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Development of the European Biotechnology Industry

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DEVELOPMENT OF THE EUROPEAN BIOTECHNOLOGY INDUSTRY†

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INTRODUCTION

What I propose to do in this Article, is to present an European Union perspective on the topic of governmental regulation of the biotechnology industry. There were two fundamental developments in the 1970s that launched the biotechnology industry in the 1980s. The first of these was the development of genetic engineering into a practicable, routine procedure that could be used outside the research laboratory; the second, of course, was Georges Köhler[1] and Cesar Milstein's demonstration of monoclonal antibody technology,[2] for which they received the Nobel Prize.[3] Both of these

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† This Article is based on a report, and draws on data, submitted to the European Parliament and the Directorate General for Research by Panos Kavanos, Elias Mossialos, and Brian Abel-Smith of the London School of Economics. I am grateful for their permission to quote from their research.

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Previously, he held the posts of Vice-Chancellor of the University of Salford (1981-90) and Chief Scientist of the Central Policy Review Staff in the Cabinet Office (1976-81) where he advised Prime Ministers Callaghan and Thatcher.

Before that, he was foundation Professor of Biology at the University of Essex, has degrees in chemistry and biochemistry and has published articles on biochemical, cell biological, genetic, physiological, and educational topics. He has been an *ex officio* member of the Advisory Board for the Research Councils, the Advisory Council for Applied Research and Development, UK Titulaire on the Comite de la Recherche Scientifique et Technique (CREST) of the EEC, UK co-chairman of the UK/USSR Joint Committee on Science and Technology, a member of the Electronics Economic Development Committee of the National Economic Development Council, the Council of the Economic and Social Research Council, and Chairman of the National Accreditation Council for Certification Bodies (BSI), the Board of the National Computer Centre and the Technical Advisory Committee, Jaguar Cars Limited.

He is currently a non-executive Director of Granada Group plc and J. Sainsbury plc, a member of DEMOS Advisory Council, a governor of the Ditchley Foundation; and a Deputy Chairman of London First.

1. Georges Köhler was born in West Germany in 1946. In the 1970s, he went to Switzerland to study at the Institute for Immunology. In 1975, he went to Cambridge and engaged in a collaborative effort which culminated in a celebrated paper in the scientific journal, *Nature*. In late 1975, Köhler returned to Switzerland. He became a member of the European Molecular Biology Organisation. In 1985, he became the director of the Max Plank Institute. He died at the age of 48 in April of 1995. *Obituary of Georges Köhler*, THE DAILY TELEGRAPH (London), Apr. 7, 1995, at 25.

2. Antibodies are the body's defence against disease and infection. When bacteria or viruses invade–or cells become abnormal, as in the case of cancer–the B (bone marrow) lymphocyte cells of the immune system recognize them as alien by reading the biochemical signatures on their surfaces. The lymphocytes then produce complex protein molecules (antibodies which specifically react with and neutralize the invaders). Living creatures can manufacture millions of different antibodies, each fighting a particular type of foreign germ. Once a creature's lymphocytes have produced an antibody, it is immune to that particular germ.

Doctors have known for years that antibodies are ideal for treating and diagnosing disease. But the human body makes any one antibody only in minute quantities, and only when infected;

developments were based on two decades of accelerating understanding and research into molecular biology and genetics.

The traditional pharmaceutical industry was based on the chemical and biochemical sciences. Although the industry was very well used to high levels of research and development spending in the 1980s, it was slow to realize the potential of these molecular biology developments. Thus, from its inception, the biotechnology industry has been characterized by small, new technology based firms (NTBFs in the jargon) started by scientists impatient with the slow and ponderous behavior of the large pharmaceutical corporations. Now, in the 1990s, every pharmaceutical company wants access to biotechnology. Since the late 1980s, a quieter revolution has been taking place within the laboratories of the established pharmaceutical firms. The procedures and some of the products of the NTBFs have been blended with the traditional chemical and biochemical strengths of the older pharmaceutical companies to produce a new kind of pharmaceutical entity: the biopharmaceutical corporation.[4]

There have, however, been significant differences in the rate at which these processes have occurred in different countries and there are now very clear differences in the comparative advantage perceived by the three dominant industrial players in our global economy: the United States, the European Union, and, of course, Japan. This Article evaluates the competi-

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and techniques for creating antibodies in animals never produced pure vaccines or reliable diagnostic tests. Köhler found his work with lymphocytes difficult because they cannot be maintained in a laboratory culture for more than a few days. In 1973 he attended a lecture given by Cesar Milstein, a senior scientist at the Cambridge Molecular Biology Laboratory, who was studying the abnormal way in which cancer cells produce antibodies. Cancer cells multiply out of control, and can be used to make laboratory cultures that are "immortal." From his conversations with Milstein, Köhler realized that there might be a way of mass-producing any required antibody outside the human body in a pure form, and so immortalizing its production.

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To make an antibody to human cancer cells–to diagnose cancer and direct drug intake–cancer cells are first injected into a mouse. The mouse begins making antibodies, which are taken out of the mouse and fused with a strong-growing cell culture in the laboratory. This hybrid culture, the hybridoma, will manufacture the antibody indefinitely and in any amount. Antibodies made in this way are called monoclonal because they are made from a single cell line.

. . . .

Monoclonal antibodies have had a huge impact in diagnostics, allowing precision and purity in tests. They are now being evolved for use in therapy, and are already used in transplantation for immuno-suppression, where they allow the production of crucial vaccines.

Id.

3. Georges Köhler, Cesar Milstein, and Niels Jerne received the Nobel Prize for Physiology and Medicine in 1984, nine years after their paper on monoclanal antibodies was first published. *Id.*

4. Biotechnology companies and established pharmaceutical companies are increasingly pursuing the commercial development of biotechnology through joint efforts. The biopharmaceutical corporation is forged usually through acquisition or merger, to enable the two entities to pool their strengths and compete in concert. The biotechnology companies' strengths include innovative research and technological capabilities which, when combined with monetary, regulatory, and marketing strengths of established pharmaceutical companies, translate into new pharmaceutical products. U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, BIOTECHNOLOGY IN GLOBAL INDUSTRY 94.

tive position of the European Union in the evolving biopharmaceutical and biotechnological areas. By analyzing the nature and extent of the United States and, to a lesser extent, the Japanese presence in Europe, we may hopefully put that competitive position into perspective.

BACKGROUND OF THE EUROPEAN BIOPHARMACEUTICAL INDUSTRY

The European Union has maintained its position as a leading producer of pharmaceuticals. The fifteen member states of the European Union[5] accounted for 32% of world production in 1993, just ahead of the United States at 31%, and Japan at 18%. Within the European Union, the German industry is the largest national producer, supplying approximately one quarter of the total European Union output. The next largest national producers are the United Kingdom, Italy, and France, with about 15% to 20% each. Interestingly, Spain is the fastest developing producer. What I just summarized may be seen in Figure 1.[6]

5. The fifteen member countries of the European Union are as follows: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom.

6. The sources used to compile this table are as follows: European Federation of Pharmaceutical Industries' Association (EFPIA), Pharmaceutical Research and Manufacturers Association of America (PhRMA), Japan Pharmaceutical Manufacturer's Association (JPMA).

FIGURE 1

Basic Indicators of the European, US and Japanese Pharmaceutical Industries				
	Production (1993) in ECUm	Consumption (1993)* in ECUm	Employment (1993) (employees)	R & D (1992) in ECUm
EU-12	61,358	46,631	451,138	7,789
Germany	15,941	13,057	122,485	2,268
U.K.	12,186	4,888	80,400	1,961
France	16,290	11,508	100,000	1,606
Italy	10,143	8,430	68,600	1,024
Spain	4,877	4,069	38,800	266
U.S.A.	$84,900	na	353,743	$12,500
Japan	Y5,574,000	na	150,452**	Y666,000

*Total consumption (including ambulatory, hospitals, OTC), at ex-factory prices.

**JPMA Member companies only.

As well as being the largest pharmaceutical producer, the European Union also represents one of the largest potential markets in the world, with approximately 46 billion ECU[7] in 1993.[8] Thus, the European Union represents the largest potential market with about 46 billion ECU, or 30.8%, of the world market. The United States comprises 29%, and Japan comprises 19%. However, this is a somewhat misleading way of presenting this data, for the fifteen member states of the European Union have still largely retained their separate and different practices and priorities. Major internal barriers to trade and harmonization of regulatory practices still exist.[9] Harmonization of regulatory practices, although occurring, is proceeding quite slowly.[10] The single market in pharmaceuticals in the European Union is still but an aspiration rather than a reality.

There are a number of very serious consequences, as I shall go on to illustrate, for the structure of the developing biopharmaceutical industry in Europe. But first, I would like to finish this brief background summary by pointing out that although large and growing, the pharmaceutical industry only accounts for 0.62% of total European Union industrial production and contributes a mere 0.78% to the European Union's gross domestic product (GDP). Thus, although it is a very important industry to us, and although it is clearly developing into a major force, it is still not yet large enough to attract the attention of European politicians.

CONSEQUENCES OF THE STRUCTURE OF THE EUROPEAN BIOPHARMACEUTICAL INDUSTRY

Disturbingly, the cash employment positions noted in Figure 1 clearly illustrate that the productivity of the European Union industry in terms of sales per employee is approximately 50% of the United States figure and 45% of the Japanese figure. In absolute terms, the number of qualified scientists and engineers employed in the United States and the European Union is very similar. The over-staffing in the European Union is concentrated in those functions such as sales and marketing and regulatory affairs, which are needed to cope with the fifteen different markets and their different medical

7. ECU (European Currency Unit) is pronounced "e-que," with a French accent, and is currently equal to one dollar and twenty-six cents. For an overview of the ECU, see ECONOMIC AND MONETARY INTEGRATION EUROPEAN UPDATE, 1991 WL 11671 (D.R.T.) (last update May 20, 1996); *Currency Trading,* WALL ST. J., Nov. 1, 1996, at C16.

8. G. Steven Burrill, *The European Biotech Industry: Gathering Momentum,* BIOPHARM, May 1995, at 12, *available in* WL, Magazine file.

9. BIOTECHNOLOGY IN A GLOBAL ECONOMY 21, 122-24 (Brown, Bart, ed., Oct. 1991).

10. Harmonization is a process in which various nations' patent, intellectual property, and biotechnology regulations and practices are structured uniformally to enable consistent application throughout the global industry. For instance, procedural distinctions between the laws of various nations are receiving increased attention in forums convened to harmonize international patent law. U.S. CONGRESS, BIOTECHNOLOGY IN A GLOBAL INDUSTRY, OFFICE OF TECHNOLOGY ASSESSMENT 18-24 (1991).

practices, ethics, health care systems and policies. Therefore, the efficiency costs of not having a true internal market in the European Union is high and the purpose of the London School of Economics (LSE) report, from which this talk is drawn, was in part to highlight and substantiate these costs.

Given this situation, it is not surprising that the United States industry also appears to be more research orientated, devoting 23.4% of its work force to research and development, compared to the European Union's 13.4%. Although expenditures on research and development have grown in the European Union by an annual 15% over the last decade, and was estimated to have exceeded 8 billion ECU in 1993, both as a percentage of sales and in absolute terms, there is a growing gap between the United States and the European Union.

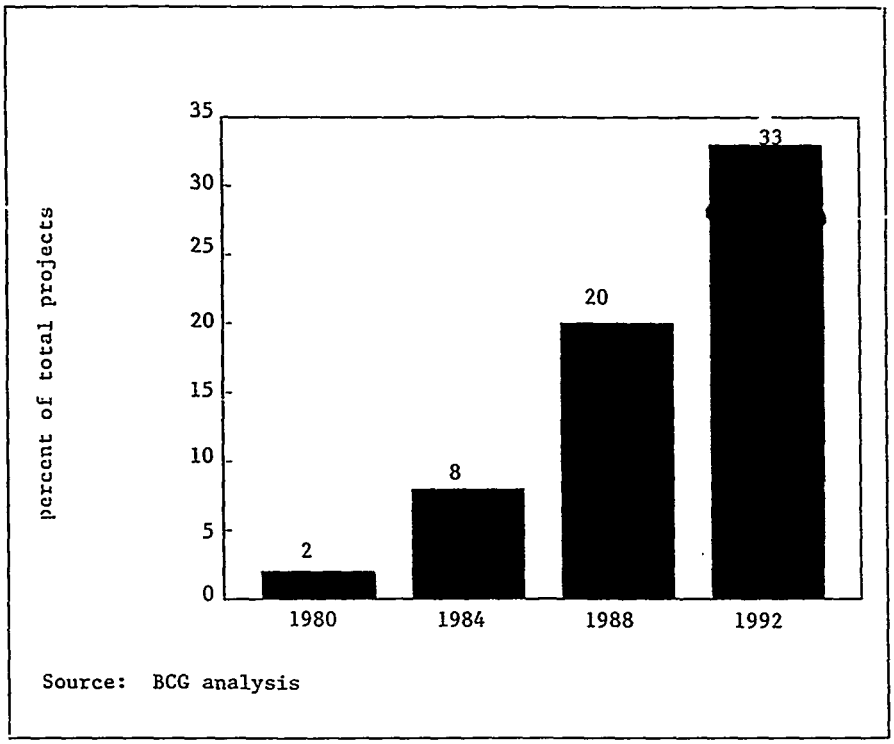
The general picture, therefore, is of an historically important industrial sector in the European Union that is slowly being overtaken. It is unable to draw the strength it should from its internal market and is weakest in the fastest growing sectors. This shows up most clearly in the trade figures. If one defines an index, which for the economists amongst you is usually known as the Balassa index,[11] then the European Union has shown a decline from 0.39 in 1981 to 0.16 in 1990. That is a very serious decline. By comparison, the United States had a value of 0.27 in 1989–just another way of expressing the fact that the European Union industry as a whole is declining in the fastest growing sectors.

Let me now turn from the pharmaceutical industry in general to the impact of biotechnology and in particular, that of the developing biopharmaceutical industry in Europe. Today, biotechnology permeates both large and small companies within the pharmaceutical industry. The LSE survey of eight large multinational corporations in Europe shows that approximately one-third of their research and development projects were in biotechnology. Yet Figure 2 shows that the rate of growth has really been very slight.

11. The ratio of the sum of exports, plus imports, over the difference of exports, minus imports:

$$\frac{\text{Exports} + \text{Imports}}{\text{Exports} - \text{Imports}} = \text{Index}$$

FIGURE 2



Biotechnology R&D Projects as a percent of
Total Projects at Pharmaceutical Companies

Within the European Union, research and development expenditures on biotechnology projects are concentrated in the United Kingdom, Germany, and France. A closer examination of these three countries, however, shows marked differences in their comparative competitive positions. These can be summarized in terms of six key parameters:

1. a pre-existing pharmaceutical industry;
2. the amount and type of government support;
3. relationships between universities and industrial sponsors;
4. availability of private venture capital;
5. the legal framework for environmental protection and safety at work and patenting; and
6. research and development expenditures and policies.

I want to mention each of these six areas briefly in the European Union context, but my conclusion probably will not surprise you. In the biotechnology industry, as in many others, the United Kingdom's situation looks much more like the United States' than do the French or German situations, with all the strengths and weaknesses of the Anglo-Saxon capitalist structure compared with the Continental European, or Rhenish, model.[12]

In terms of the pre-existing industrial base, Germany, the largest single European Union biopharmaceutical producer, has historically possessed considerable assets in terms of its chemical expertise. Ironically, these assets have inhibited the rapid development of biotechnology within German chemically-based pharmaceutical companies.[13] The situation in France appears to be similar. Furthermore, there has been no development of a small NTBF biotechnology sector in those countries to compensate for the caution of the large, traditional, chemically-based pharmaceutical companies. Only in the United Kingdom does one see a significant number of the small, entrepreneurial firms such as CellTech, ChiroScience, and British Biotechnology based on university spinoffs, which is such a feature of the United States industry. You do not see companies such as these in France or Germany.

Governmental support and initiatives, shown in Figure 3, have reinforced this trend in the United Kingdom. Europeans envy the way in which the United States government funds new biotechnology developments through at

12. Unlike the Anglo-Saxon capitalist structure in the United States and the United Kingdom, which is an economically liberal free-market model, the Continent Capitalist structure is more illiberal, with labor and capital operating within allotted roles. For further information regarding the differences between the Anglo-Saxon and Continental capitalism models, see *The End of Never-Never-Land,* THE ECONOMIST, Feb. 13, 1993, at 17; James Ball, *The European Union: The Road to Nowhere,* 8 EUR. BUS. J. 31 (1996).

13. The strength of Germany's traditional chemically-based pharmaceutical companies has placed them in a comfortable niche. Thus, these pharmaceutical companies seem hesitant to compromise their positions by venturing forth into the more experimental biotechnology market.

least six major competing departments: National Institute of Health (NIH),[14] National Science Foundation (NSF),[15] the Department of Energy,[16] the Department of Agriculture,[17] the Environmental Protection Agency,[18] and

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14. The NIH is a federal agency that underwrites research in its own laboratories, as well as in those at private and public institutions by awarding grants and contracts.

> In the area of biotechnology, NIH-supported research can be divided in two categories. The first is basic research directly related to biotechnology, which includes recombinant DNA techniques; gene mapping and DNA sequencing; isolation, separation, and detection of DNA; the creation of hybridomas; the production of monoclonal antibodies; protein engineering; production of antibody-torn chimeras (immunotoxins); and the computer analysis of DNA and protein sequences. The second category relates to the broad research underlying biotechnology and refers to studies in the fields of genetics, cellular and molecular biology, biological chemistry, biophysics, immunology, virology, macromolecular structure and pharmacology. For the basic research studies directly related to biotechnology, NIH provided an estimated $1.19 billion in fiscal year 1990. For the broadly based research area, NIH provided and estimated $1.7 billion in fiscal year 1990. Thus, for fiscal year 1990, NIH provided an estimated $2.9 billion for biotechnological research through its research grants and contracts mechanisms for its intramural component.

U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, BIOTECHNOLOGY IN A GLOBAL ECONOMY 249 (1991).

15. The NSF is a federal agency that supports basic research in the United States' colleges and universities. In fiscal year 1990, the NSF budget comprised about 7% of the federal nondefense budget for research and development. About 94% of the NSF budget is used to support basic research; about 6% of the NSF budget supports applied research.

> NSF specifies a category of work as related to biotechnology if it includes research activities related to the following: environmental applications; bioprocessing and bioconservation; bimolecular materials; bioelectronics and bionetworks; agricultural applications; medical applications; and impact of biotechnology.
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> . . . .
>
> NSF's total support for biotechnology-related research in fiscal year 1990 was $167.9 million.

Id. at 251-52.

16. The Department of Energy (DOE) funds biotechnology research through three main programs: Basic Energy Sciences, Biological and Environmental Research (both of which are part of the Office of Energy Research), and Conservation and Renewable Energy.

The Basic Energy Sciences program, which focuses on the transformation of biomass into other forms, was funded at approximately $20.4 million in fiscal year 1990. *Id.*

The Biological and Environmental Research program, which focuses primarily on human genome and structural biology programs, was funded at $54.9 million in fiscal year 1990.

The Conservation and Renewable Energy program focuses on bioprocessing industrial and municipal wastes into fuels, and was funded at $6.9 million in fiscal year 1990.

17. The Department of Agriculture (USDA) funds biotechnology research and development through four different agencies: the Agricultural Research Service (ARS), the Cooperative State Research Service (CSRS), the Forest Service, and the Economic Research Service (ERS).

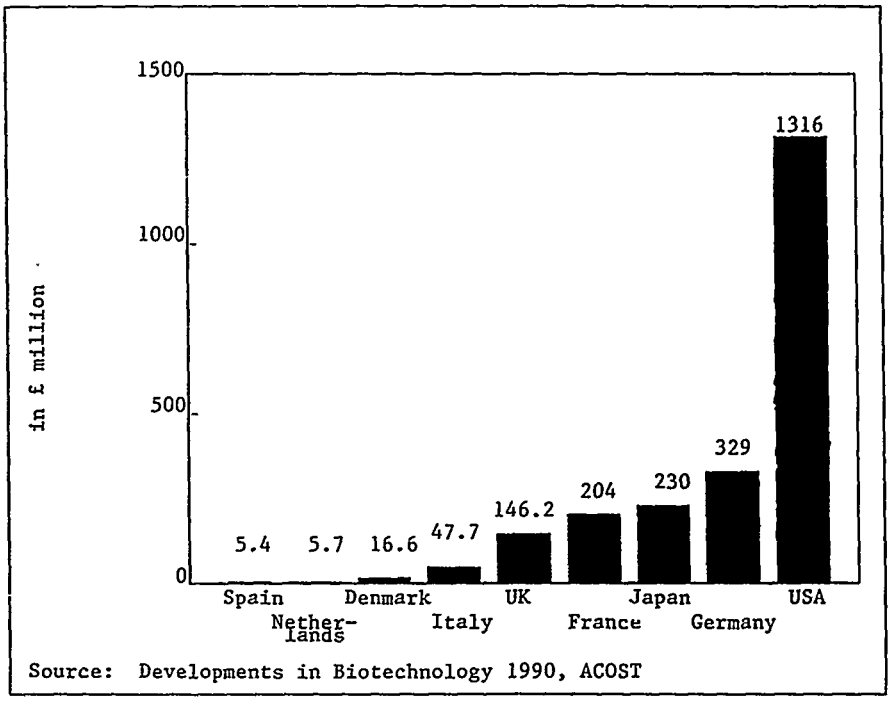
The ARS is the USDA's main research agency. ARS funds processes in order to solve agricultural problems. In fiscal year 1990, ARS received approximately $59.2 million in funding.

The CSRS is the USDA's liaison to the state university system. The CSRS handles diverse funding to university research projects, and was funded at about $52.2 million in fiscal year 1990.

The Forest Service funds biotechnology research to improve the cultivation of trees and plants by improving their growth and resistance to disease. The Forest Service also funds the testing and development of new industrial processes for wood. In fiscal year 1990, the Forest

the Food and Drug Administration.[19] This funding stimulates and supports a highly competitive industrial and regulatory structure. The European Union picture is much smaller and much more bureaucratic.

FIGURE 3



Public Funding of Biotechnology in selected countries

Service was funded at approximately $3.6 million.

ERS analyzes developments in agricultural technology and studies their potential foreign and domestic economic impacts. Research in the area of biotechnology includes forecasting the economic conditions under which animal growth hormones should be utilized and risk-management in biotechnology. ERS expended roughly $250,000 on economic analysis of biotechnology in fiscal year 1990. *Id.* at 253-54.

18. Although largely a regulatory agency, the Environmental Protection Agency (EPA) has a significant budget for research and development to produce a scientific basis for its regulations. EPA focuses on biotechnology risk assessment, particularly the impact of genetically-altered microorganism on humans and the environment. EPS' total biotechnology funding in fiscal year 1990 was $8.3 million. *Id.* at 255.

19. The Food and Drug Administration (FDA), which is responsible for the safety of foods, cosmetics, drugs, biologics, medical devices, and radiological products, monitors and evaluates the industry to assure products which are produced are safe and effective. Biotechnology has had a major impact on the development of products that the FDA regulates. The agency's focus is to maintain a research expertise in the field in order to have the knowledge necessary to approve new pharmaceuticals and other items regulated by the FDA in a minimum of time. The FDA spent approximately $19.4 million on biotechnology research in fiscal year 1990. *Id.* at 256.

Community research and development money is largely channeled through Bimolecular Engineering Programme and Biotechnology Action Programme, which are funded at nowhere near the extent of their United States equivalents.[20] This competitive use of public money is paralleled by its flourishing venture capital market in the United States, which is unknown in Continental Europe, and exists only to a much more minor extent in the United Kingdom.

The consequence is that in much of the European Union, large multinational corporations such as Bayer, Roche, and Glaxo, either set up laboratories in the United States[21] or compensate for the shortcomings in the European Union situation by buying into United States research, developments, and firms. I do not totally accept the notion that this implies that the United States taxpayer is giving something away for free, because it seems to me that the European Union firms have paid top-dollar for some of their investments. However, I leave that perhaps to discussion.

Martine Kraus addresses the legal situation of this area in more detail in her article.[22] Let me just briefly mention that the European Union regulations were only adopted at the Community level in March 1990 for the contained use and deliberate release of genetically engineered organisms. The regulatory situation is still uncertain and there is considerable room for legal conflicts and different interpretations.

Public opinion has had an important impact in this area, as has been sadly illustrated by the current "mad-cow disease" crisis in Europe.[23] Public

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20. The Biotechnology Action Programme (BAP) is a community organization which, among other things, supports biotechnology research and development and coordinates efforts for harmonization. BAP was established in 1985 and funded at $50 million. Mark Dibner, *Biotechnology in Europe*, SCIENCE, June 13, 1986, at 1367.

21. All of these companies have laboratories in the United States.

22. *See generally*, Martine Kraus, Ph.D., *A Comparison of Drug Approval at the FDA and the EMEA/CPMP*, 33 CAL. W. L. REV. 101 (1996) (this volume).

23. Bovine spongiform encephalopathy, more commonly known as "mad-cow" disease, is a brain disease which affects beef and dairy cattle. Mad-cow disease was first identified in 1986. The foremost theory for the origin of mad-cow is that it came from scrapie, a fatal viral disease found in sheep. (Scrapie is characterized by twitching, excitability, excessive thirst, weakness, and, in its latter stages, paralysis).

Britain, which has a $7.5 billion-per-year beef industry, is the only European country in which mad-cow disease exists. This is typically explained by citing the presence of a number of factors, including a high infection rate of sheep with scrapie and the practice of grinding and then feeding to cows sheep brains as a protein supplement.

In November 1995, some scientists theorized that there is a close link between mad-cow disease and Creutzfeldt-Jakob Disease (CJD), a rare but fatal human brain disease that had recently claimed the lives of ten Britons. The theory was expanded to hypothesize that the human disease could be traced to an abnormal protein in the cell membrane which, if consumed, could be transferred and damage proteins in the host. Although the Ministry of Agriculture, Fisheries and Food produced a number of scientists who showed that it was unlikely for the disease to be transmitted across species, other scientists disagreed. Debates regarding this link were common in British medical journals.

Although no conclusive link could be proved or disproved, public opinion regarding the matter was clear. In January 1996, Nielsen statistics showed that 1.4 million households had ceased to buy British beef. From November to mid-December, beef sales declined by 25% from the similar period in 1994. The most notable decline occurred in hamburger sales, which fell by

opinion has led to a general over-concentration in the biotechnology sector on the regulation of genetic engineering processes. This differs from the United States, which concentrates on the nature of the products produced.[24] The European concentration has slowed the construction of a secure regulatory environment and led to great conflicts in the one we have already partially constructed.[25]

In the area of intellectual property rights, the issue seems to have been solved, at least at the European Union level, with the adoption of a European Council regulation in April 1994[26]; however, the biotechnology industry has expressed serious concerns regarding the practicality of the interpretation and form of that regulation.[27] Quite simply, this means that we will be mired in the European courts for a long time, trying to decide exactly what that European Council regulation means.

Europeans believe that the United States grants patents with much broader scope and claims than would be allowed in the European Union and at the national level. Of course, the standards and intellectual property rights regimes vary amongst the members of the European Union and, often in a confusing and bewildering way, between the European Patent Office in Munich and the various national legal authorities. This muddle is being sorted out, but it is taking far too much time in the view of industrialists who

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40%. John Darnton, *Fear of Mad-Cow Disease Spoils Britain's Appetite*, N.Y. TIMES, Jan. 12, 1996, at A1.

Then, in March 1996, Health Secretary Stephen Dorrell reported to the House of Commons that the most likely explanation for the recent outbreak of CJD was exposure to mad-cow disease. Nearly every country in the European Union, as well as other countries around the world, imposed bans on the importing of British beef. But the worst blow came on March 27, 1996, when the European Commission imposed a world-wide ban on the exporting of British beef and a variety of products containing beef byproducts. John Darnton, *Europe Orders Ban on Exports of British Beef*, N.Y. TIMES, Mar. 28, 1996, at A1.

Almost three months later, on June 22, 1996, the European Commission agreed to a plan that would gradually repeal the ban on British beef. The plan, however, contains no specific dates for an end to the ban, and requires Britain to destroy approximately 120,000 cattle. John Darnton, *For the British Beef War: A Truce but No Victory*, N.Y. TIMES, June 24, 1996, at A9.

The impact of the mad-cow scare on the British economy was severe. The Office for National Statistics reported that the decline in beef sales resulting from the mad-cow scare reduced Britain's quarterly GDP growth by a tenth of a percentage point for the second quarter of 1996. Although forecasted to do so to a lesser extent, the mad-cow scare is also likely to impact Britain's third quarter GDP figures as well. *Farm Woes Curb British Growth*, N.Y. TIMES, July 27, 1996, § 1, at 40.

24. *See* Michael J. Malinowski, *A False Start? The Impact to Federal Policy on the Genotechnology Industry*, 13 YALE J. ON REG. 163 *passim* (1996).

25. Thomas C. Vinje, *Recent Developments in European Intellectual Property Law: How Will They Affect You and When?* 13 J.L. & COM. 301, 313 (1994); Richard Evans, *The Banking and Currency Power, Technology and the Future of the Market Economy*, 12 SANTA CLARA COMPUTER & HIGH TECH. L.J. 381, 401-01 (1996); Victor Vadebeck, *Realizing the European Community Market by Unifying Intellectual Property Law: Deadline 1992*, 1990 B.Y.U.L. REV. 1605 *passim* (1992).

26. Council Decision 110/94, 1994 O.J. (L126).

27. R.R., *Sun Could Set on British Biotech Unless Regulations Lighten Up*, BIOTECHNOLOGY NEWSWATCH, Oct. 18, 1993, at 1; Harold C. Wegner, *Impact of the TRIPs Agreement on Specific Discipline Patentable Invention*, 29 VAND. J. TRANSNAT'L L. 535 (1996).

are only too aware of the speed with which the technology and underlying science is developing.[28]

UNIVERSITY AND INDUSTRY RELATIONS

Finally, I wish to mention university-industry relations. It is important to remember that, aside from the United States, only the United Kingdom regards universities as legally autonomous institutions. In most of Europe, universities are part of the state, and university faculty are therefore civil servants.[29] As civil servants, the university faculty were forbidden, at least until very recently, to accept consultancy payments or enter into exclusive deals with commercial interests. This, together with the lack of a mature venture capital market, largely accounts for the absence of flourishing small biotechnology firms.

In Britain, it was largely cultural, rather than legal, difficulties that inhibited entrepreneurial academic commercial activity. To an American eye, the United Kingdom universities would probably appear in these terms to be behaving much as the United States did fifteen or twenty years ago.[30] Within the United Kingdom, as well as in the European Union more generally, both the legal and cultural frameworks are quickly changing.[31] We all recognize that in a knowledge-driven industrial world, there is no place for the academic ivory towers of old.

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28. To what extent have the uncertain intellectual property rights regimes limited investment? The simple answer is that it must have inhibited it a lot. It is one of those factors which, for example, led ChiroScience, one of our more successful small companies, to trade on the New York Stock Exchange rather than in the city of London. The uncertainty has meant that in this sector, the United Kingdom has tried to be a colony of America, rather than a free entity in its own right.

29. In France, for example, not only are they civil servants, but the elite of them, who work not in the universities but in the Grand Zecal, are issued with uniforms and swords on formal occasions.

30. It is a useful rule of thumb that says that whatever America is doing now, we in the United Kingdom will do in fifteen or twenty years' time. It seems that in this area, that rule of thumb holds.

31. The United Kingdom scientists are becoming entrepreneurs. They are no longer confined by government. British universities are legally autonomous and, starting with Mrs. Thatcher's administration in 1980, the government funding for universities has been decreasing. In the 1980s, between 80% and 90% of a typical university's income, (excepting Oxford and Cambridge) came directly from the government. Now the figure is between 30% and 50%.

The pressure of these budget cuts has led the academics to routinely predict the end of civilization as they know it and go out and raise more money. Although this has generated an enormous amount of whining and complaining, it has led the legal powers which were always there to set up companies and engage in the kind of activities which I can remember seeing with so much amazement when I was in the United States 30 years ago. That is now being redeveloped. The French and the Germans are looking with equal interest at what the United Kingdom and the United States are doing. They are also changing their legal status as well. It is now possible for German academics to engage in consultancy, to sign exclusive consultantships with companies, and so on and so forth. I think given five or ten years, you will see much more of what we still regard as typically U.S. behavior.

FUTURE DEVELOPMENTS IN THE EUROPEAN UNIONS BIOPHARMACEUTICAL INDUSTRY

Given this recital of ancient strengths and gradually appearing contemporary weaknesses, how are the European Union firms likely to respond? It is clear that they will seek to compensate for the rigidities and fragmented market structures within the European Union, which is fated to last for at least the next five to ten years. The firms will compensate first by directing an increasing fraction of their investments to the United States.

Figure 4 compares what was happening in 1980 with what was happening in 1988. The trends shown here have been accelerating since 1988.

FIGURE 4
Stocks of Inter-regional Direct Investment in Pharmaceuticals[32]
in millions of U.S. dollars

Origin	Destination				
-	United States	Western Europe	Japan	Rest of World	Total
End 1980					
United States		5,080	604	3,366	9,050
Western Europe	2,558	-	268	na	2,826
Japan	9	4	-	47	60
Rest of World	377	na	na	-	377
Total	2,944	5,084	872	3,413	12,313
End 1988					
United States	-	13,830	3,047	3,366	22,087
Western Europe	10,818	-	2,660	na	13,487
Japan	436	150	-	47	993
Rest of World	829	na	na	-	829
Total	12,083	13,980	5,707	3,413	37,387

32. Source: Secretary for Trade Industry (STI) review, Organization for Economic Cooperation and Development (OECD), 1993.

Look first of all at where investment capital was coming from, which is the origin, and then look at where it went. You can see that in 1980, the United States invested some 5 million U.S. dollars in Western Europe, whereas it invested nearly $14 million in 1988, an increase of nearly three-fold. But compare that with the increase of Western European investments in the United States from just over $2 billion in 1980, to nearly $11 billion in 1988, a five-fold increase. Although we are all investing in each others' markets, the Western Europeans are investing faster in the United States than the United States is reciprocating by investing in Western Europe.[33] This is a marked pattern, and one that I expect will continue. It is also interesting that although starting from a very small base, all of us are beginning to invest quite heavily in Japan.

As the European Union firms invest in the United States, the United States firms will seek to buy market shares in the European Union. Remember, the European Union is still the largest market. When the internal barriers are finally removed, it will be an extremely attractive market to be in, and the United States companies realize this[34]; but note that the motivation for their investment is rather different. European Union firms are investing to gain knowledge, investing in research and development, purchasing, merging, acquiring, or having strategic allegiances with some of

33. The lack of venture capital in Europe may be attributed to varying situations amongst the different countries. In Germany, for example, the banks have traditionally played the role which, in America, venture capitalists play. Banks such as the Deutsche Bank routinely have large stocks of shares in companies they support. Furthermore, the industrial structure is much more akin to that of the Japanese, which has a bank that owns the stock of a cluster of companies around it. And in France, the state has traditionally played, since the days of Colbert, the role of industrial sponsor.

In the United Kingdom, we have a situation much more akin to that in America, except that the United Kingdom is a much smaller economy; one must remember that, in economic terms, the whole of the United Kingdom is smaller than California. Although there is a venture capital sector, it has never grown at quite the same rate as the American sector. One of the reasons for this is that for a venture capitalist in the city of London, it always seems more attractive to put your money in America than it does in the United Kingdom. This is simply because the market sizes are so different. The clever men who draw the economic analyses will always tell one to invest in the United States.

34. In response to Commissioner Lehman's forecast of a trade war, Bruce Lehman, *Major Biotechnology Issues for the U.S. Patent and Trademark Office*, 33 CAL. W. L. REV. 49, 60-61 (1996) (this volume), I instead foresee robust negotiations between the European Union the United States. Ultimately, it will be in everybody's interest to come to a mutually satisfactory outcome because we have a shared interest in having a successful industry. Furthermore, if you believe in the theories of globalization, then that industry must be worldwide; it cannot be restricted to one geographical area. However, I do not want to challenge the Commissioner's predictions entirely. The Commissioner was absolutely right when he noted the deep-seated philosophical differences which have understandable legal and historical bases such as the European Patent Office's and the United States' differing approaches to the problems of patenting mice. Although I do not believe there will be a major trade war, there will be a tremendous row from time to time.

those small biotechnology companies.[35] In fact, Chiron has a number of such relationships. This is the cash equivalent of those deals in Figure 4.

The motivation for the United States firms is quite different. They are buying into a market. They already have the research and development, and they already have the knowledge. They are buying into a market and buying a market share. This increase in mutual reciprocal investment is but a specific example of the globalization we hear so much of from the management gurus. Not surprisingly, one can see it in a very clear and unambiguous form here, because this is a technology-driven, high-technology industry. This is where the cutting edge of globalization is most clear.

An important part of European Union investments in the United States is alliance, merger, or acquisition activity between large European Union pharmaceutical corporations and small United States biotechnology companies. I am sure we will see much more of that in the future, together with a developing European Union sector of small biotechnology start-up companies paralleling the American experience about fifteen or twenty years later. British BioTech shares, for example, have gone from £4 to £30 in the past 18 months. This has attracted a lot of attention, not only from American venture capitalists, but also from the growing number of European capitalists as well. I am sure that one or two successes like British Biotech will be followed up by European Union investors.

CONCLUSION

The one policy conclusion for the European Union from all of this is clear: In this industrial sector above all, the European Union really must create the Single Market that was the dream of those who signed the Treaty of Rome[36] all those years ago and which still has evaded their successes, at least in this area of industrial activity.

35. An example of this may be found in Dr. Edward Penhoet's Article. Edward Penhoet, Ph.D., *Science & Technology Policy: A CEO's View*, 33 CAL. W. L. REV. 15, 20 (1996) (this volume).

36. Treaty Establishing the European Community, Mar. 25, 1957, 298 U.N.T.S. 167.