BIOTECHNOLOGY IN WESTERN EUROPE

U.S. DEPARTMENT OF COMMERCE
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Robert T. Yuan, Ph.D.

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FOREWORD

These reports on biotechnology in France; Federal Republic of Germany; Italy; the Netherlands; Norway, Finland and Denmark; Spain; Sweden; Switzerland; the United Kingdom; and the European Economic Community were prepared for the International Trade Administration, Department of Commerce, by Dr. Robert T. Yuan during his tenure as a Foreign Commercial Service Officer at the U.S. Embassy, London, United Kingdom.

Dr. Yuan currently is professor of microbiology at the University of Maryland at College Park, MD. He has extensive training in molecular biology. Prior to this assignment he taught at the Basel Biocentrum, Switzerland and Edinburgh University, Scotland. Additionally, he performed postdoctoral research at Harvard University. He is multilingual with significant knowledge of the culture and customs of many European and Asian peoples.

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INTRODUCTION

This report is the result of a study carried out by the Biotechnology Program of the U.S. Department of Commerce. The Biotechnology Program is an experimental project of the International Trade Administration (ITA) and the U.S. and Foreign Commercial Service (US&FCS). It was established to carry out a technical and industrial assessment in the major industrial nations of Western Europe and the Far East. Its objectives are to:

- determine the government policies in support of biotechnology,
- identify the principal research laboratories and their activities,
- identify the principal companies involved in biotechnology and their activities, and
- study the various mechanisms for technology transfer from the research laboratories to the industrial sector.

In order to carry out this mission, two senior scientists were selected for posting to the U.S. Embassies in London and Tokyo. They were chosen on the basis of scientific expertise, work experience overseas, language proficiency, and the appropriate cultural affinities. Their efforts were coordinated through the ITA in Washington, D.C.

During the initial phase of this project, some 30 U.S. biotechnology companies were visited over a period of five months. This enabled the technical assessment officers to familiarize themselves with U.S. industry and its concerns. Contacts were made with the scientific attaches at the appropriate foreign embassies in Washington, to acquire information and names of individuals familiar with biotechnology in their respective countries. Once in London, lists of organizations and individuals involved in biotechnology in each country were obtained from three different sources: (a) colleagues in the scientific community, (b) the U.S. Embassy, and (c) officials of foreign governments. These lists were cross-checked against each other and against published articles and reports. A list of key individuals was generated and the appropriate U.S. Embassy made the necessary arrangements for a field trip. Usually, extensive reading and briefings took place prior to the actual interviews. The meetings also provided an opportunity to obtain further documents (frequently in the original language). Once the field visits to a given country were completed, the documents and notes were used in the preparation of a country report. Each of the country reports was reviewed by the U.S. Embassy FCS staff and knowledgeable individuals in that country. Their corrections and comments were incorporated prior to submission of the country reports to ITA in Washington.

The project in Western Europe had a duration of 16 months. It could not have been done without the enthusiastic cooperation of the U.S. missions abroad and of hosts of European officials, scientists, and corporate managers. It is inevitable that certain country reports are less thorough and complete than others, and there is the unfortunate omission of Belgium and Ireland. Such occurrences were not deliberate and must be understood in the context of problems with scheduling, logistics, and budgets.

This program was conceived and coordinated by Dr. Alfred Hellman, ITA, Washington, D.C. Mr. Michael Mercurio, Commercial Attache at the U.S. Embassy in London, provided invaluable support and Ms. Emily Arakaki, ITA, Washington, D.C., was a continuous source of information on the economics of biotechnology. The author is grateful for the assistance of Ms. Becky Roberts, US&FCS, U.S. Embassy, London, who provided invaluable research and editorial support. Finally, without the continuous support of Mr. Michael T. Kelley, Deputy Assistant Secretary for Basic Industries in ITA, Washington D.C., the program would not have been possible.

Unlike previous studies of this type, this one has both the advantages and disadvantages of having been done by one individual over a period of 16 months. As a senior scientist with extensive experience in Western Europe, he could deal with the same issues and make comparisons in country after country.

In addition to the country reports, the Biotechnology Program can count other accomplishments to its credit:

- creation of a network of trade specialists knowledgeable about biotechnology at several of the U.S. Embassies in Europe,

- provision of support for U.S. sponsored trade events in biotechnology, and

- provision of information and assistance to U.S. biotechnology companies interested in operating in Western Europe.

The Biotechnology Program is an experiment in technology and industrial assessment. Unlike earlier studies, it was envisioned as a continuing effort based at the U.S. Embassies in London and Tokyo, and could be used as a model for similar programs in other high technology sectors. As such, the program deserves careful review and evaluation.

EXECUTIVE SUMMARY

A respected analyst of government policy and technology development remarked, in the course of a lengthy discussion, that certain factors are required for success in the development of high technology industries. They are: (1) a first-class science base or access to it, (2) an intelligent and supple management style, (3) sources of capital, and (4) a global strategy. "You Americans have an abundance of the first three," he pointed out. "It is on the fourth one that you lose out."

It is the objective of this study to provide an understanding of biotechnology in Western Europe. Each country report describes in some detail the national environment for biotechnology. Each is unique. This summary focuses on general characteristics and patterns, in particular, government policy, the science and industrial bases, and technology transfer. The last sections deal specifically with the U.S. competitive position and those issues relevant to an international strategy for U.S. biotechnology.

Biotechnology, as defined by the Office of Technology Assessment (OTA), is any technique that uses living organisms (or parts thereof) to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses. For the purposes of this study, the focus is on the techniques of recombinant DNA, cell fusion and novel bioprocessing methods. The growth of biotechnology in Western Europe has coincided with national policies directed towards restructuring the economy away from traditional manufacturing and towards high technology sectors. Therefore, a great deal of what has been observed in biotechnology is probably also true for other rapidly developing high technologies such as computers and advanced materials.

Eleven countries in Western Europe are included in this study: the Netherlands, Norway, Finland, France, Germany, Switzerland, Spain, Italy, the United Kingdom, Denmark, and Sweden. Table 1 provides a brief summary of the principal characteristics of biotechnology in Western Europe.

I. GOVERNMENT POLICY

National governments and large established firms play the major roles in biotechnology in the absence of significant numbers of new biotechnology companies (except in the U.K. and Sweden). Table 2 summarizes the efforts of the European governments in support of biotechnology. The U.S. and Japan are included to provide a frame of reference. Government involvement has been divided into three separate categories: basic research, applied R&D and industrial activities.

Basic research is a major responsibility of the government in all countries studied. The most common form of government involvement is the funding of research carried out at universities. In addition, seven European countries and Japan have government research institutes, frequently organized into networks, such as the CNRS in France, the MRC in the United Kingdom (U.K.), and the Max Planck Society in West Germany. The closest U.S. equivalents are the National Institutes of Health (NIH) and certain biological programs in the National Laboratories.

Table 1.
CHARACTERISTICS OF BIOTECHNOLOGY IN WESTERN EUROPE

1. The basic research is world class in a number of key areas.

2. The R&D system provides few opportunities for independent research by young scientists and frequently fosters a negative attitude towards industrial activities.

3. The state plays an important, sometimes key role in industrial development.

4. Biotechnology is concentrated in large, established companies with long term R&D programs and strong cash reserves.

5. Venture capital is not readily available to new, small companies.

6. European companies are more likely to enter into partnerships with U.S. firms than with their European counterparts.

Table 2.
THE ROLE OF GOVERNMENT IN BIOTECHNOLOGY

	Basic Research		Applied R&D			Industrial Activity		
	Research Funding	Research Institutes	Technology Transfer Institutes	Funding Univ/Inst	Funding Industry	Tax Credits	Loans/ Grants	Risk Capital
Finland	+		+					
Norway	+	+						
Italy	+			+	+			
Spain	+	+	planned	+	+		+	+
Switzerland	+		+[1]	+/-[2]				
Denmark	+		+	+	+		+	
Sweden	+	+	+	+	+		+	+
Netherlands	+		+	+	+	+	+	+
France	+	+	+	+	+	+	+	
U.K.	+	+	+	+	+	+	+	+
Germany	+	+	+	+	+	+	+	+
Japan	+	+	+	+	+	+	+[3]	+
U.S.	+	NIH			+	+		

[1]Some activities at Swiss Federal Institute of Technology, Zurich
[2]Limited funding.
[3]Development banks/low interest

Support for universities is intrinsic to the health of the research establishment. In most governments, funding of universities is administered separately from that of basic research. So frequently, increases in research funding have gone hand in hand with massive cuts at the universities. This has resulted in a weakening of the scientific infrastructure and in projected shortages of skilled manpower.

The European university system has been slow in responding to the rapid growth of biological knowledge. One of the key concerns of university officials is the need for curriculum reform due to the interdisciplinary nature of biotechnology. This is compounded by the shortage of faculty positions which prevents the hiring of specialists in new fields, such as molecular immunology or plant molecular biology.

National biotechnology programs have been established in four countries and proposed in three others. Among them are two major countries (France and West Germany). In the U.K. and Japan, individual ministries and agencies have coordinated programs for biotechnology. Six countries have government involvement at all levels, from basic research to commercialization (Table 2). This is intended to speed up industrialization of new research findings. Government programs include, in applied R&D:

- o technology transfer institutes,
- o funding of applied R&D in universities, research institutes, and private companies;

and in industrial policy:

- o tax credits for industrial R&D and innovations,
- o loans and grants for new processes and products, and
- o risk capital for new companies.

In almost all countries, and particularly those with national programs in biotechnology, total actual funding has increased.

In addition to increases in funding support and changes in the structure of the research establishment, national programs also serve an important function in establishing a political consensus in support of biotechnology. Regional and local government can be an important element in the development of biotechnology. In most European countries, political and financial authority is highly centralized. In these countries, decentralization has become a major political issue, while in certain other countries (Switzerland, West Germany, and to a lesser degree, the Netherlands) provincial and local governments are responsible for the university system and its associated research establishments, as well as industrial development. Effective regional policy can play a pivotal role in technology transfer in such situations.

The pace of industrial development in biotechnology is set by government policy. The investment of industrial resources in a new technology such as biotechnology, depends on the overall environment in a specific country.

This is determined in large part by government policy on:

- o industrial participation in policy decisions,
- o support of R&D (particularly industry related),
- o fiscal measures,
- o tax and labor laws,
- o government pricing of both products and raw materials,
- o technology transfer,
- o government funding of new companies,
- o privatization of government-controlled companies, and
- o regulation of biotechnology.

The industrial sector (which is dominated by large companies) prefers indirect measures, such as the first five listed above. The government is concerned about the conservatism of industrial management, and active intervention is the rule rather than the exception (Table 2). National policy is limited by the ability of multinational companies to operate beyond national borders.

A major responsibility of government is the safety of new biotechnology products and processes. The lack of scientific knowledge about new genetically engineered organisms and their products, resulted in the imposition of strict research guidelines. No actual health hazard has emerged up to now, so the principal thrust of government policy is to support research on risk assessment, and use the results to develop safe procedures.

Restrictive legislation can sharply inhibit industrial applications of biotechnology. There has been serious concern about the potential risks associated with biotechnology which has led to the adoption of stringent regulations, such as those in Denmark (and proposed in West Germany). Such legislation can inhibit basic research and be an obstacle to industrial development in any country. The most rigorous legislation, however, can only have limited results if it disregards the general standards in existence in other countries. This has been a compelling argument for international cooperation to:

- o conduct rigorous scientific assessment of risks,
- o establish regulatory systems for research and industry, and
- o expand such regulations to less developed countries and those in the Eastern bloc.

The acquisition and dissemination of biotechnology information is a major function and one which could be a legitimate role of government. The extremely rapid pace of biological research has resulted in an exponential growth in information. This information can be purely scientific and/or commercial, for example:

- o DNA, RNA, and protein sequences,
- o structural data on biological molecules,
- o listings of microorganisms, plant and animal cell lines,

- patent registration,
- clinical trials, and
- regulations.

Both individual countries (e.g., France and West Germany) and European organizations (European Molecular Biology Laboratory and the European Economic Community) have begun data projects. The most important of these is probably EBIP (European Biotechnology Information Project), a collaboration between the British Library and the European Economic Community (EEC). Information projects require technical expertise and timely dissemination. They also raise the issue of whether they are the proper function of the government or of autonomous non-profit institutions.

II. SCIENCE BASE

Taken as an aggregate, Europe has the second largest science base in biology and is moving to expand it. In looking at the science base, it is useful not only to look at the relative strengths of individual countries, but also at their performance in individual research areas. The research areas are the same ones used by the OTA in a 1984 study on "Commercial Biotechnology: An International Analysis":

- pharmaceuticals (proteins, antibiotics, vaccines, diagnostics),
- specialty chemicals and food additives (enzymes, sweeteners, amino acids),
- agricultural (breeding of plants and animals, biological fertilizers and pesticides),
- commodity chemicals and energy products (ethanol, solvents, mineral leaching),
- environmental applications (treatment of solid and liquid wastes), and
- bioelectronics (biosensors, biochips).

A summary of research and industrial activities in the U.S., Japan, and 11 countries in Western Europe appears in Table 3. These relate specifically to the novel technologies defined earlier. The country with the broadest spectrum of research activities is the U.K. (and Japan) followed by West Germany, the U.S., and the Netherlands. All countries, without exception, have focused on pharmaceuticals and human health care. There are much lower levels of research activity in agriculture, specialty chemicals, and food.

The major countries have programs to expand the breadth of their biological research. Some of the smaller countries have concentrated their efforts on subjects relevant to their own industry. U.S. research shows a pronounced bias towards the biomedical area.

Table 3.
BIOTECHNOLOGY ACTIVITIES IN WESTERN EUROPE

	Pharmaceuticals	Specialty Chemicals & Food Additives	Agriculturals	Commodity Chemicals & Energy Production	Environmental Applications	Bioelectronics
Finland	R/I	R/I	R*/I			
Norway	R	R	R			
Italy	R/I	R/I	R*			
Spain	R/I		R*			
Switzerland	R/I	R/I	R/I*			R*
Denmark	R/I	R/I	R			
Sweden	R/I	R/I	R/I		R/I*	R
Netherlands	R/I	R/I	R/I*		R/I	
France	R/I	R/I*	R			R*
U.K.	R/I	R/I	R/I	R	R/I*	R/I*
Germany	R/I	R/I	R		R	R
Japan	R/I	R/I	R/I	R/I*	R/I*	R/I*
U.S.	R/I	R/I	R/I		R*	R*

R=Basic Research
I=Industrial Activities
R*=Limited Activities
I*=Preliminary Activities

The rapid growth of the knowledge base will be limited by a number of "choke points." Modern biological research has developed, starting with bacterial and phage genetics, moving on to molecular and cell biology of simple organisms, proceeding to animal virology and, more recently, to molecular biology of plant and animal cells and novel fermentation and downstream processing technologies. The research activities of the principal laboratories in any given country have seldom been the result of conscious planning, but more often have been due to investigator initiative and peer review (determining government funding) and to the historical development of the laboratories. European governments and research organizations have become increasingly aware of the limited efforts being made in critical research areas. Certain ones are so important that they can limit the overall rate of biological research. These so-called "choke points" may vary somewhat from country to country, but there is surprising agreement on the following:

- genetics and physiology of industrially relevant microorganisms (including industrial fermentation conditions),
- enzymology (including use in production),
- protein engineering,
- genetics and physiology of plant and animal cells (including industrial fermentation conditions),
- plant biochemistry,
- use of microorganisms in bioconversion (including waste treatment),
- use of enzymes and antibodies in biosensors,
- risk assessment, and
- bioreactor design, separation technology.

International cooperation is a potential solution to the problem of "choke points." Realistically, funding of research projects across national borders is rare, except in the context of the EEC and EUREKA programs. One of the most common mechanisms for expanding the science base of a given country is to send postdoctoral fellows and visiting scientists for training and research abroad. The most frequent host country is the U.S. The number of U.S. visiting scientists in European laboratories has decreased. This is considered to have had a negative effect on European science. It is also likely to have affected technology transfer from Europe to the U.S.

III. INDUSTRIAL BASE

Most analyses suggest that the first clients of biotechnological products and processes are likely to be industries. Industrial activities in biotechnology in Western Europe are to be found in large, diversified multinationals (mainly in pharmaceuticals and chemicals), mid-sized multinationals (mainly in pharmaceuticals and specialty chemicals), and small new biotechnology companies (principally in contract R&D). Table 3 summarizes industrial activities in Western Europe, Japan and the U.S. Industrial activity (i.e., application of the new technologies) not only encompasses the manufacture of products and processes, but also contract R&D. As in basic research, the U.K. has the broadest spectrum of industrial activities (as does Japan) though their commercial success has been limited. There is a heavy emphasis on pharmaceuticals, followed at much lower levels by specialty chemicals and agriculturals.

The expansion and diversification of industrial activities has been promoted by government policy. This has usually been done by industrial innovation in established companies or, less frequently, by the creation of new companies. Table 3 shows that the impact of the new biotechnology programs on diversification has yet to be felt.

There is an important difference between the strength of the industrial base of a country and the strength of individual corporations based in that country. A number of small countries have major multinationals with well defined market niches, such as, Ciba-Geigy (Switzerland), and AKZO (Netherlands). These multinationals make the contribution of such countries to specific business sectors and their associated R&D very important.

The large multinationals are integrated, product-oriented, and endowed with extensive financial and technical resources. They have been generally conservative about biotechnology, but their acceptance of industrial innovation has made them purchasers of U.S. technology and companies. The mid-sized multinationals have specialized in biological processes and used them to develop global markets. Good examples are Pharmacia (separation technology), Novo (industrial enzymes), and Amersham (radioactive labeled compounds). The advent of the new biotechnology has provided them with new potential markets and the means to generate new products. The only European countries with significant numbers of new start-ups are the U.K., Sweden, and to a lesser degree, the Netherlands. The dynamics of such entrepreneurial firms requires them to move aggressively into new business sectors. Both small and medium-sized companies require industrial customers that are both profitable and compatible in technologies. When such partners cannot be found in the domestic environment, they must be sought abroad. The symbiotic relationship between small, new companies and large, established multinationals does not exist at present in Western Europe.

European companies are willing to take a long view, but usually along well defined product lines. At the same time, there is an increasing realization that they must acquire the technical capabilities now, in order not to be left behind in the future.

The widespread application of biotechnology to a variety of industries is also likely to encounter a number of "choke points." These can fall into the realms of science, government policy, and availability of capital. The technical "choke points" have already been discussed in the preceding section. As regards government policy, the ones considered most critical are:

- o funding of basic research and training,
- o government pricing,
- o regulatory policy, and
- o tax and labor laws.

Availability of capital is often presented as a crucial "choke point" in the rapid development of biotechnology. In discussing this highly controversial issue, one must distinguish between the established, large multinationals and the struggling, small start-ups. An examination of the country reports will show that many of the large corporations are highly profitable and have amassed large cash reserves and/or raised additional capital, e.g., Glaxo (U.K.) had 1985 sales of $1.83 billion and profits of $345.7 million. Its cash reserves represent 40 percent of group assets. AKZO (the Netherlands) had 1984 sales of $5.15 billion and profits of $234 million, while accumulating an acquisition fund of $311 million. Capital is not a significant problem for such large multinationals.

Start-ups in Western Europe face obstacles in financing and in the business and cultural environments in which they operate. European governments have felt that the slow pace of industrial innovation is due to the limited number of small, new, high technology companies. The shortage of risk capital is viewed as one of the principal reasons for this situation. European entrepreneurs often find that they have to raise small amounts from a variety of sources (versus finding a small number of large investors as is the case in the U.S.) The amount of venture capital available in the EEC has been estimated at ECU 7 billion ($4.31 billion), which is quite a respectable sum, though considerably less than that available in the U.S. The U.K. has the largest share with 43 percent, followed by the Netherlands (18 percent), France (14 percent), and West Germany (9 percent). As important as the amount of venture capital, is the manner in which it is used. It has been observed that:

- o only half of the total venture capital is invested in small businesses,

- o over the period 1980-84, only 10 percent of the agreements involved foreign partners, and

- o good quality technology investments were more often found in the U.S. rather than in Europe.

These have been taken as indicators of the conservativeness of European venture capital organizations. In spite of this, more than half of the investments went into technology in general, and 4.5 percent into biotechnology specifically.

The business environment favors large established companies. A number of factors inhibit the formation of new companies:

- o tax structure (lack of incentives for investment in new, high technology firms),

- o labor laws and pension plans (discourage job mobility),
- o administrative costs and costs associated with raising capital in public markets are high,
- o pricing policies that favor established products,
- o access to distribution networks, and
- o differing technical standards from country to country.

The cultural environment is the most difficult to evaluate and to change, and is considered to encourage conservative attitudes. It includes:

- o favorable attitudes towards seniority and job security,
- o intrinsic respect towards large organizations and corporations,
- o high job prestige for university faculty and researchers, low for entrepreneurs,
- o high value is given to tangible assets, while new concepts and processes are considered of negligible value, and
- o failure has a negative connotation and no redeeming value as part of a learning process.

The limited number of independent positions for young scientists, and/or the length of the educational process, raises the average age at which scientists reach positions of responsibility. Though the variation in the structure of European research establishments is quite large, it is common that a scientist reaches an independent position with his own group in his late thirties or early forties. His American counterpart usually reaches his first independent position in his early thirties, and acquires a number of important skills, such as directing research, writing grant proposals, dealing with budgets, and managing a small group. Many of these skills are easily transposable to an industrial environment. If the acquisition of such skills occurs early, it is much more likely to lead to risk taking and an entrepreneurial attitude. Therefore, the combination of age and the seniority system are likely to have a profound effect on the pool of entrepreneurs.

A significant number of large and medium-sized European multinationals raise capital in foreign financial markets. This not only provides them with access to different sources of financing, but also gives them the flexibility to take advantage of different interest rates and changes in currency exchange rates.

IV. TECHNOLOGY TRANSFER

Technology transfer is the process by which the findings of research laboratories are introduced into the industrial sector and converted into new products. The principal mechanism of technology transfer in the U.S. is the