferred over fluidized beds or other continuous bioreactor because are well characterized and standarized. A reluctance to innovate appears to be retarding continuous bioreactor development. Forecasts made in the early 80s estimated US sales of bioreactors at $270 million by 1989. Such forecasts have turned out to be over-optimistic[12]. In any event, the advantages of continuous reactors are so distinctive that many

biotechnology company executives believe the 1990s will see continuous bioreactors become firmly established in the production arena. Some companies presently use bioreactors, as opposed to fermenters, to produce reagents employed in clinical diagnostics.

2. BIOSENSORS

It was predicted for the year 1988 that the global biosensor market would be $46 million, soaring to $1-2 billion by the end of the century[10].

Presently, few instruments are available for real-time analysis of cell function, nutrient concentration and molecular configuration. Biosensor monitoring devices, operating on the combined principles of biological and electronic response mechanisms, are a promising answer to this problem.

They provide rapid response time, high specificity (ability to identify correctly), and high sensitivity (ability to measure what they have identified)[13]. Biosensor monitoring is already used in cancer detection, sepsis determination, virus detection and genetic testing.

In the environmental area, there are current applications in air and water monitoring, and in food quality surveillance. Military applications include the detection of nerve gases and other chemical agents of chemical warfare.

3. HUMAN GENOME RESEARCH

Two years ago the US government launched a 15-year, $3 billion federal programme dedicated to deciphering the genetic configurations of the human chromosome.

This programme will vastly increase the base for further exciting progress in genetic diagnostics and molecular engineering. As more genes become definitively characterized, researchers expect prolific commercial opportunities. The automated identification, separation and cloning of DNA units is one of the primary outcomes expected from this line of research.

An exciting business opportunity is evident in the need to gather, organize and manage biotechnological information generated by these research programmes.

III. SELECTED ECONOMIC INDICATORS and TRENDS IN THE SPANISH AND CANADIAN ECONOMIES

This summary of the Spanish and Canadian economies is intended to provide a general background against which biotechnology activities may be evaluated.

R & D budgets are important indicators of a country's vision of the future, and of the importance attached to creative activity in science and technology. R & D commitments reflect a nation's response to social, economic and environmental imperatives to develop new and more effective products and services.

R & D budgets and allocations are discussed below, together with other relevant economic,social, and fiscal data.

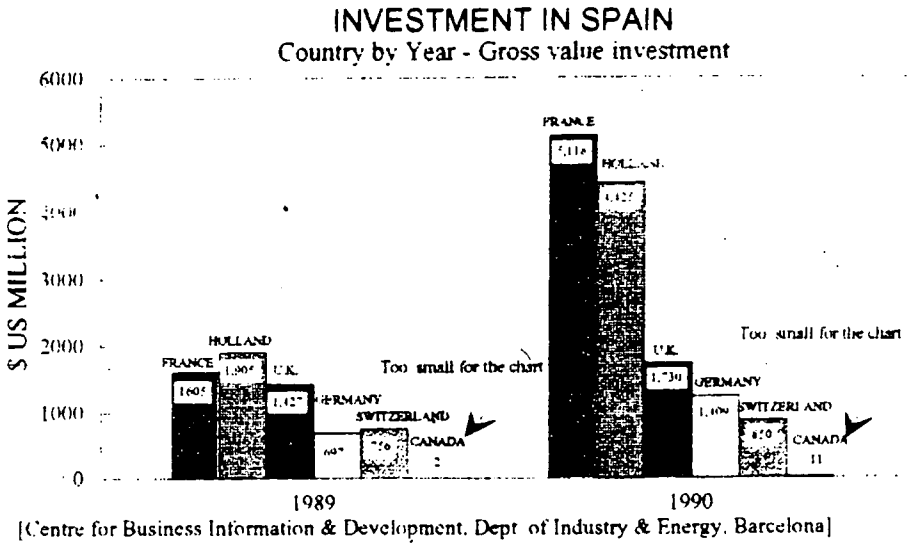
A. SPAIN

The Kingdom of Spain, the second largest country in western Europe, has a population of 40 million. It is a parliamentary democracy with a political structure similar to that of Canada. It consists of 17 regions with their own self-governments. Aproximately 25 % of the country's national budget is administered by these regional governments.

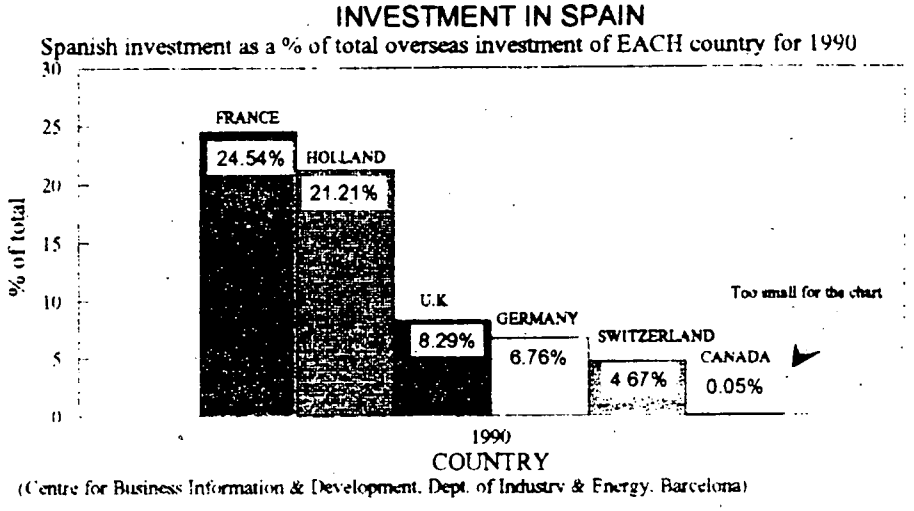
By the size of its Gross Domestic Product ($ 526 billion in 1991), it ranks the ninth largest economy in the world and the fifth largest in western Europe.

Spain has been the fastest growing member of the European Economic Community since joining in 1986, due largely to its export sector, and to the increase in foreign and domestic investment (Figure 2). It receives more direct investment than any other country except the United Kingdom and the USA. Spain's economy is maintaining a level of activity higher than the average of the industrialized countries as a whole. According to the National Institute of Statistics, the growth of the GDP in 1991 was 2.4%, above the average for the European Community.[14] The country has traditionally followed high-tariff policies by governments that too often have been interventionist.

Over the past 25 years, Spain has evolved from a rather isolated agricultural economy into a major industrial power[15]. Its trade deficit was the industrial world's third largest in 1990 ($43,8 billion)[16]. This is not of immediate concern because economic growth is investment-led, and rapid growth in foreign investment assures adequate financing. Also its reserves,



[Centre for Business Information & Development. Dept of Industry & Energy. Barcelona]



(Centre for Business Information & Development. Dept. of Industry & Energy. Barcelona)

FIGURE 2

$64.2 billion in 1991 (the world's fourth largest), provide important coverage of the national debt.

Unemployment has been persistently high since 1985, when reached 22 % of the labour force. A source of concern for Spanish industry is competitivity. Training and process management in Spain could represent major business opportunities for Canadian companies and training organizations.

Spain's membership in the European Community has loosened foreign investment restraints. Restraints were completely removed in February 1992

for individuals and firms resident in Spain. Since June 1989, the peseta has been integrated with the European Monetary System, and in September of the same year was pegged against the ECU (European Currency Unit), (Figure 3). The peseta maintains its role as the strongest currency in the exchange rate mechanism of the European Monetary System and in early 1992 came close to the maximum allowable appreciation limits.

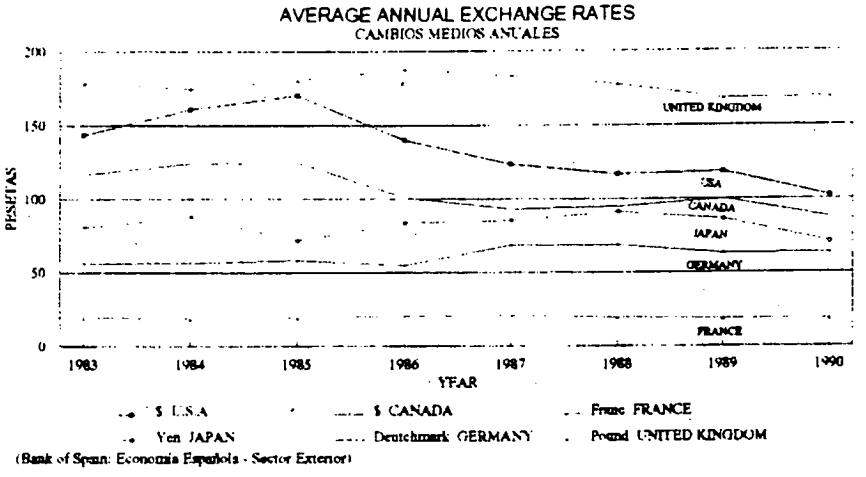


FIGURE 3

1. INDUSTRY

Industry accounts for 35.4 % of Spain's GDP. The leading industries are motor vehicles (the world's sixth larger car exporter), steel, chemicals, machine tools, shoes, leather goods, clothing and rubber products. The principal imports in 1991 were petroleum and petroleum products, machinery, electrical equipment, vehicles, and chemicals. Industrial productivity levels are one of the reasons for the present 15.6% unemployment, and has been a major source of concern for recent governments. Spanish companies have undertaken widespread restructuring and modernization programs including cross-border mergers and acquisitions since its membership in the EC in 1986. The country is a net importer of energy particularly oil which meets 52 % of the country's energy requirements. The main destinations of foreign Investment in 1991 were Madrid and Catalonia.

Although the labour-cost differential have to a certain extent diminished (See Table 1), Spain still has substantially lower costs than most European countries and North America.

TABLE 1

1990 Labour Costs per Hour in Manufacturing for OCDE Countries

COUNTRY	TOTAL	DIRECT WAGES	NON-WAGE	INDEX(USA=100)
West Germany	23.38	12.61	10.77	156.7
Switzerland	22.68	15.07	7.61	152.0
Sweden	21.78	12.46	9.32	146.0
Norway	20.21	13.34	6.87	135.5
Denmark	18.85	15.14	8.71	126.3
Netherlands	18.74	10.38	8.36	125.6
Belgium	18.55	10.08	8.47	124.3
Italy	18.41	9.07	9.34	123.4
Luxembourg	17.65	11.88	5.77	118.3
Austria	17.57	8.96	8.61	117.8
CANADA	**16.50**	**12.22**	**4.28**	**110.6**
Japan	15.96	12.27	3.69	107.0
France	15.83	8.40	7.43	106.1
UK	15.26	10.67	4.59	102.3
USA	14.92	10.83	4.09	100.0
Australia	14.22	9.81	4.41	95.3
SPAIN	**13.51**	**8.39**	**5.12**	**90.5**
Ireland	12.62	8.79	3.83	84.6
Greece	6.47	3.93	2.54	43.4
Portugal	4.41	2.53	1.88	29.5
Turkey	2.20	0.79	1.41	14.7

2. AGRICULTURE

Agriculture accounts for 5 % of the GDP and the country is largely self-sufficient. Traditionally, the Spanish agriculture has had low productivity, and although technological advances and irrigation has resulted in considerable gains, the country still lags behind the most efficient European countries. The relatively inefficient livestock sector suffers from European imports but Spanish fruit and vegetable producers are benefiting from their access to the EC markets.

3. TOURISM

Tourism is a major industry as well as a vital source of foreign exchange. With 50 million foreign visitors per year, Spain is one of the world's leading tourist countries. Tourism receipts were $18 billion in 1990[17].

4. CANADIAN INVESTMENT IN SPAIN

Direct Canadian investment in Spain was Cdn $272 million in 1989. At the present time 20 important Canadian companies maintain investments in Spain which ranks 17th among Canadian investments overseas. These companies include: Cominco, McCain, Denison, Canada North West Energy, Petrocanada, Royal Bank, Seagrams, Hirem Walker, Cognos, Dominion Textile, MacMillan Bloedel, Air Canada, Molson, Curragh Resources, ABC Group, and Canstar.

5. RESEARCH AND DEVELOPMENT

The country is behind in its industrial and social potential. It devoted 1.1 % of the GDP to R & D in 1991 with only 0.5 % of it coming from the private sector. Although the funds devoted to R & D have doubled in six years, there is an important gap with the most advanced industrialized countries which spend 2-3 % of their GDP. According to Spain's Instituto de Estudios Economicos for the country to achieve a satisfactory competitivity level, investment in R & D should reach 2 % of the GDP by the year 2000[18].

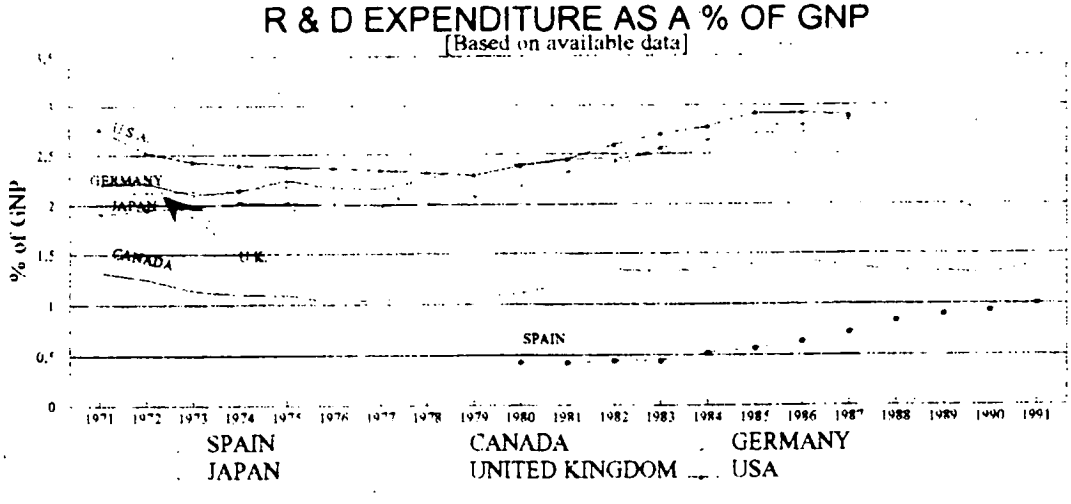


FIGURE 4

Although it exists in both the private sector and public institutions an increasing awareness of innovation and technology being the most effective means to improve productivity, Spain is a major importer of technology[19]. In 1991 the deficit in the Technology Trade balance was $2 billion[20]. Nevertheless, the R & D policy of the Government appears to be paying off as the technology trade coverage was 13.5 % in 1987 , in 1990 the coverage grew to 19.3 % and in mid-1991 reached 29.8 %.[21].

Of the sectors carrying out extensive R & D activity, the pharmaceutical industry is the most important, especially in connection with antibiotics technology. Important R & D investment is also found in food technology, biotechnology, medical and chemical sectors, and in the electronics and computer industries. Most of the R & D activity is located in Madrid followed by Barcelona.

Important opportunities for Canadian firms lie in the areas of waste water treatment and the environment (Spanish industry will have to spend Cdn $ 13.3 billion over the next four years to meet the European Community environmental standards). Other major sources of opportunities are in the pharmaceutical and agrifood industries, medical and hospital equipment, wood-forest processing, telecommunication technology, energy conservation products and services, automotive parts, precision machining, electronics, computers and peripherals, laser equipment, and new materials.

6. CANADIAN EXPORTS TO SPAIN AND OTHER OPPORTUNITIES

Canadian exports to Spain include copper mineral, pulp and paper, computer equipment,construction materials, aircraft, asbestos, cattle, iron, and steel. The potential for commercial growth in both directions is excellent as Canada only supplied 0.3 % of all Spanish imports in 1991 valued at $482 million.

The removal of trade barriers under EC transition makes Spain an attractive investment country. Additional factors favouring investment includes, political stability, availability of both skilled and unskilled labour, size and purchasing power of the population, its position as a platform to the rest of the Community, temperate climate and attractive culture, and special historical and commercial ties with the 350 million Hispanic American market. To complete the picture, it would be convenient to recall that in Europe, 1992 has been called the year of Spain. Not only is Barcelona a host to the Olympic Games, and opens the biggest world's fair ever, Expo'92 in Seville (four times the size of Expo '67 in Montreal), but also Madrid is the nominated European capital of the culture. The year will mark the 500 anniversary of the Spanish discovery (for the Europeans) of

America, and finally the year of the European Community's integration. All these events are having vast economic repercussions in Spain's infrastructure and economic performance.

B. CANADA

Canada, the second largest country in the world with a surface four times larger than that of the European Community, has a population of 26 million people, 80 % of which is concentrated within 160 Km of the US border. Like Spain, Canada is a constitutional monarchy, it has a federal government and ten provincial governments. Canada is, by external reference, economically and socially one of the most successful and prosperous societies in the world. The country is the world's eighth largest economy by the size of its gross domestic product and a member of the G-7, the economic club of the seven most advanced industrial democracies. On January 1st, 1989, Canada signed the Free Trade Agreement (FTA) with the USA. Over a 10-year period, the FTA will remove all tariffs and virtually all import and export restrictions, and will liberalize rules in several areas including agriculture, services, energy, financial services, investment, and government procurement. This trade agreement is expected to be expanded with the incorporation of Mexico in the near future thus becoming the largest trading block in the world.

During the period 1983-1989 Canada's GDP growth was the highest in the industrialized world after Japan. Abundant natural resources, skilled labour force, engineering and scientific expertise, and high-tech industrialization characterize the Canadian economy. The mineral industry, forest products, and agriculture have been major factors in the country's economic development. The spectacular growth of Canadian manufacturing, particularly since the 1950s, has transformed the nation from a rural agricultural society into one that is primarily industrial and urban. Canada was in 1989 the seventh world's largest exporter.

1. INDUSTRY

Industry, including mining, manufacturing, construction, and power generation, is the leading segment of the nation's economy. It employs 25.4 % of the work force and provides 40 % of the GDP. Canada is the world's largest producer of zinc, potash, uranium, and nickel ; the second largest producer of silver, titanium, sulphur, gypsum, and asbestos, and a leading producer of molybdenum, aluminum, cobalt, gold, lead, copper, iron, and platinum. Canada ranks first in the world in mineral exports and third in mineral production after the USA and Russia. Canada is a major producer of hydroelectricity, oil (produces 500 million barrels/year), and natural gas.

Unlike most of its industrial competitors the country is a net exporter of energy (primarily gas and electricity). Canada's exports and imports of oil are in near balance. Oil reserves were well above 6.8 billion barrels. Major manufacturing industries were transport equipment, food products, paper and paper products (Canada is the world's leading producer of newsprint), machinery, chemical products, base metals, wood products, and petroleum refineries The principal industrial exports in 1990 were motor vehicles and parts, lumber, wood pulp and paper, mineral fuels, and telecommunications equipment. Main imports consisted of foodstuffs, chemicals, machinery, motor vehicles, and computers.

2. AGRICULTURE

Agriculture, including forestry and fishing, contributed about 4 % of GDP in 1989. In 1989 Canada was the world's largest exporter (in terms of value) of fish and seafood. The main crops are wheat, barley, and other cereals, which with livestock production (chiefly cattle and pigs) provide an important source of export earnings. Main agricultural imports are fresh fruits and vegetables, and livestock. Forests cover about half of Canada area, and forest products exports represent 15 % of Canada's total export trade.

3. TOURISM

Canada received over 38 million visitors in 1989 (36.1 from the US), who spent over $7 billion.

4. SPANISH INVESTMENT IN CANADA

Spanish direct investment in Canada was only Cnd $18 million in 1989. Spain ranks 28th among countries investing in Canada. Spanish companies with a presence in Canada include Banco Central of Canada, Lois Canada (jeans), Lemur Canada (children's clothing); Investronica Canada (Software); Sproma (vegetables distributor), and Abressa Canada (Abrasives).In 1991, a joint venture was established between a Quebec company and Tafisa to produce fibreboard,plywood, and hardwood for the furniture industry. Most of the Spanish investment has been directed to the province of Quebec, the only Canadian province which maintains an active and effective presence in Spain.

5. RESEARCH AND DEVELOPMENT

At 1.33 % of Gross Domestic Product for 1988, and 1.30 in 1990, Canada's relative R & D effort continues to rank low in comparison to the more industrialized OECD countries (e.g. in 1987, the ratio for the USA was 2.9 %, Germany is 2.8 %, and Japan is 2.9 %). Investment on R & D as a percent of

the GDP have remained virtually constant since 1971 (See Figure 4). Total investment on R & D in 1990 were Cdn $9.1 billion. The private sector accounted for 56 % of the total expending ($5.1 billion). That is 0.8% of the GDP, a low percentage by comparison to companies from countries like USA, Germany, and Japan. In spite of these figures, companies are beginning to see R & D as an investment and not as an expense to be reduced in times of economic crises. The highest increase in R & D expenditures over the period of 1987 to 1991 was achieved by transportation equipment manufacturing, pharmaceuticals and medicine, and metal mines. Most funds (52 %) were spent in Ontario than in any other province in 1991. Quebec was the second largest recipient of federal funds (20 %). The number of person engaged in R & D in 1989 were 52,065, out of which 30,160 were in Ontario, followed by Quebec with 13,530.

In the balance for technological services, Canada in 1989 showed a deficit, smaller than that of Spain, of $64 million [22]. Canadian engineering consulting firms have major involvement in foreign projects specially in infrastructure, pulp and paper, energy transformation, and metallurgy. Indeed Canada is the second largest engineering exporter in the world. However, the investment in R & D of Canadian engineering firms is rather limited[23]. The European Community encourages its member-states to participate in R&D joint projects with non-European members provided that two of the participants are European. Canada, through collaboration with Spanish firms and institutions could benefit from these funds. In this regard, Ryerson Polytechnical Institute (Toronto), and the Universidad de Alcala de Henares (Madrid) and Universidad Politécnica de Madrid are establishing collaboration agreements leading to the creation of research programs, exchange of students and faculty, etc.

Canada's R&D infrastructure is based on exceptional telecommunication facilities (probably the best in the world), public research institutions well endowed with human and physical resources, public libraries with information easily retrievable, agile administration (bureaucracy is not the insuperable obstacle observed in some European countries), a labour force well trained, and statistical data bases very current, accessible, and reliable. The overall quality of the universities tend to be better than those of USA, Canada having fewer world class ones but also fewer lowest ranked.

6. SPANISH EXPORTS TO CANADA AND OTHER OPPORTUNITIES

Canadian imports of Spanish products reached a total of $496 million in 1990. The principal imports were iron and steel, petroleum, fuel for aircraft, automotive parts, secondary machinery, fruit and vegetables,

pharmaceuticals, shoes, tires, wines and sherry. Spain represents only 0.4 % of the total Canadian imports.

The North American Free Trade Zone is a major trade opportunity for Canadian-Spanish companies. Specially after the eventual incorporation of Mexico thus increasing the size of the market to over 350 million consumers. Canada will be making in 1992 decisive choices which will shape its future. These choices are not only institutional but also in their working policies. Competitivity, and innovation are bound to take a different meaning as the world's social and economic forces are more dynamic than ever[24]. Canadian society, including the productive sector, are immersed in an unprecedented, rapid structural change. Their pragmatism has made Canadians a tolerant and prosperous society. This historical pragmatism will lead in all likelihood to a new quantum jump in their quality of life already considered one of the highest in the industrialized world.

A few comparative parameters of the Canadian and Spanish economies might contribute to a better understanding of their respective size and potentials.

C. SPAIN-CANADA: SELECTED SOCIAL AND ECONOMIC INDICATORS

TABLE 2

		CANADA	SPAIN
GEOGRAPHIC	Surface Area, sq.km	9,976,140	504,750
	Population	26,734,000	40,011,000
	Major Cities & Population	Toronto - 3,893,000	Madrid - 4,900,000
		Montreal - 3,127,000	Barcelona - 4,700,000
		Vancouver - 1,602,000	Valencia - 2,100,000
		Ottawa - 920,857	Sevilla - 1,600,000
ECONOMIC	Gross Domestic Product 1991, Cdn $	$690 billion	$615 billion
	Income per Capita 1991, Cdn $	$25,842	$15,385
	World Ranking by GDP	8th.	9th.
	World Ranking by Trade Volume 1990	8th.	12th.
	- Imports 1990 Cdn $billion	119.1	88.6
	- Exports 1989 Cdn $billion	131.7	56.2
	Industrial Production (1 year)	-1.9%	+6.3%
	Average GDP Growth 1980-1989	3.4%	2.9%
	Growth of Real GDP, 1992	3.1%	3.0%
	Inflation Rate, 1992	2.5	5.9
	Unemployment, 1992	10.6%	15.3%
	Prime Lending Rate, 1992	7.5%	16.0%
	Foreign Reserves, 1992, $billion	16.3	64.2
	Public Debt, % of GNP, 1991	73.0%	43.0%
HEALTH	Life Expectancy, 1990	MALE: 74 yrs FEMALE: 81 yrs	MALE: 75 yrs FEMALE: 82 yrs
	Infant Mortality/1000 births, 1990	7	6
	Hospitals	1226	1054
	Physicians/10,000 people	19.6	31.3
	Dentists/10,000 people	5	2
EDUCATION	Literacy rate	99%	97%
	University Students, 1989	1,465,159	826,306
	GDP for Education	7.4%	3.2%
	R & D, 1990 % of GDP	1.3	1.1

Sources: The Economist, Feb. 1st ,1992, Anuario El Pais 1991, The Europa World Year Book 1991

IV. THE BIOTECHNOLOGICAL COMPANY

For entrepreneurs and business people not every invention or scientific breakthrough deserves the investment effort leading to commercialization and profit. From a business perspective, the importance of any discovery is founded first on its market potential rather than in its scientific significance however significant this might be. Thus the ultimate, albeit not the sole, criterion for establishing successfully a firm in biotechnology is the market. However, before undertaking a preliminary business plan, entrepreneurs should test their technology as only an affirmative answer deserves further advance in establishing such venture. These initial plans should answer the following questions satisfactorily:

1. Is the product unique?
2. Will the product or process serve a market large enough to justify the costs of its commercial development?
3. Does the technology leads to one single product or multiple subsequent products
4. Is there any way to protect the product from similar late comers.
5. Should the technology be patented?
6. Is the transition from lab. scale to industrial scale smooth?
7. Does the product offer any major obstacle to its development and commercialization?

If all the above questions are answered adequately a second phase involving the design of the company starts. It is in this second phase where the entrepreneur's decision plays a major role. This stage which entails the development of the company's framework deals with the creation of the management team whose essential components might be:

(a) A reputable scientist or engineer specialized in the process or technology under consideration
(b) A capable business manager with proven experience in business start-ups
(c) An experienced regulatory expert
(d) A resourceful manufacturing/operation manager with strong background in the scale up of processes
(e) A versatile sales and marketing manager.

The final stage would involve the development and implementation of a realistic business plan objective. A business plan is an art as well as a science. In it, well founded objectives and hard data are blended with forecasts of uncertain origins and questionable value, along with personal intuition and experience.

As a result a business plan is often unique in space and time and seldom repeatable since the market is dynamic by nature. In biotechnology those considerations are even more pronounced given the marked difference existing between different industries in both business attitudes, technology development,political climate and market potential. In spite of those differences a business plan should include the analysis of the following variables[25]:

* The Reason of Being (also called mission) of the company and the products
* Market analysis and strategies
* R&D goals and its funding
* Plans for Manufacturing and Operations
* Organization and personnel
* General financing strategy
* Tax Planning, etc.[26].

Any of the above considerations can damage irreparably the success of a biotechnology company if not properly evaluated, and their evaluation seldom is easy. The rapid attrition of independent biotechnology companies has been predicted for the last six years. However, because of the periodic availability of both capital through stock sales and limited R & D partnerships and corporate alliances, bankruptcies and other eroding factors like mergers and buy-outs have been few. For how long will this trend persist? How many independent companies will exist at the end of the 1990s ? In early February 1990, Genentech executives, in part citing an inability to fund all the promising research in their labs, sold 60 % of the company to Roche Holding Ltd. for $2.1 billion. Genentech was at the time the largest independent biotechnology company and had developed four of the major biotechnological products that had been approved to date. The emergence of Amgen, another biotech success story, has been generally attributed to investors wishing to give biopharmaceuticals a second chance.

The future prospects of the industrial applications of biotechnology appears to be bright by all indicators. G. Rathman, former CEO of Amgen predicts a marked increase of biotech companies throughout the '90s, even after mergers and takeovers are taken in consideration. "There is plenty of room for an awful lot of companies". Although this view is not universally accepted, a recent survey of USA biotech industries show that 39% of the firms will be absorbed by larger firms within five years, and 47 % hope to acquire a smaller firm in the industry during the same period[27]. That kind of information could cautiously be extended to Canada.

With such a data it is unrealistic to predict the rate of attrition of biotech firms in the 1990s, or what the next Genentech or Amgen will be. Analysts are looking for the exceptionally successful company from samples of young

companies expected to begin turning a profit in the mid-1990s. In this regard, it appears however, that during the 1990s industrial applications of biotechnology will follow the trend observed in the late '80s, and they will be as unpredictable and dynamic. In fact for investors looking to make money in biotech, patience is the key. In the end, ".. most biotech ventures end up doing something different than their initial plans. What you are betting on is the resourcefulness of the people and their scientific talent"[28]. In addition, the health of the financing environment, the strength of intellectual property protection, and the ability of regulators to better recognize the major social benefits of biotechnology in making the process more expeditious, will be decisive for companies to expand and prosper.

V. FACTORS DETERMINING THE COMMERCIAL DEVELOPMENT OF BIOTECHNOLOGY

A number of factors determine the success of a biotech venture. According to their impact such a commercial venture can be classified as primary, secondary and tertiary. Primary factors are: a) Financing and tax incentives for companies; b) Government funding of basic and applied research; and c) Personnel availability and training. The Secondary factors are a) Health and safety; b) Environmental regulations; c) Intellectual property laws; d) University-industry relationships. Finally, Tertiary factors include a) International technology transfer, investment, and trade; b) Government targeting policies; and c) Public perception.

A brief discussion of the three most relevant factors will clarify by some of the considerations established in the next two sections.

A. FINANCING AND TAX INCENTIVES

One of the most intriguing financial stories of the 1980s has been the successful financing, specially in the USA, of independent biotech firms. These companies have been able to raise capital on the basis of potential, rather than actual, operating results, primarily because they offer the possibility of huge returns. The availability of venture capital to start new firms, along with tax incentives provided by the governments to encourage capital formation and stimulate R & D in the private sector, are most significant in the commercial development of biotechnology. According to a recent survey in the USA[29] the average biotechnology company spends 63 % of its income on R & D. Furthermore, R & D spending per employee and year averaged $30,000. This figure was much higher for biopharmaceutical

companies which spent $47,000 per employee. Traditional pharmaceutical companies spent only $26,000 per employee.

Lacking product revenues to completely support their R & D efforts, financing demands and opportunities shape priorities. Early-stage companies burn start-up capital on R & D and building business infrastructure. Their additional capital needs drive them to seek other options of venture financing and corporate alliances. As companies mature, they approach the public equity market. Public equity (39 %) and strategic alliances (34 %) are expected to provide the bulk of biotech companies' capital needs during the next five years. Public financing reached the highest level in the history of biotechnology and strategic alliances likely to growth in high numbers in Europe, North America and Japan.

Tax incentives relevant to established companies commercializing biotechnology are those which stimulate R & D investments and those which encourage capital formation. Corporate tax rates are also important.

B. GOVERNMENT FUNDING OF RESEARCH

The ability of a company to produce significant innovations is related to the amount it spends on research and development. There is also evidence to suggest that a company's rate of productivity increase is also related to its research expenditure, but with a time lag[30].

The goal of basic research is to understand the phenomena under study without consideration for their ulterior commercial applications. Such a research is critical for advancing applied science or technology and eventually reaching a commercial target. Basic research is usually conducted at universities, and government research institutes.

On the other hand the objective of applied research, or technology development, is to gain knowledge needed to attain a process or product of social interest, and hence of commercial significance. Such a research is funded by both industry and governments, and it is carried out mostly in company labs and university labs. Applied research in biotechnology includes among others, the development of bioreactors, screening of microorganisms for potential products and, the understanding of the genetics and biochemical processes of industrially important microorganisms.

Some controversy exists over government support of basic and applied research. In general, it is accepted that the development of a technology within a country will progress faster if companies have access to local basic

research scientists for consulting and research contracts. The Japanese model for the commercialization of semiconductors is often used as a reference for biotechnology commercialization. The pattern of funding in Japan gives priority to applied research to the detriment of basic research. Since the USA. and other countries show limited restrictions in the publication of basic research, Japan might rely on that free and available information to advance faster and cheaper in the direction of commercial feasibility[31].

C. PERSONNEL AND TRAINING

Properly trained scientific and technical personnel are vital to any country's industrial competitiveness in biotechnology. The commercial development of biotechnology will require several specific types of technical personnel such as: specialists in DNA and monoclonal antibodies technology (MAb) like molecular biologists and immunologists; industrial microbiologists and biochemists; enzymologists and cell culture specialists; and as biotech companies move more into continuous processes and bioreactors,chemical and biochemical engineers. Shortages of these types of specialists will be a limiting factor in the rate of growth and commercial success in biotech companies. In that sense training programs must be a permanent consideration in the governments research policies.

Apart from the above factors, there are other aspects that play a role difficult to quantify but nevertheless important. The abundance or scarcity of raw materials can determine the direction of biotechnology in a country. Risk taking is associated with innovation, and innovation is now widely recognized as being a cornerstone of the success of economic ventures. This is particularly true in biotechnology. North Americans are in general more willing to risk than Europeans and this, to date has manifested itself in the vigour and number of biotech companies in North America.

VI. BIOTECHNOLOGY IN SPAIN

Compared to other scientific disciplines, Spain has traditionally had the highest scientific level of achievement in the biological sciences. Two of its Nobel laureates are from medicine, and molecular biology. However, until 1986 scientific research and development took place in Spain without a framework with which the Administration could undertake appropriate planning and coordination. In 1986 the National Plan for Scientific Research and Technological Development was established. The absence of such a plan has

affected, to a certain extent, a more vigorous development of the sciences and new technologies in general, and of biotechnology in particular. The present section describes major aspects of Spain's policies in biotechnology, and the R&D effort within the country. In this sense two institutions deserve special mention in conjunction with biotechnology. These are : The Consejo Superior de Investigaciones Cientificas (CSIC) or Higher Centre for Scientific Research, and the Centre for Industrial Technological Development (CDTI). In addition to these research institutions, there will be a description of human resources in biotechnology. Finally the section will deal with Spanish R & D as associated with the EC, the biotechnology industrial sectors, and the status of intellectual property in the country.

A. GOVERNMENT SCIENCE POLICY

The above National Plan was set to cover activities at the National, Sectoral, Provincial, and International level. The goals of the Plan were four: I. Planning and coordination of the national R & D activities, II. Intensification of research efforts in areas in which Spain has an acceptable level of scientific achievement, and exploration and development of areas of special interest, III. Mobilization of private resources and stimulation of industrial innovation in the private sector, and IV. Renewal of scientific personnel.

To reach the above objectives concrete programs were developed in the following areas: 1) Training of scientific personnel; 2) Selection and financing of research programs; 3) Enhancement of Spain's experimental infrastructure; 4) Design of programs to stimulate innovation and competitivity in the industry.

The previous areas were implemented for the period 1988-1991 in four major research programs with R & D funding exceeding Cdn $1.5 billion. Of the four major research programs the second one, called Natural Resources and Quality of Life gives maximum relevance to the development and application of Biotechnology. This program has the following lines of activity:

1) Fundamental research in biotechnology
2) Biopharmaceuticals
3) Health
4) Agriculture
5) Livestock
6) Marine resources and aquaculture
7) Food technology
8) Forest research and technology
9) Conservation of the national heritage and environmental degradation.

A distirubtion of the projects approved in this area (Quality of Life) is shown in Figure 5.

To redress some deficiencies in connection with biotechnology in the 1986 National Plan of R & D , a National Biotechnology Program was set in place for the period 1988-1992. The aim of the program was to implement more effectively, reinforce and expand to six working areas the four areas established in the 1986 National Plan. These areas were as follows:

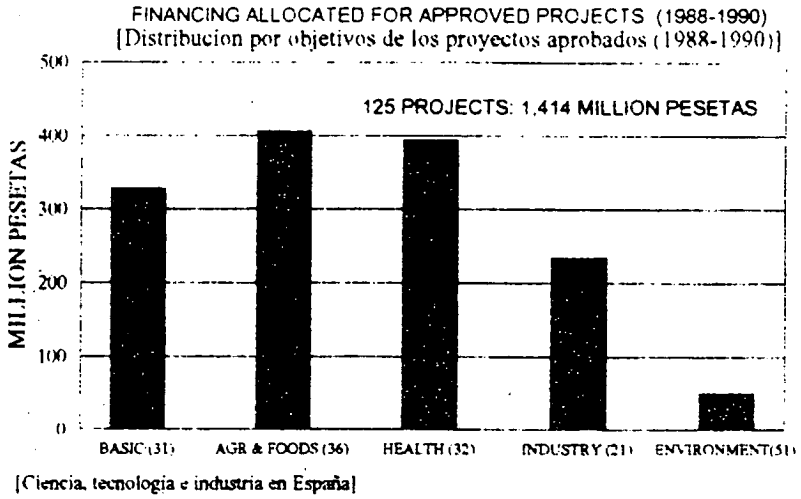


Figure 5

A. Training and increase in R & D personnel,
B. Creation of infrastructure and equipment,
C. Funding of discrete R & D projects and joint research projects with the industry,
D. Development and implementation of programs with other countries,
E. Development and construction of a National Biotechnology Centre in Madrid by 1991
F. Exploration and development of promising new areas in biotechnology.

Spanish biotechnology develops mostly within a number of Ministries specially the Ministry of Industry and Energy, the Ministry of Science and Education, and the Ministry of Agriculture, Fisheries, and Food. The financing of the National Biotechnology program comprised over 10% of the budget of the National Plan of R&D that is 5,487 million ptas. Figure 6 shows a breakdown of the budget.

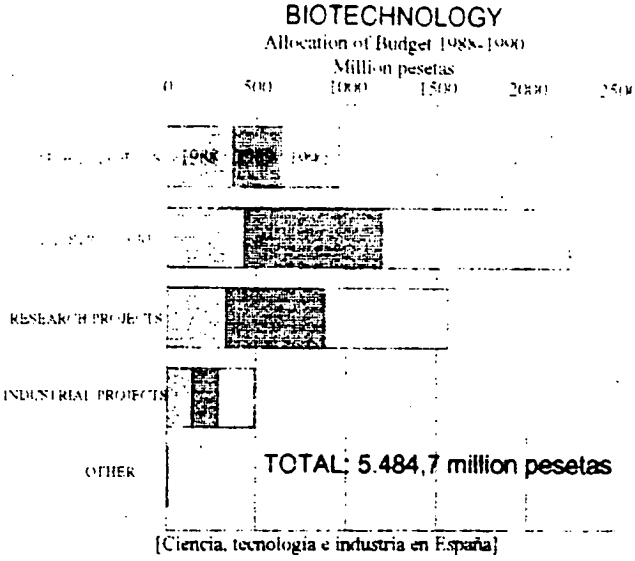


Figure 6

B. AREAS OF MAXIMUM PRIORITY

The Spanish Administration considers of maximum priority the following areas:

1. APPLICATIONS RESEARCH

* Genetic manipulation of microorganisms
* Cultures of plant and animal cells in relation with their applications
* Applications of biochemical processes and enzymology

2. AGRICULTURE AND NUTRITION

* Genetic improvement of plants
* Nitrogen fixation
* Enhancement of fermentation processes (wines, beer, dairy products)
* Improvement of starter microbiological cultures
* Bioconversion of lignocellulose materials
* Biomass production and conversion
* Insecticides, fungicides, and herbicides

3. BIO-DEGRADATION & POLLUTION CONTROL

* Treatment of waste water and toxic residues from industrial effluents
* Biodepuration of water
* Elimination of heavy metals and processing of industrial solid wastes

4. HUMAN & ANIMAL HEALTH

* New generation of antibiotics
* Monoclonal antibody technology
* Vaccines, diagnostic reagents, antigens,and allergens
* Blood derivatives
* Neuropeptide, protein and enzyme applications

5. INDUSTRY

* Application of microorganisms to mineral leaching
* Recovery of heavy metals
* Production of specialty chemicals (amino acids, organic acids)

Other biotechnology projects not included in the area of Quality of Life (Figure 6) are shown in Figure 7.

C. PRINCIPAL R & D INSTITUTIONS

Biotechnology is supported in Spain at three levels of government, the regional or provincial, the national, and the European. Three main

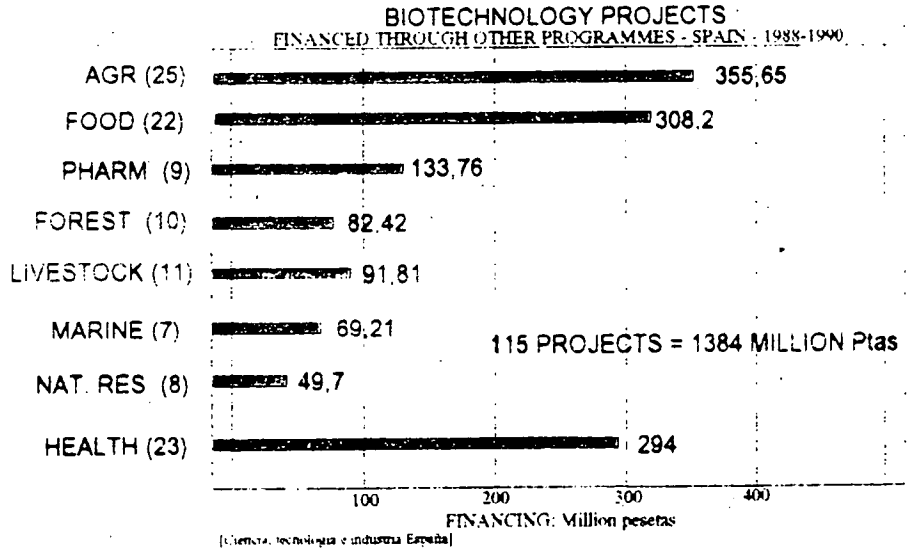


Figure 7

institutions are involved in the coordination, funding, and R & D of biotechnology. These are : the Interministerial Committee for Science and Technology (CICYT)[32], the Centre for the Industrial Promotion of Technology (CDTY), and the Public Research Institutions. Given the importance of these institutions in potential Spanish-Canadian ventures we briefly discuss them

1. INTERMINISTERIAL COMMITTEE FOR SCIENCE AND TECHNOLOGY (CICYT)

This is the national agency responsible for the coordination, funding and implementation of R & D national effort. CICYT consists of representatives from Ministerial Departments appointed by the Government and chaired by either the Minister of Industry and Energy or the Ministry of Science and Education. Other ministries represented include: Agriculture, Fisheries, and Food; Health and Consumer Affairs; Defense; Public Works; Transport and Communications; Culture; Economy and Finance.

The CICYT through its General Secretariat has four major duties, these are:

1) Coordination of the national and international R & D programs

2) Budget management

3) Administration of the R & D national plans

4) Technical evaluation and monitoring of the plan's objectives

2. THE CENTRE FOR INDUSTRIAL TECHNOLOGY DEVELOPMENT (CDTI)

The Centre for Industrial Technology Development (CDTI) was established in 1978 by the Ministry of Industry and Energy to stimulate industrial research and innovation.This organization deals mostly with medium and small size firms. CDTI, which has a major influence in the development of Biotechnology in Spain, is responsible for the following functions:

A. Identification of priority technologies,
B. Funding of pre-commercial research and development, and marketing of new products and processes,
C. Analysis of the results from European projects (EUREKA, BRIDGE, ECLAIR, FLAIR, etc.) and feed back to the Interministerial Commission for Science and Technology.

CDTI funds two type of projects: technology development projects and concerted projects. In the former case a company can negotiate an ample set of funding formulas ranging from credits with preferential interests, to risk and venture credits, purchase of shares in capital-risk operations. In the latter case the credits are addressed to projects at a pre-competitive stage, and take the form of interest-free loans which cover up to 70 % of the project cost. The CDTI budget for 1989-1991 was over Cdn $300 million and $215 million for 1991-1992. CDTI funds an average of 33 % of the total project, the duration of the them range between 2 and 6 years, for credits in the range of Cdn $250,000 to 2 million per project.

3. PUBLIC RESEARCH INSTITUTIONS (OPI)

The Organismos Publicos de Investigacion or Public Research Institutions (PRI) take part not only in the Sectoral Programs of their relevant Ministerial Departments, but also participate in the various National Programs. Some of the most important PRIs with biotechnology programs include the National Institute for Agricultural Research, the Institute of Oceanography, both dependent on the Ministry of Agriculture, Fisheries and Food; the National Institute of Health, dependent on the Ministry of Helath and Consumer Affairs; the Centre for Energy and Environmental Research (CIEMAT) dependent on the Ministry of Industry and Energy; and the Higher Centre for Scientific Research (CSIC). A brief discussion of the last two institutions follows.

Centre for Energy and Environmental Technology Research (CIEMAT)

CIEMAT is involved in two areas of biotechnology namely, the environment and the impact of various types of exposures on human health. In the former case CIEMAT has active programs in the biotreatment of effluents from the pulp and paper industry, and on urban solid wastes. In the area of human health CIEMAT is involved in projects dealing with occupational health, blood cell dammage through radiation, parvovirus MVM infections, and gene therapy. Full time research personnel was 550 in 1989, and the R & D budget exceeded $ 90 million.

The Higher Centre for Scientific Research (CSIC)

El Consejo Superior de Investigaciones Cientificas (CSIC), dependent on the Ministry of Science and Education, is the Spanish counterpart of the National Research Council (NRC). CSIC is the largest public R & D institution. It has 90 centres and over 7,000 employees including 2,100 research professionals. The CSIC's total available funds for R & D in 1991 were Cdn $390 million. It has an international reputation in biology,

medicine, solid state physics, and food science and technology. An ample description of the activities of the CSIC is given in Reference.[33]

A recent major addition to the research centres of the CSIC is the Centro Nacional de Biotecnología (CNB).

THE NATIONAL BIOTECHNOLOGY CENTRE (CNB)

In 1991 it was officially opened in Madrid as a dependent on the CSIC. The centre was conceived in 1984 and construction began in 1986. The CNB facilities exceeds 18,000 m^2 area, staffs more than 400 professionals and technical personnel, and it is associated with the Universidad Autónoma de Madrid. Total investment in this centre exceeds $60 million. The design, construction, facilities and equipment are state of the art. CNB has three major lines of activity namely, a) cell and molecular biology with a strong emphasis in immunology, b) microbial biotechnology directed to its application in biopharmaceuticals, agriculture and the environment, and c) plant biotechnology, emphasizing genetic improvement and resistance to plant disease and environmental stress in plants. A board of trustees including representatives from the industry administer CNB. Several multinationals established in Spain plan to launch a series of products developed in collaboration with CNB. CNB which is most interested in establishing various areas of collaboration with Canadian firms and institutions, could develop important links with its sister organization in Canada the Biotechnology Research Institute of Montreal.

Other centres of CSIC involved in Biotechnology include the Centro de Biología Molecular (Madrid), Centro de Investigación y Desarrollo (Barcelona), Instituto de Investigaciones Biomédicas (Madrid), Instituto de Biología Vegetal and Fotosíntesis (Sevilla), Instituto de Farmacología y Toxicología (Madrid), Instituto de Microbiología (Salamanca).

D. SPANISH BIOTECHNOLOGY & THE EUROPEAN ECONOMIC COMMUNITY

A number of factors has hindered the development of Biotechnology in Europe. In the first place, the multiplicity of regulations and intellectual property laws. Then political considerations related to the subsidies for fermentation feedstock have made uneconomic the development of certain areas in biotechnology. On balance, the European Community (EC) lags behind the USA.

The III EC Framework Program (1991-1994) with a Cdn $1.067 billion budget includes three major sub-programs dealing with Biotechnology.[34]

These are:

1. PROGRAM BRIDGE (Biotechnology Research for Innovation, Development and Growth in Europe)

Period: (1991-1993)

Goal: To foster transnational research, and produce biological data, materials, and processes for their industrial biotech applications.

Budget: Cdn $144 million.

Type of Projects :There are two types of projects, N (Network, acquisition of data of industrial interest) and T (Target, of immediate industrial application). Some typical N projects include: Protein design and molecular models, evaluation "in vitro" of pharmacological toxicity of certain molecules, safety, evaluation of genetically modified microorganisms, etc. Example of T projects include: Sequencing of yeasts genoms, molecular identification of new plant genes, modification of bacteria of lactic acid, etc.

Participation: The EC provides up to 50 % of the cost of the project the rest must be provided by the industrial partners from more than one EC country. There are more than 600 European laboratories and research institutions involved in this program, 40 of which are Spanish. Canada could participate with Spanish and other European partners. To date more than 45 % of the successful projects counted with Spanish participation.

2. PROGRAM ECLAIR (European Collaborative Linkage of Agriculture and Industry Through Research)

Duration: (1989-1993)

Goal: To foster industrial integration of European agriculture utilizing biotechnology and other advanced technologies. The program encourages collaboration among industrial and agricultural sectors, and among state members. It promotes pre-commercial R & D, and facilitates interchange and training of R & D personnel.

Budget: Cdn $115 million.

Type of Projects: The program deals with four major sectors. These are: 1.Production of biological resources for agriculture/industrial applications, 2. Harvesting and conditioning for agro-industrial applications, 3. Fractionation and/or extraction methods, 4. Transformation and control methods.

Participation: The EC funds no more than 50 % of the project's cost, industrial partners, two at least from two EC countries, contribute the rest. Spain has participated in 21 out of 43 successful projects in 1991.

3. PROGRAM FLAIR (Food Linked Agro-Industrial Research)

Duration: 1989-1993

Goal:This program is divided in three major areas, namely, 1. Evaluation and improvement of food quality, 2. Hygiene, safety, and toxicology in plant and animal foods. 3. Nutrition and health.

Budget: Cdn $36 million.

Participation: As in the above programs. The successor of this program will pursue the areas initiated by FLAIR and will include to aquaculture. The established budget is Cdn $480 million.

4. PROGRAM EUREKA. (European Agency for the Coordination of R & D)

Of major industrial significance is the biotechnology area of the EUREKA Program. In this program the participation of large firms is also important. Project budgets tend to be considerably higher than those seen above. **Spain's financial contribution** is 17.2 % of the total budget. The biotechnology effort of the Eureka program consists of more than 64 projects, 33 in the area of human health, 11 in plant biology, and the rest in food processing, and specialty chemicals. Until mid-1991 Spain was participating in more than 22 projects (out the total 64 mentioned) with a Spanish contribution of more than Cdn $78 million (out of a total of Cdn $174 million[34a]). Some examples of successful projects include, the development of several diagnostic kits for allergies and occupational skin disorders between a Spanish and a Dutch pharmaceutical companies. The project had a total budget of Cdn $9.5 million. Other projects like fish husbandry and aquaculture, drug delivery systems, novel method for the production of proteins of medical interest, utilizing recombining DNA techniques, greenhouse cultivation of saffron, etc. had budgets in the Cdn $ 3-130 million, and project duration from 3 to 7 years. Spain has participated preferentially with France (67 %), U.K (62 %) and Germany (53%). In addition, in 23 % of the projects one of the Spanish partners was not member of the European Community.

From 1990 onwards there has been an increment in the participation of Spanish firms in these programs, the industrial sector however, has been

slow at participating in the R & D effort, and clearly, has not matched the effort made by government research.

A long list of Spanish participants, from industry, universities, and government laboratories, in the BRIDGE, FLAIR, and ECLAIR programs as well as the project titles can be found in reference [34].

E. THE INDUSTRIAL SECTOR

Recent estimations of the volume of sales of biotech industrial products exceeds 15 % of Spain's GDP or (Cdn $92 billion). 71 % of the 80 firms with manufacturing facilities actively involved in biotechnology are Spanish. In the diagnostics sector that figure was 100 % and in fine chemicals and pharmaceuticals it was 40 %. More than 40, 000 people are involved in the industrial application of biotechnology, 5,000 of them in technology development and nearly 2,000 in R & D. Information, albeit in need of updating, concerning public and private sector biotechnology groups, focus of activity, and patents issued can be found in the References at the end of this document[32].

Active Sectors include:

1. AGRIFOOD

Over 400 firms[34b] with a manufacturing volume of Cdn $50 billion constitute the Spanish agrifood sector. An excessive dependence on external technologies makes this area a major player in the future of Spanish industrial biotechnology. Spain is already a leader in the area of citrus plants and products. Main areas of activity are in genetic improvement of seeds, disease resistant plants, and development of plants resistant to drought and hard water. Other areas are in the production of wines and beers with low alcohol content, and in the manufacture of cheese, ham and other meat products. The food industry appears to be taking rapid steps toward the incorporation of new biotech methods. In 1991 there were over 2,000 scientists and engineers involved in more than 600 industrial projects in this sector.

2. PHARMACEUTICALS

Pharmaceuticals firms constitute 39 % of the companies involved in biotechnology. In 1990 the volume of sales of this sector exceeded Cdn

$4.8 billion, from which $300 millions were from biopharmaceuticals. The percentage on sales devoted to R & D was 12%[35], that effort was preferentially focused in recombinant DNA technology and the development of new generations of antibiotics. Antibiotics firms are well represented by the size of their R & D programs and by the volume of sales.

3. DIAGNOSTICS

More than 11 % of the biotech companies are involved in diagnostics and develop their products through very active R & D programs. Vaccines, DNA probes and biotech kits are important areas.

4. ENVIRONMENTAL

Government estimates show that for the next four years the cost of compliance with the environmental regulations of the EC would be as high as Cdn $13.3 billion (1.2 Trillions[d] PTAS)[36]. Until recently Spanish compliance with national environmental regulations had somewhat to be desired. A recent industrial survey indicated that more than 71 % of Spanish companies did not have an environmental coordinator, and more than 35 % of the firms surveyed were not aware of the environmental regulations issued by the EC. That in contrast with 92 % of other European firms which considered the environmental issue very important. The budget allocated for environmental compliance by the Spanish Administration for the period 1990-1994 exceeds Cdn $1.4 billion and will be managed by the Programa Industrial Tecnológico Medioambiental (PITMA). A large part of these funds are addressed to small and medium size firms.

The lag of nearly 15 years relative to the most environmentally advanced EC countries will have to be eliminated within the next 4 years lest Spanish industrial competitivity suffers severe consequences. In waste water treatment, the National Plan for Industrial Waste which ends in 1993 has among other objectives, the elimination of 12,000 tons of PCBs and over 96,000 tons of industrial waste oils. An area of great concern is that of personnel training for which there are more than $380 millions assigned.

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d The official figures are "1.2 billones de pesetas". The Spanish billion(one million of millions) not to be confused with the Canadian billion (one thousand millions)

Drastic measures applied from Brussels are already forcing Spanish national and provincial governments and industries to meet European environmental criteria. In this aspect the potential opportunities for Canadian firms in the area of waste water treatment, air quality control, toxic wastes, environmental audits, etc., are excellent.

F. HUMAN RESOURCES

The training of R & D professionals is contemplated in the National Plan and for the period 1988-1991 were allocated Cdn $323 million. The main objectives of this Training Program are:

* To increase the number of R & D personnel in Spain
* To ensure the proper distribution of the human resources according to established priorities
* To facilitate training abroad in understaffed fields
* To encourage short-term visits by foreign experts to Spanish research groups
* To facilitate scientific personnel exchange between the industry, public research institutions, and universities

According to 1991 statistics there were 320 different groups comprising 1,500 scientists and engineers working in biotechnology R & D projects. Most of these groups were located in Madrid (40 %) and Barcelona. Most of them hold postgraduate degrees at the Ph.D level. Projects are funded by both the Spanish Government in fundamental biotechnology, fine chemicals, and new materials,and by the European Community through the programs EUREKA, BRIDGE, ECLAIR, and FLAIR. The distribution by R & D activity in Biotechnology is as follows[37]:

* 33 % Food and nutrition
* 28 % Fundamental biotechnology
* 25 % Human and animal health
* 9 % Specialty chemicals,industry, energy, and minerals
* 5 % Biomass and Pollution control

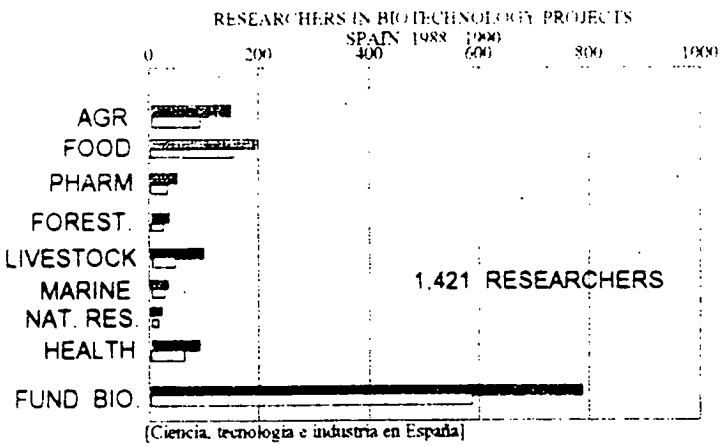

Figure 8

The scientific level of Spain in Biotechnology is by the quality and quantity of its scientists and research centres, comparable to the best in Europe[38, 39]. There is, however, a considerable gap between the fundamental and applied level of Spanish biotechnology as until recently the private sector failed to see the benefits brought about by innovation through guidance and funding of Spanish and EC agencies. An additional reason for concern is the potential shortage of Spanish engineers and applied scientists. Spanish engineering programs tend to be highly demanding with stringent entrance examinations and heavy work loads. Present enrolment in science and engineering, however, is insufficient for the requirements of the impending single European market.

G. INTELLECTUAL PROPERTY IN SPAIN

The legislation of intellectual property in Spain is based on the Patent Law (Ley 11/1986) of March 20,1986, the Trade Marks Law (Ley 32/1988) of November 10, 1988 and the Law of topography for semiconductors (Ley 11/1988). In addition, Spain is a signatory of the Paris Union Convention for the Protection of Insdustrial Property, of the Munich Convention of October 7, 1973, of the European Patent Agreement in 1986, and of the Patent Cooperation Treaty (PCT).

Spain is a signatory of the 1977 Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, and it has requested from the world Organization for Intellectual Property, the granting of official statute of International Authority of Deposit of Microorganisms.

The Munich Convention implies patent protection to any applicant of a EC country not only within the European Community but also this protection is extended to non members like Sweden, Switzerland, Austria and Liechtenstein. The Patent Cooperation Treaty extends the protection of an invention to the 42 countries signatory members.

Patents are granted by the Industrial Property Registry (Registro de la Propiedad Industrial) for a period of 20 years and are not renewable thereafter. Trademarks must be registred to be legally protected. They are registred for a 20-year period and are renewable. Copyright belongs to the author until his death and to his heirs for 60 years thereafter.

As stated earlier Spain is a net importer of technology. In 1990, 120 patents in biotechnology were filed which represents 1.1 % of the total number of

Spanish patents. Spanish and foreign distribution by areas were as follows : 49% of patents are on fermentation processes, 23 % were on diagnostics, 22 % on monoclonal antibodies, vaccines, and genetic engineering, and 6 % on molecular biology[39]. The number of European and PCT applications that included Spain were 787 and 513 respectively. A distribution of the registered Biotechnology patents in 1990 is shown in Table 3.

TABLE 3

DISTRIBUTION BY COMPANIES OF BIOTECHNOLOGY PATENTS FILED IN 1990 IN SPAIN

Applicant	No of Patents
Sandoz (Switz.)	8
Boehringer-Mannheim (Germ.)	6
Oncogen (USA)	5
Genentech (USA)	4
Sanofi (Fran.)	4
Gist-Brocades (Holl.)	3
CSIC (Spain)	3
Hoffman-La Roche (Switz.)	3
Other	84

Although an important number of inventors in the above patents are Spanish citizen their work with foreign multinationals exclude them from ownership or patent title. A more detailed information on the patents law in Spain is given in references found at the end of this document[40,41]. The EC is expected to adopt a common policy on patents during 1992. Drug approval will be considerably speeded up as the approval in one country will be valid for the rest of the Community.

VII. BIOTECHNOLOGY IN CANADA

Canada's biotechnological industries are among the world's most innovative, forward looking and successful. Biotechnology has a solid institutional and industrial base, employing an important nucleus of world-renowned researchers. Canadians have been innovators in fields related to biotechnology, for example insulin, discovered at the University of Toronto, and canola, are major examples of agrifood biotechnology.

Canada has been a country with an excellent scientific record. Its five Nobel prizes in the physical and biological sciences bear witness to it. An excellent educational system has produced a solid scientific and engineering base which together with good entrepreneurship has given rise to a highly developed biotechnology. Its research and development system, as opposed to that of Spain, was well established with the arrival of the new biotechnology in the mid-70s. This allowed a fast response to the increasingly evident importance of those technologies. This section will give an overview of the activities in conjunction with biotechnology of the Canadian Government. A brief description of the National Research Council and some of the public centres associated with it involved in the development of biotechnology follows. A section on Canadian human resources in R&D, biotechnological industries, and Intellectual property in Canada will be commented upon.

A. GOVERNMENT SCIENTIFIC POLICY

In 1983 the federal government of Canada formally considered biotechnology a national priority for economic growth. Identifying seven strategically important areas. These were:

1. Aquaculture
2. Forestry
3. Human and animal health care
4. Plant strain development
5. Nitrogen fixation
6. Mineral leaching and metal recovery
7. Cellulose utilization and waste treatment

These areas were felt to satisfy the resource- rich and advanced industrial nature of the Canadian economy. The above objectives were to be implemented by the following measures:

A. Creation of the National Biotechnology Advisory Committee (NBAC) to advise and evaluate the progress.

B. Establishment of networks to develop and promote links between research institutions and users.

C. Creation of an interministerial committee

The NBAC is appointed by the Minister of Science and provides advice to him. Representatives from the private sector, universities, and government form the 24-member committee. The major areas for advice include:

1) The development of strategic plans for the near and longer term incorporation of biotechnology in industry;

2) The continued strengthening of the science and technology infrastructure to support the industrial development and application of biotechnology;

3) To study both, the approaches to biotechnology being pursued by other nations and the opportunities and appropriate mechanisms for Canada to foster international collaboration in this field.

4) To develop programs, policies, regulations, etc., which are capable of influencing the course of industrial and human resource development in Canadian biotechnology.

These guidelines aim at developing policies and strategies for the harmonic economic growth of Canada. This economic growth is to be achieved by enhancing international competitiveness of Canadian industry through the development, application, and commercialization of biotechnology[42].

B. AREAS OF PRIORITY

The areas identified by the National Biotechnology Advisory Committee are similar to those development by the Spanish Government except for Forestry, included by Canada but assigned a lesser role by Spain, and Industry and Applications Research included by Spain. These are Canada's strategic areas with their division into other subareas :

1. FORESTRY

- the pulp and paper industry
- regeneration of harvested forests
- protection of existing and new forest resources;

2. WASTE TREATMENT

- promote the Wastewater Treatment Centre, Burlington, Ontario

3. AGRICULTURE & FOOD

- promote Agriculture Canada as the Ministry responsible for R & D coordination and identification of strategic areas in agriculture and food processing industries

- Agriculture Canada to further foster the development and use of probiotics for commercialization.

4. HUMAN BIOPHARMACEUTICALS

- development and construction of a fermentation facility ,designed to Good Manufacturing Practice (GMP) standards.

Public expenditure for the period 1988-1989 exceeded Cnd $11.1 billion. A distribution of these expenditures is shown in Figure 9. World-class collaborative research projects are being carried out at 14 National Centres of Excellence. Biotechnology is a major component in 7 out of those 14 Centres which count with the participation and support of the federal government, over 40 companies, and 35 universities. Areas of research include:

1. Bacterial diseases: molecular strategies for the study and control of bacterial pathogens of humans, fish, and plants

2. Biotechnology for insect pest management

3. Genetic basis of human disease: innovations for health care

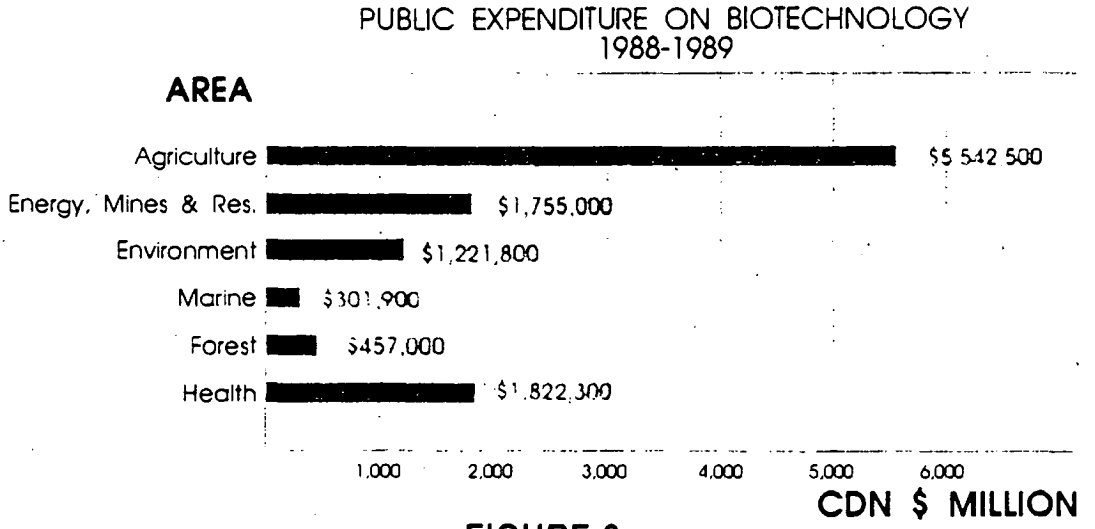

FIGURE 9

4. Neural regeneration functional recovery

5. Protein engineering : 3D structure, function and design

6. Respiratory health network of centres of excellence

7. Ocean production enhancement network

C. PRINCIPAL R & D INSTITUTIONS

The Government of Canada provides tax credits to companies involved in R & D in Canada. The amount of the credit varies, depending on the size of the company, from 20 to 35%. Canada has also perhaps the most competitive corporate tax treatment for R & D out of the ten most industrialized countries.

The Ministry of Industry, Science, and Technology provides financial assistance for the development of biotechnology through the Strategic Technologies Program. The **budget** for biotechnology is $40 million, and the type of projects includes feasibility studies, R & D alliances and technology application alliances. Projects accepted can qualify up to 50 % of the eligible costs. There is no maximum per project.

In addition to the technical and financial agencies of the federal government the provincial governments have independent programs to promote R & D and innovation in industry.

1. THE NATIONAL RESEARCH COUNCIL (NRC)

NRC is Canada's largest research granting agency, channelling over $480 million annually into university research and the training of new scientists and engineers. This figure constitutes 8% of the federal government funds for scientific activities ($5.6 billion in 1990-1991). It includes other agencies like the National Science and Engineering Research Council (NSERC), the Medical Research Council (MRC).

NSERC focuses on the funding of university-based research and offers a wide range of programs including the following: university-industry collaborative: Industrial research fellowships, research personnel exchanges, university-industry affiliations, co-operative R & D activities, etc. The **budget** for the period 1989-1990 was $20 million. Spanish firms could participate with Canadian partners.

The Industrial Research Assistance Program (IRAP) is the best Canadian program for financial and technical assistance to medium and small firms. It is especially designed for companies interested in R & D activity and innovation. Some 5,000 firms were helped in 1990 through IRAP. This program offers technical and financial support (up to 50 % to a maximum of $500,000) for promising research projects where the substantial risk to the

company would make it difficult to undertake alone. Over 13 % of IRAP collaborative research projects have been carried out in partnership with foreign countries including Spain.

Another source of funding within the NRC is the Medical Research Council of Canada. The budget for biotechnology is $43 million. Projects range from basic molecular biology to gene mapping and molecular diagnosis applied to patients[43].

NSERC biotechnology effort is the largest in Canada. Its industrial support comes from four major institutes namely, the Biotechnology Research Institute in Montreal, the Plant Biotechnology Institute in Saskatoon, the Institute for Marine Biosciences in Halifax, and the Institute for Biological Sciences in Ottawa. There is in addition, a network of research stations across the country wihich depend of the Ministry of Agriculture and Forestry.

A number of publications describe in detail the available technical and financial assistance offered by the government of Canada to industrial firms[44].

2. THE BIOTECHNOLOGY RESEARCH INSTITUTE (MONTREAL)

The BRI, opened in 1987, has become an international centre for excellence in the research, technology development and commercialization of biotechnology product. Although associated to the National Research Council, it is strongly oriented toward partnership with the industry. Thus universities, the private sector, and government participate in the management and activities of the BRI. In this regard,the Institute has reserved seven out of thirteen seats on the board of directors for business representatives. BRI has 220 employees including 180 scientists, engineers, and technical personnel, and it is endowed with a 1500 m^2 pilot plant. Its research has been structured in four principal areas, these are: biochemical engineering, genetic engineering, protein engineering, and cell fusion and molecular immunology.

3. THE INSTITUTE FOR MARINE BIOSCIENCES (IMB) (HALIFAX)

The mandate of IMB is to foster economic development and protect public health and safety by doing research into the chemistry and biology of marine organisms. Along with institutes in Japan and USA ranks as one of the largest marine biotechnology enterprises in the world. In some of the research areas, like shellfish toxins identification, marine microbiology, and marine biology including aquaculture and culture development, IMB is a world leader.

4. PLANT BIOTECHNOLOGY INSTITUTE (PBI) (SASKATOON)

PBI is responsible for keeping Canada abreast of research in plant biotechnology, and to develop enabling technologies in select areas vital to the country's agricultural and forest economy. PBI focuses on genes and metabolic regulators that better adapt to Canada's environment, genes that offer cold-tolerance, salinity tolerance, resistance to diseases and insects, and genes that improve plant product quality. There are two main themes to PBI's varied R & D program: the identification and definition of valued genes; and the development of transgenic plants that express these genes.

Other non-public research centre is the Wastewater Technology Centre in Burlington, Ontario. Established in 1972 by the Ministry of the Environment, this private centre has become an important Canadian facility in the development and evaluation of treatment and disposal technology for municipal and industrial wastewaters and associated residues.

Recently two of the Centres of Excellence of the province of Ontario have been linked with associates in The Four Motors of Europe (Catalonia, Spain; Wurttemburg, Germany; Rhone-Alps, France; Kombardy,Italy)[45]. However, most of the collaborative efforts with other European institutions are insignificant.

D. THE INDUSTRIAL SECTOR

There are more companies per capita engaged in biotech R & D in Canada than in US or Japan.

Prior to 1983 very few companies could be identified as operating in the field of biotechnology. A survey of the Science Council of Canada in 1985 showed that only 33 companies were performing R & D in biotechnology. In 1987 they grew to 125 companies. By 1989 the number raised to 220, and in 1991 they were over 450 companies developing or marketing over 10,000 biotech products. Biotechnology is well distributed all over the country with 36 % of the companies in Ontario, 25 % in Quebec and 11 % in British Columbia. Industrial research by the private sector is small compared to that of the most innovative countries although has improved during the last 20 years.

Strategic alliances play an important role in the transition from the R & D phase to commercial production. 87 % of Canadian firms surveyed in 1989 had alliances with other firms and organizations, with an average of 8.7 per

company [46]. Half of the alliances were with foreign firms, 33 % from the USA and 13 % from Europe. The top major factors for selecting a foreign partner were credibility, marketing expertise and access to technology.

Industrial biotechnology in Canada is largely made up of small firms. In fact only 20 % of the firms engaged in biotechnology have over 135 employees. Presently there are 13 publicly traded biotech firms in Canada[47]. Some of the largest firms include Allelix Biopharmaceuticals Inc., BioChem Pharma Inc., Biomira Inc., Cangene, Quadra Logic Technologies Inc. and RML Medical Laboratories Inc. Revenues in 1989 reached $660 million.

A list of firms involved in the commercialization of biotechnology can be found in various federal and provincial publications (43,48,49,50).

1. AGRIFOOD

In 1988, agriculture and food production, processing and distribution made 4.5 % of the GDP of Canada, and exports reached $10.2 billion. Of the 70 companies active in agrifood biotechnology, 39 are involved in improving crop yield and animal production. Average revenues per biotech company for 1992 are $16.8 million for agriculture and $2.5 million for food and beverages. Annual sales in the industry for biotech products could rise to $5 billion in 1992.

A major market potential for advanced bovine and porcine vaccines and other animal health products exists in the US, with smaller markets in Western Europe and Hispanic America. In probiotics the potential market exceeds $4.4 billion. These market could be readily accessed by Canadian companies with Spanish partners. Other areas of commercial development include, artificial insemination, and cloning, biosensors for food toxins, for example Salmonella, development of fermenters and bioreactors, etc. are being developed by Canadian firms.

A number of firms are active participants in the Transgenic Plant Centre of Saskatoon (a new section of the Plant Biotechnology Institute) assessing the first genetically engineered plants to come out of the laboratory[51]. The following areas of development are pursued by Canadian firms: cereal grain (genetic modification of the freezing tolerance of wheat and rye), and legume grain biotechnology, etc.

Another area of great interest in this context is aquaculture. Canada has the conditions to become one of the world's players in culture-based fisheries.

In salmon farming Canada produced 21,000 tons and a revenue of $150 million in 1991. This makes Canada the third largest salmon farming nation in the world. Other species like Rainbow trout are being successfully developed in Ontario[52]. The fact that Spain is one of the largest fish and seafood consumers in the world, and the first in Europe makes it worthwhile to explore areas of collaboration in aquaculture between the two countries. Some products and areas of development include, vaccines for fish grown by aquaculture, fish health monitoring systems, diagnostic tests for the detection of fish pathogens, etc.

2. BIOPHARMACEUTICALS

The Canadian pharmaceutical manufacturers see themselves as the kind of industry that the country needs for the future; technology and research based, with large value added products. It is after telecommunications, and aerospace industries, the sector spending the greatest percent of sales in R & D (8,8 %)[53]. Also, Canada is one of the ten largest pharmaceutical markets with sales of $4 billion of prescription drugs a year[54]. When the National Biotechnology Strategy was developed in 1983 Canada had a minor presence in the international pharmaceutical industry. Through the 1980s, this sector has emerged as a strong and dynamic one within the biotech industry. There are two reason for this upsurge of biopharmaceuticals in Canada. The strength of R & D in health care, and the dramatic increase in R & D investment.

Much of the Canadian pharmaceutical industry (about 85 %) is multinational. According to the third annual report of the Patented Medicine Prices Review Board, R & D investment in 1990 by patent-holding drug companies totalled $281.3 million or 8.8 % of sales. That is three times the level of 1987. Ontario, and particularly the Toronto area, accounts for 50 % of the manufacturing firms of the pharmaceutical industry, followed by the province of Quebec with 34 %.

In 1991 there were in Canada nearly 10 medium sized firms in the diagnostic kits or biopharmaceuticals capable of having a good level of R & D. These companies as indicated earlier have 50-100 employees. Many Canadian firms have commercial kits on the market.

Clinical diagnostics is the fastest growing sub-sector of this industry with a sales volume over $600 million extrapolatable to $1 billion by the year 2000. Canadian owned firms amount to 87 and sold only $100 million in 1991.

The industry is involved in a wide spectrum of R & D activities which include: anti-inflammatory drug development, antibody/radioisotope

technology for detection and treatment of cancer (this project is the result of one of Canada's largest-ever biotech R & D ventures)[55], tissue repair proteins, drug delivery systems, gene synthesis, protein biochemistry,etc.

The Canadian drug approval process is presently under review as the government is moving ahead with approaches to speed up the process[54].

3. ENVIRONMENT

The legal framework for Canada's environmental program is the Canadian Environmental Protection Act; one of the toughest pieces of environmental legislation in the world. Current estimates regarding the environmental costs of complying with these and new regulations controlling only pulp mill effluent in Canada are estimated to be $4 billion. Gross expenditure by government agencies in the construction and maintenance of sewage and waterworks systems is estimated at $2.5 billion. The North American market for water supply and waste water treatment facilities, products and services now exceeds $30 billion per year. These figures are eloquent enough to explain the potential of biotech waste water treatment.

To address these needs, municipalities and companies seeking technologies to enhance the operation of existing treatment facilities normally engage the services of a consulting engineering firm. About a dozen consulting engineering companies specialize in the design of waste water treatment facilities. Of these, only three have active in-house research programs. Canada has recognized strengths in fields like: biological waste treatment, bioremediation of contaminated sites, and pulp and paper industrial effluent treatment. A view of this area and companies involved in biotech environmental applications is given in reference[56].

4. FORESTRY

The forestry and forest products sector is one of Canada's most important industries. More than 5,000 companies work in this sector generating over $40 billion in sales annually. Canada is the world's second largest producer of pulp, and the largest producer of newsprint. About 1 million hectares are cut each year in Canada. Reforestation, the protection of existing forests, and the creation of new forest resources is a major concern for this industry. Efficient procedures for embryogenetic micropropagation and development of transgenic trees is in this sense a very much developed area. Also, Canada is the world leader in somatic embryogenesis, a new type of tissue culture for trees. This technology could drastically reduce the time it takes to deliver improved trees to the forest.

E. HUMAN RESOURCES

Canadian firms involved in biotechnology consider scientific and management expertise their most important assets for competitive purposes. Their most valuable source of advice tends to be universities, followed by in-house expertise, and the federal government. The industrial application of biotechnology in Canada will generate an almost 100 % increase from 1988 to 1992 in which the number of employees, only in the private sector, will rise to 11,638[46]. The average number of employees in 1992 for large biotech firms is expected to be 80, and for small companies the average figure is 50 employees.

The sectoral distribution of employees is 65 % for the area of diagnostics, followed by therapeutics with 33 %, 20 % aquaculture, 8 % environmental biotechnology, and the rest would be involved preferentially in consulting, and mining. The percentage of personnel involved in the food and agriculture sectors was 5%. Thus there is a considerable difference between the distribution of employees in Canada and that in Spain. This can be easily explained in terms of the more advanced stage of commercial biotechnology in Canada (a much larger number of biotech firms) and also in terms of the strategic areas of each country. For example, most of the Canadian personnel involved in biotechnology (37.6 %) are in production, followed by R & D (34.1 %), and sales and marketing (10.4 %).

Canada like the European Community and the USA might experience a serious shortage of professional such as biochemists, molecular biologists, chemical engineers, bioengineers, and senior management.

F. INTELLECTUAL PROPERTY IN CANADA

The legislation of intellectual property in Canada is based on the Canadian Patent Act. Patents in Canada are granted by the Canadian Patent Office and protect the owner for a period of 17 years if the patent was filed before 1989, or 20 years if the filing took place after 1989.

Canada is a signatory of the Patent Co-operation Treaty (PCT), administered by the World Intellectual Property Organization in Geneva[57]. This provides a standarized filing procedure, which is shared by Canada's main trading partners including the USA, Japan, and the EC. The country is considering becoming a signatory of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure.

Canada, like Spain, is a net importer of intellectual property, including patents. Of the more than 30 million patents in the world only 1.2 million are Canadian patents.

VII. COMPARATIVE EVALUATION OF BUSINESS OPPORTUNITIES IN SPANISH-CANADIAN RELATIONS

The objective of this document is to introduce Canadian and Spanish professionals, from the private or public sectors, to biotechnology opportunities in both countries. To describe those specific opportunities in a coherent and extensive manner is beyond the scope of this introductory report. Nevertheless, during its preparation, public and private organizations in both countries have expressed a great deal of interest in exploring areas of mutual interest. The forms of collaboration range from representations, and distribution of products to strategic alliances in manufacturing and R & D. These companies or institutions are referred in Appendix I and II. Some of them have a lot to offer since they have the mandate and the economic means to implement agreements of interest to both countries. Therefore, the lists described in the above appendices are not the result of a systematic market exploration but a small but important sample of the interest existing. Concrete opportunities and threats will be identified if market and data analyses are conducted in a subsequent report. In that sense, this document highlights major biotech areas worth exploring. The description of those areas of opportunities are described in the following three lines of investigation:

A. AREAS OF OPPORTUNITY FOR CANADIAN MANUFACTURING, TECHNOLOGY TRANSFER, AND R & D

1. Forest and forest products (pulp and paper technologies), reforestation technologies

2. Waste water treatment, and toxic waste

3. Food technology transfer, including fermentation technology

4. Aquaculture, specially fish farming

5. Animal health vaccines and probiotics

6. Biopharmaceuticals and diagnostic kits to be distributed or manufactured under license in Spain, and joint R & D projects

7. Training for R & D professionals and highly qualified technical personnel.

8. Access to R & D European Research funds of which Spain is a net contributor.

B. OPPORTUNITIES FOR SPANISH MANUFACTURING, TECHNOLOGY TRANSFER AND R & D

1. Food technology transfer, particularly for cured meats and cheese

2. Fermentation technology transfer, wine and beer with low alcohol content

3. Aquaculture technology transfer, development of fine fish species and seafood

4. Biopharmaceuticals especially antibiotics and diagnostic kits

5. Access to the North American Free Trade Zone.

C. AREAS OF COLLABORATION AND BALANCED JOINT-VENTURES

1. Canadian-Spanish ventures in the Hispanic American Market particularly with Mexico, Venezuela, and Argentina.

2. R & D joint projects with Canadian and Spanish agencies. Projects of interest includes:- bioreactor design and development, development of fragrances and flavours, development of diagnostic kits.

3. Collaboration agreements between the National Research Council (Canada) and the Consejo Superior de Investigaciones Científicas (Spain).

4. Well focused collaboration agreements among the Centres of Excellence of various Canadian provinces and their equivalent in Spanish regions.

IX. CONCLUSIONS

The objective of this report has been to introduce the reader to the Canadian and Spanish economies and give an overview of biotechnology present trends and commercial applications. These are the major findings of this document:

1. Two of the ten largest economies in the world, Canada and Spain, have insignificant levels of trade and investment.

2. Biotechnology, known as the third technological revolution of the century, forms part, in both countries, of the strategic technologies fostered to promote productivity and competitivity.

3. The success of a biotech venture requires not only an unique technology, but a high R & D level based on well qualified scientists and engineers. In addition, financing and tax incentives, government funding of fundamental and applied research, and personnel availability and training are major components in the commercial success of a biotech company.

4. In Spain, biotechnology R & D are developed along five areas of maximum priority. These are: Applications Research; Agriculture and Nutrition; Biodegradation and Pollution Control, Human and Animal Health; and Industrial Applications.

5. The level of funding of Spanish research and innovation, either through national or European programs, is excellent, and only limitations in the availability of scientific personnel makes funding lower. The major sources of Spanish industrial R & D financing come from CDTI and CSIC (in Spain), and the biotechnology programs of the EC Eureka, Bridge, Flair and Eclair.

6. The scientific and technical level of Spanish human resources in biotechnology is comparable to those of France, Germany or U.K., but there is an important lag between the amount of R & D done by the private sector of those countries and that of Spain. Training of scientific personnel is one of the major needs of Spanish biotechnology.

7. The industrial sectors of greater impact in Spain's economy and hence sectors of strategic relevance are: Agrifood; Pharmaceuticals and Diagnostics; and Environment

8. The Canadian government considers the following seven areas of maximum priority in the development of biotechnology: Aquaculture;

Forestry; Human and Animal Health Care; Plant Straint Development; Nitrogen Fixation; Mineral Leaching and Metal Recovery; and Waste Treatment.

9. In Canada, the Ministry of Science and Technology through the Strategic Technologies Program, and NSERC through the Industrial Research Assistance Program are the main sources of funding of R & D and industrial innovation.

10. Canadian scientific and technical human resources, as well as R & D experimental infrastructure, are excellent. The average level of research and education in universities and higher learning institutions is very good. Canada has also the best system of telecommunications in the world, with first rate libraries, information data bases, and an agile civil administration. These factors facilitate the creation of strategic ventures among firms and collaboration among industry, university, and government.

11. The industrial applications of Canadian biotechnology is directed along those sectors with a major impact in the country's GDP. These four sectors are: Agrifood; Pharmaceuticals; Environment; and Forestry. In areas like waste treatment, forestry and forest technology, fish and seafood farming, and specific R & D biopharmaceuticals, Canada is among the most advanced countries in the world.

12. Canadian companies are very receptive to strategic alliances and more so with European partners. Half of Canadian biotech firms are engaged in joint ventures, strategic alliances, or R & D joint projects, with either American or European partners. The principal factors in selecting a foreign partner is credibility, marketing expertise, and access to technology.

X. RECOMMENDATIONS

Based on the comparative evaluation of business opportunities in both countries and the conclusions established in the previous section, the following recommendations to impulse business opportunities in biotechnology between Canada and Spain are put forward:

1. TO IDENTIFY AND SELECT BY SECTORS, CANADIAN COMPANIES AND THEIR SPANISH COUNTERPARTS IN THE FOLLOWING INDUSTRIES OR SERVICES:

   A) HUMAN AND ANIMAL HEALTH CARE
   B) AGRIFOOD INDUSTRIES
   C) ENVIRONMENTAL APPLICATIONS
   D) FORESTRY
   E) TRAINING AND EDUCATION

This selection should produce a well focused document of Spanish and Canadian firms seeking strategic alliances in manufacturing, services, investment, and technology transfer. A detailed description of the policies and programs in biotechnology of Canadian and Spanish regional (provincial) governments should be incorporated to this document.

2. SIMULTANEOUSLY AND IN CONJUNCTION WITH RECOMMENDATION 1., WE PROPOSE THE IMMEDIATE PREPARATION OF TWO BIOTECHNOLOGY SEMINARS ON SELECTED INDUSTRIES, ONE TO BE HELD IN MADRID AND THE SECOND IN OTTAWA. THE DOCUMENT RECOMMENDED IN 1., SHOULD BE MADE AVAILABLE TO THE PARTICIPANTS OF THESE SEMINARS. TO FACILITATE EXPLORATORY MEETINGS AMONG THE COMPANIES PARTICIPATING SHOULD BE ONE OF THE MAJOR OBJECTIVES OF THESE SEMINARS.

3. IN PARALLEL WITH RECOMMENDATION 1., WE PROPOSE THE INMEDIATE INITIATION OF EXPLORATORY DISCUSSIONS BETWEEN THE FOLLOWING CANADIAN AND SPANISH INSTITUTIONS:

   A) CENTRO NACIONAL DE BIOTECNOLOGIA (MADRID) AND THE BIOTECHNOLOGY RESEARCH INSTITUTE (MONTREAL).

   B) THE NATIONAL RESEARCH COUNCIL (OTTAWA) WITH ITS SPANISH EQUIVALENT, CONSEJO SUPERIOR DE INVESTIGACIONES

CIENTIFICAS, AND THE SPANISH RESEARCH FUNDING AGENCIES CDTI AND CICYT, WITH EQUIVALENT AUTHORITIES IN INVESTMENT CANADA AND INDUSTRY SCIENCE AND TECHNOLOGY CANADA.

To implement the above we propose

4. TO DEVELOP THE NECESSARY INSTRUMENTS WHICH PERMIT TO FACILITATE, FOLLOW UP, AND EVALUATE THE PREVIOUS INITIATIVES.

APPENDICES

A. APPENDIX I

ADDRESSES OF RELEVANT CANADIAN AND SPANISH FIRMS AND INSTITUTIONS

During the preparation of this document a number of major organizations and institutions in Spain and Canada have shown strong interest in exploring possible avenues of collaboration with each other. As mentioned earlier this list is not the result of a systematic analysis of the Spanish and Canadian market, which was not the objective of this report, but it is an indicator of the interest revealed by both parties. The size of some of the firms and institutions listed here justifies in itself the follow up to this report. The names listed follow no deliberate classification.

CANADIAN FIRMS AND INSTITUTIONS

1. CMS Group Inc. Mr. Jack Grant, Chairman
2. Allelix Biopharmaceuticals, Dr. G. Strachan, President and Chief Executive Officer.
3. Pollutech Environmental Ltd, Mr. R.V. Laughton, President
4. W.H.E. Process Technology Group , Mr. V. Harding and Mr P. Hallman Executive Vice-president and Vice-president of Sales respectively.
5. Investment Canada, Mr. R. S. Peters, Manager for Europe
6. Gore & Storrie Ltd, Environmental Consulting Engineers and Scientists. Dr. W. Hargrave, Executive Vice-president.
7. Ryerson Polytechnical Institute, Dr. W.E. White, Dean of the Faculty of Engineering and Applied Science.
8. University of British Columbia, Dr. J.R.Grace, Dean of the Faculty of Graduate Studies.
9. University of Toronto, Dr. L.L. Diosady, Professor of Food Engineering
10. Apotex Health Care Group, Dr.Michael Spino, Vicepresident of R & D.
11. Wastewater Technology Centre, Dr. B.E. Jank, Chief Executive Officer

B. APPENDIX II

SPANISH FIRMS AND INSTITUTIONS

1. Centro Nacional de Biotecnologia, Dr. J. López Carrascosa, Director
2. Centre for the Development of Industrial Technology (CDTI), Dr. J.R. Pellón, Director of Bilateral Programs
3. Isolux Wat, Mr. J. Llorens, Director General Adjunto
4. La Corporación Banesto, Mr. V. Lopez-Pinto, Director General Adjunto al Consejero Delegado
5. Camara de Comercio de Barcelona, Mr. C. Oliete i Canela, Dirección Técnica de Promocion Tecnológica
6. Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria, Mr. F.J. Martinez Vasallo, Director Técnico
7. Laboratorios Leti, Mr. J. Grego Mayor, Assistant Financial Director
8. Universidad de Alcalá de Henares, Dr. M. Najera Aleson, Director of OTRI
9. Universidad Politécnica de Madrid, Escuela Técnica Superior de Ingenieros Industrial, Dr. L. Ortiz Berrocal, Director
10. Centro de Investigaciones Energeticas Medioambientales and Tecnologicas (CIEMAT), Dr. Gabriel Maganto, Jefe U.O. Oficina Tecnica del Instituto del Medioambiente.

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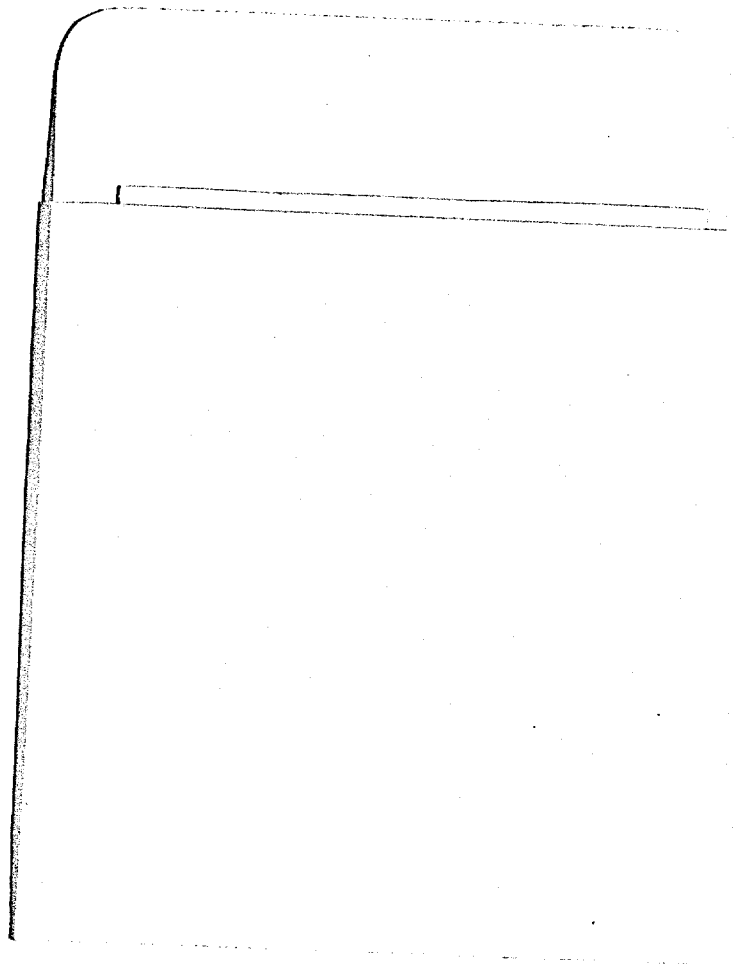

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