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Working Party on Biotechnology

ECONOMIC ASPECTS OF BIOTECHNOLOGIES RELATED TO HUMAN HEALTH

PART II: BIOTECHNOLOGY, MEDICAL INNOVATION AND THE ECONOMY: THE KEY RELATIONSHIPS

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FOREWORD

Health care in the developed world is facing a massive surge of new knowledge and new technologies, deriving in particular from modern biotechnology and genomics, and driven forward by the pharmaceutical and biopharmaceutical industry. How should governments react, respond or intelligently anticipate the resulting implications for public policy? In February 1995, the OECD established under the Working Party on Biotechnology (WPB) of its Committee for Scientific and Technological Policy (CSTP) a working group on Human-Health-Related Biotechnologies. The first responsibility of this group was to oversee a major study on the economic aspects of such innovations.

The study has from the start reflected a certain ambivalence for public authorities faced with the prospects and promises of innovation. There are high hopes, among patients, clinicians and scientists, about the promise and potential of the new technologies, particularly for currently incurable diseases; strong economic interests in play, given the requirement for heavy and protracted investments in research and development; but also concerns about the rising costs of health care in national budgets, and uncertainty as to whether the new technologies are part of the problem, or part of the solution -- or both.

The present report is the second of two volumes presenting the results of the study. The first volume, published in early 1998, is titled, "*Economic Aspects of Biotechnology related to Human Health: Part I: Biotechnology and Medical Innovation: Socio-Economic Assessment of the Technology, the Potential and the Products*" **[OCDE/GD(97)205]**. As the title indicates, this focuses on the details of the technology and on methods of economic evaluation, and presented illustrative case studies. It addresses the increasing interest in such methods, not only of governments, but of academic researchers having interests in public policy, and in economics; and of the industrial firms, large and small, whose innovations are expected to withstand such appraisal.

Economic appraisal and decisions e.g. on reimbursement are one important dimension of socio-economic assessment, but governments have wider responsibilities and influence in relation to medical innovation. These wider dimensions are the focus of this second report. It is in the public interest, indeed essential for survival and competitiveness in an open world economy, that governments encourage innovation and provide appropriate conditions within which companies may successfully launch products and services, profiting from the general rapid progress of knowledge and scientific understanding. The first three papers in the present volume focus on innovation, on the determinants of market structure in the biopharmaceutical industry, and on the restructuring which the changes in the new knowledge system are provoking in the pharmaceutical sector. The increasing information-intensity of the sector underlines the importance of intellectual property, the topic of the fourth paper.

Finally, three papers address the topic of regulation. This is a topic of central importance: the regulatory framework stands at the interface, holds the balance between innovation and application, between supply and demand, between the public authority with its multiple responsibilities, and the potential fruits of the knowledge system in the form of new technologies, services and products.

The Glossary published in the Part I report is repeated here for convenience, since many of the terms appear also in this volume.

Financial support for this OECD work has been provided by extra-budgetary grants: from the industry association Interpharma in Switzerland, with the support of the government of that country, and from the United Kingdom's Department of Health; general support for OECD's work in biotechnology has also been provided by the Japanese government. This support is acknowledged with grateful thanks.

Thanks are due also to the members of the Steering Group, designated by Member governments, who have overseen and advised on the study throughout. Individual chapters have been drafted by the expert consultants as indicated, and the overall report co-ordinated by Elettra Ronchi of the Secretariat.

A "Policy Summary" based on the material presented here will be published by OECD shortly. Full details of these and other publications and activities of the OECD in biotechnology can be found on website <http://www.oecd.org/dsti/biotech>.

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EXECUTIVE SUMMARY

Introduction. Objectives of the study, aims and content of the Part II Report

This report comprises Part II of a study on the Economic Aspects of Biotechnologies Related to Human Health. The study from its beginning reflected the conviction that recent progress in the life sciences and technologies represents an enormous opportunity, in human and economic terms. Its objective was to provide:

- a background on current and potential applications of biotechnology in health care; and
- a description and analysis, based on carefully chosen case studies, of the process of development and adoption of specific biotechnological innovations;

addressing such issues as improved quality of life and cost-effectiveness of the new approaches, and setting the specific analysis in a wider macro-economic perspective and policy context.

Part I of this study, "Biotechnology and Medical Innovation: Socio-economic Assessment of the Technology, the Potential and the Products"[1], provides a synthesis of the achievements of biotechnology in health care and considers how methods of economic evaluation may be applied to appraise costs, benefits, and the wider implications of new and emerging medical innovations. It highlights the need to resolve problems of comparability and international transferability of results, and the challenges specific to the assessment of emerging technologies.

The earlier report also emphasizes the common goals of public policy-makers and industry, to encourage the maximum effective contribution of biotechnology to health care, while sustaining innovation and competitiveness in the global market. The report advocates the introduction of clear public health goals, and rigorous evaluation in relation to the potential explosion in applications such as genetic testing; and suggests increased dialogue between governments and biopharmaceuticals concerning the generation of relevant clinical and economic data.

Part II completes this study by addressing the regulatory environment and several other major factors that affect market structure in the international biopharmaceutical industry. For this phase of the project, three specific objectives were formulated through this consultative process:

- review the impacts of regulatory frameworks on the cycle of innovation in biotechnology;
- review the determinants of market structure in the international pharmaceutical industry;
- identify incentives and disincentives to the transfer, wider diffusion and growth of biotechnology.

It was agreed that in addressing these objectives, the report should provide examples of the impact of public policies on the research, development, approval and marketing of new biotechnology-derived biopharmaceuticals; and consider also the impact of legislation on intellectual property.

Given the complex nature of the biotechnology industry, its close interaction with the pharmaceuticals sector, and the dependence of this sector on public policy, the present report focuses on the total framework for biotechnological innovation, and develops a fuller picture of the several key interfaces between public authorities and the industry.

Government policy and regulations can have both positive and negative effects on the innovation process, especially in such a high-technology, resource-intensive sector. A theme which recurs throughout this report, is *the relation between regulation and innovation; a relation sometimes of tension, but in which a sound regulatory framework is recognised as essential for acceptance and success of innovation*. This dichotomy is used to classify into two groups the papers comprising the report, and to present in this Executive Summary the main points of the report under the same two headings; while recognising that each paper can be read either in isolation, or as part of this broader policy dialogue. Overall conclusions are summed up in the final section of this Summary.

This study has benefited from an extended process of consultation with experts from OECD Member countries, as acknowledged briefly in the Preface. This has strengthened many points; while inevitably delaying completion of the publication. Some of the data in the papers has been updated, but in general the analyses and recommendations are not sensitive to the presence or omission of the latest data points.

Innovation in biotechnology: the key players: academia, industry and the knowledge system

The first three chapters of the present report describe and analyse, on an international comparative basis, the systems and structures by which advances in biological understanding and technological development are generated and translated into industrial innovation and commercial products.

- Ronchi in Chapter 1 describes the innovation "cycle" in the health-care sector; a scene-setting paper outlining the total system from basic research via industrial development of processes and products, to commercialisation; a system much influenced, constrained and driven by regulatory policies.
- Kanavos in Chapter 2 gives an extended overview of the determinants of the market structure of the biopharmaceutical industry, in different countries, analysing the factors which make for a favourable climate. Particular account is taken of the specific characteristics of pharmaceuticals, and of financial aspects.
- In Chapter 3, Cantley discusses the transformations in progress, the "knowledge-intensification", as the pharmaceutical sector digests the surge of insights and innovations flowing from modern biotechnology; as background to a report by Dibner, of the results of an attempt to obtain a snapshot of this process by a survey of dedicated biotechnology companies in the United States.

The major determinants of market structure in the international biopharmaceutical industry include a number of factors, of which the following are addressed in the above-mentioned chapters of the report, and in the case study (Chapter 4) concerning Canada's policy experience with intellectual property rights for pharmaceuticals:

- the research system and its linkages;
- industrial structures;
- financing of innovation;

- intellectual property;
- public perceptions.

These factors play a crucial role in determining the activities and structure of the biopharmaceutical industry and the innovation system; some key points, drawn from the papers are summarily presented below. Regulatory aspects are addressed in the following section.

Policies to foster relationships between academic institutions and industrial partners

The development of biotechnology presupposes a strong science base and the ability to form horizontal links with other disciplines, mobilising and managing an inter-disciplinary activity. Countries that are successful in the biopharmaceutical field -- the United States and, to some extent, Japan -- have a long-term commitment to biotechnology, which is partly evident in their funding to academic institutions. The case of the United Kingdom is rather different: its very strong scientific base has never been entirely dependent on public sector support and has always had to obtain some of its resources elsewhere, from private foundations and through good links with the corporate sector.

In the opening chapter, Ronchi discusses the gradual but necessary blurring of the boundaries between academia and industry. University-industry links constitute powerful channels for the development of new technology. Significant private sector involvement in biomedical research highlights two major features of today's research systems. First, with the introduction of modern biotechnology, research outputs are more easily transferred to the private sector so that the distinction between basic and applied research has become less clear.[2] Second, recent public policy has profoundly changed the constraints and incentives which influence the development of new medical technologies and products. The United States provides an environment conducive to successful co-operation between university-based research and corporate efforts. In Japan, current policy initiatives are seeking to strengthen collaborative mission-oriented research between industry and public institutions. In Europe, university-industry collaborations are comparatively less frequent than in the US, with the exception of the United Kingdom.

In general, industry-academia relationships are short-lived. Thus, universities cannot depend heavily on industry to support their research and infrastructure and cannot hope to offset public budget reductions with this source. This is an area where US public funding (in particular via the National Institutes of Health) has laid a basis for long-term competitive strength.

In several countries with strong science bases, public policy increasingly encourages the most qualified academic and research institutions to work with private firms to improve basic research, technology development, and technology transfer. However, the issue of conflict of interests must be addressed, especially for university scientists. Guidelines for resolving such conflicts of interest should be introduced, as a necessary element to facilitate the development and practical application of the results of academic research.

In place of subsidies, consideration might be given to the use of tax incentives for qualifying research expenditures and for companies' expenditures on, or in support of, university-based research. In Europe and Japan, there is a clear need to fund basic research in a manner that encourages close collaboration between the industry and universities and research centres. Cost-sharing projects, especially in biotechnology, should be expanded.

Industrial structures for innovation: large companies vs. Small and Medium-sized Enterprises (SMEs)

Kanavos in Chapter 2 examines on an inter-connected basis the factors affecting industrial structure, conduct and performance, noting especially those specific to the pharmaceutical sector, such as the three-tier demand system (patient, doctor and reimbursing agency), and implications such as the intimate dependence on the actions of governments. There are also clear economies of scale in research and marketing (the trend to outsourcing of research is another response to research costs and scope, but a separate issue).

At first glance, notes Kanavos, it might therefore appear that the future of the pharmaceutical/biopharmaceutical industry in OECD countries depends only on generous pricing of newly patented products and further mergers of firms that lack the size apparently now required to stay in the top league. Mergers are indeed necessary and are already occurring at an increasing pace. Governments are not, however, in a position to know either which mergers should occur or which are likely to be successful. This must be left to the industry. There are already near monopolies in the world market for certain new therapies, and, given the patent system, these may be inevitable in the short run. Mergers and acquisitions may, however, reduce research options and the likelihood of technological advances, since the vitality of any industry depends on new entrants. Thus, policies need to be reinforced to strengthen the innovative potential of SMEs, particularly in Europe and Japan, where the entrepreneurial spirit must also become more aggressive, the incentives for its expression clearer. So far, given the broad scope of scientific research, large biotechnology companies and SMEs co-exist and complement each other.

Kanavos argues that policy on the development of SMEs is successful in the United States, but remains fragmented in Europe, particularly since each European Union (EU) member state has a policy of its own. What is generally lacking is explicit support of the high-technology SME sector of which biotechnology is an integral part.

Financing innovation

The financing of innovation in biotechnology presents considerable differences across countries, and both Kanavos and Ronchi make clear the multiplicity of steps and obstacles to be overcome. An important aspect of finance is the facility for start-up biotechnology companies to reach the stage where they can seek listing in capital markets and raise capital from them. Their small size and the fact that in most cases these companies in their early years do not have a product on which to trade, makes listing difficult.

The United States has the largest pool of venture capital, necessary for the initial phases of biotechnology product development; with an active "over the counter" market for the trading of unlisted securities, and relatively simple listing requirements for the NASDAQ (National Association of Securities Dealers Automated Quotations), now one of the busiest financial sites on the Internet, offering early "exit routes" through which to realise capital gains. Such facilities encourage investment by "business angels" and venture capitalists in companies needing start-up and early-stage finance. In the United States, experienced brokers with in-house biotechnology specialists can "shepherd" young companies through the preparation of their initial public offerings (IPOs) on the public stock market. Such support is gradually also developing in other OECD countries.

In Europe, venture capital exists, but at a lower scale, due to the fragmentation of European markets and to regulations which in some countries make it more difficult for early investors to realise capital gains via the "exit route" of public flotation. The London Stock Exchange (followed by the Tokyo Stock

Exchange) have for this purpose relaxed their listing rules for biotechnology companies, and the creation of EASDAQ, the London "Alternative Investment Market" (AIM), and the "New Markets" in Brussels, Paris and Frankfurt, similar in concept to the NASDAQ, have similarly expanded opportunities for European companies.

Despite the availability of a number of sources of finance for biotechnology, including IPOs and R&D limited partnerships, these sources are subject to market volatility, and short-term expectations about product launches and net revenue streams. For these reasons, strategic alliances between biotechnology and pharmaceutical companies have become the most popular and less risky way of financing innovation in the former.

The role of national governments (and supra-national institutions, such as the European Commission) in financing innovation is very important, but varies across the OECD countries. The US government is the most active supporter of innovation through generous (when compared with other countries) funding of biotechnology R&D in national laboratories and universities. Moreover, an appropriate legislative framework is in place for the transfer of technology from national laboratories to the private sector for development. In the EU, public sector research is perceived to be fragmented and national initiatives, though important, may lead to duplication of the research effort. In terms of scale, the United Kingdom, Germany and France spend a lot more per capita than other EU Member States. The European Commission, through the EU research budget, has supported priorities identified at the European level, and has made the development of biotechnology one of these. However, the funds committed to biomedicine and health at the European level are only a fraction of the US equivalent.

Japan has also identified biotechnology as one of its priorities and actively funds research in specific areas. Government and industry pursue active international policies, through research collaborations and private sector investments, thus adding strength and breadth to the domestic research base for industrial development.

In summary, Kanavos (Chapter 2) lists a number of features as desirable attributes of a financing environment conducive to the development of biotechnology, including the following:

- a large and non-fragmented (financial) market, from which venture capitalists can draw financial resources;
- relative investment freedom for mutual funds and pension funds; in that way important resources can be released and partly used to support high risk investments;
- lower capital requirements for securities issuing houses;
- shortening of the period within which quoted investment companies can sell stakes in companies without being liable to tax;
- shortening of the period within which banks and investment advisers can be held liable for the contents of prospectuses and their own advice;
- definition of an appropriate level for personal and corporate taxes (e.g. on capital gains) to stimulate risk capital;
- high demand for equities helps companies, including biotechnology companies and SMEs in general, to raise equity finance - and such demand is encouraged for example, by the introduction or expansion of equity-based pension funds;

- capital availability at the start-up level, i.e. when new companies need it most, and when ideas are taking shape;
- overall tax policy for Small and Medium-sized Enterprises (SMEs), particularly carry forward of tax credits which can be used when such SMEs become profitable or negotiate an alliance with a large (bio)pharmaceutical company.

Intellectual property rights

Common to the first three chapters is an emphasis on the ever-increasing importance of intellectual property rights (IPR), a topic addressed specifically by a case study paper (Chapter 4), in which Pazderka describes the Canadian experience -- the pressures and arguments which led them to legislate improved protection for research-based pharmaceuticals companies, and the uncertain evidence of its effects over the following years. Gosse *et al.* (see below) also touch upon aspects of IPR in the US regulatory context.

The evolution of internationally accepted regimes for intellectual property is of great significance for biotechnology as it enters the age of genomics, as is emphasized in Chapter 3. In a research-intensive industry, effective protection of intellectual property rights is crucial. Patenting in biotechnology, and particularly in connection with human genes and/or living organisms (such as transgenic mice) and with "bio-prospecting" for genetic resources[3] has become highly controversial, both within countries and in the international context. The subject will again be highlighted during the 1999 review of the World Trade Organization's "TRIPS" agreement (on Trade-Related Intellectual Property); but the current and prospective policy discussions are part of a protracted international debate.

The OECD first addressed IPR aspects of biotechnology in a 1982 survey, the report on which pointed to "the unchanged if not increasing interest and concern which industry and inventors demonstrate for the patent system". The same report, reviewing numerous legal differences between OECD countries, noted that "United States law and Japanese law are on the whole more open and flexible towards the new developments in biotechnology than are the laws of many other OECD countries". In response to that challenge, the European Commission put forward in 1988 a proposed Directive "on the protection of biotechnological inventions", which triggered wide-ranging and protracted discussion over the following ten years. In 1998, this finally culminated in adoption by the European Parliament and Council of a Directive clarifying and harmonizing key elements of patent law as it relates to biotechnology.

Apart from the question of patent legislation itself, there are side-issues related not to the nature of the legislation but to its implementation: the backlog of applications (which increases both costs and uncertainty); enforcement (Russia, for instance, is said to possess a pharmaceutical patent law, but it is not enforced and it may take decades for a patent infringement suit to reach the courts); or licensing requirements (once Canada relaxed licensing requirements after introducing a new patent law, R&D investment increased threefold).

Public perception and acceptance of innovation

Kanavos emphasizes the importance of public perception and demand as a factor influencing the acceptability and speed of innovation. Where needs are strongly felt [e.g. in Autoimmune Deficiency Syndrome (AIDS), cancer, and genetic diseases], patients' organisations have played a significant political role in the pressure for research support and demands to modify regulatory procedures, in order to facilitate early availability and diffusion of new therapeutics.

In assessing public acceptance of innovation and the potential impact of biotechnology, one must be aware of the different, though not necessarily opposing, views of consumer groups, on the one hand, and specific patient/disease groups, on the other. An opinion widely shared among representatives of consumers and patients is that the degree of public acceptability of an innovation, particularly in the field of biotechnology/pharmaceuticals, will depend on the degree to which a drug or new technology meets "real" needs.

Regulation, rationale, reaction and refinement

Regulatory reform, regulation in health care

This study was conceived at a time when the OECD was charged by Council with examining the significance, direction and means of reform in regulatory regimes in Member countries.[4] The preamble noted that:

"Governments seek to promote the economic and social well-being of their people in a wide variety of ways, which include policies aimed at macroeconomic stability, increased employment, improved education and training, equality of opportunity, promotion of innovation and entrepreneurship, and high standards of environmental quality, health, and safety"; thus embracing both aspects of the present report.

Chapters 5, 6 and 7 of the report concentrate primarily on regulatory aspects of health-care systems.

- In Chapter 5, Gosse and colleagues from the Tufts Center for the Study of Drug development present a comprehensive history of the developments over the past ten years, in US regulatory policies affecting the research, development and approval of biopharmaceuticals derived through modern biotechnology. The current process is the outcome of a succession of regulatory initiatives in response to political pressures from industry, patients or others; and successive refinements as shortcomings are addressed. Industry is concerned at the financial implications of delay; patients' groups (particularly sufferers from AIDS and cancer) have exerted pressure for expanded access and accelerated procedures for investigational new drugs. Various licensing steps have been simplified or eliminated. For biotechnology, and for the patient groups concerned, one of the most important regulatory innovations has been the development and operationalisation of the concept of "Orphan Drugs": of vital significance in opening up opportunities for the biopharmaceutical sector. They review matters under current debate, concerning reform of the Food and Drug Administration (FDA), and the continuing efforts to streamline regulatory review without compromising safety. They compare US with other international experience and efforts of other countries to address some of the recent regulatory challenges arising in five areas: human gene therapy, xenotransplantation, cellular therapy, transgenic animals and AIDS vaccines. Finally they discuss progress of, and prospects for further international regulatory standardisation and its effect on world-wide biopharmaceutical development.
- A specific and perennially contentious point is delay, which not only adds to costs but leads to tension between the needs of patients suffering from life-threatening diseases; and the depth and thoroughness of the review procedures which past experience and prudent risk management have shown to be necessary. McAuslane and Walker of the Centre for Medicines Research in a short paper (Chapter 6) give an international comparative survey of

regulatory review times and their determinants, but caution against over-simple comparisons, given the differences in other factors.

- One of the innovations developed in the US environment (see Gosse *et al.*), to bridge an apparent gap between public interest or need, and the motivations of industry, was the concept of "orphan drugs". Philipon (Chapter 7) reviews this experience, and that of Japan, which implemented a similar initiative; as background to a discussion of the ongoing arguments about the need for legislative steps to implement the concept in the European environment, while recognising the partial possibilities which exist under current structures and dispositions.

The rationale for regulation in health care

Ronchi emphasizes uncertainty as one of the main reasons for intense government intervention in the health-care industry. Other related reasons include ensuring equity, equality of access, and transparent provision of information for consumer awareness. The pervasive influence of risk and uncertainty on the market for health care has long been recognised. Patients do not know when they will need health care, nor for how long. In addition patients lack information to evaluate what is offered and possible alternatives. Moreover, for many of the industry's products, their influence is a matter of life and death (or may be so perceived by patients). Indeed, the consequences of ill-informed purchase of care may include irreversible damage or death; and there is no certainty whether the long-term effects of new medicines will be beneficial or harmful.

In this context, regulation -- defined as the exercise of sustained control over an activity by a public agency (and including both authorisation for release of products, and post-release monitoring) -- can be seen as an instrument for reducing and protecting people from the risks linked to such uncertainty.

In developing regulatory guidelines for new technologies, policy-makers are challenged to strike a balance between public concern over unknown technological risks and guidelines that foster, not impede, research on promising new treatments. Biotechnology provides a useful example of the difficulties and complexities that regulatory authorities face, since in this field governments seek also to reconcile their role in promoting and maintaining a strong, internationally competitive research-based industry with their regulatory objectives in health and safety policies, and public expenditure goals.

Thus, Ronchi argues that regulations should strike a balance between the public policy objectives of providing for pharmaceutical innovation, and promoting mechanisms for containing risk and controlling health-care expenditure.

Over the last five years the regulatory arena has seen a number of changes which have the potential to have a major impact on both review times and the relationship between the health-care industry and regulatory authorities. Biotechnology, as applied to the development of human therapeutic products, has provided and will continue to provide innovative technologies to aid the discovery of new disease mechanisms, the genetic basis of human diseases, and novel therapies. In order to realise the potential in this technology, governments must create policies to foster innovation through regulatory practices, economic incentives, investment in research and development, and an expressed commitment to provide for its citizens the benefit of these technological advances. Concise regulatory practices must be aimed specifically at protection of the population from potentially harmful or ineffective products while allowing innovative research and development to flourish.

Regulatory regimes affecting R&D of new biopharmaceutical products

Biotechnology-derived pharmaceuticals are subjected to the same regulatory rules as conventional pharmaceuticals. Speed of approval is essential for marketing and capture of market share, as it is for revenues accruing from sales in large markets. Biotechnology companies are more sensitive in this respect due to the capital constraints they face. In Europe, the establishment of the European Medicines Evaluation Agency and its centralised authorisation procedure for all biotechnology products facilitates market access.

Slow product approval remains a problem, more so in the United States than in Europe, although the FDA is making considerable efforts in this direction, as described by Gosse *et al*. Long approval times add substantially to biotechnology companies' costs, thereby increasing the need for funds, so that the formation of strategic partnerships with larger corporations becomes a condition of survival; here as in other ways, the regulatory environment influences the financial requirements and hence the structure of the industry. The introduction of user fees partly solves the problem, for although it adds to the short-term costs of biopharmaceutical firms, the gain in time offers on average a significant net benefit.

The reasons for differences in review times between countries merit examination, as all authorities have the same basic tenets, to protect and promote public health and to review dossiers based on the three criteria of quality, safety and efficacy. In order to understand the reasons behind these differences, McAuslane and Walker draw attention to other factors which need to be assessed, such as the quality of dossiers, companies' response time to authorities' questions, and the ability of authorities to manage the review effectively and efficiently.

The US Orphan Drug Act of 1983 provides the financial incentives that have encouraged pharmaceutical manufacturers to develop new orphan drugs. These incentives include exclusive marketing rights for seven years and tax credits for clinical research, among others. According to the National Organisation for Rare Disorders (NORD), a non-profit voluntary health agency, many important new therapies have been or are being developed in response to the legislation. The situation is similar in Japan, where orphan drug legislation has existed since the early 1990s.

EU countries have no specific criteria for funding research activities leading to the development of orphan drugs. Legislation or institutions are also lacking at EU level, although efforts in that direction are in preparation. In the United States, the Office of Orphan Products Development (OPD) of the FDA encourages, through its grants programme, the clinical development of products for use in rare diseases or conditions. The products studied may be drugs, biologicals, medical devices, or medical foods. OPD grants support clinical trials on the safety and effectiveness of orphan products and encourage clinical development of orphan indications for already approved products; they do not support basic research.

Health-care reform

Health-care reform is on the agenda of most OECD countries. Cost containment and efficient use of resources are the most important directions in health sector reform. Unavoidably, pharmaceutical products, accounting for between 10 and 27 per cent of the health budget in different countries, are subjected to a large array of cost control measures.

The emphasis on cost containment is expected to influence the dissemination of biopharmaceutical products, due to their high cost, unless the therapeutic gain exceeds (and is seen to exceed) current and future costs of treatment.

Very few OECD governments allow the pharmaceutical industry to set prices freely. In addition, as the effort to contain costs increases, an effective mechanism is needed to guarantee a certain price level for the industry and some success in holding down pharmaceutical spending. Various systems have proved ineffective, including the German version of reference prices; a possible exception is the United Kingdom's Pharmaceutical Price Regulation Scheme, coupled with incentives to doctors to prescribe rationally. Free pricing remains a long-standing demand from the industry, but it is doubtful whether governments that impose pharmaceutical price controls will accept free pricing, without additional measures that would keep the pharmaceutical budget under control.

In this context, the challenge for biotechnology is twofold. First is whether it can deliver therapies for a wide range of diseases. Policy-makers are faced, in the short to medium term, with the question of whether or not to adopt expensive new biotechnologically derived therapies without solid proof that costs will be reduced in the long run. Second is whether the new technology will make it possible to move towards effective prevention of disease by understanding the underlying aetiology, in which case the long-term benefits, in terms of public health, decreased mortality, and increased quality of life, will outstrip the short-term costs.

Overall conclusions

The Part I report confirmed the potential of the technology -- for more fundamental understanding of disease processes, which may lead to treatments for currently unmet needs; for efficient production of previously scarce molecules of therapeutic value; for safe and effective vaccines; and for novel, sensitive and specific tests. This surge of innovations -- many of them initially expensive, and potentially creating new demands -- has stimulated an expansion of health technology assessment. An underlying and continuing question is whether technological innovation is part of the problem of rising costs in health care; part of its solution; or both -- meeting some needs more cost-effectively, but offering new potential for quality of life improvements which will increase total expenditure.

This Part II report addresses a broader challenge, looking at the total context of public policy which can influence the processes through which innovations are generated by modern biotechnology, and brought into application in health care. Recurrent throughout the report is a tension between regulation and innovation.

Evidently both are essential, and serve the public interest; the former addressing issues of risk and safety, the latter the source of continuing hope for improving current practices and products, and addressing needs currently unmet. Governments are faced with the problem of managing a complex process, with a range of policy instruments, uncertainties about their effects, and a continuing surge of new scientific knowledge and potential innovations. The process has been described in the papers of this report, the potentials more fully in the earlier, Part I report.

Governments are also faced with numerous pressures, sometimes contradictory, demanding action and responses, not least to the promises and potential of the innovations apparently on offer as a result of biotechnology. Information about all aspects of the system, but particularly about scientific and technological breakthroughs, is instantaneously available, world-wide, in formats ranging from scientific or clinical research papers and data, to tabloid newspaper headlines. The information is almost equally

accessible to patients, in organised groups or as individuals; and the pressures exerted have encouraged or obliged public authorities to alter their procedures, for example as described in the Tufts paper regarding the US Food and Drug Administration. Although many of the references in the report are to the US scene, no country is an "island", able to isolate itself from such information and the resulting pressures.

The international exchange of information (not least, through international or inter-governmental bodies such as OECD) offers speed and economy of learning, through exchange of experience and data. Through harmonization, standardization, mutual acceptance of test results and data, further economy of effort and the facilitation of collaboration and trade are obtainable; market access and economies of scale encourage and facilitate corresponding internationalisation of the industry, and the innovation process.

This report is addressed, in the first instance, to policy-advisers in OECD Member countries, and to the wider interested communities. In an era sometimes characterised by "single-issue politics", it offers a message inescapably pluralist: government has many faces, many objectives, and many instruments available to it. It has to play many roles in the contexts of science, industry and health-care policies. From the papers in this report, recommendations to policy-makers could be summarised as emphasizing the simultaneous roles of government as **promoter** (of research and innovation), **controller** (of costs, market access, reimbursement), and **"intelligent facilitator"**:

- supporting basic research and infrastructure for the life sciences and technologies (through national facilities, or good national connections to international facilities);
- facilitating academic-industrial collaboration;
- setting targets and incentive structures to orient research and innovation towards priority and unmet needs (vaccines, orphan drugs, ...);
- facilitating financing conditions at all phases of innovation, from academic-industrial collaborations and start-ups, to IPOs;
- facilitating clear terms for IPR and its enforcement, nationally and internationally;
- where needs are urgent, facilitating early release and diffusion of promising new therapies, with appropriate oversight and monitoring;
- facilitating innovation by establishing reimbursement conditions compatible with a return on investment consistent with the (high) risks involved in developing innovative drugs.

These recommendations include, indirectly, means to promote and protect domestic research capabilities and infant industries; but in ways compatible with commitments to an open world trading environment, and benefiting from the pressure of international -- indeed global -- competition in stimulating innovation and controlling costs.

NOTES

1 OECD, 1998; available for full-text download from website <http://www.oecd.org/dsti/biotech>

2 The Frascati manual (OECD, 1994) gives the following definitions for basic and applied research: "*Basic research* is experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, without any particular application or use in view". "*Applied research* is original investigation undertaken in order to acquire new knowledge; and is directed primarily towards a specific practical aim or objective".

3 See " *Intellectual Property, Technology Transfer and Genetic Resources: An OECD Survey of Current Practices and Policies*" (OECD, 1996); and "*Biotechnology and Patent Protection: An International Review*" (OECD, 1985).

4 See OECD (1997), *The OECD Report on Regulatory Reform, Synthesis*, OECD, Paris.

SECTION I: INNOVATION IN BIOTECHNOLOGY: THE KEY PLAYERS AND THE KNOWLEDGE SYSTEM

THE CYCLE OF INNOVATION

by

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Introduction

This chapter offers an introductory overview of the innovation cycle in the health care sector, with particular reference to the biopharmaceutical sector. It shows how modern biotechnology is affecting the structures and processes of innovation, and reviews some aspects of the regulation of the new products setting the scene for fuller discussion of these matters in the subsequent chapters. The report uses case studies as a basis for assessing the impact of government intervention on innovation in biotechnology, and for examining how such intervention has sought to adapt to the evolving nature of the biopharmaceutical sector, its technology and its products. A conclusion, or theme, which emerges in this chapter and recurs throughout the report, is *the continuing interplay, the tension between regulation and innovation*.

In the biotechnology sector, industrial performance is usually viewed in terms of product competition rather than price competition. As industrial success and long-term profitability are based on the ability to compete with new products, innovation is the ultimate source of competitiveness in this sector. Government regulation can clearly influence the innovation process. While price regulation is one of the most visible aspects of intervention, product safety regulations or rules on patenting may have even stronger impacts. Stringent product safety regulations, for example, may not only make development of new drugs more expensive, they may also raise barriers to entry.

Uncertainty is a main reason for the level of government intervention in the health care industry. The pervasive effects of risk and uncertainty in the market for health care have long been recognised. People do not know when they will require health care or for how long. In addition, patients lack the information, and often the capability to evaluate what is offered and possible alternatives. Moreover, most of the industry's products are perceived as a matter of life and death. Indeed, ill-informed purchase of care may result in irreversible damage or even death, and it cannot be said with certainty whether the long-term effects of new medicines will be beneficial or harmful (Abel Smith, 1976).

In this context, regulation -- defined as the exercise of sustained control over an activity by a public agency -- can be viewed as an instrument for reducing risk and for protecting people against risks related to uncertainty. However, governments also seek to reconcile their regulatory objectives in health and safety policies with their efforts to promote and maintain a strong, internationally competitive, research-based industry, and with their public expenditure goals. Regulation needs to strike a balance between the public policy objectives of promoting pharmaceutical innovation and providing mechanisms to contain risk and control health-care expenditure.

The role of scientific knowledge and basic research

New scientific knowledge is the primary source of innovation. It is the very first step in new product development and is thus a significant source of economic growth. Since the 1950s, models of economic growth have recognised technical advance as a driving factor of the economy.

Recent shifts in OECD economies towards high-technology investments, high-technology industries, and more highly skilled labour mean that science systems are ever more important to growth. Today, economists use the term "knowledge-based economies" in recognition of the increasingly important role of science and technology.

In all OECD countries, large quantities of human resources are employed in science. In 1991, for example, 85 000 PhD scientists were engaged in research in the physical, environmental and life sciences in the United States (National Science Foundation, 1994). In 1993, basic research budgets for these fields represented about $13 billion and applied research budgets about $17 billion (US National Science Board, 1993).

Despite these significant levels of investment, government-financed research and development (R&D) as a proportion of total R&D expenditure has gradually decreased in recent years (see Table 1). Industry now funds almost 60 per cent of OECD R&D activities (OECD, 1997) and carries out about 67 per cent of total research.

Policies to foster relationships between academic institutions and industry

The gradual blurring of the boundaries between academia and industry is highlighted by the fact that most publications are now the result of collaborative research between industry and the academic sector. In the United States alone, 45 per cent of biomedical articles are co-authored by industry and academia, a rise of over 50 per cent between 1981 and 1994 (Paula and Stephan, 1996). In 1994, companies in the United States funded more than 6 000 projects and spent nearly $1.5 billion for academic research in the life sciences.

Significant private sector involvement in biomedical research highlights two major features of today's research systems. First, with the introduction of modern biotechnology, research outputs are more easily transferred to the private sector so that the distinction between basic and applied research loses some of its original meaning.[1] *Second, recent public policy has profoundly changed the incentives for developing new medical technologies and products.*

In one way or another, almost all OECD governments have reduced public spending, including support for basic research, to curb their national debt burdens and budget deficits. At the same time, almost all OECD governments have developed policies to foster collaboration among the public, private and higher education sectors to promote research synergies and stimulate innovation. With these measures, governments hope that industry will "pick up the tab" and replace lost government support.

It is widely understood that advances in knowledge and science are not mere chance events. R&D is influenced by the expectation of rewards, primarily financial in nature, and many OECD countries use fiscal incentives as an instrument to encourage R&D. These include: accelerated depreciation of investment in capital stock used for R&D activities, full deductibility of current R&D expenditures from taxable income, additional tax allowances enabling firms to deduct more than 100 per cent of their R&D expenditures from taxable income, and tax credits allowing firms to deduct a percentage of their R&D expenditures from their tax liabilities (OECD, 1996; OECD, 1998). Venture capital schemes are another means of filling "funding gaps" (see OECD, 1998).

Table 1. **Financing of expenditures on R&D by source**
percentage

	Business enterprise						Government					
	1981	1985	1989	1991	1993	1995	1981	1985	1989	1991	1993	1995
United States	48.8	50.0	52.2	57.6 [10]	58.4	59.9	49.3	48.3	45.6	38.7 [10]	37.7	36.1
Canada	40.8	40.0	41.5	41.3	44.8	46.7	50.6	48.1	44.7	43.7	40.1	37.7
Mexico	..	..	..	..	14.3	22.4	..	..	..	..	73.4	53.4
Japan (adj.)	67.7	74.0	77.1	77.4	73.4	72.4	24.9	19.1	16.8	16.4	19.7	20.5
Australia (1,2)	20.2	37.5	41.1	43.9	..	45.7	72.8	59.2	54.9	50.3	..	48.3
New Zealand	..	..	33.2	27.4 [10]	33.9	..	..	..	64.7	61.8 [10]	54.8	..
Austria	50.2	49.1	53.0	50.2	49.0	48.0	46.9	48.1	43.4	46.5	48.0	49.1
Belgium	..	66.5	63.9 [10]	64.8	62.7	..	..	31.6	32.0 [10]	31.3	32.5	..
Czech Republic	..	..	..	..	..	63.1	..	..	..	..	..	32.3
Denmark	42.5	48.9	46.8	51.4	50.0	..	53.5	46.0	45.5	39.7	37.7	..
Finland	54.5	..	62.2	56.3	56.6	..	43.4	..	35.3 [10]	40.9	39.8	..
France (2)	40.9	41.4	43.9	42.5	47.0 [10]	48.7	53.4	52.9	48.1	48.8	43.5 [10]	41.6
Germany (3)	57.9	61.8	63.3 [10]	61.7 [10]	61.4 [10]	60.9	40.7	36.7	34.1 [10]	35.8 [10]	36.7 [10]	37.1
Greece (4)	21.4	23.2	19.4 [10]	21.7	20.2	..	78.6	74.4	68.9 [10]	57.7	46.9	..
Hungary (5)	..	..	..	56.0	53.1	43.0 [10]	..	..	..	40.0	40.5	47.9 [10]
Iceland	5.7	24.1	23.9	24.5	31.6	31.6	85.6	64.3	65.8	69.7	62.9	62.9
Ireland	37.7	45.7	55.4	60.6	61.7	67.4	56.5	46.1	34.0	27.8	28.8	22.6
Italy	50.1	44.6	46.4	47.8	48.2	48.7	47.2	51.7	49.5	46.6	47.8	47.4
Netherlands (2)	46.3	51.7 [10]	53.4	47.8 [10]	44.1	44.8 [10]	47.2	44.2 [10]	41.8	48.6 [10]	48.5	43.8 [10]
Norway	40.1	51.6 [10]	45.6	44.5	44.3	..	57.2	45.3 [10]	50.8	49.5	49.1	..
Poland	..	..	..	..	..	31.8	..	..	..	..	..	64.4
Portugal (1,6)	30.0	26.8	27.0	20.2	..	18.9	61.9	63.5	61.8	59.4	..	65.2
Spain (2)	42.8	47.2	47.8	48.1	41.0 [10]	40.3	56.0	47.7	46.8	45.7	51.6 [10]	52.4
Sweden	54.9	60.9	58.6	61.9	63.0 [5,10]	..	42.3	36.4	38.1	34.0	31.5 [5,10]	..
Switzerland (4,7)	75.1	78.9 [10]	73.9 [10]	67.4	..	..	24.9	21.1 [10]	23.2 [10]	28.4	..	..
Turkey	..	..	..	28.5	31.8	30.8	..	..	..	70.1	65.2	64.5
United Kingdom	42.0	45.9 [10]	50.6 [10]	49.6	51.2	48.0	48.1	43.5 [10]	36.4 [10]	35.0	33.4	33.3
North America (8)	48.4	49.5	51.7	56.5	57.4	58.7	49.4	48.3	45.6	39.2	38.1	36.4
Asia-Pacific (OECD)	64.5	71.2	74.8	75.0	71.1	70.3	30.7	23.6	20.6	20.1	23.7	24.6
European Union (2,3)	48.6	51.2	53.2	52.2	52.8	52.9	46.7	44.0	40.5	40.9	40.0	39.2
Total OECD (2,3,8,9)	51.2	54.0	56.7	58.8	58.6	58.8	45.0	42.3	38.8	35.7	35.5	34.9

1. 1986 instead of 1985, 1990 instead of 1989 and 1992 instead of 1991. 2. 1994 instead of 1995. 3. Figures for Germany from 1991 onwards refer to unified Germany. 4. 1986 instead of 1985. 5. Percentages do not sum up to 100 because of an incomplete breakdown. 6. 1982 instead of 1981. 7. 1992 instead of 1991. 8. Including Mexico from 1991 onwards. 9. Excluding Czech Republic, Hungary and Poland. 10. Change in survey methods or coverage.

Source: OECD, MSTI and STIU databases (DSTI/EAS Division), March 1997.

Recent initiatives to strengthen science-industry links in biotechnology include the establishment of centres of excellence, co-operative R&D centres, and biotechnology science parks. Furthermore, governments have facilitated these interactions through a variety of mechanisms, such as national or transnational financial programmes, funding for collaborative projects, and the removal of legal obstacles and constraints on personnel mobility and academic rules (OECD, in press). The success of these initiatives varies considerably.

Impacts on innovation

One way to measure the implications of such policies is to examine the products that reach the market. However, because of the long time needed to develop new pharmaceuticals (on average 12 years; Kobelt-Nguyen, 1997), new products give little insight into the impact of recent policies. This reflects how difficult it is, in general, to measure effects of policies on technology, and on advances in technology, in this sector. Despite their obvious limitations, numbers of patents registered by a country or a firm and market introduction of new products are among the most used measures of the success of a policy or technology (Mogee and Kolar, 1994). In addition, the introduction of new chemical entities is a good indicator of R&D intensity (Chakrabati, 1990).

In the United States, over 90 per cent of life sciences companies have some relationship with academia. The most prevalent type of relationship is the use of university faculty members as consultants (88 per cent). Furthermore, more than half of life-science companies (59 per cent) support university research, and 38 per cent participate in training by providing grants, fellowships or scholarships.

A recent survey by the Health Policy Research and Development Unit of the Massachussetts General Hospital (Blumenthal *et al*., 1996) suggests that these relationships are more common today than in 1984. However, they are also short-lived. For 84 per cent of respondents whose firms have relationships with academia, the typical relationship lasts two years or less. Furthermore, 71 per cent are funded at less than $100 000. In consequence, universities cannot depend heavily on industry to support their research and infrastructure and cannot hope to offset public budget reductions with this source. This is generally true for most OECD countries, where industry generally funds less than 5 per cent of university research.

For industry, relationships with university are generally rewarding. Numbers of patents and products resulting from university research supported by industry are comparable to, if not slightly higher than, those resulting from industry-supported research elsewhere (Blumenthal *et al*., 1996).

In terms of agreements on proprietary information, however, industry-university relationships seem to be less satisfactory. Universities are often opposed to restricting information flows, and academic scientists have to publish their research in order to advance their career. Industry, on the other hand, demands confidentiality to allow for the filing of patent applications.

As patent-to-science linkages are increasing at a rapid rate, clear international policies are needed in this area.

In 1994, the National Institutes of Health (NIH) released a policy statement, *Developing sponsored research agreements: considerations for recipients of NIH grants and contracts.* In this document, the NIH indicated 30-60 days as a "reasonable" period to delay the release of information to allow for filing a patent application. However, companies generally request confidentiality and some form of "secrecy" for longer periods (Blumenthal *et al*. 1996).

The linear model of innovation (industrial clustering and biotechnology science parks)

Several OECD governments have established biotechnology science parks as a means to strengthen industry-university links and create new employment. This reflects an assumption that innovation is the product of a linear pattern of events in which, briefly, innovation is initiated by basic scientific research, which is followed by applied and more product-oriented research activities, clinical development and testing, commercial manufacturing, and finally marketing and diffusion (Figure 1). The assumption is that, if technological innovation is strongly linked to basic scientific research, science parks or the "clustering" of young firms around a basic research centre would provide an "incubator" conducive to more rapid and effective technology transfer.

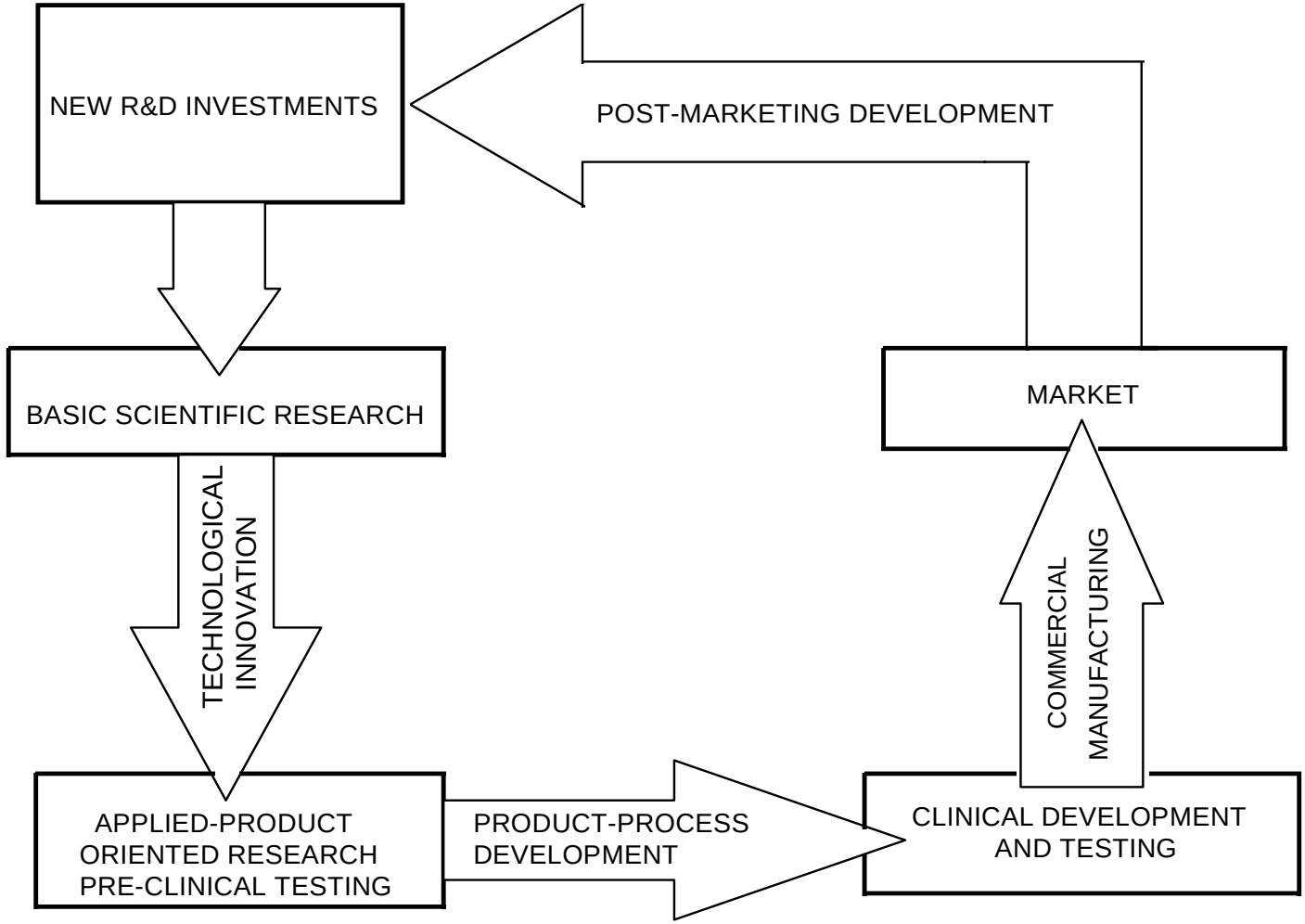
In support of this linear concept, Jaffe (1989) has shown for the United States that university research causes industry R&D and not *vice versa*. In addition, university research, particularly in biotechnology, seems to increase local innovation by attracting clusters of similar firms to one geographical area (Acs and Audretsch, 1993). Moreover, the history of the biotechnology industry confirms these assumptions. The biotechnology industry originated in California, near San Francisco, in an area where several research centres were located, and firms were founded in co-operation with academic scientists at those centres (Prevezer, 1996).

There are obvious benefits to being part of a cluster. On the supply side, they include availability of specialised labour, specialised intermediate inputs, and knowledge spillovers (Krugman, 1991). On the demand side, the strength of some high-technology sectors may come from clustering with important users in other industries or domestic users (von Hippel, 1988).

Some of the drawbacks of clustering include congestion costs and increased competition. By 1991, in the United States, 50 per cent of the biotechnology industry was still significantly clustered (Figure 2). Science parks were created in the hope that clusters of young firms around a science base could foster innovation. However, several recent studies seem to indicate that science park firms are not more innovative than other firms (Westhead, 1997).

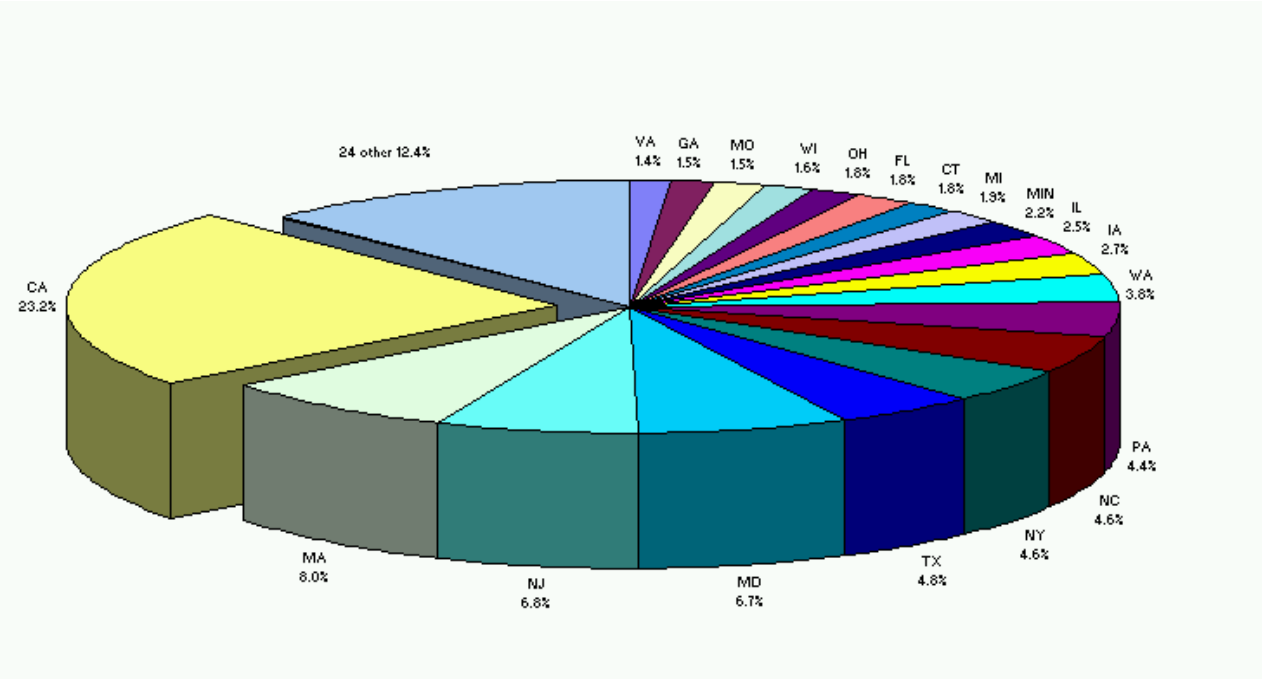
A recent analysis of the dynamics of industrial clustering in biotechnology points to some of the reasons. The science base attracts new biotechnology firms in sectors where entries are already flourishing. However, the effects on firm growth are negative in some other biotechnology sectors and much weaker in others. This means that new firms can absorb "spillovers" from within their own and closely related sectors but are not good at absorbing spillovers from the science base of other sectors. In the biotechnology industry, intersectoral feedback or links do not seem to encourage entry. This is due in part to the fact that the various biotechnology sectors do not all share technological links. For example, developments in the health care sector do not necessarily lead to entries in sectors such as chemicals and food (Swann *et al*., 1996). Furthermore, strength of employment in a specific sector in a cluster seems to discourage similar firms from entering, perhaps for reasons of competition (Swann and Prevezer, 1996).

Figure 1. **The drug development process**



Source: Author.

Figure 2. **Distribution of biotechnology companies by states in the United States (1991)**



Key

CA	California	MO	Missouri
CT	Connecticut	NC	North Carolina
FL	Florida	NJ	New Jersey
GA	Georgia	NY	New York
IA	Iowa	OH	Ohio
IL	Illinois	PA	Pennsylvania
MA	Massachusetts	TX	Texas
MD	Maryland	VA	Virginia
MI	Mississippi	WA	Washington
MN	Minnesota	WI	Wisconsin

Source: Swann and Prevezer, 1996.

Product and process development: impact of policies

As suggested above, a main reason for government intervention is to protect citizens from the uncertainties and risks of new technologies. *In addition, all governments have developed mechanisms to steer research into priority areas, to ban controversial or undesirable research, and to balance innovation against the need to contain health-care costs.*

What are the effects of government policies on product and process development and how does uncertainty about these policies affect output in the health care sector? To address these questions, this section summarises some of the main results of this report.

Effects of regulatory policies on development and approval of new biotechnology-derived biopharmaceuticals in the United States

Over the past decade, both the individual states and the federal government have adopted measures designed to ease the financial and regulatory burden on the biotechnology sector, to take account of the circumstances unique to early stages of product development in this industry; and to respond to public health concerns that innovative products be made available to patients as quickly as possible. Many of the intended effects of these policies and proposals relate to reducing out-of-pocket costs, making the process more predictable, and moving effective and safe products to market faster. If realised, any of these effects will increase incentives for firms to engage in and for investors to invest in biopharmaceutical R&D.

What is the cost of clinical trials and of regulatory times as a whole?

As highlighted by Gosse *et al*. (part II: Biotechnology, Medical Innovation and the Economy; A Survey of the Key Relationships), developing new biopharmaceuticals and getting them approved for marketing is a lengthy, uncertain, and costly process. The times from the initiation of clinical testing in the United States to submission of a product license application (PLA) with the Food and Drug Administration (FDA), and to approval of the PLA by the FDA, averaged 3.9 and 5.7 years, respectively, for new biopharmaceuticals approved in the United States between 1990 and 1994 (Gosse and Mannochia, 1996). Policies to reduce these times would lower the cost of bringing new biopharmaceuticals to market and increase the returns that may be expected from successful product introductions.

Although new drug development costs can change significantly over time, the relative contributions of various components of the development and regulatory review processes are likely to be much more stable and can be assessed. DiMasi *et al*. (1991) estimated R&D costs for a sample of new drugs that first entered clinical testing anywhere in the world from 1970 to 1982. When the costs of research failures and preclinical expenditures are included in cost estimations, they found that time costs represent more than half of total costs. Time costs are measured as the amount that could have been earned if the funds spent on R&D expenditures up to the date of marketing approval had instead been invested in a financial instrument of similar risk. Thus, reductions in the amount of time spent in development or regulatory review can significantly reduce costs. Table 2 shows the percentage declines in cost per approved new drug (failures included) that can be achieved from a reduction of one year in the clinical trial and regulatory review phases. The cost savings indicated in the table assume that out-of-pocket costs[2] remain the same. If the reductions in time to market are also associated with lower out-of-pocket expenditures, then the cost savings will be even greater. In addition, a product that reaches the market faster will have a longer effective patent lifetime and so higher net returns to the investment in R&D. Lower costs and higher returns translate into greater incentives to pursue new drug development. The benefits to speedier development and regulatory review are particularly important for start-up biotechnology firms, which generally have cash flow problems (Lee and Burrill 1994).

Since the late 1980s, several aspects of the drug development and review process have been modified to reduce the time to market for new therapies.[3] Initially, the changes were introduced to improve access to new therapies to treat serious or life-threatening conditions. Investigational new drug (IND) regulations allowed for patient access to new therapies outside standard clinical trials. Fast-track initiatives (Subpart E regulations and accelerated approval regulations) were implemented to expedite time to market of drugs for life-threatening illnesses. This was accomplished by allowing more lenient risk-benefit ratios and clinical endpoints.[4]

Table 2. **Percentage declines in cost per approved new drug from a one-year reduction in average phase length***

One-year reduction in phase	Percentage decline in time cost	Percentage decline in total cost
Phase I	11.1	5.6
Phase II	13.7	6.9
Phase III	15.4	7.8
New Drug Application review	16.2	8.2

Note: *Based on a sample of 93 new investigational chemical entities which first entered clinical testing in 1970-82.

Source: DiMasi *et al.*, 1991.

Since 1993, under the authority of the *Prescription Drug User Fee Act of 1992* (PDUFA-Public Law No. 102-571), the FDA has collected user fees from applicants seeking FDA approval for certain new drug applications (NDAs), PLAs, and supplemental applications. The Act established a five-year programme for the payment of user fees, which generated almost $80 million in fiscal year 1996.

The pharmaceutical and biotechnology industries' expectations for speedier FDA review of applications for new drugs and biologics have figured prominently in the implementation of the user fee programme. A crucial component of the programme is a series of performance goals designed to achieve specific incremental improvements in the speed and efficiency of the drug review process, the ultimate goal being review and ruling on an application within 12 months. In 1996, the agency took action on 269 original applications, with 131 approvals.[5] Of these, 53 were new molecular entities (NMEs), i.e. a drug based on active ingredients never marketed before.

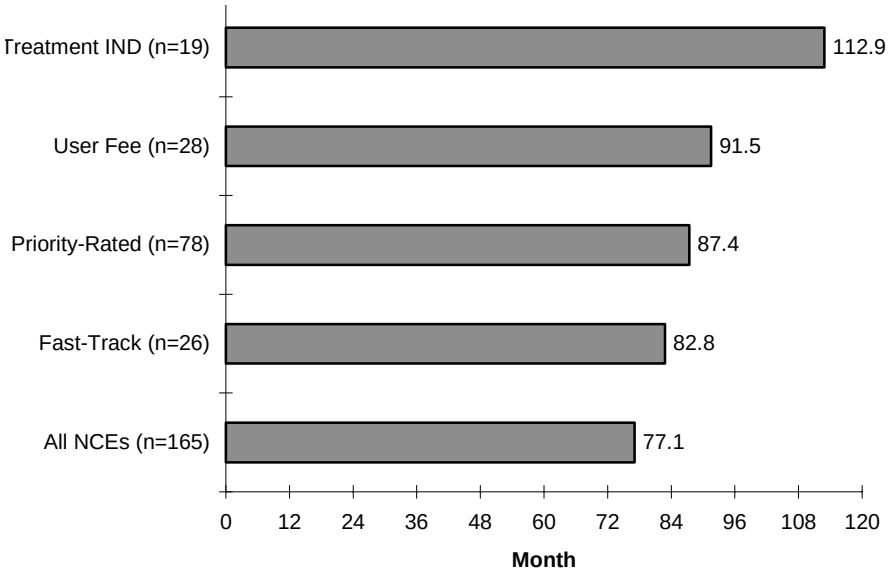
NMEs approved in a given year are an important industry marker and an indicator of the rate of innovation. By charting the number of NMEs and median approval times since 1986 (Table 3 and Figure 3), it is apparent that even if not designed specifically to expedite regulatory review, early access, together with fast track mechanisms and PDUFA, have been successful regulatory reforms.

Table 3. **Median times of approval for NMEs**

Calendar year	Number	Median time to approval (months)
1996	53	14.3
1995	28	18.2
1994	22	17.5
1993	25	23.0
1992	26	22.6
1991	30	22.1
1990	23	24.3
1989	23	29.3
1988	20	27.2
1987	21	29.9
1986	20	32.9

Source: PDUFA speech, 1997.

Figure 3. **Mean IND phase times for NCEs approved from 1987 to 1995 that were part of a treatment IND program, were part of the user fee programme, were priority-rated by the FDA, or were subject to a fast–track initiative (Subpart E or accelerated approval)**



Source: DiMasi and Mannocchia, 1997.

Note: "All NCEs" also include drugs approved by standard new drug application process.

On the other hand, treatment IND regulations are also associated with longer clinical development times. The longer development time may reflect difficulties in expanding distribution and monitoring to physicians and patients who would not ordinarily be included in the compressed clinical trial protocols (DiMasi and Manocchia, 1997).

The feedback loop between technology and regulations

It is widely recognised that R&D is influenced by public policy. What is less understood is the reverse, i.e. the extent to which new technological developments can influence policy making and regulatory bodies. It is apparent that the relation between regulatory frameworks and new science and technology is increasingly complex.

There is no doubt that the application of molecular biological techniques has spurred a revolution in drug development.[6] Since many of these biopharmaceutical products have altered traditional drug development by targeting innovative therapeutic methods or treatments of the genetic basis of disease, the policies and regulations mandated by regulatory agencies in all OECD countries have required modification. Regulations, some dating from 1902, had not kept pace with technological change (Korwek 1995). Thus, proposals for regulatory reform were advocated by government, industrial, and academic groups.

In developing regulatory guidelines for new technologies, policy makers are challenged to strike a balance between public concern over unknown technological risks, and guidelines that foster, rather than impede, research on promising new treatments. Biotechnology provides a useful example of the difficulties and complexities that regulatory authorities face. Two mechanisms for the oversight of

recombinant DNA technology in the United States and the United Kingdom and their evolution over time are reviewed below.

The Recombinant Advisory Committee (RAC) was founded in 1974 to advise the Secretary of Health and Human Services, the Assistant Secretary of Health, and the Director of the NIH on "the current state of knowledge and technology regarding DNA recombinants and to recommend guidelines to be followed by investigators with recombinant DNA" (*The Blue Sheet* 1994). *The RAC's role was to assure the public that genetic research was being done in the open and in the right way.*

Over the years, the RAC has proved useful in addressing sensitive issues of safety and medical ethics in a public forum; proposing (and progressively adapting) guidelines for recombinant DNA experiments, generation of transgenic animals, and, more recently, human gene therapy protocols. The RAC met quarterly to review these protocols and to ensure that proposals fell within the guidelines of an NIH points-to-consider document (NIH Guidelines, 1996). Prior to mid-1995, all gene therapy protocols arising from federally funded research had to be submitted for RAC review. The RAC proceeded to make specific recommendations, ensured that safety precautions were addressed, and reviewed the scientific and ethical basis of the proposal. The time needed to obtain RAC approval of a protocol was affected by the limited meeting schedule. The Director of the NIH awarded final NIH approval.

The second federal government mechanism to approve a human gene therapy trial is the standard IND submitted to the FDA. *As gene research moved into the mainstream, the apparent redundancy of the two review mechanisms seemed cumbersome.*

The dual review process increased the time to commencement of human clinical trials. Thus, the seemingly redundant process of protocol review by the NIH and the FDA drew criticism from industry, academia, and AIDS activists. This prompted the director of the NIH to reconsider the role and function of the RAC (Marshall, 1996). As a result, RAC is no longer responsible for approvals, but is responsible for identifying novel human gene transfer experiments deserving public discussion and transmitting comments/recommendations to the NIH, for identifying novel ethical issues relevant to specific human applications of gene transfer, for identifying novel scientific and safety issues relevant to specific human applications of gene transfer, and for publicly reviewing human gene transfer clinical trial data.

The RAC set a precedent for the review of human gene therapy trials. In 1989, the government of the United Kingdom established the Committee on the Ethics of Gene Therapy, under the chairmanship of Sir Cecil Clothier. Based upon the recommendations of the Clothier Committee, the UK Gene Therapy Advisory Committee (GTAC) was established in 1992 to review proposals for genetic therapy for human disease. The GTAC has prepared a manual, the *GTAC Guidance on Making Proposals to Conduct Gene Therapy Research on Human Subjects*, for preparing human gene therapy proposals in the United Kingdom (GTAC 1994). GTAC serves to complement local research ethics committees (LREC) and at the present time, will not consider proposals for germ cell gene therapy. Outside of the United States, GTAC is the closest equivalent to the RAC. The GTAC review of a human gene therapy protocol is similar to the initial US RAC/FDA separate and parallel review; the GTAC and the Medicines Control Agency (MCA, the UK counterpart of the FDA) receive the proposal simultaneously. GTAC evaluations and recommendations are then submitted to the MCA, LREC, and the principal applicant. Although the GTAC is similar to the RAC, GTAC does not have a history of public debate and access. It is a smaller group, is more likely to seek external *ad hoc* reviewers and thus is ultimately more able to streamline review.

Intellectual property rights

The function of intellectual property[7]

"Industrial property" systems (e.g. patents, trade secrets, trademarks, design protection, etc.) have been developed by states as a means for recognising and promoting innovation. Patents, for example, protect the innovator for a limited period against use by third parties of the protected subject matter (i.e. the patented invention) without his consent. Patent systems promote innovation by encouraging the early and effective public disclosure of inventions. They universally involve publication of a full description of the invention upon grant or, in many systems, 18 months after patent protection is originally sought. A patent cannot hamper the free use of whatever is already in the public domain; it can only control the use by others of the inventor's novel addition to the previously existing technology. The principle of providing a temporary period of legal protection encourages the climate for innovation, to the ultimate benefit of the public as a whole. This period of protection is not yet uniform in all countries, but the period is most commonly set at 20 years from the patent application date, subject to the payment of annual renewal fees. Patents also encourage investment in R&D and in the production and marketing of new products and processes.

Statutory intellectual property rights provide a basic framework for voluntary technology transfer through intellectual property right licensing, supplemented and reinforced by provisions based on the supply of know-how and other factors which may be less easy to define. Patent law demands clear definition of the protected technology and thereby establishes the scope of the rights of the innovator, identifies what is transferred to a licensee, and allows for the corresponding freedoms of third parties to be assessed.

Subject to international agreements designed to improve and unify patent protection throughout the world, a country is free to develop its own policy towards legal protection systems and legal enforceability procedures. Thus, a country is free to develop and implement measures to encourage technological innovation, technology transfer and other technology-related objectives, provided these measures conform to the minimum standards of protection mandated by the TRIPS Agreement[8] and other multilateral treaties in the field of intellectual property law.

Important factors affecting national patent policy are:

- the current level of national technology transfer from the research base and expectations as to its future development;
- the need to encourage technology transfer from other countries;
- the desire to attract foreign investment to the country or region (a strong patent system is more likely to do so).

The freedom to carry out research is safeguarded under patent laws. Under patent law "experimental use" for research purposes is not considered to be an infringement of the rights of the patent owner. But what is purely experimental (rather than experimental for commercial purposes) is a matter of interpretation, mainly through case law, and can therefore vary according to national jurisprudence. The freedom to commercialise the products of research depends on whether or not patents are infringed, or for plants, whether they are essentially derived or dependent varieties under plant variety rights.[9]

Intellectual property rights for pharmaceutical innovation

To develop a new drug requires an average of 12 years and $300-500 million (see Kobelt-Nguyen, 1997). Regulations governing clinical research are also one of the primary reasons for rising R&D costs. Most of the industry's innovative efforts, as mentioned previously (Figure 1) proceed in a fairly linear manner, with clearly defined stages, many of them determined and regulated by law. Pharmaceutical companies must follow a lengthy R&D process. Pre-clinical tests study the potential risks that a compound poses to humans and the environment by using animals, tissue cultures, and other test systems to examine the relationship between factors such as dose level, frequency of administration, and duration of exposure to both the short-and long-term survival of living organisms. This is followed by three phases of clinical testing to assess both safety and efficacy in humans.[10]

Since companies typically patent early during pre-clinical testing, the development and approval process, discussed above, can consume a significant portion of a new chemical entity's patent life. Today, when a drug reaches the market, it typically has 8-11 years of patent protection remaining, (often including patent term extension, which restores time eroded by regulatory delays) a number that has been declining steadily for the past three decades. When the patent on a pharmaceutical product expires, other companies can make generic copies without spending hundreds of millions of dollars on discovery, development and testing.

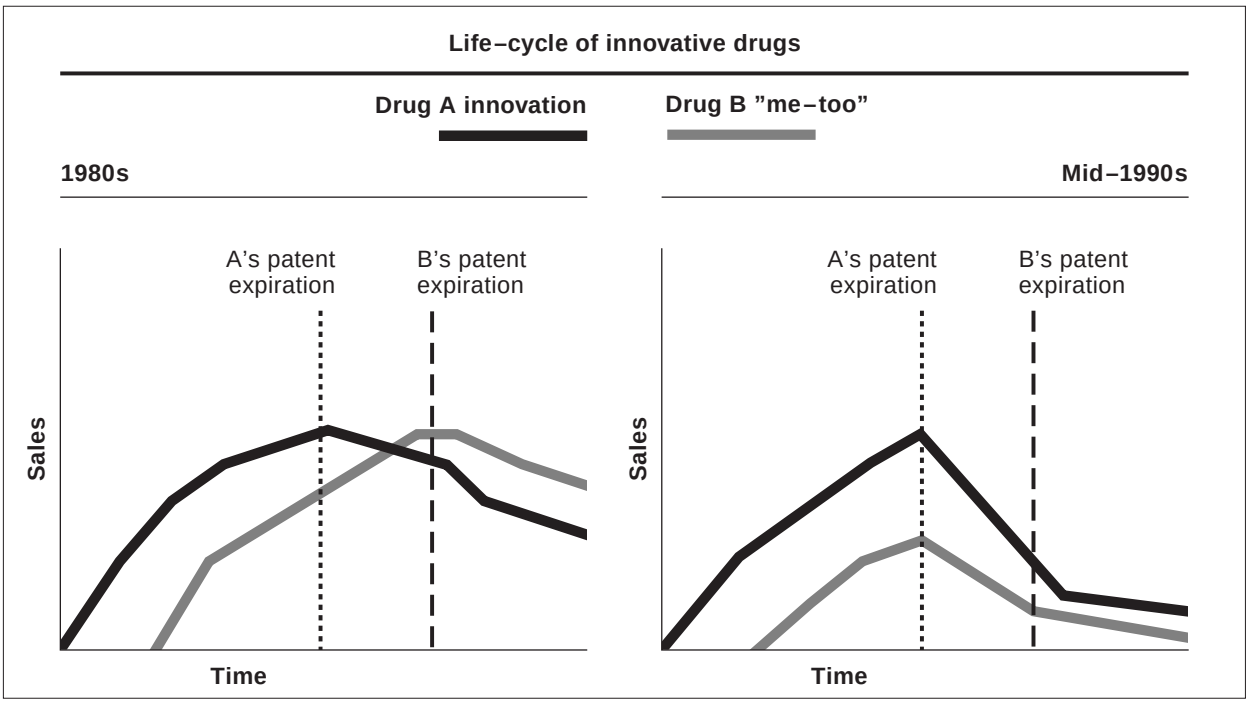
The second or third product in a class, the so-called "me-too's", will often be marketed at a discount. As part of the efforts to contain costs, purchasers will shift prescriptions to generic products as early as possible, and this will include extensive use of the first generic available in a class of products. The price of generics may be as low as 20-30 per cent of that of the branded product, and it has been shown that, in the United States for example, sales of a branded product will drop as much as 50-70 per cent within one year after its patent expires; in addition, there will be a substantial effect on the second and third product in the class (Figure 4).[11]

Thus, the pharmaceutical industry is more dependent on strong intellectual property protection than any other industry. If pharmaceutical companies could not patent their drugs they would be unlikely to invest in new research.

Furthermore, it is frequently argued that relatively weak intellectual property rights protection in a country may lower the probability that firms will invest there, and that, if they do, they may restrict investment to their own subsidiaries and will also restrict the transfer of "know-how".

In Canada, for example, for almost two decades (between 1969 and 1987), patent protection of prescription drugs was weakened by allowing compulsory licensing of drug imports.[12] Compulsory licensing facilitated the proliferation of cheaper generic substitutes for brand-name prescription drugs and contributed in a major way to the development of a strong, mostly Canadian-owned generic drug industry. The multinational drug companies objected to the weakening of their intellectual property rights and publicised their reluctance to invest and conduct R&D in Canada. Pressure to repeal the legislation gained additional impetus when compulsory licensing became an obstacle to successful completion of the free trade agreement between Canada and the United States. In 1987, the government enacted Bill C-22, which provided for protection from compulsory licensing for a period of seven years in the case of licence to manufacture, and ten years in the case of licence to import. Bill C-91, which was enacted in 1992, abolished compulsory licensing completely, in accordance with the provisions of the General Agreement on Tariffs and Trade (GATT) and the North American Free Trade Agreement (NAFTA).

Figure 4. **Development of the effect of patent expiration on innovative and me-too products**



Note: During the 1980s it could be expected that a second entrant of the same class of products to the market could still reach sales similar to the first entrant, even after patent expiry of the latter. Only the branded product was affected by its generic equivalent. Today, the first generic product launched in a class will affect the sales level of the entire class, regardless of the expiration of the patent on individual products.

Source: *Spectrum*, 1994.

A number of indicators of pharmaceutical R&D spending in Canada show an increase in R&D activity starting around the year 1987 (the time of enactment of Bill C-22 and of the Investment Tax Credit).

A survey of institutions belonging to the "Canadian biotechnology community" (Heller, 1995) reported average annual growth of R&D expenditures of 41 per cent during the period 1989-93, with the agri-food sector growing at 112 per cent a year, followed by the health care sector at 77 per cent. The slowest growth (5 per cent a year) was recorded in the research sector, where federal government biotechnology expenditures were affected by government spending restrictions.

Measured in terms of total revenue, the Canadian biotechnology industry is today about 5.6 per cent that of the United States (Table 5), up from 2.9 per cent in 1994. Furthermore, the total number of core biotechnology companies increased from 121 in 1994 to 224 in 1997 with the small and very small companies accounting for 42 per cent and 30 per cent, respectively. Industry revenues have increased from $353 million to $1.1 billion, and total financing activity during 1996 exceeded $1 billion, approximately the same amount of financing as was raised in total over the preceding five years (1991-95).

It would be difficult to explain the dramatic increase in R&D activity in the Canadian pharmaceutical industry exclusively in terms of the economics of patent protection and it is unlikely that the economic

benefits of increased patent protection alone would cause such an increase. Indeed other contributing factors should be noted. For example, the Canadian pharmaceutical companies made a commitment during the debate on the merits of Bill C-22 to double the ratio of R&D to sales from less than 5 per cent in 1984 to 10 per cent in 1996. In addition between 1985 and 1987 legislation on tax incentives for R&D was amended to include experimental development, and to extend the carry forward period for R&D tax credit from seven to ten years (see Pazderka, 1998). However, inadequate patent protection certainly deters investment, as revenue is lost if cheap identical products made by unauthorised producers appear on the market. Biotechnology firms are particularly affected since provision of investment capital is contingent on the ownership of or access to patentable technology. Thus, intellectual property protection remains a crucial incentive for market entry and the growth of the pharmaceutical industry.

NOTES

1 The Frascati manual (OECD, 1994) gives the following definitions for basic and applied research: "*Basic research* is experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, without any particular application or use in view". "*Applied research* is original investigation undertaken in order to acquire new knowledge; and is directed primarily towards a specific practical aim or objective".

2 Out-of-pocket costs are the direct costs that firms incur in the course of development. Capitalised costs are the sum of out-of-pocket costs and time costs.

3 For an in-depth review of these changes see Gosse *et al.*, 1998.

4 For a discussion on endpoints see Drummond *et al.*, OECD, 1997.

5 An "action" for the purposes of the Act constitutes one of three responses by the FDA: the issuance of an approvable letter, an approval letter, or a non-approvable letter.

6 See E. Ronchi in OECD, 1997.

7 This paragraph draws on the OECD publication: *Intellectual Property, Technology Transfer and Genetic resources: An OECD Survey of Current Practices and Policies*, OECD, 1996.

8 The Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS Agreement) signed on 15 April 1994 in Marrakesh, stipulated for the first time in the history of international industry property protection the obligation of all members of the World Trade Organization (WTO) to provide patents for both product and process inventions in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. For more details see OECD, 1996.

9 Although patents for certain types of plants have been available under US law since 1930, patent law in most other countries was originally considered unsuitable for protecting new plant varieties developed by traditional breeding methods. Special national laws of plant breeders rights (also called plant variety rights) were therefore established in the 1960s in some countries, as well as the International Union for the Protection of New Varieties of Plant (UPOV). For more information see OECD, 1996.

10 Phase I establishes the tolerance of healthy human subjects to the new chemical entity at different doses, defines the entity's pharmacological effects and studies the patterns of its behavior in humans.
Phase II involves a small number of patients in controlled clinical trials to determine a compound's potential usefulness and short-term risks.
Phase III studies are much broader, involving several hundred to several thousand subjects in clinical trials of a drug's safety and effectiveness in hospital and outpatient settings.

11 Source: Kobelt-Nguyen, 1997.

12 This issue is addressed to some extent by B. Pazderka, in Chapter 5, by a review of the impacts on R&D, of changes in Canada's intellectual property legislation.

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DETERMINANTS OF MARKET STRUCTURE IN THE INTERNATIONAL BIOPHARMACEUTICAL INDUSTRY

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1. Introduction

Various theories of industrial organisation have pointed out a variety of factors that affect market structure.[1] Empirical evidence indicates that if an industry is dominated by a handful of firms in one country, it is also likely to be dominated by a handful of firms elsewhere. Most studies argue in favour of such a pattern and interpret it as a reflection of the fact that technology and tastes in a given market may be expected to be similar across different countries. Earlier literature in the field attempted to explain differences in concentration across industries by reference to a small number of key variables taken to reflect basic industry characteristics such as the extent of scale economies, capital intensity, the level of R&D expenditure and the intensity of advertising (Bain, 1956). However, recent theoretical frameworks have moved away from early empirical literature and examine factors affecting structure, conduct, and performance in an interrelated way (Sutton, 1991). We have adopted this latter approach in our study.

Thus, in examining the determinants of market structure in the international biopharmaceutical industry, this study looks at the importance of traditional factors affecting ease of entry such as research and development (R&D), the financial context, advertising intensity, and concentration; and in explaining structure analyses the relevance of these factors to the biopharmaceutical industry. Given the complex nature of the biotechnology industry, its close interaction with the pharmaceuticals sector, and its reliance on adequate public policy, this study also seeks to explain the importance of purely exogenous factors for the industry's structure.

To this end, the study reviews the impact of the regulatory and financing environment, and intellectual property rights protection on market structure within the OECD area. Furthermore, it investigates the effect of public opinion on biotechnology in general and on biopharmaceuticals, in particular; the availability of policies to encourage SMEs, and the extent to which the presence of a skilled workforce influences investment in the biopharmaceutical industry. Finally, it suggests some policy options for encouraging biopharmaceutical investment and the development of biotechnology/pharmaceutical industry in OECD countries.

2. The international biopharmaceutical industry

2.1. The context

Over the past three decades, research on molecular biology has increased dramatically. As a result of the new knowledge and understanding gained, it is now possible to manipulate genetic material and use genes for a wide range of hitherto unimagined purposes. Among them are many that may profoundly influence medical practice and human health. Two revolutionary advances of the 1970s -- the invention of genetic engineering and monoclonal antibody technology -- launched the biotechnology industry in the 1980s.

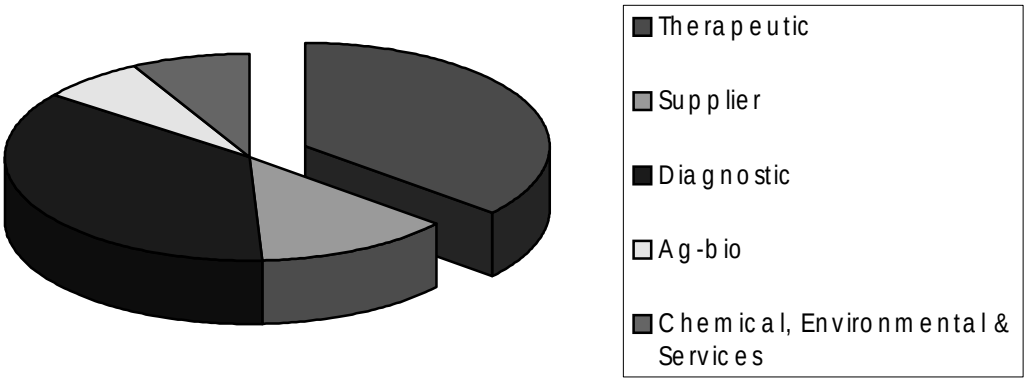
Biotechnology is a process that finds wide applications in a number of fields, such as the food industry, health care, diagnostics, and environmental technology.

The traditional R&D-based pharmaceutical industry embraced and integrated these technologies and invested heavily in order to take advantage of cutting-edge biomedical research. While much attention has been paid to the creation of the new biotechnology industry, a further revolution has been taking place in the laboratories of established pharmaceutical companies: the technology that biotechnology

companies use to develop and manufacture their products have been incorporated in pharmaceutical production.

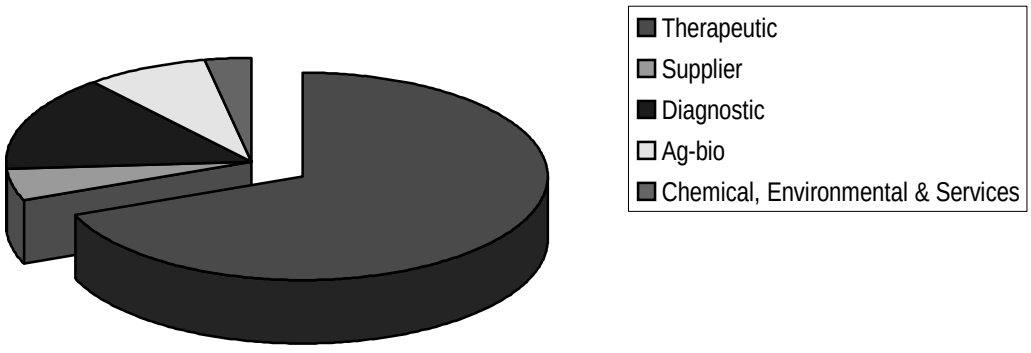
Indeed, the largest segment of the international biotechnology industry is human health therapeutics (biopharmaceuticals) and accounts for approximately 42 per cent of biotechnology assets world-wide. Other segments include diagnostics (26 per cent of total assets), chemical, environmental, and services (9 per cent), agricultural biotechnology (8 per cent)[2], and supplier (15 per cent) (Figure 2.1). Public sector biopharmaceuticals, which depend heavily on public sources of capital, account for 69 per cent of the sector's biotechnology assets world-wide (Figure 2.2).

Figure 2.1. **The total biotechnology industry by market segment**



Source: Ernst & Young, 1995.

Figure 2.2. **The public biotechnology industry by market segment**



Source: Ernst & Young, 1995.

2.2. New technologies and the need for new medical treatments

The development of biotechnology/biopharmaceuticals is expected to open new avenues in the treatment and cure of disease. Currently, the vast majority of drugs are meant for symptomatic and

palliative treatment rather than radical cure of disease. As the process of discovering clinically useful new products appears to have reached a point of diminishing returns, the question is whether scientific progress can lead to treatment of the underlying pathology of each disease; in other words, whether apart from being able to "diagnose and treat illness" to increasingly be able to "predict and prevent disease". In this respect, biotechnology has an important role to play. However, the setting of priorities and the shaping of plans for further drug development will depend on the perspectives and the motivation of the different players. For pharmaceutical companies, an important consideration must be the interests of shareholders, and these will be influenced by factors such as market size, profitability, the stage reached in their research programme, and the amount of investment required to explore new areas. Clinicians will be influenced by their own speciality interests, the medical problems they address, their understanding of the status of research in relevant areas, and the opportunities they see to exploit recent advances and innovations. The perspective of patients is not easily articulated since they rarely have the requisite knowledge or ready access to vehicles of expression, but it concerns their desire for prevention or cure of illness where possible, or at least extension of the quality and duration of life. In some countries, means are being explored to give more formal recognition to patients' rights; which can have a significant impact on health policy.

Owing to the discovery and implementation of new technologies, medical information has increased tremendously, with major impacts on pharmaceutical R&D. Refined models of disease mechanisms suggest new lines of research that may produce new drugs. Each project now undertaken is far more precise and the mechanisms involved are better understood. However, as the research targets become more precise, they also become more numerous (Office of Technology Assessment, 1993). Over the past 15 years, this new orientation, together with the discovery of new techniques such as genetics, combinatorial chemistry, rational drug design, and nanotechnology, has meant very significant changes in drug discovery research.

New technologies are expected to fill some of the gaps in new drug development, although this process may be a lengthy one. Pharmaceutical R&D has considerable risks and the lack of effective treatment or cure for a number of the above conditions can be attributed in part to the risks and uncertainties of basic research and is associated with the availability of research tools and new research techniques. There is empirical evidence from Japan and the United States (JPMA, 1992), on the number of therapeutic areas for which research is difficult and for which there are few therapeutic alternatives. This evidence was based on a survey conducted on research specialists both in US and Japanese research laboratories, by investigating scientific uncertainty and the economic risks within eight therapeutic categories (cardiovasculars, CNS, anti-infectives, cancer, immunology/inflammation, metabolic/endocrine, genito-urinary disorders, and all other), and 81 therapeutic sub-categories. The researchers' views were ranked according to a risk index, under which a higher figure denotes greater perceived scientific uncertainty. This evidence suggests that the greatest scientific uncertainty concerns cancer, genito-urinary diseases, CNS, and metabolic/endocrine disorders (Table 2.1). For both US and Japanese scientists, the riskiest therapeutic sub-category is neurodegeneration, followed by cognitive impairment and autism, all of which belong to the CNS area (Table 2.2). Myocardial ischaemia and restenosis were ranked first in the cardiovascular category, emphysema and growth factors in immunology/inflammation, hepatic encephalopathy and vascular collagen in the metabolic/endocrine area, and polycystitis and nephritis in genito-urinary disorders.

Table 2.1. **Risk assessment for new R&D**
Ranking of therapeutic categories according to perceived scientific uncertainty

Category	Japan		United States	
	Mean value	Rank	Mean value	Rank
Cancer	4.607	1	5.054	1
Genito-urinary	4.140	2	4.393	2
CNS	4.105	3	4.240	3
Metabolic/endocrine	4.016	4	4.090	4
Immunology/inflammation	3.822	5	3.870	5
Cardiovascular	3.801	6	3.787	6
Anti-infective	3.723	7	3.209	7
Other	3.602	8	3.600	8
Average	**3.967**		**4.031**	

Source: Japanese Pharmaceutical Manufacturers Association, 1992.

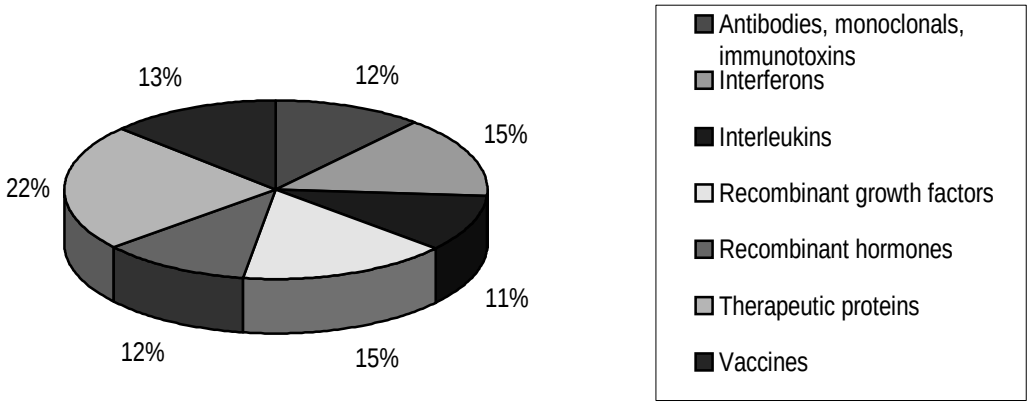
Table 2.2. **Risk assessment for new R&D**
Ranking of therapeutic sub-categories according to perceived scientific uncertainty

Japan Sub-category	Rank	United States Sub-category
Neurodegeneration	1	Cognitive impairment
Cognitive impairment	2	Neurodegeneration
Autism	3	Autism
Antiviral (AIDS)	4	Bone cancer
Bone cancer	5	Hearing disorders
Lung cancer	6	Growth factors (imm.)
Spinal injury	7	Lung cancer
Hearing disorders	8	Nerve injury
Nerve injury	9	Gastro-intestinal cancer
Hepatic encephalitis	10	Growth factors (can)

Source: Japanese Pharmaceutical Manufacturers Association, 1992.

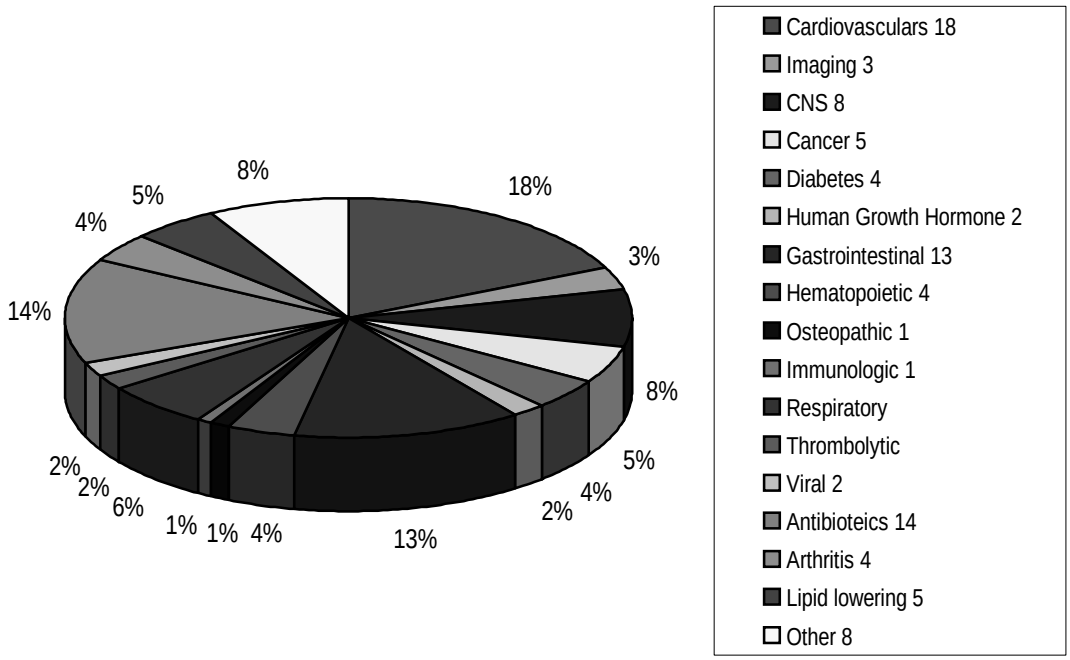
Nonetheless, over the past 15 years, biotechnology has already contributed a significant number of new chemical entities, which include therapeutic proteins, recombinant growth factors, interferons, monoclonal antibodies and vaccines (Figure 2.3 gives a detailed breakdown). The number of drugs in development in 1995 has risen sharply since 1993, and so have the number of diseases under clinical investigation (PhRMA, 1995, 1996). Cancer is the disease most targeted, but there are also products being tested to treat AIDS, Lou Gehrig's disease, asthma, diabetes, heart disease, Lyme disease, multiple sclerosis, rheumatoid arthritis, stroke and viral infections. Cardiovasculars, antibiotics, and drugs for the digestive system are the main therapeutic categories and account for 45 per cent of the total market (Figure 2.4). Drugs for the treatment of central nervous system (CNS) disorders, of various types of cancer, and of diabetes are high on the list. In terms of products with the largest sales, Amgen's Neupogen (Granulocyte colony-stimulating factor) and Novo's Novolin (human insulin) are the leaders (Table 2.3). With the exception of Novo Nordisk, all companies that have developed biopharmaceutical "blockbusters" are of US origin and/or ownership.

Figure 2.3. **Major groups of novel biopharmaceuticals launched world-wide, 1983-1991**



Source: Netherlands Foreign Investment Agency, 1995.

Figure 2.4. **US blockbuster sales by therapeutic category, 1994**



Source: PhRMA, 1996.

Table 2.3. **Sales of biopharmaceutical products by geographic region, 1993 (US$ millions)**

Product	Sales (US$ million)					Brand name(s) & revenue in US$ m	Developer	Marketer
	United States	Europe	Japan	Rest of world	Total			
Alpha-interferon	145	435	665	45	1 290	Intron A, 572; Roferon A, 172	Biogen; Genentech	Schering-Plough; Roche
Beta-interferon	-	15	205	-	220	Betaferon	Biogen	Schering-Plough
Erythropoietin	735	305	355	170	1 565	Epogen, 587; Eprex, 670; Procrit, 500	Amgen; Johnson & Johnson; Amgen	Amgen; Johnson & Johnson; Ortho Biotech
Factor VIII[1]	155	85	25	10	275			
Gamma-interferon	5	3	2	-	10			
Granulocyte colony-stimulating factor (G-CSF)	580	125	240	50	995	Neupogen, 719	Amgen	Amgen
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	40	20	15	10	85	Neupogen, 719	Amgen	Amgen
Hepatitis B vaccine	560	315	135	45	1,055	Engerix B, 480	Genentech	SKB
Human growth hormone	300	340	325	75	1,040	Protropin, 217; Humatrope, 210 Genotropin	Genentech; Eli Lilly; Pharmacia-Upjohn	Genentech; Eli Lilly; Pharmacia-Upjohn
Human insulin	380	280	130	55	825	Humulin, 560; Novolin 980	Genentech; Novo Nordisk	Eli Lilly; Novo Nordisk
Interleukin-2	12	20	3	-	35			
Orthoclone OKT3	40	30	5	10	85			
Tissue plasminogen activator (tPA)	165	40	40	20	265	Activase, (236)	Genentech	Genentech
Total	3 117	1 983	2 145	490	7 745			

1. Includes immuno-purified and recombinant versions.

Note: As is the case with estimates (from different sources) they do **not** add up normally. Total sales in penultimate column are sales of final good, whereas company revenues (last column) may include licensing fees / royalty payments / transfer pricing.

Source: Heller, 1995, for first six columns and author's compilations from company annual reports.

2.3. The cost of new technology

Although new technology is generally praised for the considerable improvement in patient mortality rates, it is very often blamed for the escalating costs of health care. Two issues closely related to the development and adoption of new biotechnology are, therefore, of relevance: firstly, whether new biotechnologies will speed the discovery of new drugs; secondly, whether uncovering disease subtypes will make clinical testing more precise. For both, there are cost considerations. Genetics, for instance, may prove useful in identifying groups of patients more likely to respond to a given agent. If so, the process of demonstrating a drug's effectiveness would be simplified, and the drug approval process would be expedited. Furthermore, narrowing the population requiring clinical assessment could cut the cost of clinical trials dramatically. However, tests of efficacy and safety might also proliferate, as well as the number of tests regulators might demand, thereby leading to an indeterminate net cost effect. Moreover, it is uncertain whether, *ceteris paribus*, the new approaches to drug discovery will reduce (R&D) costs. The direction taken by R&D costs will depend largely on whether the drug development cycle is shorter or longer as a result of the new technologies, as further discussed by Gosse *et al*. in "Effects of US Regulatory Policies on the Research, Development, and Approval of New Biotechnology Derived Biopharmaceuticals: Points to Consider for OECD Member Countries".

It has been argued that developing new therapeutic drugs is likely to become more difficult over time, as the easiest to discover are found and the tasks of discovering further therapeutic agents become more difficult (Office of Technology Assessment, 1993). Unless the new technologies expedite drug discovery sufficiently to compensate for the increasing difficulty of finding new agents, costs will rise.

As a result, large pharmaceutical manufacturers are tending to narrow their research portfolio. Once they have identified a number of disease areas, they carry out research on them and focus on potentially promising results. On the other hand, some new technologies (particularly combinatorial chemistry and rational drug design) allow them to "sweep the floor" in their search for new agents. This is clearly a strategy for many top pharmaceutical MNCs, including GlaxoWellcome, SmithKline Beecham and Hoffmann-La Roche.[3]

2.4. Key features of the biotechnology industry

The international biopharmaceutical industry is highly research-oriented. It is characterised by a very small number of large firms, the rest being of small and medium size (SMEs). Such firms [alternatively called dedicated biotechnology firms (DBFs)] in this sector need to invest for a number of years before they can expect a reasonable stream of revenues.

The market size of most biopharmaceutical companies is small, except for a handful, mainly in the United States. Amgen, Genentech, Chiron, Biogen and Genzyme are the leaders, followed by a myriad of dynamic small technology-intensive enterprises. R&D intensity is quite high, and expenditure on R&D in most start-up biopharmaceutical companies is increasing as a sunk cost in anticipation of high future yields. Few countries can rival the United States, with the possible exception of the United Kingdom, though on a smaller scale.

Dedicated biotechnology companies (DBCs) are almost exclusively a US phenomenon; no other country has a remotely comparable number. These companies depend on venture capital, stock offerings, and relationships with established pharmaceutical companies for their finance and must bear their initial (research) costs without any internally generated revenue.

Many biotechnology firms originally planned to become fully integrated, but the economics of the pharmaceutical industry have made this very difficult. As a result, many new DBCs have been founded with the intention of targeting niche markets and, at times, seeking to be acquired by a large pharmaceutical firm. Table 2.4 shows a number of major mergers and acquisitions (M&As) involving pharmaceutical and biopharmaceutical firms in the last four years. There are also many kinds of strategic alliances, but the most common type of agreement is licensing, which may include joint development of specific products as well as the exchange of marketing rights for financial support.

Table 2.4. **A selection of important alliances in pharmaceuticals and biopharmaceuticals**

Source company	Target company	Year of alliance	Value in US$ m	Activity
Novartis	Sandoz & Ciba	1996	merger	R&D/manufacturing/marketing
Rhone-Poulenc-Rorer	Fisons	1995	2 700	R&D/manufacturing/marketing
Pharmacia	Upjohn	1995	merger	R&D/manufacturing/marketing
BASF	Boots Pharmaceuticals	1995	1 300	R&D/manufacturing/marketing
GlaxoWellcome	Affymax	1995	553	R&D/manufacturing/marketing
Glaxo	Wellcome	1995	13 750	R&D/manufacturing/marketing
Sandoz	Genetic Therapy	1995	295	Biotechnology R&D
Monsanto	Calgene (49%)	1995	230	R&D
Ligand	Glycomed	1995	95	R&D
Hoechst-Roussel	Marion Merrell Dow	1995	7 100	R&D/manufacturing/marketing
American Home Products	Cyanamid	1994	9 700	R&D/manufacturing/marketing
Amgen	Synergen	1994	258	Biotechnology R&D
Ciba-Geigy	Chiron	1994	2 100	Biotechnology R&D
Genzyme	Biosurface	1994	26	Biotechnology R&D
Rhone-Poulenc Rorer	Applied Immune Sciences (60%)	1993	113	Biotechnology R&D
Lederle	Immunex	1992	730	Biotechnology R&D
Pharmos	Pharmatec	1992	65	Biotechnology R&D
Enzon	Genex	1992	13	Biotechnology R&D
Roche	Syntex	1994	5 300	R&D/manufacturing/marketing
Chiron	Cetus	1991	660	Biotechnology R&D
American Home Products	Genetics Institute (60%)	1991	666	Biotechnology R&D
Sandoz	Systemix (60%)	1991	392	Biotechnology R&D
Roche	Genentech (60%)	1990	2 100	Biotechnology R&D
Eli Lilly	Hybritech	1986	480	Biotechnology R&D
Bristol Myers-Squibb	Genetic Systems	1986	294	Biotechnology R&D

Source: Author's compilations from various sources.

2.5. R&D intensity of biotechnology companies

The spending ratio of R&D to sales is much higher for DBCs than for conventional pharmaceutical firms. Empirical evidence suggests that the ratio of R&D to sales is 69 per cent for DBCs (Ernst & Young, 1995); in 1995, the top US pharmaceuticals companies spent close to 17 per cent of sales on R&D. Both biotechnology and pharmaceutical companies face years of costly research, development and testing, with no guarantee of returns on their investment; and even for the drugs which are eventually marketed, only 30 per cent recover their R&D costs. The risk involved in bringing a new molecule to the market place is high, since only a small fraction is eventually marketed, having gone through all the

regulatory controls. It is possible, but as yet unproven, that the development of new technologies will increase the probability of more molecules matching disease patterns, enhancing both therapeutic efficacy and the prospect of commercial success.

2.6. Situation in different geographical areas

The United States

In the triad of the United States, the European Union, and Japan, the first is currently the most impressive reservoir of biotechnology expertise in the world. Indicative of the United States' advantage over the European Union and Japan is the pattern of investment: over 90 per cent of European investment in biotechnology is directed towards the United States (Booz *et al.*, 1991). The US biotechnology industry can be seen to have two main components: the small recently established DBCs and the established corporations that use the new technology as part of their overall corporate R&D efforts. Over the last 20 years, more than 1 300 new biotechnology firms were established in the United States. A large proportion of these DBCs emerged from universities. Mostly small in size, they have been a tremendous source of new technology (and to a certain extent of new products). Over two-thirds of these companies are active in health care (biopharmaceuticals), and many, founded in the United States in the late 1970s and the 1980s[4], have commercialised successfully their research breakthroughs.

The European Union

There are fewer start-up biotechnology companies in Europe (approximately 500) than in the United States. Biotechnology contributed to European GDP approximately $45 billion in 1993 and current estimates indicate that this figure will exceed $100 billion by the turn of the century.[5] Biopharmaceutical companies constitute the largest proportion of the biotechnology sector and are mostly concentrated in the United Kingdom, and, although less so, in Denmark, France, Germany and The Netherlands. Large European pharmaceutical multinationals have invested heavily in biotechnology over the last decade and some of them have already marketed the resulting products.[6] By contrast, promising European start-up biotechnology companies have had little success in launching products onto the market.

It is very difficult to speak of the EU as a homogeneous entity since in different Member States the relation between health and industrial policy differs considerably. Most member states support the development of biotechnology, although the organisation and the direction of such policies differ. The organisation of academic science, a springboard for biotechnology development, varies widely, with the United Kingdom coming closer to the US model. In other member states, particularly Germany, the tradition of academic elitism persists, which tends to discourage commercial involvement. The European Commission, as will be discussed in some detail in section 7.4, has developed a number of policies to encourage biotechnology and has included the sector as a priority in its R&D framework programmes. However, biotechnology policy at the European level still suffers from a lack of protection of intellectual property rights and from the different systems of pricing and financing drugs. The establishment of the European Medicines Evaluation Agency (EMEA), with its centralised approval procedure for all biotechnology-derived pharmaceuticals, is expected to harmonise European approval procedures.

Japan

The structure of the biotechnology industry in Japan is quite different from that of the United States (Yuan and Dibner, 1990). While the US biotechnology industry is made up of a large number of small firms, the Japanese biotechnology industry presents exactly the opposite picture with few small firms and the involvement of many large pharmaceutical and food corporations, which diversify into biotechnology. The biotechnology market in Japan was valued at approximately $8 billion in 1995, with biopharmaceuticals accounting for 46 per cent of this figure (Japan BioIndustry Association, 1996). Sales of recombinant DNA products accounted for over half the total sales in the industry in 1995, followed by cell fusion and cell culture.

There are a number of reasons for the lack of small biotechnology firms in Japan. Firstly, venture capital is less readily available than in the United States or Europe. Secondly, traditional and larger companies control pharmaceutical marketing channels, making them less accessible to smaller firms. Furthermore, the pricing system for pharmaceuticals (R-zone)[7] as well as recent trends towards reference pricing are thought to create difficulties for the survival of smaller companies owing to strong competition and small markets. Thirdly, business practices and the entrepreneurial ethos differ from those of the United States (Yuan and Dibner, 1990). Many US biotechnology companies are founded by researchers from universities, who draw on breakthrough research results. As basic research is weaker in Japan's universities, fewer potential founders of biotechnology companies are available. In addition, government programmes are usually not open to small businesses.

As a consequence, start-up biopharmaceutical companies on the US model do not exist in Japan. Health-care-related companies (i.e. therapeutics, diagnostics, and vaccines) account for about half of the Japanese companies active in biotechnology. Biotechnologically based pharmaceuticals are being developed and produced by established pharmaceutical companies or by companies moving into the pharmaceutical area for the first time.

3. Traditional barriers to entry in the biopharmaceutical industry

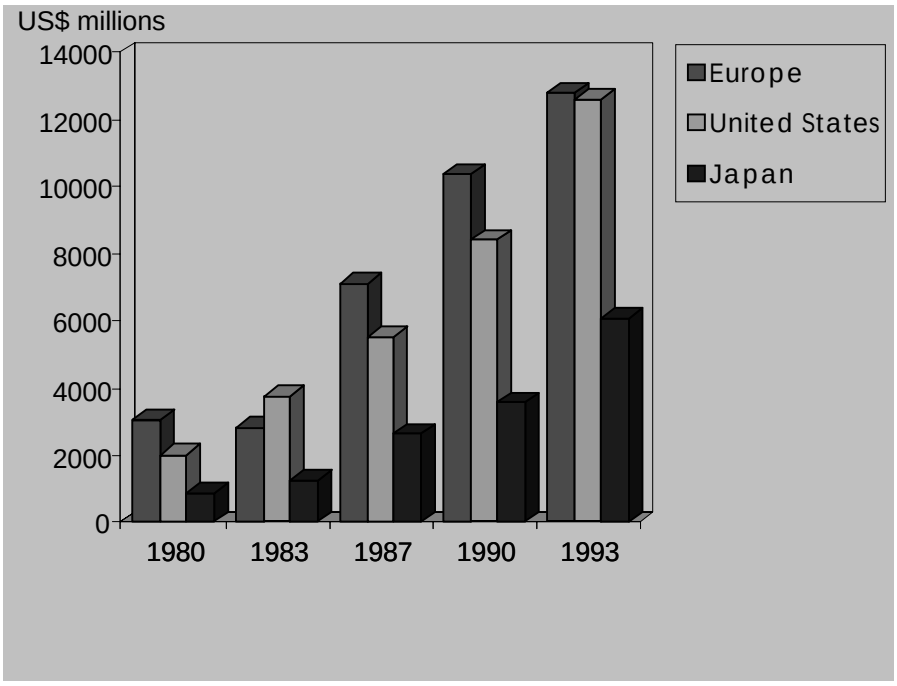
3.1. R&D

World pharmaceutical sales[8] was estimated at approximately $240 billion in 1994. The largest single markets are the United States (23.9 per cent), Europe (27 per cent), and Japan (19 per cent). The main producers are located in the United States, the European Union, and Japan.

The pharmaceutical industry is heavily dependent on continuous innovation, more so than any other research-based industry world-wide.[9] The proportion of income spent on R&D has increased over the past 30 years, owing in part to an increase in concerns about safety and a decrease in returns from conventional screening techniques for drug discovery. R&D spending has escalated dramatically over the past 15 years (Figure 3.1). The cost of bringing a new drug to the market is said to have increased from $54 million in 1976 to $359 million in 1990 (EFPIA, 1995). High R&D spending is a necessary but not a sufficient condition for the development of innovative medicines. A considerable amount of R&D may be devoted to imitation and duplication of the research performed by others, in different geographical areas, or for the adaptation of the product to specific local market conditions. At times, national governments indirectly impose specific requirements on pharmaceutical companies, two of them being to conduct pharmaceutical R&D locally or/and use the local market as a base for exports (Kanavos *et al.*, 1995).

Despite the considerable increase in the global R&D outlays, this, with the exception of Japan, does not appear to have led to a significant increase in innovation, as measured by the number of new chemical entities (NCEs) introduced in the market over the past 20 years. On the contrary, there has been an absolute fall in the number of NCE introductions and a significant change in the location where they are produced, with a considerable improvement in Japanese-based production and a notable decline in Europe (Figure 3.2). R&D spending and NCE introduction cannot on their own provide evidence on corporate innovative performance and other indicators need to be co-examined for this purpose. Such indicators include the level of patents and the contributions by public institutions and are examined in the industrial policy section.

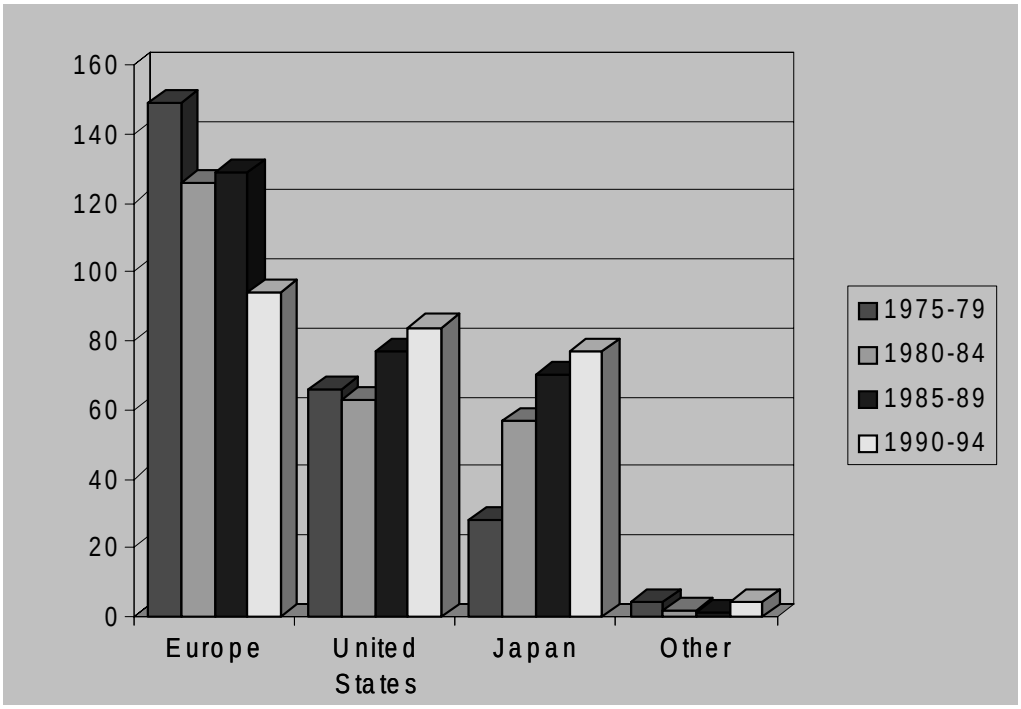
Figure 3.1. **Pharmaceutical R&D in Europe, the United States, and Japan, 1980-1993**



Sources: EFPIA, 1996; PhRMA, 1996; JPMA, 1995.

Although both large pharmaceutical multinationals and small dedicated (bio)pharmaceutical companies (DBCs) are interested in the commercial exploitation of their research, there is a clear distinction between the sort of pressures and constraints that they experience in the process that paves the way to the discovery of new products. For one, the size of pharmaceutical R&D outlays, associated with long periods of basic and clinical research, development and authorisation procedures, imposes a more severe constraint on DBCs. From the DBCs' point of view, the barriers to entry are related to the scale of the resources needed to conduct research and to develop a product further. Most DBCs would need a large and financially independent partner at this stage to fund their innovation process.

Figure 3.2. **New chemical entity introductions by geographical area, 1975-1994**



Source: Barral, 1995.

3.2. Market penetration

Exports and foreign direct investment (FDI) are alternative ways to establish an international presence (UNIDO, 1992), but the evidence suggests that the pharmaceutical industry has always preferred the latter (Kanavos *et al.*, 1995; Remit Consultants, 1995). The United States is the largest originator of pharmaceutical FDI, although its share has declined over time owing to the emergence of pharmaceutical FDI from Europe and, to a lesser extent, from Japan (OECD, 1994*b*). The extensive requirements of human clinical trials, the specific requirements of local regulatory frameworks regarding registration and approval procedures, as well as the pricing and reimbursement of new drugs and the adaptation of products to local epidemiological patterns are thought to be behind the increasing internationalisation of pharmaceutical production. The result has been high levels of penetration of most national markets, possibly excepting Japan, although this seems to be changing (Table 3.1). There is extensive market penetration in Europe, where the pharmaceutical market is still fragmented to a large extent and companies find it worthwhile to improve market share in neighbouring countries by investing locally.[10] Subsidiaries of large multinationals (MNCs) are taking an increasing share of national markets. However, patterns of corporate internationalisation differ considerably. For instance, Japanese companies depend almost exclusively on the Japanese market (Table 3.2), although this is changing slowly. By contrast, US and European companies have considerable activities in Europe and the United States, respectively.

Table 3.1. **1993 company market share in Europe, the United States, and Japan by company nationality**

(percentage of the pharmaceutical market in each country)

	Company's country of origin											
Market	**Germany**	**Belgium**	**Denmark**	**Spain**	**France**	**Italy**	**Netherlands**	**United Kingdom**	**Sweden**	**Switzerland**	**United States**	**Japan**
Germany	52.5	1.6	1.1	0.3	4.3	0.5	1.5	5.8	3.9	8.0	18.6	1.4
Belgium	12.3	9.5	1.8	0.0	10.6	1.6	1.4	16.5	3.6	9.9	30.2	0.8
Spain	14.6	1.6	1.2	29.3	5.1	4.3	0.8	9.8	3.6	11.3	17.5	0.6
France	11.5	2.3	0.6	0.0	45.0	0.7	1.0	8.5	2.2	6.5	20.6	0.8
Italy	14.0	0.5	0.3	0.0	5.6	33.7	0.4	9.2	3.7	11.6	20.2	0.5
Netherlands	11.7	1.9	3.9	0.0	3.8	1.1	15.6	16.7	7.9	11.6	22.5	1.7
Portugal	12.2	2.8	0.6	3.4	11.1	3.7	0.8	9.6	2.2	12.9	25.4	0.5
United Kingdom	9.4	1.1	2.1	0.1	4.5	0.0	1.2	32.6	7.2	7.8	25.5	0.5
United States	4.7	0.3	0.2	0.0	1.5	0.0	0.1	15.1	0.2	7.7	69.2	0.3
Japan	3.9	0.1	0.3	0.0	0.3	0.0	0.1	2.6	0.3	3.3	6.4	82.3

Source: The French Pharmaceutical Industry: Facts and Figures, SNIP, 1996.

Table 3.2. **Dependence of Japanese, US and European companies on their domestic markets**

Importance of Japanese market to top 10 Japanese players[1]	%	Importance of US market to top 10 US players[1]	%	Importance of European market to top 10 European players[1]	%
Eisai	95.4	Merck	61.3	Glaxo	36.7
Sankyo	91.9	BMS	54.5	RPR	67.7
Daiichi	90.8	Lilly	66.6	Astra	75.0
Shionogi	99.0	Pfizer	60.5	Sandoz	45.7
Fujisawa	90.4	Syntex	73.4	SKB	33.7
Takeda	89.5	MMD	78.8	Hoechst	50.7
Yamanouchi	93.4	AHP	76.8	Ciba	31.0
Chugai	96.0	Upjohn	72.5	Roche	41.1
Tanabe	78.7	Schering-Pl	56.5	Bayer	43.2
Merck-Banyu	9.9	J&J	56.3	Zeneca	37.1

1. Only the top ten companies originating from this segment are accounted for.

Sources: *LSE Health (1994)*, based on Datamonitor (reported in *Marketletter*, 11 April 1994), and Barclays De Zoete Wedd (reported in *Financial Times*, 10 March 1994) and company annual reports.

3.3. Concentration levels and competition policy

Competition in the pharmaceutical industry is intense, although the largest pharmaceutical company does not possess a world market share in excess of 5 per cent. Between 1994 and 1995, concentration levels rose owing to a wave of industry mergers and acquisitions (M&As). The top ten companies now account for ~31 per cent of the global market compared to 28 per cent in 1994 (Table 3.3). While overall concentration levels remain low, there is product competition at the level of therapeutic sub-categories, where market shares are considerably higher, and many companies are achieving near monopoly positions in specific markets (Table 3.4).

In the highly diversified pharmaceutical market, it is very difficult for a single company to achieve a market share in excess of 10 per cent in any given country across the entire spectrum of therapeutic categories or indications. However, as mentioned above, a number of companies are achieving monopoly positions in many therapeutic categories regardless of whether there are compulsory licensing regulations in place. In the United Kingdom, for instance, a market share in excess of 25 per cent refers all relevant parties to the Monopolies and Mergers Commission (MMC) to investigate whether a monopoly is being created. However, in the case of pharmaceuticals, it is not clear at which level of aggregation the 25 per cent market share applies; if it applies to the overall pharmaceutical market, then there is no company with a 25 per cent market share; if, on the other hand, it is interpreted narrowly and applies to the therapeutic category level, then the evidence suggests that there might be candidates for referral to the MMC.

Table 3.3. **World pharmaceutical market shares by sales**

1994			1995		
Rank by sales	**Company**	**Market share %**	**Rank by sales**	**Company**	**Market share %**
1	Glaxo	3.6	1	GlaxoWellcome	4.7
2	Merck	3.4	2	Merck	3.5
3	Bristol-Myers Squibb	3.2	2	Hoechst Marion Roussel	3.5
4	Roche	2.8	4	Bristol Myers Squibb	3.1
5	Johnson and Johnson	2.7	5	American Home Products	3.0
5	Pfizer	2.7	6	Pfizer	2.9
7	SmithKline Beecham	2.5	6	Johnson and Johnson	2.9
7	Ciba	2.5	8	Roche	2.6
9	Hoechst	2.3	9	SmithKline Beecham	2.5
9	American Home Products	2.3	9	Ciba[1]	2.5
Top 10		**28.0**	**Top 10**		**31.2**
11	Bayer	2.2	11	Rhone-Poulenc	2.2
12	Eli Lilly	2.1	12	Bayer	2.1
13	Sandoz	1.9	13	Eli Lilly	2.0
14	Rhone-Poulenc	1.8	14	Sandoz[1]	1.9
14	Schering-Plough	1.8	14	Schering-Plough	1.9
16	Abbott	1.7	16	Astra	1.8
17	Astra	1.6	16	Abbott	1.8
18	Takeda	1.5	18	Pharmacia-Upjohn	1.7
18	Sankyo	1.5	19	Sankyo	1.6
20	Boehringer Ingelheim	1.4	19	Takeda	1.6
Top 20		**45.5**	**Top 20**		**49.8**

1. Ciba Geigy and Sandoz merged their activities in 1996 into the new corporate entity called Novartis. The joint company is currently number 2 in the pharmaceutical league tables in terms of sales.

Source: 1996 edition PreView/data, quoted in *Financial Times*.

Table 3.4. **World market for ethical pharmaceuticals by therapeutic class**
(1989 and 1991/92 market shares in selected therapeutic sub-markets)

Therapeutic class/indication	Drug (top company), % market share		Drug (2nd company), % market share		Drug (3rd company), % market share		Drug (4th company), % market share	
1. Cardiovasculars								
ACE-inhibitors (1989)	Vasotec (Merck)	38	Capoten (BMS)	36	Captopril (Sankyo)	8		
ACE-inhibitors (1991)	Vasotec (Merck)	41	Capoten (BMS)	38	Zestril (Zeneca)	9.4		
Ca-Antagonists (1989)	Adalat (Bayer/Takeda)	29	Cardizem (MMD)	15	Procardia (Pfizer)	11	Perpidine (Yamanouchi)	11
Ca-Antagonists (1991)	Cardizem (MMD)	18	Procardia (Pfizer)	17.3	Adalat (Bayer/Takeda)	6.5	Calan (Monsanto)	10
2. Gastro-intestinal								
H2-Antagonists (1989)	Zantac (Glaxo)	52	Tagamet (SKB)	27	Pecid (Merck)	14		
H2-Antagonists (1992)	Zantac (Glaxo)	57	Tagamet (SKB)	15.4	Gaster (Yamanouchi)	5.5		
Proton-pump inhibitors (1989)	not available							
Proton-pump inhibitors (1992)	Losec (Astra)	85						
3. Respiratory								
Asthma	Ventolin/Becotide (Glaxo)	41	Atrovent/Berodual/ Berotec/Alupent (Boehringer-Ingelheim)	15	Intal (Fisons)	11	Proventil (Schering-Plough)	10
4. Cancer treatment								
Immunomodulators (1992)	Intron-A (Schering-Plough)	31	Roferon-A (Roche)	22	Krestin (Sankyo)	19		

Source: LSE Health, 1994.

3.4. Marketing of (bio)pharmaceutical products

Marketing is an extremely costly and important part of pharmaceutical business. Launching a new product does not necessarily imply commercial success. Such success is usually determined by the number of markets in which the relevant new chemical entity (NCE) is marketed. A NCE is successful if it is considered "international", that is if it is marketed in five out of the seven largest international pharmaceutical markets (US, Japan, Germany, France, UK, Italy, Canada). Companies of different nationalities have widely different rates of success in this respect. As Table 3.5 shows, US companies are leading the way and, although they appear to have introduced fewer NCEs over the 1980-94 period (see Figure 3.2) than their European counterparts, they have managed to achieve international marketing for a larger share of their inventions.

Table 3.5. **International drugs as a percentage of total NCEs, 1994**

Country	Total NCEs	% of international drugs
Europe	112	9
USA	90	21
Japan	67	4

Source: Centre for Medicines Research, 1996.

The recent world-wide emphasis on cost containment has put pressure on pharmaceutical firms to develop cost-effective therapies and has made pricing a sensitive issue. Marketing has become more important in all major markets, including the United States, where free pricing exists for pharmaceuticals. A number of governments impose upper ceilings and/or taxes on promotional expenditure of pharmaceuticals. Such is the case in the United Kingdom, France and Spain. In order to respond to increasing pressures on their promotional activities, pharmaceutical companies have adopted strategies of co-promotion or collaboration in the promotion of new products in specific countries by using each others' distribution networks.

The issue for biotechnology/biopharmaceutical companies is that very few of them, perhaps only the most established, such as Genentech, Centocor, and Amgen, have the capacity, in terms of funds and established distribution networks, to market their products on their own. Most DBCs with approved products have licensed marketing rights to established pharmaceutical companies.

3.5. Price and product competition

Price competition in pharmaceutical products protected by a patent is very limited. This is due to the nature of the industry itself, which is the object of public intervention in most national markets, with the exception of the United States, in attempts to contain the cost of drug spending. An additional reason for non-price competition is the nature of pharmaceutical production. The pharmaceutical market is extremely fragmented and consists of a large number of therapeutic categories. Even within a single therapeutic category, there are different product classes; typical, in this respect, is the case of hypertension, which can be treated with diuretics, beta blockers, calcium-channel antagonists, angiotensin-converting enzyme (ACE) inhibitors, or a combination of the above. There is of course an element of evolution in these product categories, in that diuretics are the oldest available treatment for hypertension, whilst ACE inhibitors represent the state of the art treatment in the field. There is also a considerable difference in price, the oldest class of products being cheaper, the newest more expensive. But even within the same product group, similar products (see Table 3.4) are differentiated and suit the needs of different patients. Certain products, for example, are more effective for certain patients than they are for others; it may also be that patients react differently to different products within the same product class. There is ongoing debate about the extent to which drugs within the same therapeutic category can be considered as substitutes.

Consequently, competition in the pharmaceutical industry depends more on the introduction of new products, or classes of products and product differentiation within a therapeutic category, than merely differences in price. Tables 3.6 and 3.7 show the effect of introducing a new product on company revenue by comparing the rankings of the top ten products in 1994 and their expected revenue in 2000. Some of these products, which are currently "blockbusters", will have been replaced by the year 2000. This pattern is maintained throughout, from large markets (hypertension, ulcer treatments, antibiotics) to traditionally smaller markets (urology or dermatological conditions).

Competition through product innovation, on the other hand, requires sophisticated research capabilities and financial power. Coupled with patent protection and exclusivity rights, these confer a natural competitive advantage on producers in industrialised countries. Other characteristics, such as the high cost of marketing and the unusual standards of purity required for producing drugs strengthen the dominance of MNCs over DBCs.

Table 3.6. **Blockbuster drugs, 1994**

Brand name(s)	Generic name	Indication	Sales from marketing companies (US$ m)	Market size US$ m	Launch date
Zantac	Ranitidine	anti-ulcer, H2 antag.	Glaxo 3 657	3 657	1983-84
Adalat/ Procardia	Nifedipine	hypertension	Pfizer 1 200; Bayer 1 130	2 330	1975-89
Losec/Prilosec	Omeprazole	anti-ulcer, proton pump inh.	Astra 1 250; Merck 900; others 80	2 230	1989
Epogen/Eprex	Erythropoietin	haematology	Amgen 750; J&J 690; Kirin/Sankyo 215; Chugai 385; Boehringer Mannheim 150	2 190	1989
Vasotec	Enalapril	hypertension	Merck 2 140 (Banyu 270)	2 140	1986
Humulin/Novolin	insulin (all)	diabetes	Lilly 665; Novo 1 032; HMO 100; Yamanouchi 175	1 972	1982-92
Pravachol/Mevalotin	Pravastatin	lipid-lowering	BMS 615; Sankyo 1 270	1 885	1989-90
Prozac	Fluoxetine	anti-depressant	Lilly 1 665	1 665	1988
Cardizem/CD/SR	Ditiazem	cardiovascular	MMD 933; TAN 370; Syntex 180; Warner-Lambert 78; Rhone-Poulenc Rorer 128	1 689	1982-92
Capoten	Captopril	cardiovascular	BMS 1 460; Sankyo 80	1 540	1981

Source: Lehman Brothers, quoted in *Financial Times* 1996.

Table 3.7. **Blockbuster drugs, 2000 (projections)**

Brand name[1]	Generic name	Indication[2]	Sales for marketing companies[3] (US$ bn)	Launch date	1998 sales US$ bn	2000 sales US$ bn
Losec/Prilosec/Antra	Omeprazole	anti-ulcer, proton pump inh.	2.0+: Astra; 1.0 Astra-Merck	1989	3.78	4.0
Epogen/Eprex/ProCrit/ Epogin/Espo	Erythropoietin	haematology	1.0+: J&J, Amgen; 0.5+: Chugai; <0.5: Kirin/Sankyo, Boehringer Mannheim	1989	3.0	3.5
Prozac	Fluoxetine	anti-depressant	1.0+: Eli Lilly	1988	2.875	3.0
Zocor/Lipovas	Simvastatin	lipid lowering	2.0+: Merck	1989	2.315	2.5
Norvasc/Istin	Amiodipine	hyperten/angina	1.0+: Pfizer	1990	1.72	2.0
Vasotec	Enalapril	hypertension	1.0+: Merck	1986	2.16	2.0
Zoloft	Sertraline	anti-depressant	1.0+: Pfizer	1991	1.61	2.0
Adalat+SR/Procardia+XL	Nifedipine	hypertension	0.5+ : Bayer, Pfizer	1975-89	2.3	1.75
Pulmicort Turbuhaler	Budesonide	steroid, asthma	0.5+: Astra	1982-87	1.45	1.75
Neupogen	GCSF/filgrastim	white blood cell stim.	2.0: Amgen/Roche; <0.5: Kirin/Sank, Chugai	1991	1.35	1.65

1. Products may be known with different brand names in different markets.

2. According to the Anatomic Therapeutic Classification (ATC).

3. Expected/approximate revenues by company.

Source: Lehman Brothers, quoted in *Financial Times*, 1996.

R&D is hampered by the risks inherent in innovation and by the regulatory process. Only a very small number of new molecules eventually reach the market after undergoing lengthy pre-clinical and clinical trials for toxicity, safety and efficacy. Development costs are therefore high, the time required to achieve revenues is long, and there is a strong probability that a given product will not be commercially successful. All the above place additional constraints on new entrants.

3.6. Integration

The changing environment of the pharmaceutical industry has prompted a wave of mergers, acquisitions, and strategic alliances, and thus greater concentration. Companies' strategies for increasing their size in order to achieve economies of scale in R&D and market operations differ considerably. Some primarily integrate horizontally in order to strengthen their innovative capacity by acquiring small(er) companies with promising R&D pipelines; the Glaxo-Wellcome and Hoechst-Marion-Roussel mergers definitely fall into this category. Others mainly integrate vertically by expanding their activities into distribution of pharmaceuticals (the Merck-Medco paradigm) or by acting as health-care companies (the SmithKline Beecham paradigm).

Financial markets are usually quite receptive to new products and ideas promoted by individual biotechnology/biopharmaceutical companies. However, the availability of funds tends to be cyclical. At the peak, (several) products have successfully gone through clinical trials and pre-approval stages; the trough, instead, is characterised by the failure of such products either to get through the regulatory process or to outperform other (and at times conventional) products in terms of therapeutic-[11] or cost-effectiveness.[12]

The further development of the biotechnology industry requires a continuous flow of funds for high-risk research, which venture capital, because of its highly selective structure, does not always provide. This is one of the reasons why biotechnology companies form strategic alliances with pharmaceutical companies. These alliances not only provide a source of funding for biotechnology, they also facilitate product and technology transfer through licensing agreements which enable biotechnology firms to diversify and reduce the uncertainties in their product development. On the part of the larger pharmaceutical firms, they also reflect a more mature understanding that they cannot afford to do research in all therapeutic categories, given exponential growth in knowledge in the biological sciences and the burgeoning of cutting-edge technologies.

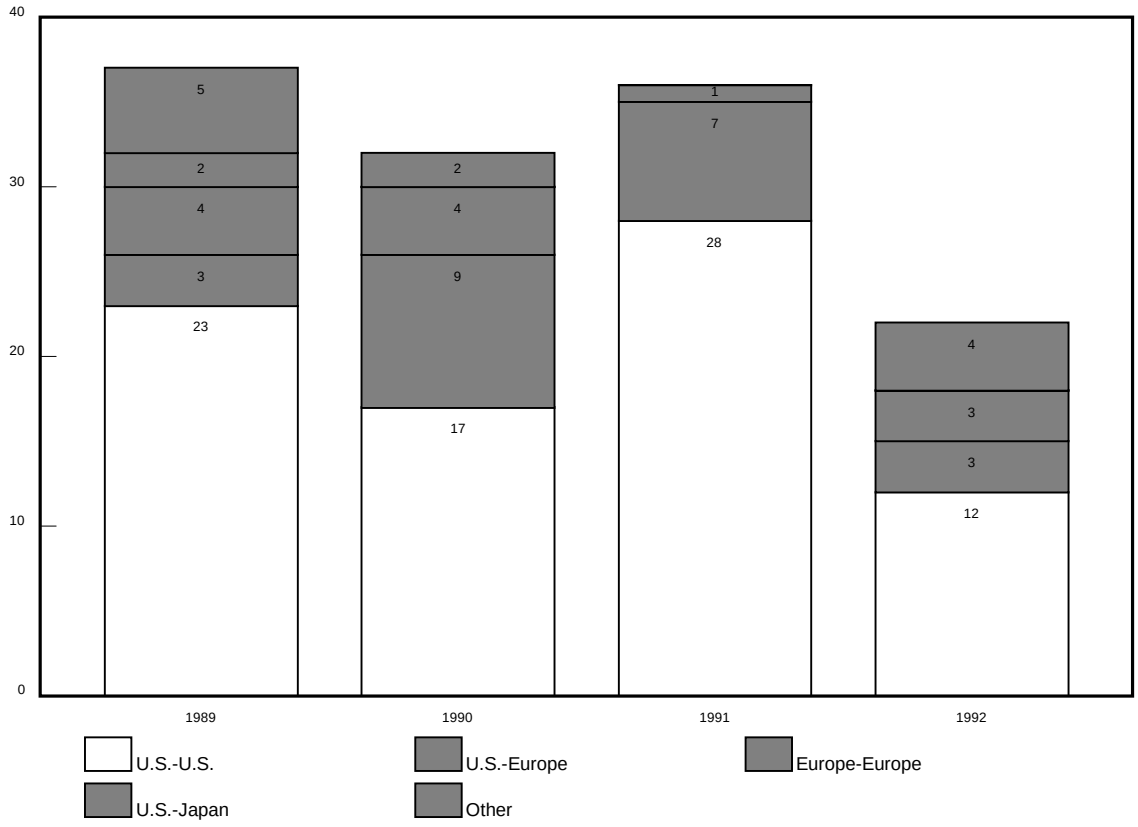
The radical changes in the international pharmaceutical industry and the changes in regulatory environments have forced companies to join forces in order to face competition. For biopharmaceutical companies, M&As and strategic alliances, either among themselves or with pharmaceutical companies, are necessary to fund expensive research, take products through authorisation procedures, and obtain access to marketing and distribution networks.

While traditional reasoning has long been that financial pressure would eventually force biotechnology companies to sell out in order to survive, pharmaceutical companies are also teaming up to achieve potential synergies and greater competitiveness in an increasingly globalised market environment. Thus, although financial markets and venture capital have played an important role in providing biopharmaceutical companies with capital, strategic alliances have emerged as the preferred way to fund research in the biopharmaceutical industry (as Figures 4.2 and 4.3 in the next section demonstrate). There are good reasons for this: first, financial markets are quite volatile and are susceptible to events such as the 1987 stock market crash and the following debt deflation period; second, decisions to invest in the stock market are usually dictated by actual or potential corporate profitability, but most biopharmaceutical

companies are far from profitable during their initial phase; third, there is not an endless source of venture capital and limitations may be imposed by national policies; fourth, most financial markets are not of a size sufficient to cater to the increased requirements of the biotechnology sector; finally, a strategic alliance may be a safer option for biotechnology companies and can facilitate the development and approval process or guarantee access to markets.

The vast majority of M&As involve companies from the United States. An indication of the order of magnitude over a four year period (1989-92) is provided in Figure 3.3; similar trends exist for 1995 and 1996 (Bio/technology, various issues). Over 55 per cent of all biopharmaceutical M&As involve activities between US companies only; over 63 per cent of all biopharmaceutical M&As involve at least one US partner; very few involve M&As among European biopharmaceutical companies. It is worth noting that European pharmaceutical companies seek to acquire stakes in US rather than European biotechnology companies. The available evidence also suggests that promising biopharmaceutical companies often merge with or are taken over by large pharmaceutical companies (as the examples of Genetics Institute/American Home Products, and Genentech/Roche demonstrate).

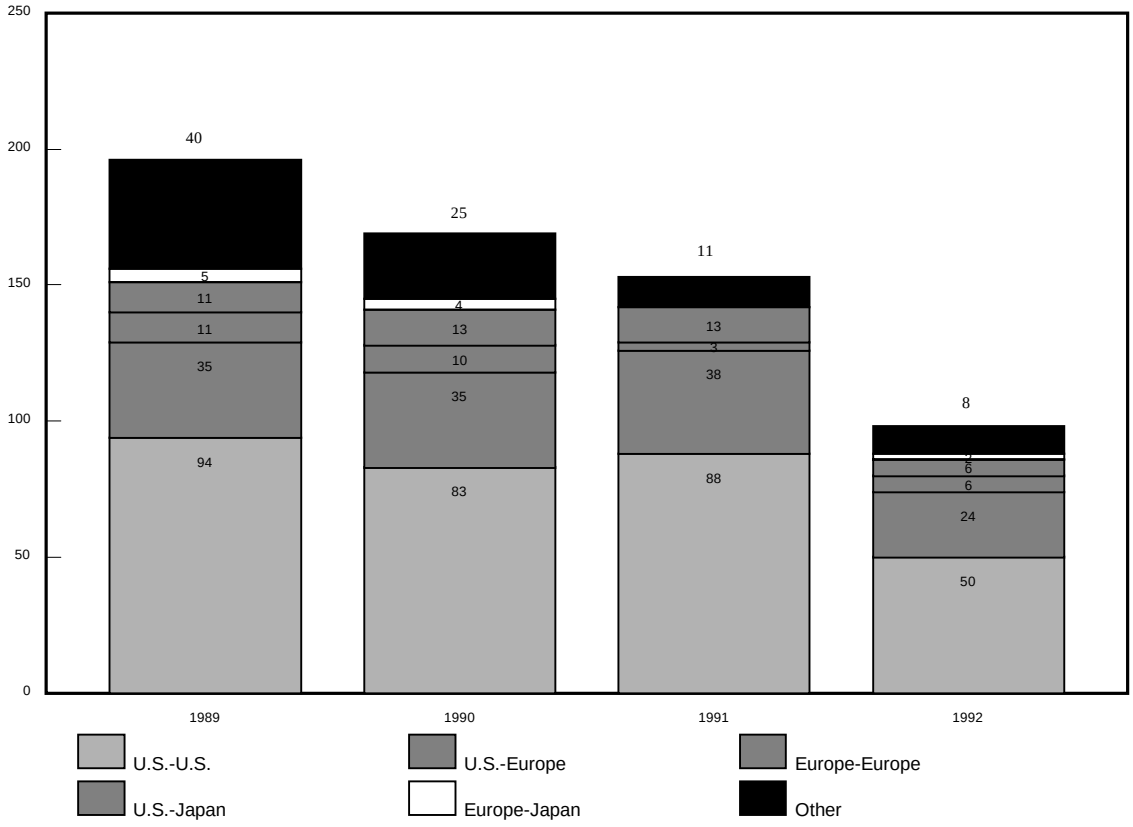
Figure 3.3. **Number of corporate mergers and acquisitions in biopharmaceuticals, 1989 -1992**



Source: Kanavos *et al.*, European Parliament, 1995.

Over two-thirds of strategic alliances (91 per cent in 1991) involve at least one partner originating from the United States; a substantial proportion of world strategic alliances in biopharmaceuticals (estimated at 40 per cent of the total for 1989-92), involves partners originating from the United States (Figure 3.4); the same trend persists for 1994 and 1995 (Bio/technology, various issues).

Figure 3.4. **Number of corporate strategic alliances in biopharmaceuticals, 1989 -1992**



Source: LSE Health.

A fair number of these alliances involve European companies (approximately 22 per cent of the total for 1988-92). The trend is for European and Japanese pharmaceutical multinationals to invest in biotechnology activities in the United States. Such investments allow them to acquire and transfer technology in areas where their expertise is limited (Kanavos *et al.*, 1995). In the vast majority of cases, US-based companies provide the technology or accumulated expertise, and their European or Japanese partners provide the funding for a new process, drug or therapy to be developed. Table 3.8 shows the number of strategic alliances formed by the top 50 pharmaceutical companies with biotechnology companies. European pharmaceutical companies figure prominently as seekers of such alliances.

The number of alliances between companies and academic institutions is increasing, especially in the United States. Many American, but also many European companies sponsor research in an academic institution in addition to entering into strategic alliances with other companies. Alliances with universities or research centres are oriented towards basic research and the academic partner is, most often, an American university (LSE Health, 1996).

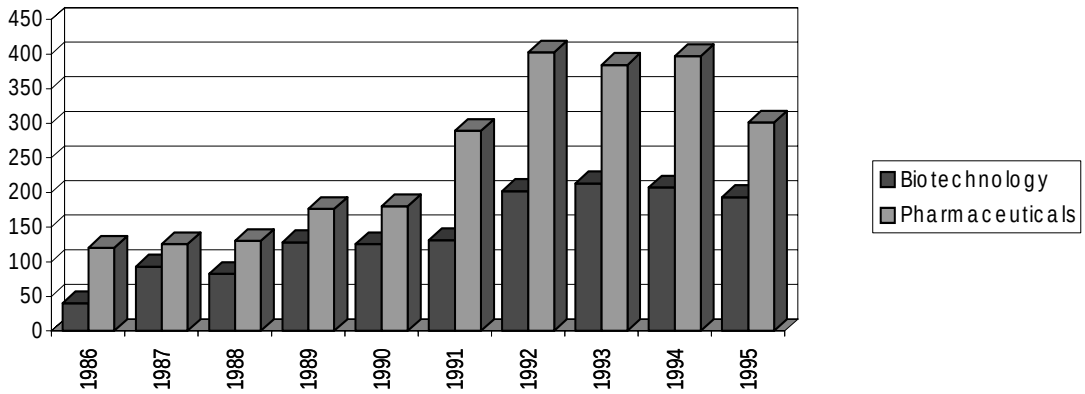
Table 3.8. **US and European biotechnology alliances, 1992-1994**
(leading US and European companies)

Ranking by 1994 global turnover	Active US companies (number of deals)	Active European companies (number of deals)
1-10	Merck (6), Bristol-Myers Squibb (1), Johnson & Johnson (3), Pfizer (1), American Home Products (1)	Glaxo (10), Hoffmann-La -Roche (14), SmithKline Beecham (13), Ciba (6), Hoechst (6)
11-20	Schering-Plough (2), Abbott (1)	Bayer (3), Sandoz (9), Rhone-Poulenc Rorer (19), Astra (2), Boehringer Ingelheim (4)
21-30	Marion Merrel Dow (1), Warner-Lambert (1), Upjohn (3)	Wellcome (9), Sanofi (2), Zeneca (1), Schering (2)
31-40	Searle (2)	Pharmacia (2), Novo Nordisk (1)
41-50	-	Akzo-nobel (10), Servier (10), E. Merck (1), Synthelabo (1), Nestle (1), BASF (2)

Source: Ansell and Sparkes, 1996.

In conclusion, the pattern of acquisition and collaborative strategies in the biopharmaceutical sector has a number of strongly interrelated aspects. First, priority is given to ensure a supply of new products, either by acquiring companies intensively oriented towards R&D or by bundling R&D activities with those of the acquired/merged company. Second, large pharmaceutical companies globalise their activities and by acquiring or linking with local biotech or pharmaceutical companies, and research institutions, also ensure access to marketing and distribution networks. Finally, the pattern of mergers, acquisitions and strategic alliances strongly suggests that there exists a flow of investment from European (and to some extent Japanese) pharmaceutical multinationals towards the United States. The trend in international strategic alliances in pharmaceuticals and biotechnology, including university deals and CROs, has been steadily growing, as Figure 3.5 suggests.

Figure 3.5. **Number of international strategic alliances in pharmaceuticals and biotechnology, 1986-1995**



Note: Strategic alliances include all corporate and university deals concerning biotech products.
Source: PhRMA, 1996.

4. The regulatory framework and financial context

The evolution of the regulatory framework is crucial to the development of biotechnology in general and biopharmaceuticals in particular and is also a determinant of inward investment. The characteristics of regulation (i.e. intellectual property rights protection, the pricing, financing, reimbursement, authorisation and approval procedures and the regulations therein, including regulations on quality, safety, efficacy, non-clinical studies and clinical trials) naturally affect the (bio)pharmaceutical industry, but other issues (such as the accessibility of the regulatory authorities) may also play an important role. Because (bio)pharmaceutical products are subjected to extensive regulatory controls (from the stage of patenting, clinical development and approval, through to the pricing and reimbursement), it is important to consider the extent to which the pursuit of industrial policy meets the objectives of health policy.

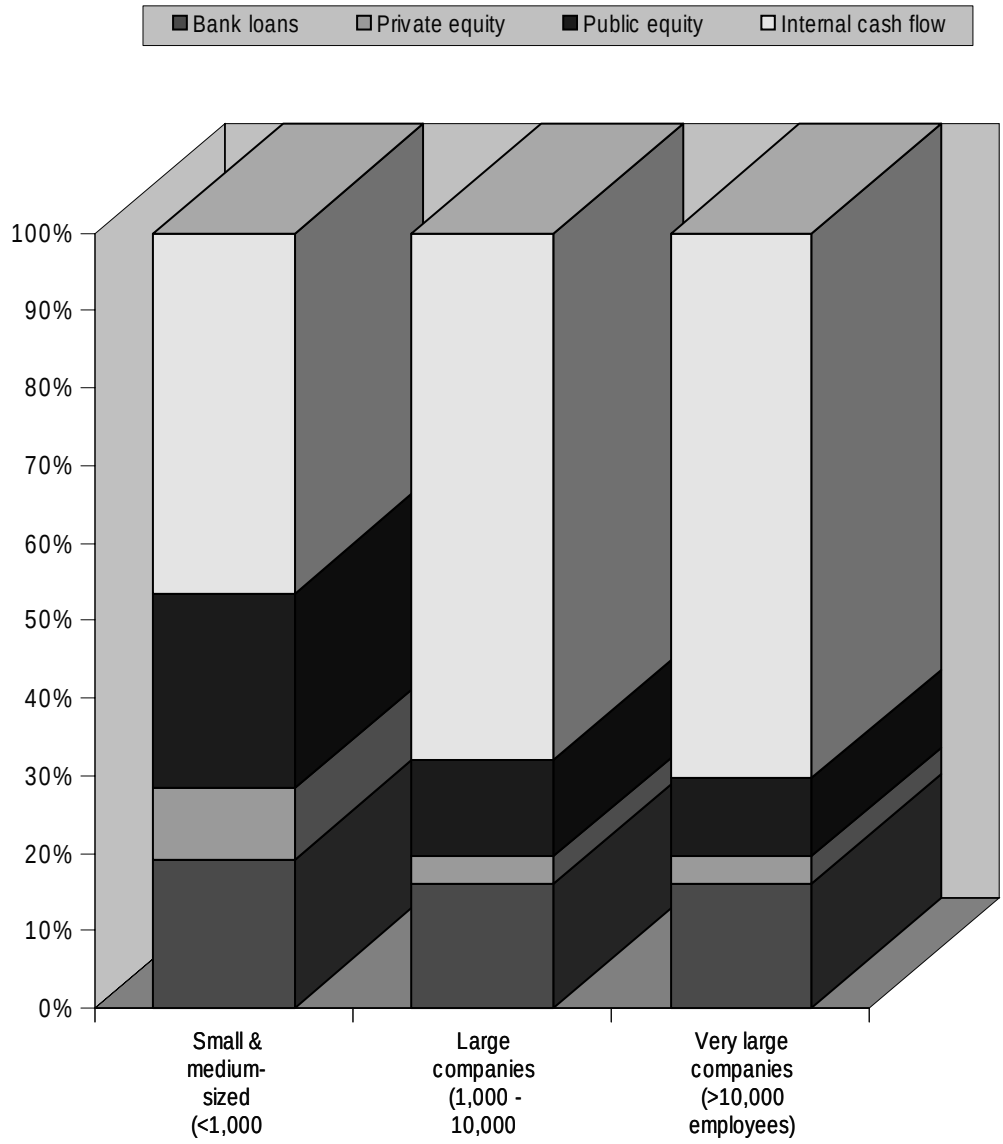
4.1. The financial context

Given the high costs of R&D, the financial strategy of dedicated biotechnology companies (DBCs) is crucial to their survival. Figure 4.1 shows the sources of finance of biotechnology companies according to a survey conducted in Europe (SAGB, 1994). It appears that small biotechnology companies rely comparatively more on public and private equity and bank loans thereby demonstrating the vulnerability of such companies and their dependence on outside sources of finance. This is clear, despite the fact that the division between small, large, and very large companies is not the conventional one.

The financing of innovation, particularly of small biotechnology companies, is determined by a number of important parameters. Firstly, the considerable risk in biotechnology research necessitates the involvement of venture capital companies; secondly, investors' perception of individual biotechnology companies' performance and potentials, and the extent to which capital can be raised from financial markets through initial placement offers; thirdly, regulation of financial markets is important in promoting such a highly sensitive industry; and finally, shortage of capital and risk "neutralisation" imply that biotech companies will be seeking collaborations with larger (pharmaceutical) companies which can afford the extra financial burden in return for a new production process or/and product.

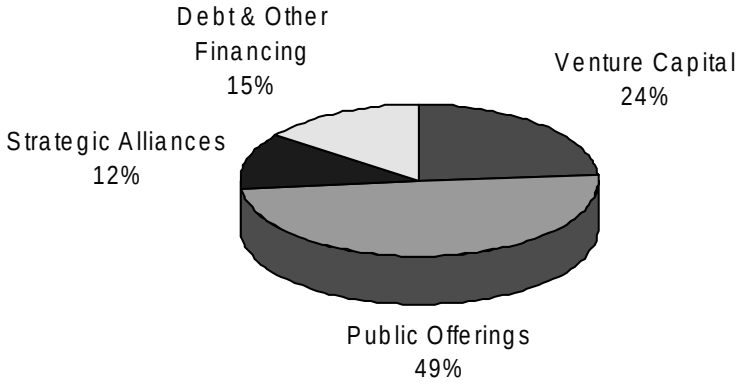
Over time, the financing of biotechnology companies has presented significant variations. In 1986, 49 per cent of total funding came from public offerings and 24 per cent from venture capital (Figure 4.2; Ernst & Young, 1986); in 1994, 27 per cent of financing came from strategic alliances, and 20 per cent from public offerings, while venture capital declined to 13.5 per cent of total funds (Figure 4.3; Ernst & Young, 1995). The above variations highlight the importance of private capital in financing biotechnology innovation and also the emergence of strategic alliances[13] as a safer means of channeling resources into innovative companies. The rise in the share of strategic alliances over time also signifies that financial markets are volatile and subject to movements of the business cycle, which influence the availability of capital and its allocation in different activities according to perceived risk.

Figure 4.1. **Sources of finance of biotechnology companies in Europe**



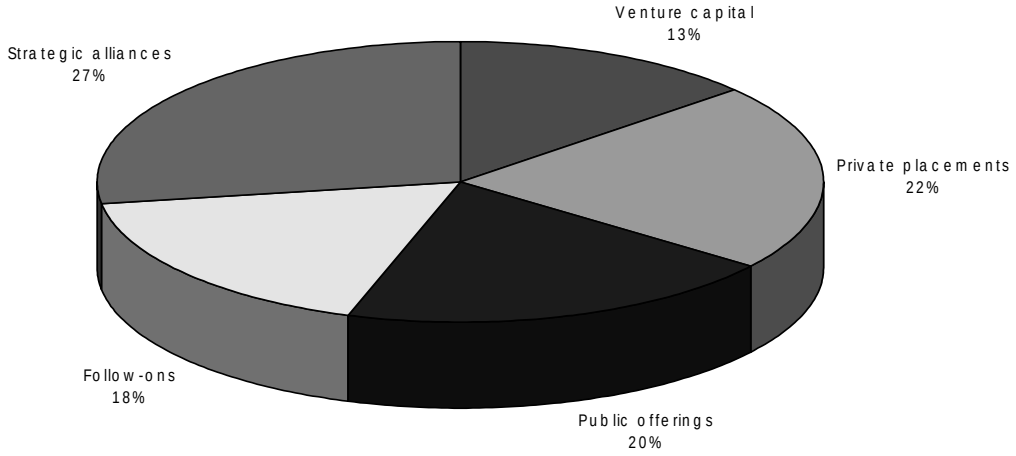
Source: Senior Advisory Group on Biotechnology, 1994.

Figure 4.2. **Sources of international biotechnology industry financing, 1986**



Source: Ernst & Young, 1986.

Figure 4.3. **Sources of biotechnology industry financing, 1993**



Source: Ernst & Young, 1994.

The trends above reflect the changing situation of the biotechnology industry, the increase in R&D activity by small start-up firms, but also the risky nature of biotechnology R&D and the difficulties faced by biotechnology companies for successfully commercialising their products.

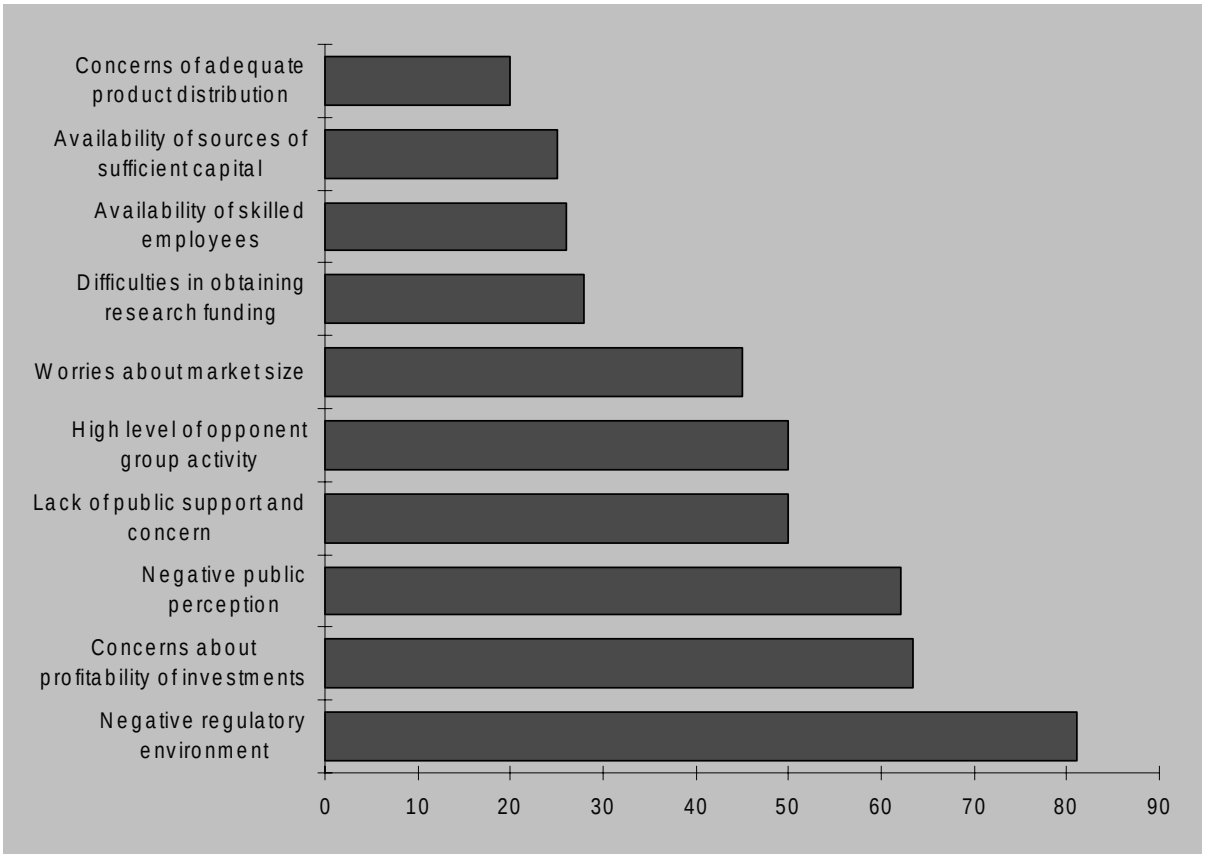
4.2. Investment in the pharmaceutical and biopharmaceutical industry

Investment in the pharmaceutical and biotechnology industry is a complex function of many parameters. Investment usually takes place if business opportunities are deemed profitable in terms of expected return on investment. Because of the special characteristics of the pharmaceutical and biotechnology industries, prospects for investments are evaluated not only in terms of an estimated rate of

return, *i*, but also against a set of qualitative variables that differ according to the national environment. These variables are of particular importance and relevance to the pharmaceutical and biotechnology sectors, due to the nature of the products and the interplay between public policy and private profit-making activities. They include among others the three-tier demand system for medicines, the interplay between health and industrial policy, the complexity of regulatory procedures at different stages of product development, and public attitudes. In addition, because of the great uncertainty in the R&D process, risk is an important residual factor, which is reduced (but never eliminated) in environments conducive to pharmaceutical research or supportive of the science base.

Thus, investment decisions of pharmaceutical or biotechnology companies appear to reflect three major sets of factors. One set concerns traditional notions of a company's revenue streams and includes market size, but also pricing, financing, and reimbursement factors. The second is an extensive list of qualitative factors, including future market potential, the regulatory environment, industrial policy (which primarily includes intellectual property rights protection and financial and/or other support of the R&D effort by public authorities), SME policy, competition policy, the science base and the relations between academia and industry, public perceptions of biotechnology, language and cultural factors in a given country (see also Figure 4.4 for the importance of some of these factors). Finally, as a residual factor, risk includes the costs of R&D and the associated output from the innovation process. These factors are summarised in a formula in Box 1.

Figure 4.4. **Constraints and factors affecting investment decision-making in Europe**



Source: SAGB, 1994.

Box 1. **The investment decision function in the pharmaceutical/biotechnology industry**

$$NPV = \left\{ \sum_{t=0}^{x} \left(R_p / (1+i)^t \right) \right\} + Q_p - U_p$$

where:

NPV is net present value of an investment;
R is expected revenue;
Q is the set of qualitative factors;
U is the uncertainty/risk residual associated with R&D;
t is the starting point from which investment is considered (in years);
x is the final year of the investment;
p is the country factor.

The literature (Remit Consultants, 1994, 1995; Kanavos *et al*., 1995) supports this broad framework of decision-making for investment in the pharmaceutical sector,[14] provided that each of the above sets of factors is applied to different environments. Thus, the decision for pharmaceutical investment does not only depend on the future stream of revenues from conducting manufacturing activities in a given country *(R_p)*. This stream of revenues is dependent on government policies regarding pricing and financing of pharmaceuticals in a given country *(p)*, and is inversely related to the number or intensity of price and reimbursement regulations prevailing. Due to the pharmaceutical industry's research-oriented nature, any stream of revenues from manufacturing and distributing products is highly dependent on successful discovery and development of new molecules. The process of discovery and development is closely related to the set of quality factors that prevail in a given country *(Q_p)*. These factors make up the overall environment for pharmaceutical investment. Finally, there is widespread agreement that pharmaceutical R&D is very risky and there is always the possibility of failure in discovering, developing or commercialising the results of R&D. Pharmaceutical companies are therefore looking for factors that would minimise this risk by choosing a specific location (area or country) which may fulfil this criterion *(U_p)*; the risk factor can therefore be country-specific and affects negatively the total stream of revenues from any investment decision.

Consequently, pharmaceutical investment is a complex decision influenced by country-specific revenue factors *(R_p)*, qualitative factors *(Q_p)* and risk factors *(U_p)*. The importance of these factors in any investment decision is far stronger in the pharmaceutical/biotechnology industry due to its special features and its close relationship with or dependence on public policy decisions.

Revenue factors

The industry has always argued the case for free pricing as a means to recoup R&D spending and sees any type of price controls as a hindrance to its development. Large market size, coupled with free pricing and few or no limitations to reimbursement would definitely attract investment; this is the case of the United States, the United Kingdom, Japan and, to a certain degree, Germany and the Netherlands. The fact that considerable expansion of pharmaceutical multinationals is taking place in the Asia-Pacific region, and the excess capacity of the European pharmaceutical industry, where subsidiaries operate in almost every EU Member State, indicate the presence of other factors affecting location decisions. For newly industrialising countries, such as those of the Asia-Pacific rim, this presence (initially through

representative offices and distribution networks rather than manufacturing and research facilities) is deemed important due to the significance these markets will acquire in the next decade or so. A reason for the overcapacity of the European pharmaceutical industry is the implicit or explicit requirement by many EU governments for performance indicators (local R&D content, contribution to the balance of payments, employment).

Country-specific qualitative factors

Surveys have shown that pharmaceutical manufacturers are particularly sensitive to the qualitative factors identified above. In particular, differences in regulatory environments (as will be discussed in section 7), especially in the context of markets with similar purchasing power, have been found to be a major influence on investment. The stability of government policies as well as their flexibility to adapt to specific investment plans are considered advantages. European firms have been investing in the United States for some time, in part owing to the cumbersome European regulatory framework. Lengthy approval times are also a problem, although this is an issue for all large pharmaceutical markets. Incentives provided by national governments are acting positively towards attracting companies.

Government support of pharmaceutical R&D has been successful where implemented and in most cases national (but also regional or provincial) governments compete with each other on incentives in order to attract inward investment. All OECD countries have adopted such policies. A different qualitative factor is the quality of the science base which has proved a very national important asset due to the nature of the pharmaceutical/biotechnology industry.

Inadequate patent protection certainly deters investment, as revenue is lost if cheap identical products made by unauthorised producers appear on the market. Pharmaceutical companies are for instance sceptical about the current potential of Eastern Europe, where patent law is still not fully enforced (Kanavos, 1996). By contrast, the introduction of the C-91 patent law in Canada is said to have led to a considerable rise in R&D spending by the Canadian pharmaceutical and biotechnology industries within a few years after its enactment (Heller, 1995). The imposition of ceilings on certain types of expenditure, particularly advertising expenditure, is also a negative point because it may lead to revenue losses in the long run.

Cultural affinity and linguistic advantages have also been mentioned in the literature. Interviews with Japanese managers have indicated[15] that an important factor for investment is the cultural affinity the Japanese felt with Britain, *vis-à-vis* other European countries, due to the "island mentality" that both countries share, as well as the greater ease of communicating in English.

Specific country factors may force domestic companies to internationalise their activities. This was certainly the case for Japan, where outward investment by domestic pharmaceutical companies increased in the aftermath of health-care reform. Recent changes in Japanese health insurance reimbursement and pricing policies are expected to have profound implications for all those who receive and deliver health care in Japan. Traditionally, the key factor for success was a constant flow of small innovations listed at higher prices, promoted by a large sales force, and distributed through a controlled wholesaler network; now, only "innovative" drugs will receive price premiums over older drugs. For manufacturers, this implies that the mission of research has largely shifted to "breakthrough" innovation.

The choice of country in which to invest is a function of geographical attributes, but also of qualitative ones. The success behind increased investment in the US biotechnology industry is, apart from the attractive regulatory environment, the existence of a superior science base coupled with an

entrepreneurial culture. The development of new technologies and the existence of a strong science base are important determinants of inward investment through the reduction in the riskiness of R&D projects they imply.

4.3. Financial regulation

Stock markets

Adequate funding is crucial to the R&D activities of biotechnology/pharmaceutical companies. Stock markets usually provide means of financing, although the small size of biotechnology companies and the risky nature of their business make raising capital on financial markets difficult. The London Stock Exchange has explicitly taken steps to encourage the listing of biotechnology companies by modifying its listing rules and adjusting them to meet the requirements of such companies (London Stock Exchange, 1996).[16] Biotechnology companies can figure on the main list of the Exchange if they meet certain requirements: first, an ability to attract funds from sophisticated investors, second, intention to raise at least £10 million pursuant to marketing at the time of listing; third, capitalisation, prior to marketing at the time of listing, of at least £20 million[17] (instead of the £100 million required for listing ordinary companies); fourth, primary reason for listing is to raise finance to bring identified products to a stage where they can generate significant revenues; and finally, if their activities are mainly research and development of drugs and if they have at least two drugs in clinical trials regulated by an internationally accepted regulatory authority. This last criterion has recently been relaxed to allow companies with potential to be listed; while the requirement to have at least two products in clinical trials remains. Another condition is the signing of collaborative agreements with other companies and proof that R&D expenditure of the order of £20 million has been incurred over at least three years and has resulted in the creation of intellectual property of significant worth. A biopharmaceutical company seeking listing must satisfy at least one of these two conditions.

As a result, a number of biopharmaceutical companies have been listed over the past three years (Table 4.1). Other European stock exchanges do not provide similar incentives to the biotechnology sector. In the United States, the New York Stock Exchange (NYSE), has particular guidelines that apply to all high-tech companies, including biotechnology/biopharmaceuticals, implementing more relaxed rules regarding profitability performance and capitalisation levels.[18] In Japan, on the recommendation of MITI, the Tokyo Stock Exchange relaxed its rules for listing "R&D-intensive" or "knowledge-intensive" companies (defined as companies spending 3 per cent or more of turnover on R&D and having dynamic market prospects) in July 1995. The Japanese criteria for listing appear to be quite flexible: even if a company does not satisfy profitability criteria or is in the red, it can be listed.[19]

Table 4.1. **The seven largest UK biotechnology companies by market capitalisation**
April 1996

Company	Market capitalisation £ m
British Biotech	1 438.0
Medeva	718.6
Scotia	487.0
Cortecs	433.2
Celltech	379.0
Oxford Molecular	186.9
Chiroscience	167.3

Source: Financial Times London Share Service.

The alternative investment market

London's Alternative Investment Market (AIM) has provided biotechnology companies with another public equity option. Its regulations are far less stringent. Potential entrants have to provide a prospectus, meet all audit requirements laid out in company law, and fulfil certain obligations such as publication of unaudited interim figures and directors' dealings. AIM gives early-stage companies with little chance of meeting the listing requirements of the London Stock Exchange access to capital markets. The success of the London AIM has induced other European countries to establish their own parallel markets. This is the case of the Paris Nouveau Marché[20] (already in operation), the Frankfurt Neuer Markt and the Brussels New Market.

Global trading systems

A single financial market that brings together investors from a broad geographical area can achieve economies of scale. In the United States, the National Association of Securities Dealers Automated Quotation (NASDAQ) provides such a vehicle, as it allows companies to register and raise capital from institutional investors.[21] The experiment has been quite successful, and European companies such as Cantab Pharmaceuticals and British Biotech have raised capital there. In Europe, EASDAQ, the European version of NASDAQ, was launched in late November 1996.

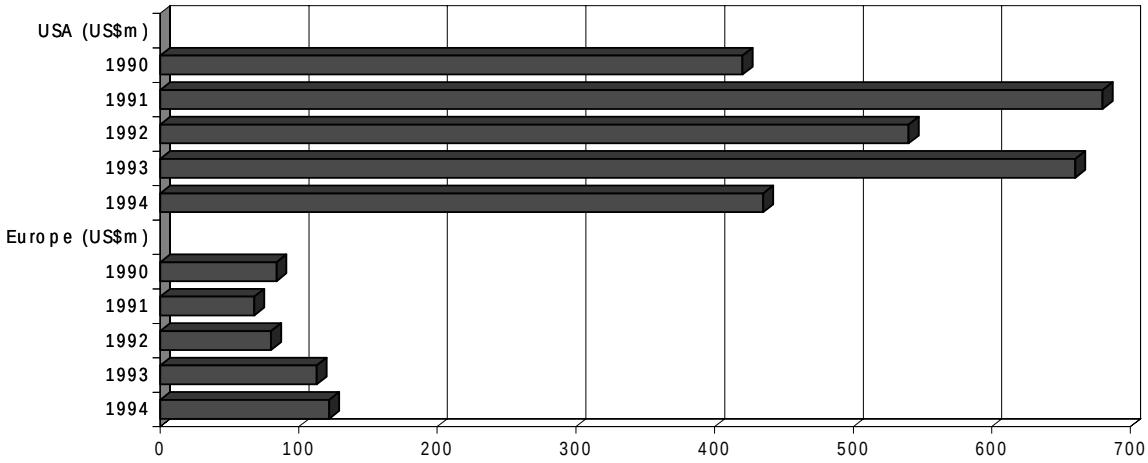
Venture capital

In terms of research objectives and capital requirements, new business firms (NBFs) can be classed according to product lines types (Smith and Fleck, 1988): those providing products and services such as monoclonal cell lines or peptides for other large producers; those involved in the development and production of diagnostic kits of various types for use on humans or animals; and those developing and producing drugs for human therapeutics. The first type usually needs minimum capital and often serves as a springboard for small start-ups by raising revenue at the early stages of development. The second is already more capital-intensive, while the third is concerned with human drugs, the most expensive products to develop, produce and sell. Many NBFs go through these three stages of development as they mature.

Regardless of their type, biopharmaceutical companies need capital not only to finance their R&D activities, but also to turn their discoveries into viable commercial products. The availability of venture capital and its accessibility vary. Figure 4.5 shows the level of venture capital disbursements in the United States and Europe over a five-year period, with disbursements in the former outnumbering those in the latter by a factor of four. Similar are the trends for 1995 and 1996, where, at least in the United States, venture capital investment reached record levels (Nature, 1996). The US capital markets are sufficiently large and are willing to finance risky projects in biopharmaceuticals. Pension funds are a significant source of venture capital financing in the United States, and financial deregulation in the mid-1970s released a large pool of cash for venture use, paticularly pension funds (Office of Technology Assessment, 1991; US Congress, 1984). Furthermore, independent private venture capital firms provide about 83 per cent of the total venture capital pool (Henderson, 1989). The availability of venture capital is subject to cyclical factors; nevertheless, the US market possesses a number of positive features, which, in part, counteract volatility caused by the business cycle. These features are related both to the availability of funds and the public perception of biotechnology. The availability of capital for venture purposes is related to the size of the market, particularly savings instruments. Americans favour saving in mutual

funds and other vehicles, which, in turn, seek appropriate investment opportunities. A more favourable environment for new products at the Food and Drug Administration (FDA), related to speedier approval procedures, is also a contributing factor.

Figure 4.5. **Venture capital financing of biotechnology in the United States and Europe, 1990 -1994 (in US$ million)**



Source: KPMG/BioWorld Financial Watch, 1995.

European capital markets, in contrast, are fragmented and neither large nor sophisticated enough to support the demand for start-up or venture capital of a large number of biopharmaceutical companies. At the same time, large pharmaceutical MNCs invested in biotechnology in the 1980s but did not encourage or support the emergence of small specialised "start-ups". Many overseas laboratories were established (particularly in the United States), and a large number of co-operation agreements were signed between European and US biotech companies. Under these agreements, the US biotechnology firms undertake research and develop new production processes at laboratory scale.

Table 4.2 shows the amounts of venture capital raised in different European countries. The sources of venture funds vary between countries and their availability is affected by those who control them. Banks largely tend to be the sources of venture capital in the United Kingdom (about 25 per cent), Denmark (50 per cent), and Germany (56 per cent). The government provides as much as 73 per cent of venture capital in countries such as Belgium and Luxembourg and nearly 40 per cent in the Netherlands. In France, insurance companies provide 23 per cent of venture capital. In other European countries, venture capital companies are relatively new.

Most venture capital investment in Europe has been channelled to consumer-related projects (14.8 per cent), computer-related projects (8.4 per cent), and industrial products and services (16 per cent) (Figure 4.6). Biotechnology received about 2.5 per cent of total disbursements in 1994.[22] This is in sharp contrast with the United States, where biotechnology received almost 24 per cent of total venture capital disbursements in 1993 (Figure 4.7). The shortage of start-up and early stage financing across Europe has been recognised, and the European Commission has recently launched two initiatives, Seed Capital and Eurotech Capital, which support new activities including biotechnology. The first of these has supported 24 new capital funds across the European Union over the period 1989-95, for a total of ECU 37 million of

early-stage investment capital. The biotechnology sector has the largest participation over this period (12.98 per cent of the total number of firms created; see Figure 4.8).[23] This initiative is expected to continue for the near future.[24] Eurotech Capital encourages financial institutions to increase their investment in cross-border high-technology projects by means of investment subsidies ranging from 4 to 50 per cent (see also Bank of England, 1990).

Table 4.2. **European biotechnology[1] venture capital by country, 1994**

	Amount (ECU 000) 1994	Amount (ECU 000) 1993	Growth over 1993	% of total amount of venture capital invested (1994)	No. of investments	% of total number of investments (1994)
Austria	0	0	0	0	0	0
Belgium	6 527.01	2 788.83	134.04	6.1	3	2.54
Denmark	1 769.88	1 298.94	36.26	9.7	2	6.06
Finland	1 611.09	0	0	6.7	9	9.09
France	6 926.66	8 371.06	-17.25	0.64	38	2.64
Germany	29 237.83	12 133.68	140.69	3.64	27	3.61
Iceland	0	0	0	0	0	0
Ireland	656.96	479.75	36.94	2.42	2	4.00
Italy	0	7 465.95	0	0.3[2]	3[2]	2.01[2]
Netherlands	9 699.77	2 078.52	366.67	3.00	24	6.00
Norway	1 453.69	397.26	265.93	2.30	8	5.30
Portugal	0	0	0	0	0	0
Spain	265.93	75.89	250.42	0.23	3	1.36
Sweden	1 150.76+	0	0	0.63	2	2.82
Switzerland	10 901.67	280.89	3 881.11	14.13	5	8.77
United Kingdom	14 200.21	28 833.76	-50.75	0.63	27	1.38

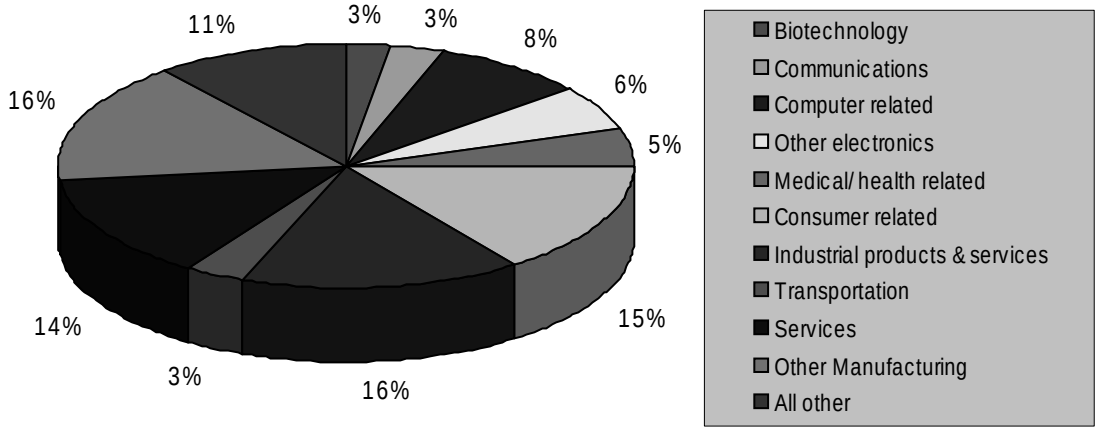
1. Biotechnology includes human medical diagnostics and therapeutics (e.g. DNA probes); agricultural/animal biotechnology (e.g. plant diagnostics); industrial biotechnology (e.g. biotechnologically derived chemicals); biosensors; biotechnology-related research and production equipment.

2. 1993 data.

Source: European Venture Capital Association, EVCA Yearbook 1995, Brussels.

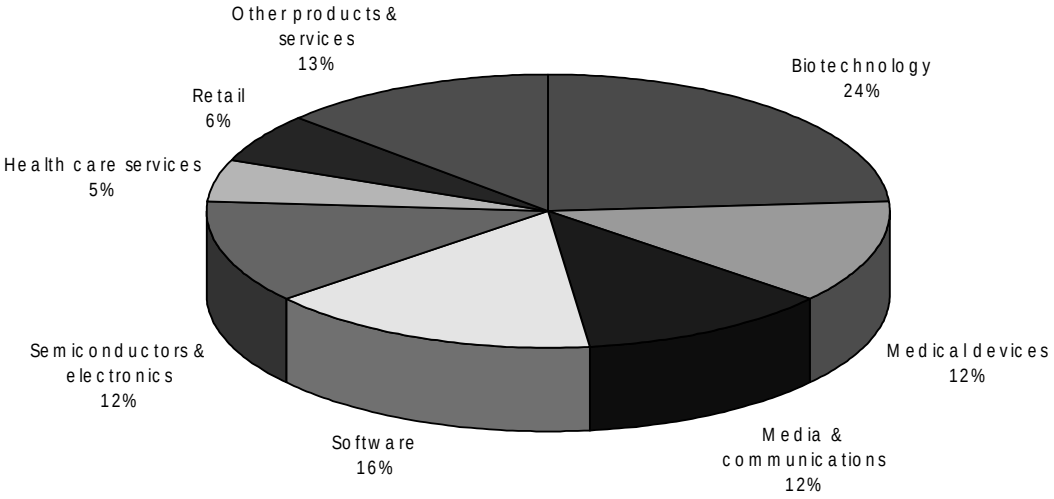
Venture capital is not readily available in Japan, and the vast majority of Japanese venture capital companies belong to large banks and brokerage houses. Most of the available capital is therefore heavily concentrated in the banking sector. Indeed, because the introduction of biotechnology in the Japanese industry is taking place through innovation within existing business sectors (e.g. pharmaceuticals), or by diversification into new businesses (e.g. bioinformatics), funding has traditionally been assured through debt finance. Until recently, the Japanese tax system did not provide private investors with incentives to establish start-up companies (Venning, 1987).

Figure 4.6. **Sectoral distribution of venture capital investment in Europe, 1994**



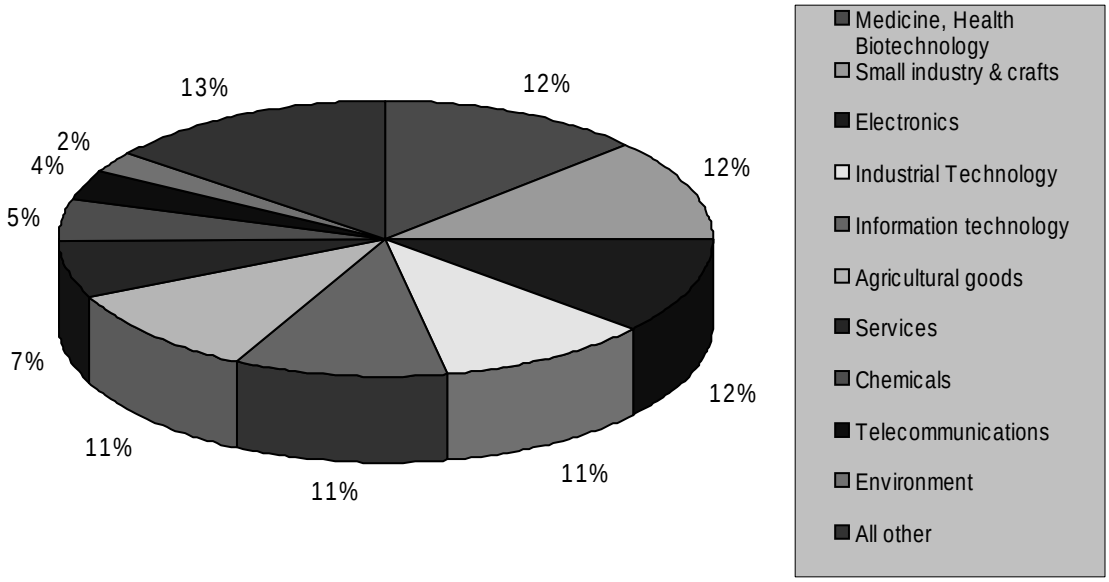
Source: European Commission, 1995.

Figure 4.7. **Venture capital distribution in the United States, 1993**



Source: B.I.O., Ernst & Young, 1995.

Figure 4.8. **Share of companies by sector benefiting from seed capital initiative in Europe, 1996**



Source: European Commission, 1996.

Over time, there has been a strategic shift in the availability and provision of venture capital. In the past, venture capital firms invested in biotechnology companies during the infant stages of a technology. Funds would be available as scientists reached one goal or another. If science proved slower or less predictable than anticipated, financing would cease. However, in 1993, the valuation of biotechnology companies dropped, and both venture backers and the public markets suffered. Venture firms have since changed the basis on which they decide to support biotechnology projects, which must be founded on mature science with identified disease targets and have a short-term revenue stream through side-line products or corporate clients (Deger, 1995). This either ensures a minimum return on investment or, at the least, reduces the riskiness of many projects. Considering that the supply of venture capital is determined by the willingness of individuals and institutional investors to allocate a portion of their investment portfolios to venture capital pools, performance is quite important and is associated with the risk incurred.[25] Biotechnology companies must therefore be in a position to prove that they possess a group of promising products rather than a single one, so that if one product fails to perform satisfactorily in the trials, other products can take its place, i.e. there must be a condition of competitive self-reliance.

Public stock offerings

Public stock offerings were a very popular method of financing biopharmaceutical companies in the past (49 per cent of total funds in 1986, see Figure 4.2), but their relative importance has declined over time (see Figure 4.3). Companies continue to have a strong focus on human health-care products, largely because capital availability has been greater for pharmaceuticals than for food or agriculture, owing to the prospect of greater market reward (Office of Technology Assessment, 1988). It is not surprising, therefore, that most discussions about the financing of biotechnology tend to be skewed toward companies working in human therapeutics and diagnostics.

In the United States a number of (now) larger companies, such as Genentech and Amgen, were able to go public, raise substantial amounts of cash, and successfully commercialise their products. For example, the top 25 US biotechnology companies were able to raise about $3.7 billion from the issue of common stock and warrants between 1987 and 1992 (General Accounting Office, 1994). The trend has continued upwards and in 1995 only, 61 US companies raised $2.1 billion in stock offerings (Nature, June 1996). In Europe, capital markets are smaller in size and have proved less willing to see increased public stock offerings for biotechnology companies.[26] This has led many European companies to seek listing in the United States, under NASD (National Association of Securities Dealers), NASDAQ, or the New York Stock Exchange (NYSE). A large number of European companies have already done so (EVCA, 1994).

However, the decision to go public is not devoid of problems, and the decline of the relative importance of this method of financing, reflects, among other things, the volatility of the biotechnology/biopharmaceutical sector. Biotechnology companies' share prices are directly related to product status in the regulatory process. Very often, profit-taking follows a period of investor concern or temporary setbacks in clinical trials or the final approval of the product by regulators. If approval is delayed, stock prices plummet. When biotechnology/biopharmaceutical companies go public, their operating results should provide an indication of future potential. In any case, most of these companies often face the speculative attacks inherent in the market.[27]

In addition to volatility, start-up biopharmaceutical companies that have raised large amounts of cash in private capital markets face pressures from investors who expect early returns and can force the company into producing them by diverting their resources into contract research for other companies or the production of non-pharmaceutical or non-innovative products. In such a case, the company may not be able to carry out R&D on genuinely innovative products or will take longer to do so.

Companies have tried to avoid such a situation and provide early revenue from their own innovative products. They use two basic kinds of strategies. In one, the company attempts to maintain its independence and support itself with a revenue stream from products it obtains, for example, by acquiring an operating unit. In this case, the company maintains its independence and acquires expertise as well as the ability to produce products rapidly. In the other, companies form some sort of alliance and lose a measure of independence. Most often, the alliance is between a small start-up biotechnology company with a very promising R&D pipeline but little capital, and a large established pharmaceutical company which can provide marketing and development expertise in exchange for an interest in a potentially innovative product (Table 4.3).

Table 4.3. **Biotechnology commercialisation strategies**

Strategy	Per cent of total number of deals
Product swap	3
Generic product line	2
Licence in late-stage technology	2
Acquire operating unit	18
Pharmaceutical to biotechnology strategic partnership	51
Biotechnology to biotechnology strategic partnership	11
Partial acquisition	4
Combine resources	8

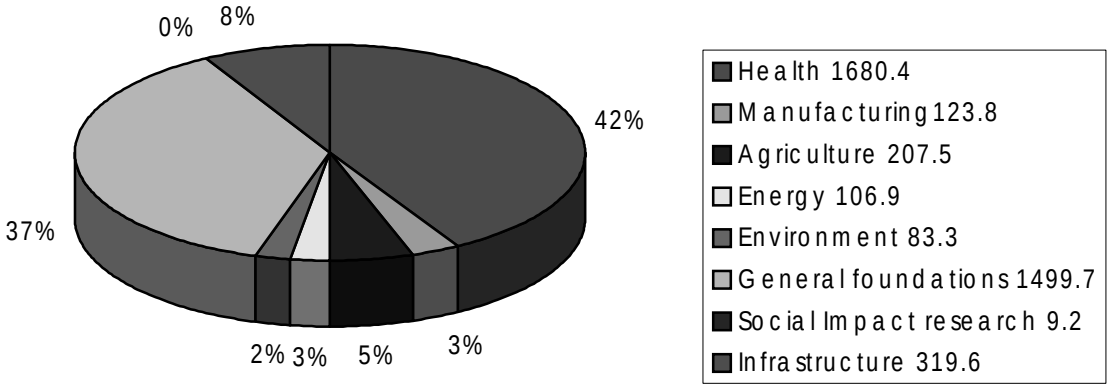
Source: Sarah Rickwood, "Global Pharmaceuticals", *Financial Times Report*, 1993.

Public funding

Public institutions are a crucial source of discovery and knowledge in Europe, the United States, and Japan. The contribution, however, of public sector research (PSR) to the creation of knowledge in the above geographical areas is subject to the availability of resources.

It is perceived that publicly funded European research lacks critical mass because it is very fragmented and not viewed as a single entity, unlike publicly funded US research (Senker, 1996). Countries in Europe pursue their own agendas and relatively little coordination exists between activities. Consequently, a duplication of the research effort and a waste of valuable resources cannot be avoided. An additional problem of European PSR is that it is undercapitalised, resulting in relatively poor quality facilities and infrastructure, when compared to US laboratories. The European Union's efforts to support life sciences have recently increased, and the European Commission, through its Framework Research Programmes, has attempted to create a common agenda of research themes across the European Union as well as encourage the mobility of researchers from one Member State to another. Biotechnology and Biomedicine and Health have been allocated a total of ECU[28] 588 million and ECU 358 million respectively for the whole of the 1994-97 period. This hardly compares with the $4 billion that was requested by the US President for biotechnology for 1993 (see Figure 4.9).

Figure 4.9. **US biotechnology proposed public research budget by area, 1993 (in % and US$ m)**



Source: *Genetic Engineering News*, March 1992.

The US government spent over $12 billion in the life sciences in 1994 (Biobusiness, June 1996), well above the total spending of the other G7 countries in the same field. It systematically sponsors research in most areas of biomedicine and biotechnology, either through public institutes, particularly the National Institutes of Health (NIH) or universities, thereby promoting university-industry collaborations. Hence, this is one of the reasons behind the success of US biotechnology companies. The Office of Technology Assessment has estimated that the federal government funds more than half of all biotechnology-related research (Office of Technology Assessment, 1988). These very substantial funds have led to the development of high-quality laboratories which, in turn, have attracted well-qualified and experienced scientists. In addition, the United States has a decentralised research system, and several cabinet-level departments have internal research divisions responsible for the research needs of their particular missions, such as improved public health (Office of Technology Assessment, 1991). Strong domestic

support of basic research and the availability of a framework for the transfer of technology from public institutions to the private sector for commercial exploitation, can lead to a strong domestic market structure, because it works against excessive (foreign) control over publicly sponsored research. In 1992, for instance, Sandoz unsuccessfully attempted to obtain first refusal rights on all R&D of the US-based Scripps Research Institute; as a result of concerns about excessive foreign control over US-sponsored research, a scaled-back agreement was reached in 1994 (Ansell and Sparks, 1996).

Japanese government support of life sciences has been significant and falls within the jurisdiction of several governmental agencies. The total funds dedicated to life sciences reached $1.2 billion in 1994. Biotechnology is supported by the Ministry of International Trade and Industry (MITI), the Science and Technology Agency, the Ministry of Health and Welfare, the Ministry of Education and the Environment Agency. In addition to Japanese companies' prowess in environmental biotechnology developments, Japan's environment agency has invested extensively in biotechnology-related pollution prevention controls.[29] Japan is also very keen to take a leading position in the relatively new field of functional genomics, which seeks to identify the function of the 95 per cent of the genes in the human genome whose function remains unknown. Despite the above developments, there is concern that the country is falling far behind in the commercial development of biotechnology. According to a panel of experts commissioned by MITI, the Japanese government needs to act fast if it hopes to catch up (Biobusiness, June 1996). A particular cause for concern is the shortage of researchers and venture-backed bioscience firms. For this purpose proposals have been put forward calling on the government to take the lead in constructing the technological infrastructure needed for basic research. That is, establishing access to biological resources, providing a means of collating biological resources and further promoting genome analysis.

Debt financing

As companies mature, debt financing becomes a means of finance which avoids giving up equity. A survey of US firms (Young, 1986) found that 13 per cent of the larger companies made use of bank loans, compared with 3 per cent of the small firms. According to another survey (SAGB, 1994), bank loans account for almost 20 per cent of finance for small biotechnology companies, compared with 14-16 per cent for large biotechnology companies (Figure 4.1).

For most biotechnology/biopharmaceutical firms, debt financing is a clear sign of maturity. As a company is obliged to service the debt it contracts almost immediately, it must have products on the market (or ready to be marketed) which would make loan repayments possible. Unless alternative methods of financing are not available, debt financing may not be desirable for companies that still require large amounts of cash to finance R&D (Office of Technology Assessment, 1988). This is the case in Japan, where companies rely more on loans due to the scarcity of venture capital; the opposite is true for US and European companies. Consequently, since debt financing is a sign of maturity and US companies have used it much more often than European ones, this is an indication of a stronger market structure in the United States than in Europe.

R&D limited partnerships

Research and development limited partnerships (RDLPs) have been an important funding mechanism for the biotechnology industry. In the United States, almost 25 per cent of the total financing of biotechnology has involved such partnerships (e.g. Merrifield, 1986; Office of Technology Assessment, 1988). They allow individuals or companies to invest in a firm's R&D and write off the investment as an

expense. Investors become limited partners and are entitled to royalty payments from future sales. The royalties are then taxed as capital gains. RDLPs provide start-up companies with a source of funding and transfer much of the risk of R&D for a new product to the limited partners who have acquired shares in the ventures. They are often seen as an alternative financing mechanism to venture capital companies and provide a vital source of capital for start-up companies.

4.4. Health policy and pharmaceutical pricing and reimbursement

Health care reform

OECD countries have carried out profound reforms in their health care systems in order to increase (macro- and micro-) efficiency, improve equity in access, equity of outcome, and patient choice (OECD, 1994*a*). At the same time, most OECD governments are faced with the escalating costs of health care, which seem to be rising faster than Gross Domestic Product (GDP). Various reasons have been put forward for the increase in health care costs and these include increased coverage, the growth in medical technology, variable practice patterns and the ageing population (Abel-Smith, 1996). The need therefore to increase the efficiency of the health service for a given amount of resources and to contain the rate of growth of health expenditures has become top priority in most OECD countries, particularly in those where health systems are financed by taxation or social insurance.

In the United States, although health care is privately provided and financed, there is recognition that spending on health is almost twice as much compared with other OECD countries, reaching 14.9 per cent of GDP in 1995. The major trend in health care provision in the US concerns the rapid expansion of managed care since the beginning of the 1980s. There has been a considerable increase in the managed care enrolment which reached approximately 90 million in 1992, compared with less than 10 million in 1980 (General Accounting Office, 1994).

Today, managed care in the United States has moved away from attempts to minimise costs by reducing the amount of hospital care and imposing barriers to access to practitioners; current policies encourage control of resource intensity in the use of clinical services while improving consumer satisfaction (Mossialos, Kanavos and Abel-Smith, 1997). For example, integrating the financing and delivery of care through contracts with selected physicians and hospitals; managing patient care through aggressive contracting or utilisation controls; controlling costs by modifying doctors' behaviour through the use of clinical guidelines; restricting the access of the insured population to physicians not affiliated with the managed care plan; and contracting with, or employing more primary care doctors and fewer specialists, with primary care physicians assuming a broader role (British Medical Association, 1995; Iglehart, 1994; General Accounting Office, 1996).

Within the European Union, Member States have been moving towards the introduction of overall budgets for health services or specific components thereof (budgets for hospitals and for pharmaceuticals), and towards more informed decisions (practice guidelines, evidence-based medicine, more explicit use of pharmacoeconomic studies in the decision-making process). Twelve Member States have established overall budgets for health services; budgets have also been allocated to parts of the health service, for instance hospitals in France and bed-day quotas in Belgium (Mossialos, Kanavos and Abel-Smith, 1997). Additional reform trends include the separation of purchasers from providers, the attempt to create internal market competition by, e.g. introducing price competition between providers; a shift towards capitation payments for first contact doctors; monitoring what doctors authorise; and further developing alternatives to hospital care (Mossialos *et al*., 1997; Robinson and Le Grand, 1994; Saltman and von Otter, 1995; Le Grand and Bartlett, 1993; Glennerster *et al*., 1994; Alban and Christiansen 1995;

OECD, 1994*a*). The wider use of practice guidelines, medical references, evidence-based medicine and economic evaluation indicate a shift towards more informed choices in health care delivery.

Additional fiscal pressures are apparent in the EU Member States within the short- to medium-term. Policy priorities throughout the European Union include the control of inflation and macroeconomic stability, through the reduction of budget deficits and overall debts. The need to meet the Treaty of the European Union (TEU) convergence criteria has compounded this effect and is expected to influence decisions in all areas of public policy, including health.

In the rest of the OECD countries health sector reform has also been on the agenda with most efforts focusing on three main directions: firstly attempts to improve micro-efficiency, particularly in the hospital and ambulatory sector; secondly to enhance geographical equity and equity of outcome; and thirdly to contain the ever increasing costs of health care (OECD, 1994*a*).

As pressures to contain costs continue, governments may find that increasing microeconomic efficiency is not enough to reconcile the demand for more health care with limited budgets; therefore, choices about priorities may be necessary (Dunning, 1996; Klein *et al*., 1996). A number of countries have developed methodologies for priority setting and establishing a package of services to be collectively financed (Abel-Smith *et al.*, 1995). Similar examples exist in the United States (Eddy, 1991).

Pharmaceutical pricing, reimbursement and cost containment

Pharmaceuticals comprise a substantial proportion of total health care costs. The share of pharmaceuticals in total health spending ranged from 10 per cent to 27 per cent in OECD countries in 1994 (Table 4.4). Being part of the health budget, governments constantly check the evolution of pharmaceutical expenditure. Public authorities' interest lies in the provision of safe and efficacious medicines at an affordable cost. Yet, pharmaceutical spending has been rising faster than total health spending in many OECD countries over the 1980-1994 period and that has sparked a series of pharmaceutical cost control measures by all OECD governments, with the exception of the United States. The measures employed largely depend on the organisation and financing of health care systems. Cost-containment measures for pharmaceuticals seek to influence doctors' prescription patterns and make both doctors (supply side) and consumers (demand side) more cost-conscious. Strategies aimed at the whole market have also been developed. Table 4.5 illustrates the main approaches to pharmaceutical cost containment introduced in OECD countries in the last decade.

The control of pharmaceutical expenditure is primarily through pricing and reimbursement policies. Most OECD governments directly influence prices by determining their level and by setting the level of reimbursement. There are few exceptions to this rule: in the United States, the pharmaceutical industry sets prices freely without any government intervention or control. In the United Kingdom, prices are set freely in the market and the only limitations are the profits of the pharmaceutical industry on sales to the British National Health Service according to the provisions set out in the Pharmaceutical Price Regulation Scheme (PPRS) and a negative list which excludes products from reimbursement. In Japan, although prices are set freely by the industry, they are subjected to periodic price reductions by the government. In Germany and Denmark, prices of new products are set freely in the market, but a reference price system exists for generic products; Denmark has a positive and Germany a negative list.

Table 4.4. **Pharmaceutical expenditure as % of total health expenditure in OECD countries, 1980 -1994**

Country	1980	1985	1990	1991	1992	1993	1994
Australia	7.9	8	9	9.6	9.6	11	n/a
Austria	12	11.7	11.1	10.8	10.5	10.6	10.2
Belgium	17.4	15.7	15.5	15.5	16.3	17.5	17.5
Canada	8.9	10.5	13.5	13.9	14.4	12.3	12.7
Denmark	9.1	9.6	8.9	10.6	10.2	10.8	11.1
Finland	10.7	9.7	9.4	9.9	10.8	11.9	12.8
France	15.9	16.2	16.7	16.7	16.6	16.8	16.5
Germany	18.7	19.7	20.5	20.2	20.8	18.9	n/a
Greece	34.8	28.9	24.1	22.7	23.5	n/a	n/a
Iceland	15.9	16.6	15.5	14	15	14.3	15.1
Ireland	11.2	10	13.6	13.2	13.2	12.6	11.5
Italy	13.9	17.9	18.4	17.9	18.1	18.1	17.4
Luxembourg	14.5	14.8	15.9	15.6	n/a	n/a	n/a
Netherlands	7.9	9	9.5	9.5	10	10.5	10.7
New Zealand	n/a	14.6	14.1	14.2	13.8	17	n/a
Norway	10	10.2	10.4	10.8	n/a	n/a	n/a
Portugal	19.9	25.4	24.9	24.3	24.7	25.6	25.2
Spain	21	20.3	17.8	17.9	18.2	n/a	n/a
Sweden	6.5	7.1	8.2	8.9	11.4	12.5	13.2
Switzerland	15.2	8.9	8.2	7.8	7.4	n/a	n/a
Turkey	n/a	13.2	26	n/a	n/a	n/a	27
United Kingdom	12.8	14.1	13.8	14	14.5	15.3	15.2
United States	8.7	8.7	8.6	8.6	8.6	8.4	8.3

Source: OECD Health Data Base, 1996.

Table 4.5. **Overview of national pharmaceutical price control and other cost containment methodologies, OECD countries, 1998**[30]

	Country
A. Supply-side strategies	
1. Fixed budgets for doctors	UK (fundholding until 1998; Primary Care Commissioning Groups from 1999)
2. Indicative budgets for doctors	UK (non-fundholding), Germany
3. Fixed budgets for drug spending	Italy
4. Practice guidelines	France, UK, Canada
5. Cost-effectiveness guidelines	UK
6. Positive and/or negative lists	All OECD countries, except US
7. Active support of generic competition	UK, Germany, the Netherlands, Denmark
8. Prescription auditing	UK (systematically); other OECD (not systematically)
9. Capitation or salary as dominant methods of paying first contact doctor	Most OECD countries, except Japan, Germany, France
10. Disease management	US, experiments in France, UK
11. Paying pharmacist a fixed fee or regressive margin	UK, and the Netherlands (flat rate), France and Germany (regressive margin)
12. Pharmacoeconomic studies to determine reimbursement level	Australia, Canada (Ontario), France (not explicitly required), Belgium (not explicitly required), Italy, Sweden, Finland
B. Demand-side strategies operating on patients	
1. Cost sharing	All OECD countries, except the Netherlands
2. Health education programmes	The Netherlands, UK
3. Developing a market for OTC products	Most OECD countries
C. Strategies aimed at the market as a whole	
1. Price controls	All OECD countries, except USA, UK, Germany, Denmark, Japan (initially)
2. Profit control	UK
3. Reference pricing	Germany, the Netherlands, Sweden, Denmark, Italy, New Zealand, Canada (Ontario and British Columbia), Czech Republic, Japan
4. Average pricing	Italy, the Netherlands
5. International price comparisons	Greece, Ireland, Luxembourg, the Netherlands, Portugal, Spain, Sweden
6. Periodic price reductions	Japan
7. Industry contributions when pharmaceutical budgets are exceeded	France, Spain
8. Ceilings on promotional expenditure	France, Spain, UK
9. Development of parallel imports market	UK, Germany, the Netherlands, Denmark

Source: Adapted from LSE Health, 1997.

Historically, most pharmaceutical cost control measures have focused on price, and this is still the main focus. Apart from traditional methods of pricing pharmaceuticals, based on product cost details provided to the authorities by pharmaceutical companies, there is currently a trend towards comparative

pricing and this has taken various forms: first, reference pricing, where a single price is established for a group of products that are considered interchangeable. A product may be priced freely in the market, however, a reference price is determined as the maximum price at which the government will reimburse (LSE Health, 1995). Second, average pricing, according to which the recommended price in the market is developed by calculating the arithmetic mean of the "standardised" national prices in other selected markets. Third, international price comparisons, where governments, in determining the price of a product in the home market, take into account neighbouring countries' (or selected countries') prices for the same product. Fourth, promotion of generic products and generic substitution, namely prescribing and dispensing off-patent products, where such alternatives exist, has emerged as a favourable form of cost containment, although its introduction is closely related with incentives for prescribing doctors (such as the fundholding scheme in the United Kingdom, where GPs are allowed to keep any saving made on their budgets), or penalties to prescribing doctors (as is the case in Germany, where the deficit in a fixed pharmaceutical budget will be met by the doctors themselves) and incentives to pharmacists (pharmacists will dispense generically if they are paid by a flat rate or a regressive margin and would have no incentive to dispense generically if remunerated on a percentage basis).

Other cost control measures that have been introduced in most OECD countries include cost sharing, where patients contribute a part of the price of drugs they consume, either on a percentage basis, or according to the pack size, or, even by imposing a flat co-payment rate, which applies to all drugs prescribed; limited lists, which can be positive (i.e including all the drugs that are reimbursed by the health service) or negative (drugs that cannot be reimbursed); ceilings and taxes on pharmaceutical promotion expenditure; and delisting of medicines from prescription-only (POM) status, to over-the-counter (OTC). A number of countries use performance indicators (exports, conduct of R&D locally, employment, clinical trials), as an indirect means for pricing pharmaceuticals.

A recent trend in many European countries, is the introduction of fixed budgets for pharmaceutical expenditure as well as fixed revenue budgets for the pharmaceutical industry; if these budgets or target revenues are exceeded, the pharmaceutical industry will return the excess amount. The escalation of health care costs and the need to reduce the rate of growth in pharmaceutical spending have also given rise to an increased demand for economic evaluations of pharmaceutical products, and in some countries, to the development of guidelines. While only few countries have explicitly adopted cost effectiveness guidelines for the pricing and financing of pharmaceuticals [Australia and Canada (in Ontario and British Columbia)], cost effectiveness studies are increasingly required by a number of governments for consideration (LSE Health, 1997). Furthermore, cost-effectiveness studies have also started to make their way into medical practice to encourage a more rational process of prescribing. Finally, in regulated markets and in view of the increase in the availability of new and expensive (biotechnology-derived) products, governments tend to earmark funds for the reimbursement of such products, or allow their consumption on a selective basis.

Despite the variety of measures introduced over time in OECD countries, very few have succeeded in curbing pharmaceutical expenditure more than temporarily (LSE Health, 1995; Abel-Smith and Mossialos, 1994). It seems that most of these measures were introduced on an *ad hoc* basis and did not constitute governments' conscious efforts to curb pharmaceutical expenditure consistently, or at least stabilise it. Cost-sharing measures have had no long-term impact in the United Kingdom and France, partly owing to extensive exemptions, while the introduction of reference prices in Germany led to increased rather than diminished spending on pharmaceuticals, as the industry increased considerably the prices of drugs not included in the reference price system. In addition, very little is known about the effectiveness of positive and negative lists, while policies to encourage prescribing and dispensing of generic drugs must also be coupled with incentives both to GPs (as in the United Kingdom's GP

Fundholding Scheme) and to pharmacists (payment by flat fee or percentage margin). Price controls and price ceilings, on the other hand, encourage consumption and have a negative impact on corporate R&D.

Of course, cost containment in the pharmaceuticals sector is not simply a matter of balancing the health budget. It has implications for the development of a high-technology industry, with very high value added, highly paid jobs, and high growth. Therefore, policy makers need to decide on measures that effectively contain expenditure without damaging the research potential of pharmaceutical and biopharmaceutical companies. The European Union has pursued policy harmonisation in pharmaceuticals by adopting general directives for distributing, packaging, labelling, and advertising pharmaceuticals. It has not as yet done so for pricing and financing, areas which are still left to national governments.

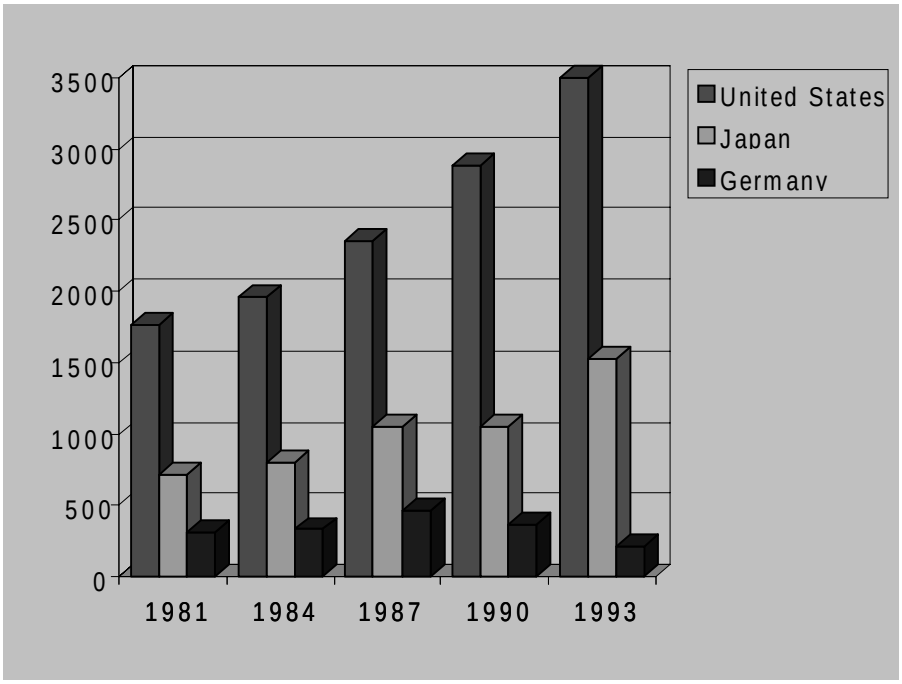
Clearly, health systems financed by taxation or social insurance face tight budget constraints[31], however, the need to meet budget constraints has to be balanced against the need for an effective industrial policy for the (bio)pharmaceutical sector, particularly in countries with (or seeking to create) a strong pharmaceutical industry. The UK Pharmaceutical Price Regulation Scheme (PPRS) achieves this goal. It is a profit-based scheme which has been in effect in various forms since 1957. It regulates the profits companies make from their sales to the National Health Service (NHS). The scheme does not cover exports of pharmaceuticals, or generic products, and operates at the level of a company's total business with the NHS rather than at the level of individual products, and measures profitability in terms of the return on the capital employed. For companies without significant capital in the United Kingdom, profitability is assessed on the basis of return on sales.[32] Under the system, a pharmaceutical company is free to determine prices for its products within the given profit margin; if profits exceed the margin, the company repays the profit in excess of a 25 per cent margin to the Department of Health. The PPRS is considered successful because it not only contributes to the existing UK industrial base but is also an important contributor to pharmaceutical inward investment.[33]

4.5. Intellectual property rights protection

Protection of intellectual property provides the temporary market conditions necessary to recoup the high costs of R&D and is therefore important to the pharmaceutical and biotechnology industries.[34] Drugs with new therapeutic potential depend on patent protection to capture and hold market shares. The pharmaceutical sector, more than any other industrial sector, regards patents as the most important form of appropriating and commercialising technology (Howells and Neary, 1995, Ch. 5; Wyatt *et al.*, 1985). Thus, patents are crucial to the competitive performance of pharmaceutical companies, and regulatory differences between countries in the treatment of pharmaceutical patents are seen by the (pharmaceutical and biotechnology) industry as important in shaping the overall competitive performance of the industry between countries.

The number of pharmaceutical patents originating from the United States and Japan has been rising over time (Figure 4.10). In contrast, the number of German patents has been declining in the past decade. While this is not conclusive evidence about Europe as a whole, it is an indicator of relative weakness in the European pharmaceutical industry, of which German pharmaceutical companies are a strong element. Similarly to the above trends, the share of European-held patents in the United States has declined from 29.8 per cent during the 1975-79 period to 24 per cent in 1990-94, while the shares of both US- and Japanese-held patents have risen over the same period (Table 4.6). This may indicate a more dynamic performance by both US and Japanese companies, or merely reflect differing practices between countries and companies.

Figure 4.10. **Pharmaceutical patents in the United States, Japan and Germany, 1981-1993**



Source: JPMA Data Book, 1995.

Table 4.6. **Trends in the distribution of US patenting in pharmaceuticals, 1975-1994 (in percentages)**

Country	75-79	80-84	85-89	90-94
Germany	11.1	10.4	9.7	7.8
United Kingdom	7.3	7.5	6.2	5.3
France	5.9	5.1	4.8	4.7
Italy	1.8	2.8	2.6	2.2
Netherlands	0.7	0.8	0.6	0.8
Denmark	0.5	0.4	0.6	0.8
Sweden	1.4	0.8	0.8	0.7
Belgium	0.6	0.8	0.6	0.6
Austria	0.3	0.3	0.4	0.4
Spain	0.3	0.1	0.3	0.3
Finland	0.1	0.1	0.3	0.2
Ireland	0.0	0.0	0.1	0.1
Greece	0.0	0.0	0.0	0.0
Portugal	0.0	0.0	0.0	0.0
European Union	29.8	29.3	27.1	24.0
Switzerland	3.6	3.3	2.3	1.9
United States	52.9	49.8	51.9	54.6
Japan	9.6	13.3	14.2	14.7
Other	4.0	4.3	4.5	4.8
Total	100.0	100.0	100.0	100.0

Source: LSE Health (1996), based on Science Policy Research Unit.

In terms of ownership of biotechnology patents by private companies, and in particular of ownership of human DNA sequence patents, US and Japanese companies are the largest holders, implying that they are also leading originators of knowledge in this field (Table 4.7). Public institutions are a crucial source of discovery and knowledge both in the United States and Japan. Through publicly funded R&D, US and Japanese institutions hold the lead in human genome patent ownership. By contrast, the absence of European institutions, with the exception of Institut Pasteur in France, is notable and quite alarming, since public institutions contribute significantly to the development of a considerable proportion of new molecules, as well as to the transfer of technology to the private sector, both in the United States and, though less so, in Japan.

Table 4.7. **Human DNA sequence patents granted worldwide. Ownership by public and private sector organisations, 1996**[1]

Company	Country of origin	Number of patents	Public institution	Country of origin	Number of patents
Takeda	Japan	63	US Department of Health and Human	US	28
Genentech	US	41	Services		
Immunex	US	23	University of California	US	13
Teijin	Japan	23	National Institute of Health	US	11
Hoffman La	Switzerland	18	University of Washington	US	11
Roche			University of Texas	US	7
Ciba-Geigy	Switzerland	16	Japan Foundation for Cancer Research	Japan	6
Suntory	Japan	18	New York State University	US	6
Sumitomo	Japan	16	Agency of Industry, Science &	Japan	5
Cetus	US	16	Technology		
Eli Lilly	US	15	Salk Institute	US	5
Shionogi	Japan	15	Pasteur Institute	France	5
Ashai	Japan	15			
Green Cross	Japan	15			

1. Includes all human DNA sequence patents granted world-wide. Where patent ownership is shared between two or more organisations, it is assumed that collaborators contributed equally. For the purpose of quantitative analysis, each party was therefore assigned an equal fraction of a patent.

Source: *Nature*, 4 April 1996.

There is a considerable difference between actual and effective patent life. The former is usually applied for prior to broad testing of the new molecule and consequently, several years are lost during clinical development. The term of effective patent life, namely the time companies have for exclusive commercial exploitation of their inventions, is thus reduced considerably. This is why the debate regarding the extension of the patent term is on the top of the agenda for many countries. In the European Union, for instance, patent protection for pharmaceuticals has been extended through the Supplementary Protection Certificate (SPC), introduced in 1993. Similarly, with the agreements signed at Marrakesh in April 1994, concluding the GATT "Uruguay Round" and establishing the World Trade Organisation (WTO), patent protection of pharmaceuticals and biotechnology-derived products was extended to 20 years within the WTO area, with the additional requirement that patent applications be published 18 months from the priority filing date.[35]

Intellectual property rights policy has been a major element of government-industry relations for the (bio)pharmaceutical sector. Several issues are involved in this debate; one is the continuing debate over the "first to invent" rather than the "first to file" approach taken in the United States. There are indications that the United States will eventually adopt the "first to file" approach. However, the US Patent Office was previously non-committal about the outcome (Burke and McGough, 1993; Kjeldgaard and Marsh, 1994; Miller, 1994).

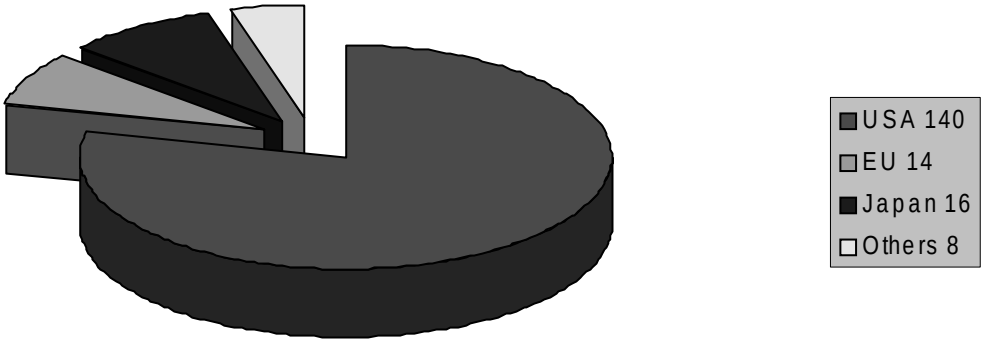
A second issue relates to differences across countries as to what concerns patentable subject matter. The European Patent Convention defines patentable subject matter as inventions that are susceptible to industrial application, are new, and involve an inventive step. Unlike the US law, which identifies patentable classes (i.e. process, machine, manufacture, and composition of matter), the European convention does not provide for precise classes of patentable inventions; it also stipulates that European patents cannot be issued for plant or animal varieties and essentially biological processes to produce plants or animals (with the exception of microbiological processes or the products thereof).

To date, the United States is the only country that has a stated patent policy regarding animals. US patent law is also noteworthy because it is generally neutral about the potential use of patented inventions. While transgenic animals are eligible for US patent protection, the "patenting life" issue was one reason why considerable delays have occurred in the introduction of the Directive on the protection of biotechnological inventions in the European Union.

After seven years of debate, the proposed EC Directive was rejected by the European Parliament in March 1995.[36] A revised proposal for a Directive was subsequently put forward in December 1995, taking account of the calls by the European Parliament for clarity and more precision, particularly in connection with ethical guidelines. The amended draft Directive sought, among others, to clarify the distinction between patentable inventions and unpatentable discoveries. The Commission submitted the new proposal to Parliament, which after extensive consultation and debate approved the Directive on the Patenting of Biotechnology Inventions on 12 May 1998. The approval took place after an amendment was incorporated which excludes the patenting and cloning of human embryos. The new legislation allows EU-based companies to patent genetically modified organisms and brings the EU in line with the US and Japan.

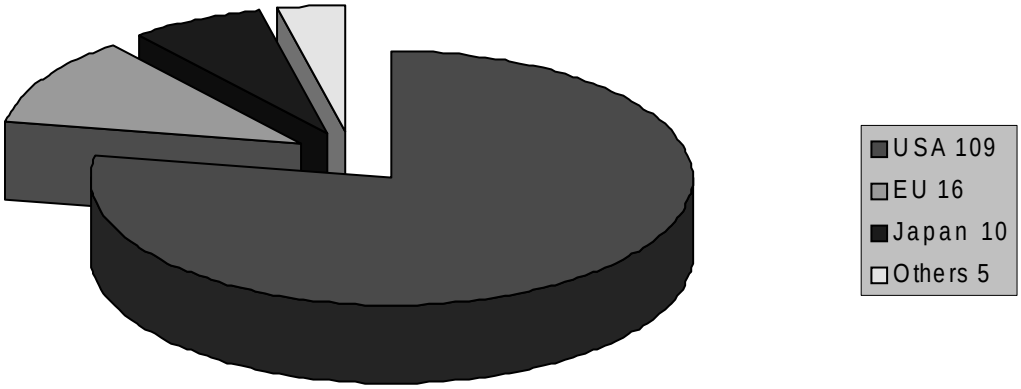
Opponents of the new legislation argue that it could stifle research by effectively allowing companies to "patent life". On the other hand, this legislation could encourage biotechnology firms to invest in biotechnology and prevent the current "brain drain" of European scientists and investment outflow to the US. Indeed, the initial failure of the European Union to provide adequate protection of biotechnology products may have had a negative impact on the further development of the biotechnology sector in general and biopharmaceuticals in particular. It is not surprising that over 85 per cent of European pharmaceutical investment is directed to the United States (Kanavos *et al.,* 1995), and biotechnology patent protection was a decisive factor in this capital outflow. This investment is channelled to the invention of novel processes or substances in US companies or/and universities. Figures 4.11 and 4.12 demonstrate the dynamism of US institutions as measured by the geographical distribution of patents in genetic engineering in 1992 and 1994; Table 4.8 summarises the most important biopharmaceutical developments in the United States by type of product over the 1989-95 period.

Figure 4.11. **Genetic engineering patents, 1992**



Source: PhRMA, 1996.

Figure 4.12. **Genetic engineering patents, 1994**



Source: PhRMA, 1996.

As a third issue, the lengthiness of the review of patent applications and action by patent offices is frequently cited as the primary impediment to commercialisation of biotechnology-related processes and products, since delays in obtaining a patent can slow efforts to commercialise a discovery. In Japan, for instance, it typically takes an average of six to seven years to issue a patent, compared to about 19 months in the United States. Another problem involves filing for protection in foreign countries. Under the Paris Convention, an applicant filing in one country has one year to file in other countries and obtain the benefit of the home patent date. Furthermore, the backlog of patent applications creates a large body of hidden knowledge, which cannot be publicly available until approved. As a result, an inventor may file an application, only to learn years later that the application is rejected because a previously filed application made the same claims or claims broad enough to encompass the claims made in the later application.

Table 4.8. **Biopharmaceutical products in development in the United States, 1989-95**

	1998	1995	1993	1991	1990	1989
Clotting factors	3	3	1	4	2	2
Colony stimulating factors	3	4	6	8	9	7
Dismutases	*	2	1	1	3	3
Erythropoietins	3	1	1	4	5	4
Gene therapy	38	17	1	*	*	*
Growth factors	21	11	9	11	7	2
Human growth hormones	5	7	4	7	5	3
Interferons	12	10	11	16	13	12
Interleukins	9	13	10	13	14	12
Monoclonal antibodies	74	69	50	58	41	25
Recombinant soluble CD4s	6	4	2	2	4	2
Tissue plasminogen activators	3	3	1	4	*	*
Tumour necrosis factors	*	1	3	2	4	4
Vaccines	77	43	20	18	15	13
Others	96	41	23	10	4	6
Total	350	229	143	158	126	95

* Category was not included in that year's survey.

Source: PhRMA, Biotechnology Medicines in Development, 1993, 1994, 1995, 1998, Washington, DC.

Other factors pertinent to the nature and scope of patent systems contribute to the creation of international differences. The costs associated with patent applications can be considerable, particularly for foreign applicants. Part of these costs are related to the translation of a patent application into the language of the country where the application is submitted, since submission in English is not allowed and/or must be accompanied by a version in the local language.[37] Companies also face difficulties in obtaining patents for pioneering inventions, defined as those involving important new technologies.[38] Practices of pre-grant opposition exist, whereby third parties can file opposition to patent applications which they believe should not be granted (pioneering inventions are often the target because of their high technological and commercial value[39]). Finally, there are side issues, such as licensing mechanisms (Heller, 1995; Vandergrift and Kanavos, 1997; see chapter by B. Pazderka: "Implications of recent changes in pharmaceutical patent legislation in Canada").

The adequacy of existing patent laws to protect inventions is a major concern for most biotechnology companies. Most patents issued in the biotechnology area concern processes, and can be crucial to the valuation of a company, especially if they involve a new process for making a known product. Again, protection of a process and the products that may emerge from it varies across countries. In Japan, patent protection is narrow in that an inventor or company must provide in their application the exact products or product types that will emerge from the invented process; if the same process is used by other companies for the derivation of a product which was not included in the initial patent application, the originator of the process will be unable to claim rights on this product. By contrast, in the United States there is no such requirement and the scope of a patent is broad, although this may result in a company holding exclusive rights to hundreds of products derived from a single process.

The emergence of biotechnology as an important field for patenting has resulted in a surge of litigation, as companies seek to enforce their rights against infringement and defend the patent grant in opposition or revocation proceedings. How the courts interpret biotechnology patent claims and how well companies protect patent rights abroad will be issues facing biotechnology companies in the years ahead. Uncertainty over patent rights will be costly and will affect the way many biotechnology-related companies structure R&D strategies. Until precedents are set in court rulings, predicting the outcome of patent litigation may be extremely difficult.

Orphan drug legislation

The existence of orphan drug legislation encourages research in disease areas for which no cure or treatment exists, which are classed as rare[40] because of their low incidence in the general population, such as Gaucher's, Huntington's and cystic fibrosis, and for which the likelihood of recouping R&D expenditure for developing treatment is very low. Legislation in various OECD countries offers incentives to researchers in the academic or business communities.

In the United States, the Orphan Drug Act of 1983 provides financial incentives to encourage pharmaceutical manufacturers to develop new orphan drugs. These incentives include exclusive marketing rights for seven years, tax credits for clinical research, and other benefits. According to the National Organisation for Rare Disorders (NORD), the law has been very successful, and many important new therapies have been or are being developed (see chapter by Patrick Philipon, The Orphans of the Health Care System).[41] In addition, the FDA's Office of Orphan Products Development (OPD), encourages, through the OPD Grants Program, the clinical development of products for use in rare diseases or conditions, usually defined as affecting fewer than 200 000 people in the United States.[42] The products studied can be drugs, biologicals, medical devices, or medical foods.

Japan enacted such legislation in 1985, specifying that "orphan drug status" is granted to products which appear to be of great therapeutic value in cases where fewer than 50 000 patients are affected in Japan.[43] The holders of orphan drugs benefit from a number of incentives, including R&D support, tax relief on R&D expenditure, and reduction in the corporate tax rate.

Within the European Union, the initial debate on the adoption of orphan drug legislation[44] has led to the development of a legal framework in which research into rare diseases is being enouraged[45], following the drafting of a regulation proposal in August 1996.[46] The draft regulation is still in the process of consultation and defines diseases as rare if they have a generally accepted prevalence in total Community population of less than five per 10 000. The new proposal puts forward an action plan, covering the 1999-2003 period. The total budget proposed for the financing of research activities of the public and/or private sector is ECU 1.3 million for the first year of the programme, with funding for the remaining four years of the programme to be determined in detail after the establishment of the future financial perspectives. It is unknown when the current draft regulation will eventually become legislation, but this is expected to occur when issues relating to the funding of research activities have been clarified between the relevant institutions.

Although the regulation of orphan drugs still remains unsettled, the research programmes initiated by the European Commission, particularly the Fourth Framework Programme currently in operation, specifically identify rare diseases and orphan drug research as an area for action in order to increase R&D on rare diseases (Fracchia and Haavisto, 1996). In Europe, assuming legislation to encourage research exists, universities and research laboratories could provide the initial stimulus for such research. Following the US example, universities rather than private companies could be the main beneficiaries of

the available grants scheme.[47] In addition, a research project need not necessarily be designated as "orphan" in order to benefit from the grant scheme. Policy makers could also set research priorities and, in this way, encourage R&D in areas involving specific social needs. This is happening in the United States, but there are no published priorities and the policy remains at the discretion of the Office of OPD. [48]

4.6. Support for research and development

The United States

The United States has a comprehensive set of policies in support of the R&D activities of the pharmaceutical/biotechnology sector (Table 4.9). Most of these policies are indirect; there is no evidence of direct subsidies. The focus is therefore mainly on the conduct of basic research. The government provides research grants to academic researchers and also performs in-house research at the NIH on which the pharmaceutical industry builds. It has been estimated that approximately 60 per cent of the NIH's total R&D budget has relevance for the pharmaceutical industry (Scherer, 1995). The impact of the US R&D policies on the pharmaceutical industry is quite dramatic: a survey revealed that 27 per cent of a sample of new products could not have been developed without previous academic research, and development of 29 per cent of the remaining new pharmaceutical products was significantly facilitated by academic research (Mansfield, 1991).

Table 4.9 **R&D tax incentives in selected OECD countries**
Summary of policies

Country	R&D tax credits	Other subsidies
Belgium		-Special deductions for R&D personnel -Exemptions from tax of distributed profits
Canada	a) at Federal level: 20% incremental up to 35% b) At province level, additional credits	-Training grants and subsidies and training tax credits; measures differ according to provincial policies
France	50% incremental	R&D grants in selected industries[1]
Germany	Tax credits on R&D equipment	Tax grants on capital investment
Ireland		Tax exemption for royalty income from innovative R&D done in Ireland
Japan	20% incremental	-Trade policies beneficial to R&D equipment[2] -R&D grants for selected technologies
Netherlands		Special allowances for R&D capital and labour
Spain	15% on R&D 30% on R&D equipment	
Sweden	30% incremental	Special allowances for R&D salaries
United States	20% incremental on R&D 20% incremental on university-based basic research 50% of clinical orphan drug R&D	
United Kingdom		Deduction of R&D facilities and machinery

1. These subsidies are provided directly to the qualifying firms; they are not administered through the tax code.

2. Beyond expending of current R&D expenditures.

Source: Adapted from United States Office of Technology Assessment, 1993.

Additional policy tools include the provision of generous grants for training and various tax advantages. Advantages specific to the pharmaceutical industry include the possibility to write off R&D expenditure as part of the industry's costs, the availability of tax credits, and a specific tax credit that allows companies to claim substantial exemptions from income tax liability by conducting manufacturing activities in certain US possessions, notably Puerto Rico (Office of Technology Assessment, 1993).

The R&D effort in the United States is implicitly assisted by technology transfer arrangements which apply to Federal laboratories, and the Federal Government has strived to promote collaboration between government-sponsored institutions and the private sector. Already since 1950, the Federal Government has explicitly required Federal employees to report inventions created during the course of their work to the Federal Government. Further steps involved making the transfer of Federal technology to the private sector a national policy and duty of Federal laboratories, through the enactment of the Stevenson-Wydler Technology Innovation Act in 1980.[49] Additional legislation in 1984 directed the US Department of Commerce to issue regulations governing the licensing of new technologies developed in Federal laboratories.[50] A subsequent legislative development[51], introduced the establishment of formal co-operative research and development agreements in which a Federal laboratory provides personnel, services, facilities, equipment and (non-financial) resources, and a non-Federal party provides funds, personnel, services or other resources for R&D[52] (Office of Technology Assessment, 1993).

Additional legislation has been enacted which has facilitated the successful commercialisation of technology by academic institutions[53] : universities, non-profit organisations and SMEs are allowed exploitation of inventions from federally sponsored research and, in return, are required to share any royalty income from patents with the scientists responsible for the invention. The law also encourages universities to make efforts to seek patents on discoveries and to look for licensees for those patents; the holders of patents must also give licensing preference to small businesses and companies that in the United States agree to manufacture any products resulting from the license.

Japan

Japan's industrial policy for pharmaceuticals and biotechnology evolved very rapidly during the 1980s, particularly after the Ministry of International Trade and Industry (MITI), in its "Next Generation Project", recognised biotechnology (along with microelectronics and new materials) as a key technology for the future. MITI's 1988 White Paper on Industrial Technology recognised that although Japan's investment in R&D was among the highest in the world, most of this investment came from the private sector[54], with the result that it was largely directed to applied R&D, to the detriment of more exploratory research. In its policy recommendations, therefore, MITI stressed that the government should take a more active role in promoting basic research.

In response, various government agencies support biotechnology research relatively generously (funds in excess of $2 billion were spent on biotechnology in 1995).[55] The Drug Organisation of the Ministry of Health and Welfare (MHW) is instrumental in supporting R&D activities by facilitating private sector R&D activities in both basic and applied research, as well as the establishment of research infrastructure (Table 4.9). In basic research, the Organisation can contribute up to 70 per cent of a company's research expenditure by purchasing stock. In applied research, it provides up to 70 per cent of expenditures for technical developments expected to lead to important health and medical solutions (for more detail, see Organisation for Drug ADR Relief, 1995).

The Japanese government also provides certain tax incentives for high-technology industries (Yuan and Dibner, 1990), including biotechnology. First, 20 per cent of R&D expenses over the highest cost

incurred in the past can be deducted from corporate tax (to a maximum of 10 per cent of corporate tax). Second, up to 7 per cent of the cost of acquiring assets or R&D in fundamental technologies can be deducted (to a maximum of 15 per cent of corporate tax). Third, up to 6 per cent of the cost of research can be deducted by SMEs (to a maximum of 15 per cent of corporate tax). Moreover, the financing of new facilities for either R&D or production can be arranged through the Japan Development Bank or through the Small Business Finance Corporation. Projects eligible for these loans are: first, the cost of acquiring special buildings and facilities to improve R&D; second, construction of demonstration plants and trial manufacture of machinery and equipment in order to develop commercial products; third, construction of production lines and development of heavy machinery for commercialising new products. The loans can cover up to 50 per cent of eligible construction costs for a period of up to 15 years.

Finally, towards the end of the 1980s, a series of joint research projects were launched in which the MHW supported the creation of a venture capital company formed by two or more Japanese pharmaceutical companies (JBA, 1996). It aimed to establish two or three such companies every year, so that eventually there would be as many as 20 companies active in different areas. The objectives of this programme were to encourage co-operation between competing pharmaceutical companies, encourage university-industry collaboration, and create an environment in which start-up biotechnology companies could obtain funding.

The European Union

In addition to the initiatives taken by national authorities, the European Commission has promoted a number of research programmes in the field of biotechnology. European Community biotechnology programmes began with the Biomolecular Engineering Programme (BEP), which disbursed ECU 15 million in support of basic research from 1982 to 1986. Although funded by the European Commission, it was not a trans-national programme. Rather, through competitive grants, BEP supported individual research groups performing isolated projects within the respective EC member states. Funding amounted to 50 per cent of project costs.

BEP was followed in 1986 by the four-year Biotechnology Action Programme (BAP), which differed from BEP in several ways. First, it focused on pre-competitive research emphasising the development of novel processes. Second, it supported trans-national co-operation by requiring groups from more than one EC member state to participate in each project. Third, through its training stimulation scheme, it encouraged scientists to work in EC laboratories outside their native countries. Finally, it enjoyed a generous budget of ECU 55 million, over four years (1985-89), subsequently increased to 75 million.

The Biotechnological Research for Industrial Development and Growth in Europe programme (BRIDGE) was planned for 1990 through 1993. Its research areas included information infrastructure and cellular biology. It had a budget of ECU 100 million. BRIDGE's objectives were to further strengthen industrial applications of biotechnology and to enhance trans-national research. To this end, it included projects focusing on providing a link between basic and applied research. In addition, two EC agro-industrial R&D programmes support biotechnology. The European Collaborative Linkage of Agriculture and Industry through Research (ECLAIR), had a four-year budget of ECU 80 million and aimed at improving the integration of farm activities with upstream (supply) and downstream (processing) industries. The related Food-linked Agro-Industrial Research (FLAIR) programme aimed at improving food quality, safety, and diversity rather than productivity. Funding for this project amounted to ECU 25 million. Agro-industrial R&D funding was substantially increased in subsequent programmes.

The European Research Co-ordination Agency (EUREKA) was originally created in 1985, purportedly in response to the US Strategic Defence Initiative (SDI). It has since evolved into a co-ordinated agency, linking advanced technology projects carried out by European industry (both within the European Union and with members of EFTA). Although biology was not an initial priority, it has become one.

Finally, the European Commission's Fourth Framework Programme (1994-97), has made special provisions in the identification of research priorities and in the funding of research in biotechnology, biomedicine, and health, particularly through its BIOTECH and BIOMED2 research programmes, administered by the Directorate General for Research (DG XII). Additional initiatives include the setting up of a task force for vaccines, with the mission of establishing priorities in vaccine development. The Commission expects significant progress from a number of priority integrated actions, merging national and Community efforts. The EU programmes on biotechnology aim at promoting broad rather than reductionist approaches and the integration of disciplines, rather than excessive specialisation. European institutions do not have competence over direct taxation[56] and therefore cannot institutionalise a tax policy at the EU level. Such policies are initiated by the individual Member States (Table 4.9), which often compete with each other for the provision of tax breaks, credits or the overall level of corporate and personal taxation (Kanavos *et al*., 1995)**.**

Canada

In Canada, support of R&D takes place at both the Federal and the Provincial levels. The federal government provides credit up to 35 per cent for funds spent on qualified R&D activities. The highest credits are available to Canadian Controlled Private Corporations (CCPC), whereas lower credits are available for non-CCPCs. The previous government strategy of using low-interest loans to support the biotechnology industry has now been modified to a strategy which focuses its financial assistance on encouraging innovation as a way of achieving the government's economic agenda, particularly through the promotion of R&D alliances, networking, training and entrepreneurship.[57]

The federal programmes aimed at supporting the innovative capacity of the biotechnology industry in Canada are supplemented by efforts at the provincial level and also include a number of non-government activities (KPMG, 1994). The province of Quebec leads the way in terms of financial incentives to biotechnology companies; these incentives include grants and tax incentive benefits up to 40 per cent of funds spent on R&D, tax concessions to investors wishing to invest in companies listed in the Montreal Stock Exchange, and training grants. Ontario is more directed towards venture backing of biotechnology R&D. In parallel, there is a 10 per cent refundable tax credit for SMEs carrying out scientific research and experimental development in Ontario, commencing in 1995. Finally, while some provinces may not offer incentives that are specific to biotech-related businesses, all provinces have their own SME programmes in place.

Concluding remarks

While most OECD countries have adopted a series of measures to support the R&D effort (particularly basic research) of biotechnology companies, giving emphasis to SMEs, it is the case that most companies will face problems at a subsequent stage, when funding is needed for expanding facilities and scaling up manufacturing. Companies then become vulnerable and search for conducive environments, or resort to creating long-term links with pharmaceutical companies.

4.7. Policies to encourage small and medium-sized enterprises

Most start-up biopharmaceutical companies are small in size and thus encounter the same problems as any other SMEs. The survival of such companies is a function of various factors, including the availability of (national or supra-national) policies to support them. Firm size affects their ability to obtain financing, to bring new products to the market, and to overcome barriers to entry (R&D costs, advertising, etc.). Therefore, special treatment of SMEs is necessary, particularly if they are involved in the creation and implementation of high technology.

The problem is much greater in Europe than in the United States (Table 4.10a) in that a much larger proportion of firms are SMEs in Europe. However, small companies are also a feature of the US biotechnology industry. According to BIO, 70 per cent of US biotechnology companies are classified as SMEs (i.e. they employ up to 135 employees).

Table 4.10a. **Size distribution of enterprises and employment share: the European Union and the United States**

Distribution by size	**% of firms**		**% of jobs**	
	EU-12	**US**	**EU-12**	**US**
Micro enterprises (0-10 employees)	93.2	78.3	31.9	12.2
Small enterprises (11-99 employees)	6.2	20.0	24.9	20.0
Medium-sized enterprises (100-499 employees)	0.5	1.4	15.1	14.4
Large enterprises (> 500 employees)	0.1	0.3	28.1	46.4
Total	100.0	100.0	100.0	100.0

Source: EU-12 (1990), European Network for SME Research, 1994; United States (1990), US Small *Business Administration, 1993.*

In addition to relaxed regulation of financial markets for SMEs, other policies to encourage their development have been adopted, although the approach varies by country. Table 4.10b summarises the policies of the United States, various EU member states[58], and Japan.

Table 4.10b. **Differences in the use of aid instruments for SMEs**
Average 1986-1990, % of funds allocated

State aid instruments	United States	Japan	Sweden	Germany	France	United Kingdom	Ireland	Italy	Netherlands
Subsidies	6.8	22.6	37.0	37.3	42.3	55.4	84.0	94.0	90.5
Soft loans	3.5	21.8	18.2	1.0	3.1	-	-		7.3
Guarantees	0.9	17.0	9.8	15.3	21.8	15.3	2.1	4.0	0.6
Equity financing	-	-	1.1	1.5	15.8	24.0	-	-	1.0
Tax relief (tax credits)	88.8	19.0	15.0	43.0	16.8	-	11.8	-	-
Mixed instruments	0.1	19.7	19.0	1.9	1.0	5.3	2.0	2.0	0.3
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Note: The figures relate to all support measures, not research support alone.

Source: European Commission, DGXII working document, 1995.

The United States clearly leads in government support and incentives for SMEs, and seven US governmental bodies promote biotechnology (NIH, the Department of Defense, the National Science Foundation, the Department of Energy, the Department of Agriculture, the Environmental Protection Agency, and the FDA). Because small business has been identified as a principal source of significant innovation, the Small Business Innovation Research (SBIR) programme was established in 1982 to strengthen the R&D role of small innovative companies. Reflecting its view of the programme's success, the Congress renewed the programme in 1992 and will have doubled the programme's funding by fiscal year 1997.[59]

Excluding national financial and qualitative incentives (which in some cases override EU funding), the main EU support to biotechnology SMEs has been channelled through a number of specific research programmes mentioned earlier. Additional support comes from the European Commission through its Multi-annual Programme for SMEs which aims to maximise their contribution to growth, competitiveness, and employment[60]; to improve their financial environment; to increase their innovative potential; and to facilitate their access to the information society.

Like the United States, Japan runs its programmes through various ministries, with MITI in the lead. In addition to the funding of biotechnology and support of SMEs, government incentives are in place to strengthen the research activities of small companies through tax breaks, research subsidies, etc. [61]

5. Other determinants of market structure

5.1. Entrepreneurship

Research departments in US academic institutions have a well-established entrepreneurial culture. Researchers are ready to attempt to commercialise their biotechnology discoveries, and many investors and entrepreneurs are willing to help them. Universities themselves foster the commercialisation of discoveries made in their laboratories. By contrast, Europe and Japan are characterised by a relative shortage of entrepreneurial sprit, either because of relative weaknesses in basic research, as in the case of Japan (Yuan and Dibner, 1990), or because of cultural and institutional features, as is the case in some European countries. In Europe, particularly in Germany, the tradition of academic elitism, which tends to discourage commercial involvement in academic science, persists. Added to this dimension are major differences in the organisation of academic science. In France, the excellent scientific base has very little incentive as it is government-financed and researchers are public employees. This bureaucratic structure implicitly discourages commercialisation of research and entrepreneurial activities by researchers. The United Kingdom comes closer to the US model and, for instance, medical research is organised in universities, as well as institutes, which collaborate with industry often with government endorsement.

5.2. Safety regulations

A legal framework that sets the "rules of the game" is very important for the development of biotechnology. Legal regulations on the contained use and deliberate release of GMOs were formulated much earlier in the United States and Japan than in Europe, and made use of existing agencies and statutory powers in a flexible manner. Apart from Germany, Denmark, and the United Kingdom, these being the first countries in Europe to introduce legislation in the field of genetic modification, many European countries had no national regulations on biotechnology for many years. European Community regulations were adopted for the first time in March 1990, through two major EC directives on the

contained use of genetically modified micro-organisms and the deliberate release into the environment of GMOs. The relationship with sectoral legislation is complex, but the marketing of biotechnology-derived pharmaceutical products has since 1987 been subject to the "centralized procedure", and since 1995 involving the European Medicines Evaluation Agency (EMEA; see below). In Japan, the Ministry of Education, Science and Culture published guidelines for manufacturing drugs by application of recombinant DNA as early as 1982.

5.3. Fragmentation and rigidity of regulatory environments

The fragmentation of policies, particularly at the European level, adds to the problems faced by (bio)pharmaceutical manufacturers, as different regulatory hurdles have to be overcome. The creation of a broad legal environment for the European Union has left national governments with enough flexibility to regulate the pharmaceutical market according to national criteria, which, broadly speaking, are in agreement with European directives. Issues such as submission of proposals to conduct clinical trials or to move from one trial phase to another, or marketing issues such as packaging, labelling, and the form in which the drug is sold are still on the agenda. National governments maintain the right to determine prices. Finally, with the establishment of the European Medicines Evaluation Agency (EMEA), authorisation and approval procedures have been harmonized.

If one compares the regulatory environments for biotechnology in the United States and the European Union, regulations appear less prescriptive in the former than in the latter on many important counts. There is no specific US legislation governing R&D work in biotechnology; while the NIH has issued guidelines, outside its funding of R&D it operates in a purely advisory capacity. Strictly speaking, its guidelines apply only to R&D funded by NIH, but most, if not all, academic and industrial organisations follow them voluntarily. The United States has consciously avoided prescriptive legislation as far as possible, and the use of titles such as "Guidelines for ..." or "Points to consider ..." is quite deliberate. FDA policy is that genetic techniques are a refinement, or an extension, of existing techniques and require no new policies, regulation, or paradigms. Finally, the US regulatory framework is very different from that of Europe. In the United States, existing legislation has been used wherever possible, and even where no directly applicable legislation exists, efforts have been made to find means of accommodating the new issues.[62]

The US approach to the regulation of biotechnology is "vertical" rather than "horizontal", i.e. it is more oriented to "products" than to "processes". The FDA has decided (Miller, 1992), that a product's characteristics, even if the product is a GMO, are the sole basis on which to assess risk, not the process by which it was created.[63] This is a fundamental difference between the United States and other regulatory systems. The biotechnology sector seems quite unhappy with the underlying assumption of EU policy, which is that genetic modification is a process that requires separate regulatory control. Although risk assessment in both the United States and Europe looks at the same aspects of the modified organism, the concentration on "process" in Europe contrasts sharply with the United States and Japanese approach, which focuses on the characteristics of the final product. There is also widespread agreement among industrialists that Europe concentrates too much on monitoring R&D and thus creates an additional administrative burden.

In the context of a rapidly developing science base, regulatory agencies continually review biotechnology legislation and guidelines to ensure that they take account of emerging science, technology, and accumulated expertise. All parties concerned praise the US government's deliberate avoidance of new legislation wherever possible. This reduces complications and facilitates the process of taking a new drug through the regulatory process.

5.4. The peculiarities of the pharmaceutical sector

Public attention on the function and performance of the pharmaceutical industry is justified by the importance of medicines for health and the alleviation of pain, the share of pharmaceutical spending on total health expenditure and the level of drug prices. Such attention may seem exaggerated (Abel-Smith, 1976), yet certain characteristics of the pharmaceutical market suggest that competition and consumer sovereignty may not suffice to produce either adequately low prices or reasonably safe and effective products.

First, the three-tier demand system creates important imperfections in the pharmaceutical market (Arrow, 1963). The demand for medicines is controlled not by the final consumer but by the physician, who has neither to pay for the product nor to consume it. For the patient, the financial costs are blurred, owing to an insurance system that bears part or all of the direct costs. Second, medicines are perceived as a matter of "life and death" and thus essential in ways that most goods are not; some may fear that, as a result, pharmaceutical companies can set whatever price they like (Taylor and Maynard, 1990). Third, effects of new medicines are uncertain (Helms, 1981); no medicine is safe *a priori*, and it may be safe only for a particular purpose, but the level of uncertainty can be reduced through clinical trials. Fourth, decision making is often delegated to a public regulatory agent on the assumption that profit incentives and market competition are unlikely to generate a socially optimal level of information or to produce socially desirable decisions by pharmaceutical companies.[64] Fifth, it has been argued that R&D raises the problem of determining the economically correct level of profit to increase innovation (for instance, the treatment of R&D expenses, the allowance for risk, etc.) (Lall, 1981). Sixth, transparency is limited, owing to the multitude of pharmaceutical products[65] in a market which is sub-divided into therapeutic groups with a high cross-elasticity of supply and demand and which can be divided into three groups -- in-patent medicines, generics, and over-the-counter drugs (OTCs). Seventh, there are economies of scale in research, production, and marketing. There are also actual threshold levels of expenditure in research and marketing.

These economic characteristics suggest that, to be profitable, companies must aim to sell their products as widely as possible. This may explain the multinational character of the industry. Eighth, the supply side is thought to be oligopolistic (Leschlin, 1982), as high profits, prices, and promotion expenditures can only exist in an industry characterised by monopoly power. Finally, one must mention the high R&D intensity of pharmaceutical activities and high dependence on effective and extensive marketing and distribution networks at the micro level.

5.5. Manpower requirements and training

Education

New biotechnology processes are often discovered in academic laboratories. A substantial number of US biotechnology/biopharmaceutical companies are follow-ups of university-based research and are commercialising an increasing number of new drugs.[66]

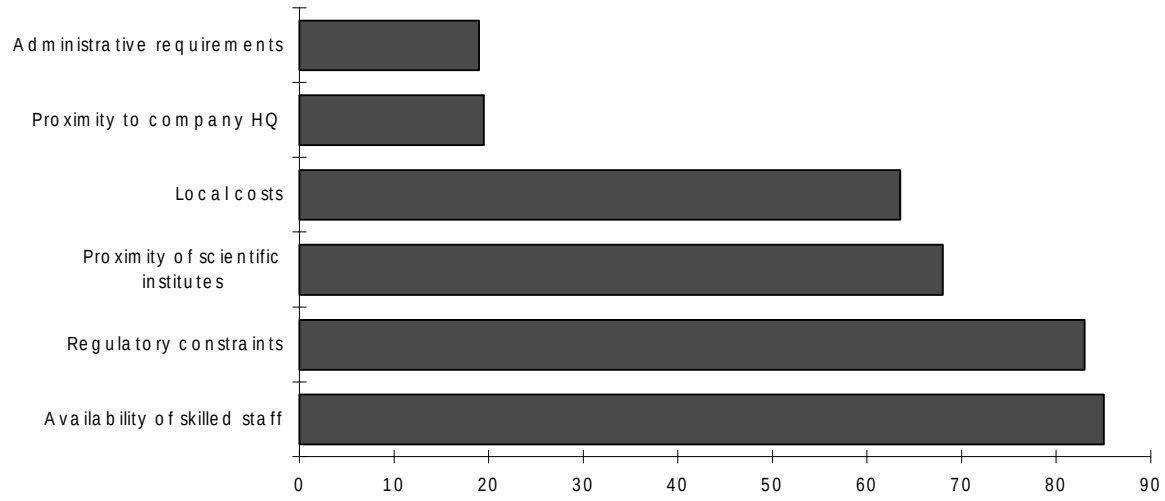
A well-developed science base is a strong determinant of a country's innovative capabilities. The discovery, development and delivery of (bio)pharmaceutical products requires a highly-skilled and trained workforce. In order to obtain such a workforce there needs to be training available not only in undergraduate and post-graduate courses but also post-doctoral research. The latter two levels are particularly important for the development of new processes. Furthermore, participation in (middle and high) vocational training is extremely important, and vocational courses can at times offer even better

training, since they are tailor-made to the needs of industrial technology and application and can channel researchers directly towards the discovery of new processes and products.

The importance of training and mobilising R&D manpower and acquiring an adequate science base lies at the heart of national policies to promote biotechnology. The two predominant features of manpower needs for biotechnology are multidisciplinarity and high levels of qualification. It is generally felt that multidisciplinary training for biotechnology should complement rather than supplant the training of specialists in the related disciplines.[67]

The importance of education can be seen in the choice of location for inward investment by pharmaceutical companies. Company decisions involve many factors and often compare situations in various areas of the world. According to a recent survey on the determinants of biotechnology inward investment (SAGB, 1994), the availability of skilled staff is the most important factor (Figure 5.1). This finding has been confirmed for the biopharmaceutical industry (Kanavos *et al.*, 1995); in fact, along with the friendliness of the regulatory environment, a high concentration of high-quality academic research has also proved to be a very important factor.

Figure 5.1. **Factors influencing the location of a biotechnology investment (in percentages)**



Source: SAGB, 1994.

University-industry links

University-industry collaboration, depending on its nature[68], provides tangible benefits to both sides. The academic world gains the opportunity to develop a new research area, recruit faculty, expand its scientific base, and, depending on the outcome of the research, generate royalty payments. Industry gains access to cutting-edge research and knowledge and achieves economies of scale, as sponsored research in universities yields four times as many patent applications per dollar as does corporate research (Blumenthal *et al.*, 1986). It has also been shown that pharmaceutical/biotechnology companies that work closely with universities have more products in development and more products on the market.[69] Such collaboration is most common in the United States, Japan, and Switzerland, much rarer in the United Kingdom and Australia, and almost non-existent in France, Germany, and Canada (Table 5.1).

Table 5.1. **Biotechnology's brightest academic stars**

Country	Academics employed by biotechnology (% of total R&D employment)	Academics linked to a company (% of total R&D employment)	Number of alliances with academics 1994[1]	Research funding of university-based research by biotech companies $ m[1]
United States	50.2	33.3	79	993
Japan	12.6	21.1	19	319
United Kingdom	7.5	9.7	11	115
France	6.1	0.0	n.a.	n.a.
Germany	5.8	0.0	7	210
Switzerland	3.6	20.0	10	357
Australia	3.4	7.1	1	20
Canada	2.4	0.0	4	45
Belgium	1.7	14.2	n.a.	n.a.
Netherlands	1.2	20.0	n.a.	n.a.

1. Approximate figures.

Source: Author's adaptation from *New Scientist*, 2 March 1996 and *Nature Biotechnology*, 14 April 1996.

The United States provide an environment conducive to successful co-operation between university-based research and corporate secondment. Indeed, university-based research was the foundation of US leadership in initial commercial applications of biotechnology. Nowadays, there are many agreements between biopharmaceutical companies and academic institutions, and a single company may have several hundred active agreements (Office of Technology Assessment, 1991) at any time.[70] The United States has, of course, an excellent scientific base, as well as accumulated scientific and technical expertise.

In Japan, the cornerstone of local biotechnology development has been the promotion of collaborative mission-oriented research between industry and public institutions. Such activities are intended to speed up and advance technology development and its transfer to private companies. There are three principal types of government-industry collaboration: collaborative projects involving government and university scientists and their industrial counterparts; research associations; and autonomous research foundations. However, it has often been suggested that the universities require reform, as many are organised into isolated faculties and provide few opportunities for independent and original research.

Europe is lagging in this area, with the exception of the United Kingdom, where the relationship between industry and the academic world is a main component of the UK initiative[71] to attract Japanese pharmaceutical investment.

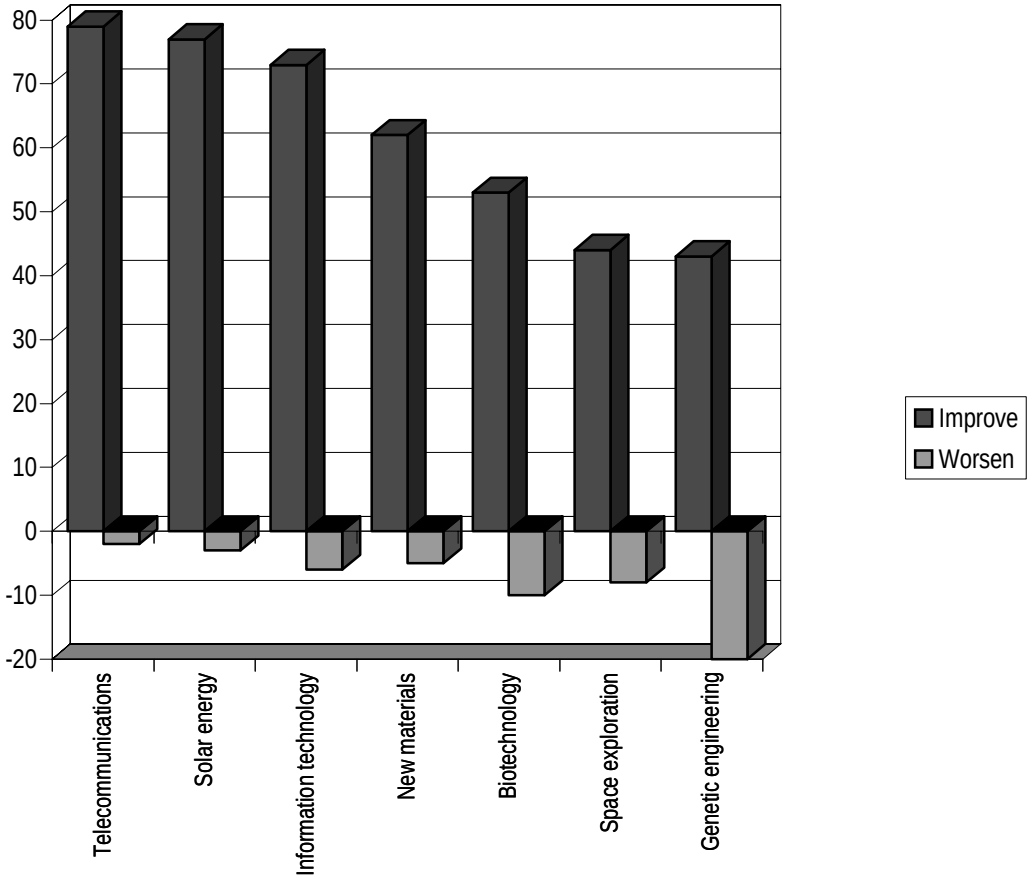
5.6. Public perception of biotechnology

Ethical dilemmas influence public opinion and perception[72] of biotechnology, and, as European experience has shown, are likely to gain importance in political and legislative debates on biotechnology. Public perception of biotechnology seems to be divided: there is concern about the environmental release of genetically modified organisms (GMOs) and intervention in the process of human birth and procreation, but there is acceptance of biotechnology as a means of meeting increasing need for medicines.

The public understanding and perception of biotechnology, and the acceptability of its products, vary widely from country to country. Comparative surveys[73] indicate that in the United States, Canada and Japan, public opinion is generally more receptive to innovative technologies than is the case within the European Union. However, within the EU countries, there is wide variation; and this has been systematically measured by successive "Eurobarometer" surveys, which in 1991 and 1993 have included a series of questions relating to biotechnology-or genetic engineering (the use of a split sample, 50 per cent being questioned using the term "biotechnology", and 50 per cent the term "genetic engineering" or equivalent, enabled the effect of terminology to be separately assessed).

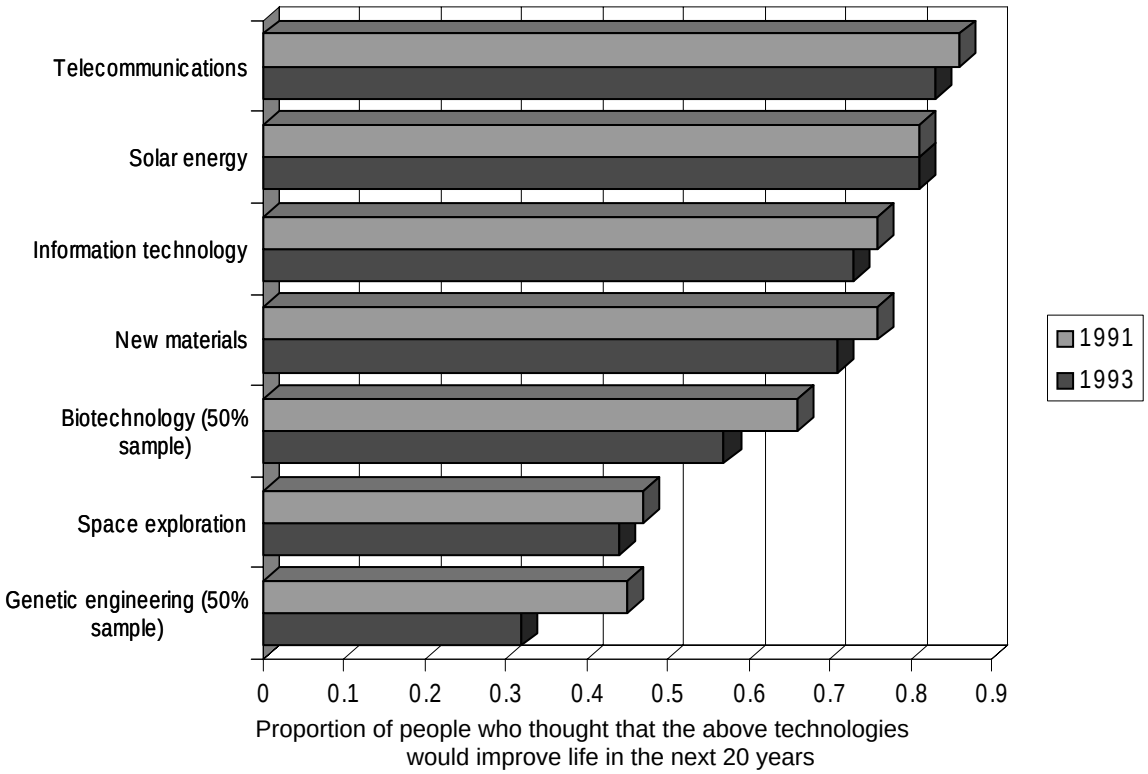
In the 1993 Eurobarometer survey, those sampled were asked for the various technologies mentioned in Figure 5.2 whether they thought each of these would improve our way of life in the next 20 years, make no difference**,** or make things worse. Although the balance is clearly on the optimistic side for all technologies, biotechnology ranks among those less favourably viewed, and "genetic engineering" still less so. Moreover, between the 1991 and 1993 surveys, there has been a shift in the pessimistic direction, as shown in Figure 5.3; this adverse shift being considerably greater for biotechnology/genetic engineering than for other technologies.

Figure 5.2. **Effects of new technologies in the next 20 years and their impact on human life**



Source: Eurobarometer 1993.

Figure 5.3. **Expected effects of new technologies: Eurobarometer 1991 and 1993**



A telephone survey in the United States gave similar results: a fifth of the respondents had negative first thoughts about genetic engineering (Hammna, 1996). As in Europe, applications to plants were more widely acceptable than animal biotechnology.

In assessing public acceptance of innovation and the potential impact of biotechnology, one must be aware of the different, though not necessarily opposing, views of consumer groups on the one hand, and specific patient/disease groups, on the other. An opinion widely shared among representatives of consumers and patients is that the degree of public acceptability of an innovation, particularly in the field of biotechnology/pharmaceuticals, will depend on the degree to which a drug or new technology meets "real" needs.

6. Conclusion and policy options for OECD countries

6.1. Broad remarks

In analysing the determinants of market structure in the international biopharmaceutical industry, one has to take into account that biopharmaceuticals are the product of biotechnology applied to activities aiming at producing treatments or cures for diseases. Biotechnology and pharmaceuticals are not ordinary industries and indeed are characterised by certain features. The involvement of health policy with industrial policy and entrepreneurship also produces a different mix compared with other industries. Furthermore, the nature of the technology and the fragmentation of the pharmaceutical market into a large number of therapeutic categories, makes the industry differ from all others and produces an industry which displays low overall levels of concentration, but very high concentration at the sub-market or product levels.

For this purpose, when analysing determinants of market structure, apart from examining the role of traditional barriers to entry, one has to take into account factors such as industrial policy, health care reform, the issue of financing innovation, public policy research and public perceptions. These factors play a crucial role in the formation of this industry.

The biopharmaceutical industry

Biotechnology has wide applications one of them being in health care therapeutics (biopharmaceuticals). The development of this technology has had significant impact on pharmaceutical R&D in that it has enabled scientists to indentify research targets with precision and increasingly improved understanding of the underlying aetiology of diseases.

There is a concentration of start-up biotechnology companies in the United States, where surveys have identified over 1 300 such companies. Fewer start-ups exist in Europe (slightly over 500 according to one source) and these are concentrated in the United Kingdom, and, less so, in France, Germany, Denmark and the Netherlands. In Japan, there are even fewer biotechnology companies and large pharmaceutical multinationals are taking the lead in biotechnology development. In Canada, there are reported to be 224 core biotechnology companies (Ernst and Young, 1997).

Biopharmaceutical companies are small in size and technology intensive. As a result, biopharmaceutical companies wishing to develop and market products face significant constraints: the long development process and the (less long) authorisation process are funds intensive; wide distribution of pharmaceutical products requires extensive distribution networks, which are expensive to set up. This is where pharmaceutical companies have considerable advantages, through scale and size. Thus, few of these biopharmaceutical companies have commercialised their products successfully in large markets; some, which have developed processes and are developing products, are building up alliances with larger partners, usually pharmaceutical companies, capable of bearing the risks and the costs of development and product commercialisation.

The advantage of biotech/pharmaceutical companies lies in their potential for the discovery and development of new processes, technologies or/and products. Such discoveries make the relevant companies attractive targets to pharmaceutical multinationals, which may imply strategic alliances for technology transfer, product development or marketing in different markets.

The financial context

The financing of innovation in biotechnology presents considerable differences across countries; the United States has the largest pool of venture capital, necessary for the initial phases of biotechnology product development; in Europe, venture capital exists, but at a lower scale, due to the fragmentation of European markets as well as regulations which in some coutnries make it more difficult for early investors to realise capital gains via the “exit route” of public flotation. In Japan, venture capital is scarce and biotechnology companies are having to contract loans, the most widely preferred form of finance, from financial institutions.

An important financial strategy for start-up biotechnology companies is to enlist in capital markets and raise capital from them. However, their small size and the fact that in most cases these companies do not have a product on which to trade, makes listing difficult. The London Stock Exchange (followed by the Tokyo Stock Exchange) have for this purpose relaxed their listing rules for biotechnology companies

and this has led many European companies to take advantages of these opportunities. As noted above, the ease of flotation also influences favourably the prospects for early stage investors.

Parallel markets also exist (or are in preparation) in many European countries; the advantage of these markets lies in the looser regulations for listing. In the United States, NASDAQ has attracted a large number of small and promising biotechnology companies and was followed by the launch of EASDAQ in Europe in November 1996.

Despite the availability of a number of sources of finance for biotechnology, which also include initial public offers and R&D limited partnerships, these sources are very often subject to market volatility, and short-term expectations about product launches and net revenue streams. For these reasons, strategic alliances between biotechnology and pharmaceutical companies have become the most popular and less risky way of financing innovation in the former. In view of these problems, the role of national governments (and supra-national institutions, such as the European Commission) in financing innovation, particularly start-up biotechnology companies, is very important, but varies across the OECD countries.

The US government is the most active supporter of innovation through generous (when compared with other countries) funding of biotechnology R&D in national laboratories and universities. Moreover, an appropriate legislative framework is in place for the transfer of technology from national laboratories to the private sector for development.

In the European Union, public sector research is perceived to be fragmented and national initiatives, though important, may lead to duplication of the research effort. In terms of scale, the United Kingdom, Germany and France spend a lot more per capita than other EU Member States. The European Commission, through the EU research budget, has supported priorities identified at the European level, and has made the development of biotechnology one of these. However, the funds committed to biomedicine and health at the European level are only a fraction of the US equivalent.

Japan has also identified biotechnology as one of its priorities and actively funds research in specific areas. However, one of the problems of Japanese research is its relative weakness in basic research.

The regulatory context

Biotechnology-derived pharmaceuticals are subjected to the same regulatory rules as conventional pharmaceuticals. Speed of approval is essential for marketing and capture of market share, as it is for revenues accruing from sales in large markets. Biotechnology companies are more sensitive in this respect due to the capital constraints they face. In Europe, the establishment of the European Medicines Evaluation Agency and its centralised authorisation procedure for all biotechnology products facilitates market access.

Intellectual property rights protection is crucial to the development of biotechnology; however, in different countries, important issues remain to be resolved. In the European Union the proposed biotechnology directive has still to be finalised and adopted by the European Parliament and Council.

The US Orphan Drug Act of 1983 provides the financial incentives that have encouraged pharmaceutical manufacturers to develop new orphan drugs. These incentives include exclusive marketing rights for seven years and tax credits for clinical research, among others. According to the National Organisation for Rare Disorders (NORD), a non-profit voluntary health agency, many important

new therapies have been or are being developed in response to the legislation. The situation is similar in Japan, where orphan drug legislation has existed since 1985.

The European Union has no specific criteria for funding research activities leading to the development of orphan drugs. Legislation or institutions are lacking at EU level, although some efforts in that direction have been made.

Health care reform is on the agenda of most OECD countries. Cost containment and macro-efficiency are the most important goals in health sector reform. Unavoidably, pharmaceutical products, accounting for between 10 and 27 per cent of the health budget in different countries, are subjected to a large array of cost control measures.

Very few countries allow free setting of pharmaceutical prices and the majority of countries impose controls. Major pharmaceutical cost containment measures within the OECD area include price-setting by governments (price controls), the use of average prices, international price comparisons, reference prices, promotion of generic products, positive and negative lists and delisting. There are also trends toward better management of health care, through fixed budgets for doctors and caps for pharmaceutical expenditure. Increasingly, governments adopt economic evaluations, either explicitly (only in a few countries), or implicitly.

The emphasis on cost containment may influence the dissemination of biopharmaceutical products, due to their high cost, unless the therapeutic gain exceeds (and is seen to exceed) current and future costs of treatment.

Direct support for small, start-up biotechnology firms exists in most OECD countries, and takes the form of subsidies, tax credits, tax relief, equity financing and soft loans. Policies vary according to country or geographical area.

New biotechnology processes are often discovered in academic institutions; the rate of such discoveries is a function of a country's science base and investment in manpower is an important determinant of scientific discovery. The two predominant manpower needs for biotechnology (and its application to pharmaceuticals) are multidisciplinarity and the high levels of qualification. The multidisciplinary nature of biotechnology, particularly its association with information technology, can perhaps explain the existence of strong SME pockets in the Western United States.

University-industry links constitute powerful channels for the development of new technology. The United States provides an environment conducive to successful co-operation between university-based research and corporate secondment. This is not the case in Japan, where biotechnology development has been the promotion of collaborative mission-oriented research between industry and public institutions. In Europe, university-industry collaborations are comparatively less frequent, with the exception of the United Kingdom.

6.2. Policy options

Large companies vs. SMEs

At first blush, it may appear that the future of the pharmaceutical/biopharmaceutical industry in OECD countries depends only on generous pricing of newly patented products and further mergers of firms that lack the size apparently now required to stay in the top league. Mergers are indeed necessary

and are already occurring at an increasing pace. Governments are not, however, in a position to know either which mergers should occur or which are likely to be successful. This must be left to the industry. There are already near monopolies in the world market for certain new therapies, and, given the patent system, these may be inevitable in the short run. Mergers and acquisitions may, however, reduce research options and the likelihood of technological advances, since the vitality of any industry depends on new entrants. Thus, policies need to be reinforced to strengthen the innovative potential of SMEs, particularly in Europe and Japan, where the entrepreneurial spirit must also become more aggressive. So far, given the broad scope of scientific research, large biotechnology companies and SMEs co-exist and complement each other.

It can be argued that policy on the development of SMEs is successful in the United States and Japan, but remains fragmented in Europe, particularly since each EU member state has a policy of its own. What is generally lacking is explicit support of the high-technology SME sector of which biotechnology is an integral part.

The growth cycle in biotechnology

Biotechnology companies generally follow a five-stage growth cycle from start-up to maturity. Each stage has its own features. Past experience indicates that phase 1 (formation and start-up) requires one year and about $3 million in funding; phase 2 (organisation and product definition) takes three to four years and between $3 million and $35 million; phase 3 (development and preparation for launch) requires an additional four to seven years and up to $300 million in funding; phases 4 and 5 (rapid growth and sustainable growth, respectively) will only take place if previous phases have been successful. The fact is that until rapid growth occurs, a substantial amount of time passes and considerable sunk costs have been incurred. The peculiarities of the (bio)pharmaceutical sector compel the adoption of specific policy measures. Such measures embrace a spectrum that includes policies for government, competition, intellectual property rights, financing, R&D, and SMEs, to mention but the most important.

The impact of new technology

Over the past 15 years, a new orientation in R&D has been identified owing to the discovery and implementation of new technologies, in particular, biotechnology: refined models of disease mechanisms suggest new lines of research that may produce new drugs. Each project now undertaken is far more precise and the mechanisms involved are better understood. However, as the targets become more precise, they also become more numerous. This new orientation, together with the discovery of new techniques or opportunities such as gene therapy, combinatorial chemistry, rational drug design, and nanotechnology, has meant very significant changes in drug discovery research, which may also imply an increase in the number of curative medicines in the long run compared with the abundance of palliative medicines that currently exist.

Most pharmaceutical and biotechnology companies are acutely aware of the potential of new technologies to complement and extend their traditional R&D activities and are striving to take full advantage of the exciting and potentially highly productive avenues opened by biotechnology and extend their research into a broader range of therapeutic indications.

In order to survive, small biotechnology companies must generate new discoveries, carve out a niche technology, focus on their core expertise, and obtain cash flow neutrality as soon as possible. Despite the fact that funding has become scarcer and that scale works in favour of bigger companies, SMEs may

benefit in the future. The escalation of R&D costs may force large companies to outsource not only an increasing proportion of their development research, but also a share of their discovery activities.

Finance

For the biopharmaceutical sector to reach its full potential, a continuous flow of funds is needed. Venture capital is one option, although its availability still depends heavily on the expected internal rate of return (IRR) and is thus affected by expectations about companies' future revenue flows. In view of the specific requirements and peculiarities of the biopharmaceutical sector, it may be essential to craft a careful policy specifically for this sector that may channel private and public funds in return for future equity.

Raising capital from financial markets is another option, shown by the success of relaxing the stock market listing rules in London and Tokyo. Nevertheless, capital markets still target companies that have already provided investors with adequate proof of their potential, so that promising companies which have yet to reach that point do not benefit. Furthermore, investors' reactions to bad news about a particular product in clinical trials can destroy a company and create an unstable (volatile) environment for the whole sector.

Although initiatives are under way in Europe to make existing main and secondary markets more receptive to biotechnology and other entrepreneurial growth companies (except perhaps in the United Kingdom), the fact remains that there is, at present, little liquidity on Europe's main and secondary markets for the biotechnology companies, which are typically backed by venture capital. The United States, by comparison, has NASDAQ, which is more targeted to this type of company; and a number of European venture-backed biopharmaceutical companies are already listed on it. The United States has also been successful in initiating the so-called R&D limited partnerships, which give individual or institutional investors the right to claim royalties from future sales.

Syndicated loans could provide an additional source of funds for biotechnology firms, and the evidence is that such investments rose considerably in Europe last year. On the one hand, syndicated loans provide additional funds to the biotechnology sector and make larger investments possible; on the other hand, they give investors access to a wider pool of expertise and spread portfolio risk.

In summary, desirable attributes of a financing environment conducive to the development of biotechnology may include:

- a large and not fragmented (financial) market size, from which venture capitalists can draw financial resources;

- relative investment freedom for mutual funds and pension funds; in that way important resources can be released and partly used to support risky activities;

- lower capital requirements for securities issuing houses;

- shortening of period in which quoted investment companies can sell stakes in companies without being liable to tax;

- shortening of the period under which banks and investment advisers can be held liable for the contents of prospectuses and their own advice;

- definition of an appropriate level for personal and corporate taxes to stimulate risk capital;

- a broader introduction of equity-based pension funds (in order to encourage more private provision for retirement) would be desirable in the countries that do not have them and are in need of reforming their social security systems;

- capital availability at the start-up level, i.e. when new companies need it most, and when ideas are taking shape;

- overall tax policy for SMEs, particularly tax credits which can be used when such SMEs become profitable or negotiate an alliance with a large (bio)pharmaceutical company;

- stimulate Anglo-Saxon type pension funds, which are large equity investors, by putting them on the same tax footing as pension reserves;

- broad(er) introduction of stock option plans for employees in countries that do not have them.

Industrial policy

Slow product approval remains a problem more so in the United States than in Europe, although the FDA is making considerable efforts in this direction. Long approval times add substantially to biotechnology companies' costs, thereby increasing the need for funds, so that the formation of strategic partnerships with larger corporations becomes a condition of survival. The introduction of user fees partly solves the problem, although it adds considerably to the costs of biopharmaceutical firms.

In a research-intensive industry, effective intellectual property rights protection is crucial. In the triad composed of the United States, the European Union, and Japan, the European Union has only recently adopted a Directive on the Patenting of Biotechnology Inventions, thus aligning itself with the United States and Japan.

Apart from the question of patent legislation itself, there are side issues related not to the nature of the legislation but to its implementation: the backlog of applications (which increases both costs and uncertainty); enforcement (Russia, for instance, is said to possess a pharmaceutical patent law, but it is not enforced and it may take decades for a patent infringement suit to reach the courts); or licensing requirements (once Canada relaxed licensing requirements after introducing a new patent law, R&D investment increased by a factor of three (Heller, 1995)).

The development of biotechnology presupposes a strong science base and the formation of horizontal links with other disciplines. Countries that are successful in the biopharmaceutical field -- the United States and, to some extent, Japan -- have a long-term commitment to biotechnology, which is partly evident in their funding to academic institutions. The case of the United Kingdom is rather different: its very strong scientific base has never been entirely dependent on public sector support but has always obtained some of its resources elsewhere. This presupposes good links with the corporate sector.

In Japan, and to some extent in Europe, the most qualified academic and research institutions work with private firms to improve basic research, technology development, and technology transfer. However, the issue of conflict of interests must be addressed, especially for university scientists. Guidelines for establishing conflict of interest standards should be introduced.

Regulatory agencies should facilitate early controlled dissemination of new medicines, coupled with more stringent post-introduction evaluation requirements.

In place of subsidies, tax incentives should be given for qualified research expenditures and for companies' expenditures for university-based research. In Europe and Japan, there is a clear need to fund basic research that encourages close collaboration between the industry and universities and research centres. Cost-sharing projects, especially in biotechnology, should be expanded. However, such support ought to focus on research in which social benefits greatly exceed private benefits and which leads to additional R&D initiatives. Development of orphan drugs, research in high-risk areas, and incentives to SMEs should be encouraged. At the moment this is not the case in Europe, Japan, or the United States (in the latter, on an *ad hoc* and discretionary basis only).

R&D

Empirical research (Drews, 1992) underlines the fact that the pharmaceutical industry spends huge amounts on R&D, but only a small fraction of its R&D outlays (estimated at 4-5 per cent of such expenditures) are spent on research in radically and fundamentally new areas for the discovery of innovative medicines. This calls for some type of evaluation of the industry's performance by technology assessment organisations; the outcomes of such assessment can be used as a basis for new initiatives and restructuring of the current policies and actions. On the other hand, there is scope for supporting R&D activities of biotechnology companies, which have spent as much as pharmaceutical companies, if not more, in real R&D.

Governments and international organisations, working together, might define a diversified set of R&D activities over a wide range of pharmaceutical research.

In areas with development potential, supranational bodies and national governments should encourage FDI in R&D and offer incentives to domestic companies to conduct co-operative R&D with foreign companies. This should generate capital, expand market access, accelerate commercialisation, profits, jobs, and creation of new technology, and strengthen corporate management through knowledge transfer. Companies wishing to pursue such avenues should be given every opportunity to do so.

Health care reform

Very few OECD governments allow the pharmaceutical industry to set prices freely. In addition, as the effort to contain costs increases, an effective mechanism is needed to guarantee a certain price level for the industry and some success in holding down pharmaceutical spending. Various systems have proved ineffective, including the German version of reference prices; a possible exception is the United Kingdom's Pharmaceutical Price Regulation Scheme, coupled with incentives to doctors to prescribe rationally (for instance through the fundholding scheme). Free pricing remains a long-standing demand from the industry, but it is doubtful whether governments that impose pharmaceutical price controls will accept free pricing, without additional measures that would keep the pharmaceutical budget under control.

In this context, the challenge for biotechnology is twofold. First is whether it can deliver therapies for a wide range of diseases. Policy makers are faced, in the short to medium term, with the question of whether or not to adopt expensive new biotechnologically derived therapies without solid proof that costs will be reduced in the long run. Second is whether the new technology will make it possible to move towards effective prevention of disease by understanding the underlying aetiology, in which case the long-term benefits, in terms of public health, decreased mortality, and increased quality of life, will

outstrip the short-term costs. These subjects are discussed extensively in Part I of this report, *Biotechnology and medical innovation: socio-economic assessment of the technology, the potential and the products*.

Public perception and acceptance of innovation

In assessing public acceptance of innovation and the potential impact of biotechnology, one must be aware of the different, though not necessarily opposing, views of consumer groups, on the one hand, and specific patient/disease groups, on the other. An opinion widely shared among representatives of consumers and patients is that the degree of public acceptability of an innovation, particularly in the field of biotechnology/pharmaceuticals, will depend on the degree to which a drug or new technology meets "real" needs.

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European Commission, DG III
European Commission, DG XXIII
OECD
London Stock Exchange
European Parliament, STOA and DG for Research
Biotechnology Industry Organisation (United States)
United States General Accounting Office
Japanese Pharmaceutical Manufacturers Association
Department of Trade and Industry (United Kingdom)
Department of Health (United Kingdom)
United Kingdom Patent Office
German Ministry of Research
French Ministry of Research
Industry Canada
Japanese BioIndustry Association
Italian BioIndustry Association

Danish BioIndustry Association
Japanese Export Trade Organisation, London Office
European Venture Capital Association
Canadian Venture Capital Association

Abbreviations

BAP:	Biotechnology Action Programme
BEP:	Biomolecular Engineering Programme
BIA:	BioIndustry Association (United Kingdom)
BIO:	Bio Industry Organisation (United States)
BRIDGE:	Biotechnological Research for Industrial Development and Growth in Europe
CEC:	Commission of the European Communities
CNRS:	Centre National de la Recherche Scientifique (France)
CNS:	Central Nervous System
DBC:	Dedicated Biotechnology Firm
EASDAQ:	European Association of Securities Dealers Automated Quotation
ECLAIR:	European Collaborative Linkage of Agriculture and Industry through Research
EFPIA:	European Federation of Pharmaceutical Industries Association
EMEA:	European Medicines Evaluation Agency
EU:	European Union
EUREKA:	European Research Coordination Agency
EVCA:	European Venture Capital Association
FDA:	Food and Drug Administration (United States)
FDI:	Foreign Direct Investment
FLAIR:	Food-Linked Agro-Industrial Research
GAO:	General Accounting Office (United States)
GMO:	Genetically Modified Organism
IPO:	Initial Public Offering
IRR:	Internal Rate of Return
JBA:	Japan BioIndustry Association
JETRO:	Japanese Export Trade Organisation
JPMA:	Japan Pharmaceutical Manufacturers Association
MESC:	Ministry of Education, Science and Culture (Japan)
MITI:	Ministry of International Trade and Industry (Japan)
MHW:	Ministry of Health and Welfare (Japan)
MMC:	Monopolies and Mergers Commission (United Kingdom)
MNC:	Multinational Corporation
NASD:	National Association of Securities Dealers (United States)
NASDAQ:	National Association of Securities Dealers Automated Quotation (United States)
NBF:	New Biotechnology Firm
NCE:	New Chemical Entity
NHS:	National Health Service (United Kingdom)
NIH:	National Institutes of Health (United States)
NORD:	National Organisation for Rare Disorders (United States)
NYSE:	New York Stock Exchange
OTC:	Over The Counter
PhRMA:	Pharmaceutical Research and Manufacturers of America
POM:	Prescription-Only Medicine
RDLP:	Research and Development Limited Partnership

rDNA:	Recombinant Deoxyribonucleic Acid
PPRS:	Pharmaceutical Price Regulation Scheme (United Kingdom)
SAGB:	Senior Advisory Group on Biotechnology
SBIR:	Small Business Innovation Research
SME:	Small and Medium-sized Enterprise
STA:	Science and Technology Agency (Japan)
WTO:	World Trade Organisation

NOTES

1 Theory on and empirical investigation of industrial organisations are extensive, and it would be unrealistic to give a few representative references. However, there are some landmarks; see for example, Bain, 1956; Baumol *et al*., 1982; and Sutton, 1991.

2 These average figures cover significant variations -- e.g. Canada is an OECD leader in the exploitation of biotechnology for agriculture.

3 Glaxo-Wellcome acquired the US-based Affymax in 1995, a company that had developed the technology that allows high throughput automated screening of different molecules; Hoffmann-La Roche acquired the US-based Genentech in 1991.

4 It is indicative of the upward trend of the early 1980s that nearly 70 new firms began operations in 1981 alone. See Office of Technology Assessment, 1988.

5 According to estimates by the Senior Advisory Group on Biotechnology.

6 For example SmithKline Beecham's recombinant hepatitis B vaccine (Engerix B), Rhone-Poulenc-Rorer's granulocyte colony stimulating factor (Granocyte), Bayer's haemophilia A agent (Kogenate), Wellcome's hairy cell leukaemia agent (launched in June 1993, prior to Wellcome's erger with Glaxo) (Wellferon injection), and Boehringer Mannheim's predialysis agent (Recormon).

7 According to which the Ministry of Health and Welfare reduces prices every two years.

8 In this context, the word "pharmaceutical" implies the ethical market only. If reference needs to be made to the generic or the over-the-counter market, this will done accordingly.

9 For an in-depth analysis of the structure of the international pharmaceutical industry, see Kanavos and Mossialos, 1996; also Mossialos *et al.*, 1994*b*; Kanavos and Abel-Smith, 1994; LSE Health, 1994; and Mossialos *et al.*, 1994*a*.

10 Meaning different regimes for pricing, financing and reimbursement of pharmaceuticals. On the other hand, the establishment of the EMEA, as well as existing legislation at the European level on packaging, labelling, and advertising constitute reforms that aim at harmonising the European pharmaceutical market.

11 As was the case with Centocor's Centoxin and Antril against septic shock. Both drugs were withdrawn after clinical trials showed that they performed badly (the first showing efficacy problems, the latter performing little better than the placebo).

12 As was the case with Genentech's tissue plasminogen activator (tPA), sold under the name Activase, whose sales plummeted in 1991 when clinical results suggested that tPA was no more effective in saving lives than a conventional and much cheaper drug, streptokinase. Further studies provided statistically significant evidence of the drug's efficacy although the results were questioned because of their lack of clinical significance (by increasing the survival rate for heart attack victims by about 1 per cent, they imply a cost effectiveness of about $100 000 per life saved).

13 In this context excluding cash flows from milestones, benchmarks, research payments, and other collaborative revenues from alliances reported in the statement of corporate operations.

14 A number of other studies review the determinants of investment in the pharmaceutical sector. Among them are Yuan and Dibner, 1990; Economists Advisory Group, 1988; and Heller, 1995.

15 Personal communication with eight executives of Japanese pharmaceutical companies in the United Kingdom; unpublished material.

16 See London Stock Exchange, *Listing Rules*, Chapter 20, December 1993. Chapter 20 has recently been amended (February 1996) and become more flexible with respect to biotechnology/pharmaceutical companies.

17 Based on the issue price and excluding the value of any securities issued in the six months prior to listing.

18 Mr. Edmund Lucas, Vice President, New York Stock Exchange, London Branch, March 1996, personal communication.

19 Japan Bioindustry Association, response to LSE Health questionnaire, April 1996.

20 But also in Paris (the *Nouveau Marché*), which was launched after London said it was setting up the AIM.

21 If a company does not want to register with the Securities and Exchange Commission (SEC) and only seeks to raise capital from institutional investors, then the NASDAQ Portal Market can be used for securities placed privately under Rule 144 A. Rule 144 A also permits resale of restricted securities without SEC registration, but only in compliance with volume limitations, manner of sale and notice requirements.

22 This is not far from the historical level of 3 per cent of total venture capital disbursements that other authors have found; see, for instance, Ooghe *et al.*, 1989.

23 For a detailed overview of the seed capital initiative within the European Union, see European Commission, DG XXIII (1996).

24 Mr. P. Poggioli, DG XXIII, personal communication.

25 In France, for instance, there may be a funding gap, owing to the low performance of the existing funds which register a 10.8 per cent net rate of return, which is not attractive enough, in light of the risk involved. In a performance study of 40 venture capital groups, 10 had negative internal rates of return (IRRs); see Anslow, 1995.

26 With the exception, perhaps, of the London Stock Exchange.

27 The case of the latest euphoria on the London Stock Exchange, with investors pouring money into the biotechnology sector, is quite typical. Of the biopharmaceutical companies listed in the main market, none has been profitable and yet share prices have seen a steep upward trend since the last quarter of 1995.

28 As of November 1996, ECU 1 is equivalent to US$ 1.1.

29 These funds amounted to US$ 300 million in 1995.

30 The list of pricing and other cost containment regimes for pharmaceuticals is not all-inclusive and appears correct at the specified point in time. Policies often change following the introduction of ad hoc reform measures or systematic changes in national cost containment strategies.

31 However, increasing health costs are also of concern in the United States, where private insurance is the main method of finance; see, for instance, Congressional Budget Office, 1993; Congressional Budget Office, 1995; General Accounting Office, 1995.

32 The existing profit range of 17 to 21 per cent is subject to review in 1996.

33 Although successful, the PPRS has been criticised because it may lead to overcapitalisation (in buildings, equipment, and personnel), once a company realises that it may exceed the allowed profit margin.

34 For a comprehensive approach to the importance of patent protection in biotechnology see, for example, Beier et al., 1985.

35 This point is of particular relevance for the United States since US patent applications remained confidential prior to issuance. Some individuals kept patent applications pending in confidence until an industry had matured or had significant infringement products on the market. Once patents were issued, the patent holders could demand much higher royalties. The new amendment which requires publishing patents 18 months after the priority filing date and then allowing patent holders to select one of two kinds of terms attempts to uncover what was known in the United States as "submarine patents".

36 Contrary to public perception, however, the rejection of this directive did not mean that "patents on life" were banned and patent offices merely continued their previous practice.

37 For instance, the costs for foreign applicants in Japan are the highest in the world, owing to translation costs and the fees charged by Japanese patent attorneys who have separate fee schedules for domestic and foreign clients; see Kanavos *et al.*, 1995.

38 A US General Accounting Office (GAO) survey concluded that many companies operating in Japan found it more difficult to obtain patents for pioneering inventions than in the United States or Europe. In addition, it is particularly difficult to obtain patents on broad, commercially valuable technologies in Japan, or on those that involve important new technologies. [see General Accounting Office].

39 As is the case in Japan, unlike the situation in the United States.

40 See chapter "The Orphans of the Health Care System".

41 For an evaluation of the Orphan Drug Act see Schulman *et al.*, 1992.

42 The terms mean any disease or condition which: a) affects less than 200 000 people, or b) affects more than 200 000 people, but for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or conditions will be recovered from sales of such a drug in the United States.

43 See "The Inauguration of a System for the Promotion of Orphan Drug Development", *Japan BioIndustry Letters*, Vol. 11, No. 1, pp. 5-6, 1994.

44 See, among others, "EU Policy on Orphan Drugs", *The Lancet*, Vol. 345, No. 2036, p. 5, July 1995; and "Health Ministers to Help Orphan Drugs", *British Medical Journal*, Vol. 310, pp. 17-18, June 1995.

45 Commission of the European Communities, *Communication from the Commission concerning a programme of Community action for rare diseases within the framework for action in the field of public health*, Brussels, September 1997.

46 Commission of the European Communities, *Proposal for a European Parliament and Council Regulation on Orphan Medicinal Products*, (preliminary draft), Brussels, 9 August 1996..

47 Under the current grants scheme, which is directly financed by the Orphan Drugs Office, 90 per cent of the grant holders are academic institutions and only 10 per cent are private companies.

48 Marlene Haffner, Director, US Office for Orphan Drugs, personal communication.

49 Public Law 96-480.

50 Public Law 98-620; 50 FR 9801; 37 CFR 404.

51 The Federal Technology Transfer Act of 1986 (Public Law 99-502).

52 Additional features of this legislation include: the entitlement of Federal employees to their own inventions, if these are deemed of having no commercial value by the Federal Government and, consequently, there is no intention to license them; and the fact that Federal agencies are required to share at least 15 per cent of royalties from any licensed invention with the inventing scientists; agencies are also directed to establish cash awards for other personnel involved in productive Federal technology transfer activities.

53 The Bayh-Dole Patent and Trademark Act of 1980 (Public Law 96-517) was one of the most important examples of this type of legislation.

54 For instance, the government's share in total R&D in 1985 was 19.4 per cent, as compared with 46.8 per cent for the United States and 42.6 per cent for the United Kingdom.

55 Such as the Science and Technology Agency (STA), the Ministry of International Trade and Industry (MITI) and the Ministry of Health & Welfare (MHW).

56 Efforts to harmonise the tax structures of Member States are limited to the approximation of indirect tax rates, including VAT rates and excise duties; currently, a share of VAT revenue finances the EU budget. The conscious efforts of the European Commission to harmonise levels of direct personal and corporate taxation have been met with opposition from the Member States, as they are seen as direct interference with the conduct of national fiscal policies. The only progress on direct taxation concerns cross-border capital movements and resolutions related to SMEs. For an overview of issues regarding tax policy in Europe, see Kanavos, 1997.

57 The extent of government and provincial support of the R&D effort balances the issue of a higher cost of capital and the definition of what can be interpreted as R&D in Canada. While in the US market analysis is included in the definition of R&D, in Canada this is not the case.

58 For a comprehensive analysis of EU policies for the SME sector, see European Commission, 1995a and 1995*b*.

59 For an assessment of the quality standards of SBIR, see General Accounting Office, 1995.

60 See the Commission Press Release IP/96/240 of 20 March 1996, on the Third Multi-annual Programme for SMEs, to run from 1997 to 2000. The Second Multi-annual Programme (1993-96) has been completed and evaluated [COM(96) 99 final].

61 For a brief exposé of such policies, see Kanavos *et al.*, 1995, and the references therein.

62 For instance, micro-organisms are defined as chemicals to allow for regulation under the Toxic Substances Control Act administered by the Environmental Protection Agency.

63 In this light, the FDA allows, for example, the commercial marketing of milk and meat from animals treated with experimental drugs, but only after scientific studies have shown that the food is safe for human consumption. In addition, although it was concluded that the US system was predominantly product-focused, it does contain elements of process regulation, the extent varying with the organism in question, the type of genetic modification employed, and the regulatory body concerned. For instance, the documentation required for the licensing of a pharmaceutical drug or a vaccine emanating from biotechnology certainly addresses aspects of both processes and products in terms of quality, safety and efficacy.

64 But here two issues may arise. First, stringent regulations on safety, prices, and profits may discourage the industry from spending on R&D, resulting in declining rates of innovation (Teeling-Smith, 1979). However Lall (1981) argues that the problem is not solely caused by strict regulation, but that the limits of scientific possibilities of new discoveries and increasing R&D costs may also cause innovation to dwindle. It must also be pointed out that a large number of "new" products are not genuinely new but involve minor changes to existing medicines and do not constitute therapeutic "breakthroughs" (me-too products). Second, the government's interest in maintaining or increasing national income may lead to strengthening of the innovative industry and its promotional activities.

65 W.D. Reekie, *The Economics of the Pharmaceutical Industry*, Macmillan, London, 1975.

66 For the importance of university-based research, see OTA, 1991.

67 For further elaboration, as well as the importance of co-ordination strategies between countries, see OECD, 1988.

68 Alliances, which are major long-term relationships between academic institutions and the corporate sector, are preferable to unrestricted grants or short-term renewable grants; see Haber, 1996.

69 Quoted in *New Scientist*, 2 March 1996.

70 As was the case with Genentech. Recent trends, however, indicate a move away from broad, lengthy agreements between universities and industry and towards numerous specific agreements.

71 Initiated by the Secretary of State for Health in late September 1994.

72 See, among others, Umeda, 1992; European Parliament, 1991; Bennett, 1995; INRA (Europe) and Commission of the European Communities, DG XII, 1993; OTA, 1987, for the issue of public acceptance; and Bauer, 1995.

73 Despite the well-known conservatism of Japanese society, a good governmental information service has helped to overcome initial public concerns; see Ishikawa, 1990. See also KPMG, 1994.

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THE IMPACT OF MODERN BIOTECHNOLOGY ON R&D IN THE LIFE SCIENCES, AND ON ORGANISATIONAL STRUCTURE AND THE MANAGEMENT OF RESEARCH IN THE BIOPHARMACEUTICAL INDUSTRY: CONCEPTS AND MEASUREMENTS[1]

by

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Concepts

Introduction: structure of the chapter

A study of the economic impact of biotechnology on health care cannot avoid consideration of its impact on the structure of the pharmaceutical industry -- starting with changes in the way in which it manages its research. This requires consideration of the ways in which recent advances in basic biological science (together with other technological changes) have altered the structure of knowledge, and the methods and requirements of research.

The chapter starts by outlining these trends -- the progressive triumph of the reductionist approach of molecular biology leading to a pervasive "molecularisation" of the life sciences; the pervasive impact of the DNA "data tape", leading and driving a trend to "informatisation" which approaches its apotheosis in the genome sequencing projects; this information intensification and the nature of modern information processing and communication tools transforming the applied life sciences towards the patterns and structures of a "knowledge-based economy"; and (at least partly) for related reasons towards "globalisation" of the pharmaceuticals sector.

This description of the driving forces for change, is followed by two approaches to describing and measuring the consequences. Firstly, some elements are presented of the changing overall shape of the pharmaceutical industry and its research expenditures, on a global basis. Secondly, the results are reported of a specially commissioned survey which aimed to capture some aspects of the ongoing pattern of change through a firm-level enquiry; the details of the results are presented in an Annex.

The molecularisation and informatisation of the life sciences

At the core of every living entity there is a data tape, written in DNA. This has been an academic cliché since Francis Crick and James Watson described the double helix; but the language of the data tape is now being read with rapidly increasing facility and falling cost. Genetic engineers are learning to edit and splice the tapes, even to write short but significant phrases. This progress is now creating massive scientific and economic opportunities; and in conjunction with modern developments in information processing and telecommunications, is transforming the structure of the corresponding economic sectors.

These developments were not evident in the early years. The molecularisation of the life sciences had a long gestation period, from the origins of molecular biology in the 1930s. Since then, the parallel progress of instrumentation technologies (the electron microscope, X-ray crystallography) led over several decades to elucidation of the structure of biological molecules, and in particular of DNA (Crick and Watson, 1953); the molecule whose key role as the carrier of genetic information had been finally demonstrated a decade previously (Avery *et al*., 1944). Further developments and discoveries, in particular of restriction enzymes, enabled Stanley Cohen and his co-workers in 1973 to use such enzymes to cut and stitch strands of bacterial DNA, i.e. the founding steps of modern "genetic engineering" (Cohen *et al*., 1973).

There are many words for pieces of DNA, the choice of terms reflecting the perspective -- a double helix, a gene, a chromosome, a genome, the carrier of genetic information. To call it a "data tape" is scarcely metaphorical, but deliberately makes the analogy and underlines the connection with the now familiar language of data processing and storage, the whole vocabulary of modern information handling and transmission. Thus "bioinformatics" becomes the hot topic, central to biological understanding and theorising. It embraces not only the handling and reading and comparison of the linear data sequences, reflecting in that linearity the limitation of the tape as a data storage medium; but, as in the living world, deriving from the one dimensional nucleotide sequences (and from other data sources), insight into the successively higher order three-dimensional structures of proteins, cells, tissues, organs, organisms, and the functioning systems in which and through which the different levels and entities interact.

In long-term planning studies in the 1980s, the US National Library of Medicine developed the concept of the "Matrix of Biological Knowledge". This phrase expressed the idea of the inter-connectedness and underlying unity of all such knowledge, about all species, and at all levels from molecular biology to populations and ecosystems; and anticipated its rapidly advancing elucidation. As elucidation of the structures and linkages advanced, the effect on the practice of biological science was indeed federating. For example, in virology, one of the youngest sub-disciplines of biology, there had been a progressive fragmentation into subspecialities: bacteriophage specialists, plant virologists, animal virologists, clinical virologists, etc. The new illumination from the molecular level forced them to recognise that the interests they had in common were now becoming more important than the reasons which had led to fragmentation; a project for a "world virus data bank" was launched, under the aegis of the International Committee on Taxonomy of Viruses.

This anecdote illustrates a wider phenomenon: it demonstrates that changes in the structure of knowledge can lead to changes in the practices and structures of research; changes also promoted or facilitated by the revolution in communication technology. The way in which research is conducted, in all areas of the life sciences and their applications, is changed, permanently.

The global "scramble" for the genomes

Managers of leading research institutes or laboratories emphasise the ruthlessly exposed nature of the modern research endeavour: there is no refuge for second-rate research. There is no protection, by distance, or transport costs, or communication difficulties and delays and charges -- in the global electronic village, everybody is next door -- including the best performers in the world. The Schumpeterian "gale of creative destruction" is today an electronic tornado, against whose effects distance and geography are no defence.

This is overstated, if we speak of all fields of application of the life sciences. Insofar as we speak of fields of application which retain some particularism -- of geography, of climate, of culture, of ecological

specificity -- there remains the protection afforded by knowledge that is specific to a crop, a region, a climate, and to those having the accumulated knowledge and practical experience specific to these. Thus, the agricultural research efforts of the International Rice Research Institute in The Philippines will not be duplicated or rendered irrelevant by the progress of soya-bean research at the University of Iowa, or potato research at the International Centre in Peru. But the barriers are diminishing, the cross-linkages increasing.

For example, in March 1994, a paper (Kurata *et al.*, 1994) by collaborating researchers located in different continents, demonstrated the close relationship between the genomes of barley, rice and wheat, descendants of a common ancestor in the Jurassic period, 60 million years ago. Since then, such demonstrations are becoming commonplace, with the progress of genome mapping and sequencing projects. The knowledge thus connected changes the researcher's reading requirements. For some piece of knowledge, about a disease specific to one cereal species, and the mechanisms of resistance to it, are suddenly relevant, the knowledge accessible to those studying apparently different, but in fact homologous, diseases and resistance mechanisms elsewhere; and the strongest evidence of the connection, the route through which the connection and translation are henceforth for ever made, is the molecular. Thus, molecularisation, informatisation and globalisation are different facets of a pattern of change, which is simultaneously illuminating, and profoundly threatening to established structures, habits and practices.

Clichés about the unity of the life sciences are given sharp operational edge by the discovery of the common genetic code; comparative genomics destroys disciplinary boundaries. The European Commission sponsored a conference in Trieste, in September 1996, to celebrate the first complete sequencing of a eukaryotic genome, the yeast *Saccharomyces cerevisiae*. Craig Venter of The Institute for Genome Research presented some of TIGR's recently published prokaryote (bacterial) sequences, remarking in the course of the discussion (with slight rhetorical exaggeration), that "it doesn't matter what species you sequence, the genes are the same". Other contributions made the same point, concerning the very high degree of sequence homology -- i.e. genetic similarity -- across species separated even by tens or hundreds of millions of years of separate evolution, including of course, *homo sapiens*.

At a gross level, inter-species homology has long been obvious, and has been widely assumed and applied: for example, toxicology to assess the safety of novel foods or medicines uses various species, in particular the mammals and especially those apparently "closer" to man such as the higher primates, because of long-standing assumption and experience of their similarity to man in terms of metabolism, physiology, nutritional requirements and responses to diseases and therapies. But the progress of molecular biology and adjacent disciplines is now revealing the intimate structure and functioning of the mechanisms on which these similarities -- and the slight but sometimes significant dissimilarities -- are based. And that changes thereafter the basis for research. For the knowledge is rapidly disseminated, globally available, pervasive and irreversible.

The accelerated technical developments of recent years have built rapidly, one could say at a frantic pace, on these breakthroughs in basic research. An OECD workshop was held in Rome in December 1996, on "Novel Systems for the Study of Human Disease: From Basic Research to Applications" (OECD, 1998). In fact the topic was the transgenic mouse: the technical breakthroughs allowing targeted specific genes to be modified, replaced, or deleted in this familiar mammal, and the vast applicability of this new armamentarium across basic and developmental research to any disease phenomena involving disorder at the level of the genetic machinery. The workshop rapporteur, Phil Minor, summarised his impressions succinctly: "It's as though we had a yeast that looks like a human being" -- i.e. combining the facility of manipulation and experimentation of the yeast, with the close similarity of the small mammal to man, a closeness that could now be intensified by appropriate gene modifications.

The pace is frantic, because the opportunities are suddenly perceived to be immense, yet the domains to be captured, although large, are finite. There are estimated to be tens of millions of distinct species, each on average containing thousands of genes; but there is a high degree of homology -- Mother Nature is economical, and reuses with minor changes the same patterns. A single broad patent can thus lay claim to a broad swathe of usefully applicable knowledge; virus resistance by the expression of the viral capsid protein in the plant is not restricted to one or a few species. Historians summarise how in the latter decades of the nineteenth century, the imperial powers competed in the "Scramble for Africa", the cartographers following the explorers and the armies to draw lines across the vast *terra* hitherto *incognita* of the "Dark Continent". The *terra incognita* of genes, genomes and genetic resources is now similarly being rapidly explored and its key economic resources appropriated by the research armies of the great powers, not by lines on a map, but by intellectual property rights.

One must be careful not to push too far the historic analogy with voyages of discovery, territorial appropriation and physical economic resources; for in the knowledge-based economy in which resources are invested to create and secure and exploit economic assets, discovery *per se* is not allowable for appropriation -- a fundamental principle of intellectual property, a topic beyond the scope of this chapter. But the nature of the "Scramble for knowledge" in the applied life sciences, in the "bio-industries", and in particular in the pharmaceutical industry, has been changed by the scientific advances and discoveries referred to.

The change in the game reshapes the players: managing the new knowledge

The change in the shape of the game is reshaping the participants. The knowledge base and the technical skills on which the competitive performance of a company depends have always been a combination of capabilities: in-house skills, some secret, some published but proprietary as in patents, and some public domain, open to all; the company's success depending in part on the quality of its technical skills and proprietary knowledge, still more on the overall management skills with which these were combined, including use of public knowledge. The recent developments, generating vast quantities of new raw data, and hence scope and need for value-added information, insights, models, new techniques and research instruments, have greatly increased the size of the total potentially relevant knowledge base. Most of these developments lie outside the company's ownership; but many of them may be relevant to the company's performance and competitiveness. To over-simplify, the research chief has to divide his time between managing internal resources, and managing the interface with the resources outside the company. In recent years, the balance has had to tilt sharply towards the latter.

To speak simply of an "inside" and an "outside" is an oversimplification. Any attempt to list the distinct categories of knowledge -- "secret", "patent", "public domain" -- quickly founders, because of the proliferation of intermediate categories, ingenious arrangements, giving various degrees of access, exclusivity, proprietary rights. A whole new taxonomy would be required to describe the different forms of relationship by which corporations buy, exchange, seek access to, share, license, and generally conduct transactions relating to the acquisition and use of knowledge. The word "network" is commonly used. Biotechnology companies seeking finance are valued on the basis of their intellectual property and their agreements with large corporations.

The life sciences sectors -- the "bio-industries" -- although they include traditional sectors addressing fundamental human needs such as agriculture and food production, as a result of the progress in molecular biology and related techniques, are becoming the information- and knowledge-intensive sectors *par excellence*. The whole health sector will be transformed, from industrial structure down to general practice, affecting health care delivery to individuals and families. In the era of pharmacogenetics and

pharmacogenomics, as the genetic profiling of individuals becomes affordable, to ignore the new information will be unacceptable -- unethical and irresponsible. The use of the new information will fragment the market for million-fold sales of standard formulations, and lead to structural changes involving the use of, and access to, information as well as the prescription, formulation and provision of medication.

Towards the "knowledge-based economy" ...

Such sectors are precisely typical of the "Knowledge-based Economy" (OECD, 1996*a*) -- a phrase much used in recent OECD work, as the economies of the developed world become increasingly based on knowledge and information, the leading sectors increasingly R&D-intensive. Knowledge is now recognised as the driver of productivity and economic growth, leading to a new focus on the role of information, technology and learning in economic performance. OECD analysis is increasingly directed to understanding the dynamics of the knowledge-based economy, and identifying corresponding "best practices". The growing codification of knowledge and its transmission through communications and computer networks has led to the emerging "*information society*".

The need for workers to acquire a range of skills, and to adapt and update them continually, underlies the "*learning economy*". The importance of knowledge and technology diffusion requires better understanding of knowledge networks and "*national innovation systems*". New issues and questions are being raised regarding the implications of the knowledge-based economy for employment, and the role of governments in the development and maintenance of the knowledge base.

In the work cited, the authors (OECD, op. cit.) acknowledge that measuring performance in a knowledge-based sector or economy poses severe challenges.

> "There are systematic obstacles to the creation of intellectual capital accounts to parallel the accounts of conventional fixed capital. At the heart of the knowledge-based economy, knowledge itself is particularly hard to quantify and also to price. ... An unknown proportion of knowledge is implicit, uncodified and stored only in the minds of individuals. Terrain such as knowledge stocks and flows, knowledge distribution and the relation between knowledge creation and economic performance is still virtually unmapped."

Yet in the knowledge-intensive modern biopharmaceutical industry, such valuations have to be made every day; it is not surprising that the values of biotechnology companies are volatile.

The survey described below illustrates some of these difficulties.

... and "Globalisation"

In conjunction with modern telecommunications, no economic factor is more easily and rapidly mobile than information. For information-intensive sectors -- such as biotechnology and pharmaceuticals -- the shift to a more knowledge-based economy is intimately connected with the phenomenon of "globalisation" -- a topic on which OECD's Industry Committee and Trade Committee submitted a joint report to the Council at ministerial level in 1994, and followed up with a series of sectoral studies (OECD, 1996*b*).

Globalisation of industry refers to an evolving pattern of cross-border activities of firms involving international investment, trade and collaboration for purposes of product development, production and sourcing, and marketing. These international activities enable firms to enter new markets, exploit their technological and organisational advantages, and reduce business costs and risks. Underlying the international expansion of firms, and in part driven by it, are technological advances, the liberalisation of markets, and increased mobility of production factors.

Globalisation in the pharmaceutical industry

The implications of globalisation, in particular for governments and public policy, are further discussed in general terms in the work cited, which includes a chapter on "Globalisation in the Pharmaceutical Industry" (Casadio Tarabusi and Vickery, 1996), presenting the results of analytical work on the recent development of the industry. Some highlights may be noted here; but the pace of recent change has been such that the judgements and conclusions have to be revised (most are confirmed) in the light of latest data -- at least, on an anecdotal basis.

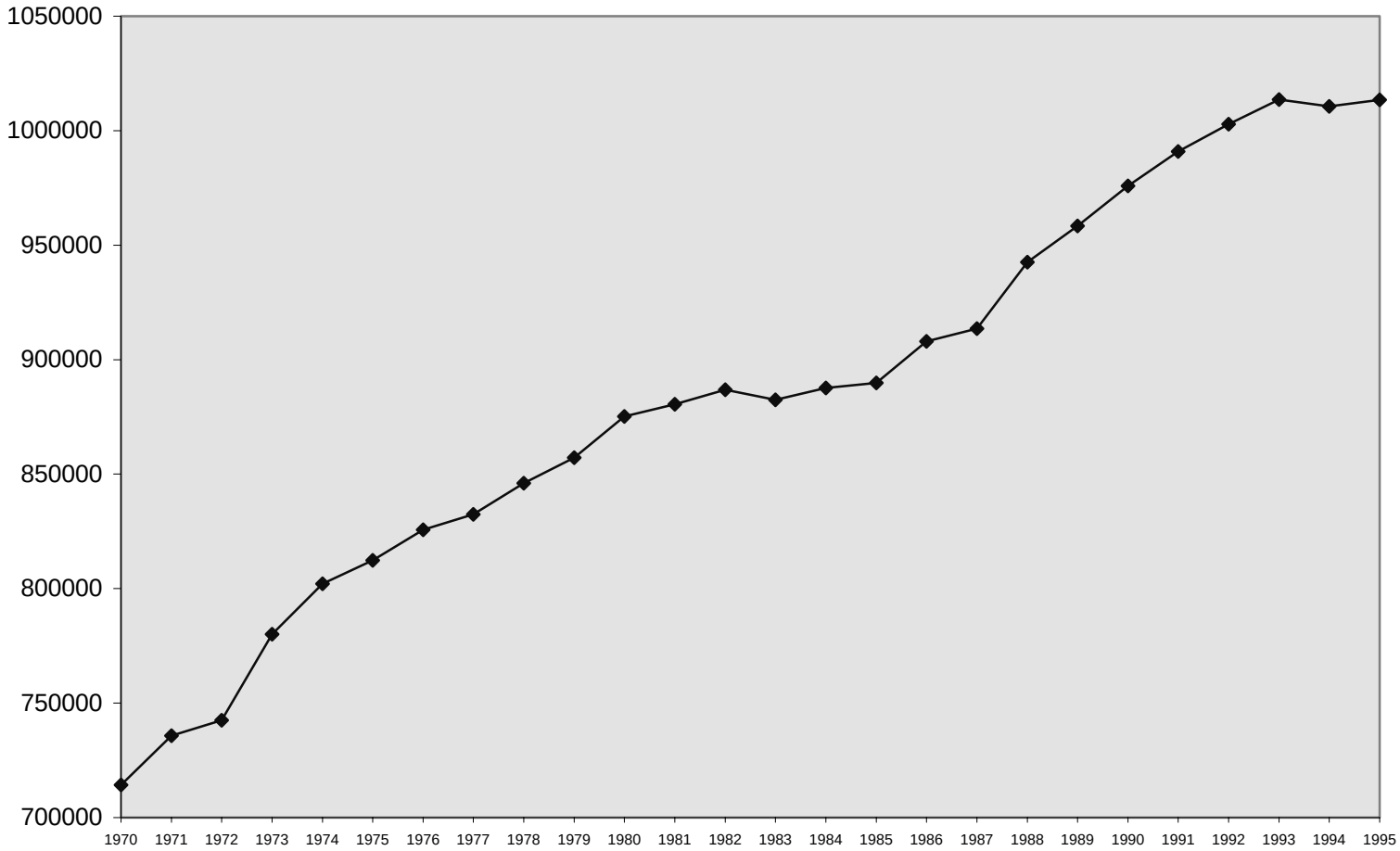
International trade in pharmaceuticals, including sourcing of intermediate inputs, is appreciably lower than in many other industries. The extent of globalisation has increased considerably as a result of cross-border acquisitions and mergers, and collaborative alliances in R&D and marketing. Pharmaceutical products are essentially "universal" in their composition and use, but markets are highly segmented because of national health and price regulations and the incidence of particular diseases and traditions of medical practice which leads to de-centralised final production, certification and marketing functions. There is a distinctive multi-country form of globalisation characterised by extensive production, finishing, packaging and marketing in countries of final sale, but with R&D still largely centralised in the home country.

The large European and US research-based firms which lead the industry and operate in all major world markets sharply increased their foreign investment activities in the late 1980s and mid-1990s. A large share of this investment in the United States and Europe has been merger and acquisitions.

Pharmaceuticals R&D still remains highly centralised in the home country, but growing cross-border consolidation and collaboration (mergers, acquisitions, joint ventures, strategic alliances) are helping firms to share risks and costs in product development, joining large firms with small biotechnology firms, and expanding markets to recoup R&D costs. New international collaboration agreements, directed mainly to product development and marketing, increased in the late 1980s at the same time as foreign investment. The United States is the overwhelming focus of international agreements between large pharmaceutical and small biotechnology firms.

Employment in pharmaceuticals has grown steadily through the 1980s and early 1990s (Figure 1), but has shown signs of levelling off in the mid 1990s, even declining. Several mergers of large-scale companies (examples are cited below) were viewed positively by the markets, because of the assumed potential for saving in manpower costs; and are likely to impinge on total employment in the pharmaceutical industry (which as indicated in Figure 1 in 1995 was just over one million for 23 OECD countries). At the same time, these structural changes in the large firms, and the growth of outsourcing (see below) including relations with new, small biotech firms, may give substance to a hope precisely expressed by Sir William Stewart, President of the (UK) BioIndustry Association, in the context of the proposed Glaxo-Wellcome and SmithKline Beecham merger: "Much is being made of the potential for job losses, particularly on the research and development side. Any such losses would be regrettable .... But what it could also mean is that a cadre of outstanding R&D staff with world class industrial experience come on to the UK market. With their skills and experience they could be in a position to develop and become involved in the expanding small and medium-sized biotech sector where the United Kingdom leads Europe". (Letter to *Financial Times*, 12 February 1998).

Figure 1. **Employment growth - pharmaceuticals, 23 OECD countries**



Source: OECD, DSTI, STAN Database, European Federation of Pharmaceutical Industry Associations (1997), and Secretariat calculations.

The industry is increasingly R&D-intensive. Business enterprise R&D expenditures doubled from under 6 to almost 12 per cent of production in the period 1973-1994 (Secretariat calculations, average for 14 OECD countries). R&D-intensity increased consistently over the period (Figure 2). R&D expenditures are very high in the United Kingdom and the Nordic countries (Sweden, Denmark, Finland, Norway), averaging close to or over 15 per cent of production. The United States was around 12 per cent, with Japan rising rapidly from a low base, Germany and France following (Figure 2).

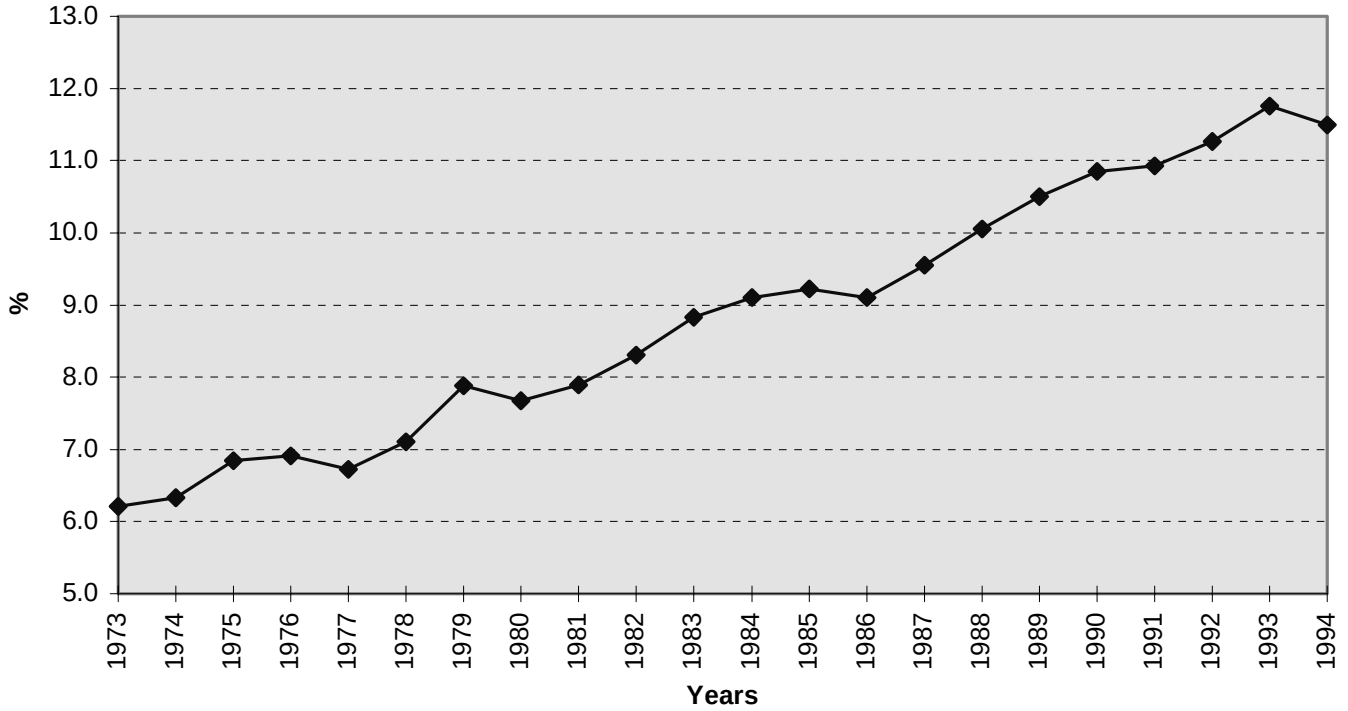
The largest international firms are even more R&D-intensive. In 1992-93, the ten largest R&D spenders spent a total of US$ 9.1 billion on R&D, an average of almost 16 per cent of sales, and estimates for 1995 show that large firms consistently increased R&D effort despite pressures on prices and profits. Research is among the most centralised activities in large pharmaceutical companies. Even the very largest carry out research and basic clinical evaluation in only a few locations, with the main centre of research in the home country. For example, in 1992 the very large Swiss pharmaceutical/chemical industry had almost one-half of R&D expenditures in Switzerland, down only marginally from the mid-1980s.

When they are set up, foreign R&D facilities are in nations with a proven record of success in innovation. US companies took the lead in setting up second and third research centres abroad. Despite centralisation, most European firms have large R&D investments in the United States. In 1986, it was estimated that 26 foreign pharmaceutical firms, primarily European-owned, had R&D facilities in the United States. A different survey showed that by 1992 there were 74 large foreign-owned biotechnology R&D facilities in the United States, of which three-quarters were European-owned (Dalton and Serapio, 1992; US Department of Commerce, 1993). By 1992 it was estimated that foreign firms in the pharmaceutical industry in the United States were the largest R&D spenders by industry and their expenditures had grown most rapidly through the 1980s to US$ 2.8 billion in 1992 in constant 1987 dollars (OTA, 1994). In current terms, US affiliates of foreign firms funded over US$ 3.8 billion of R&D in the United States in 1993, one-third of all foreign affiliate manufacturing R&D in the United States. In comparison, US firms spent over US$ 2 billion for affiliate R&D outside the United States.

Few Japanese companies have R&D centres outside Japan. But as a consequence of mounting cost-containment concerns, large Japanese companies are restructuring their R&D operations and increasingly turning to small specialist research companies, some foreign, for early-phase projects.

The pattern of R&D activities carried out abroad by R&D companies has been reshaped by the advent of modern biotechnology; much of the research being carried out by what have become known (particularly for statistical purposes) as “dedicated biotechnology companies” (DBCs). These are mostly small US-based firms which first appeared in the mid-1970s, and proliferated in the first half of the 1980s. Established pharmaceutical firms soon saw the potential impact of this new technology, but often lacked the broad-based skills to foster it. Accordingly, a web of collaboration agreements linking the large drug companies with the small DBCs was set up, to trade financial and marketing support against research resources of DBCs. A 1994 survey identified more than 1 500 DBCs in the United States and around 400 in Europe (*Financial Times*, 1994), and it was estimated that drugs produced from biotechnological processes took around 4 per cent of world pharmaceutical sales (Commission of the European Communities, 1994). Pharmaceuticals-related biotechnology (mostly R&D, in all sectors, including government) employed around 100 000 people in the United States in 1995, equivalent to over 40 per cent of pharmaceuticals manufacturing employment (OECD data).

Figure 2. **R&D intensity - pharmaceuticals, 14 OECD countries**
Business R&D/production



Source: Casadio Tarabusi and Vickery, 1996; OECD, DSTI, STAN Databases; updated by the OECD Secretariat.

New biotechnology has driven the internationalisation of the R&D function of non-US firms, which were lagging in this important area. It also suggests a new trend in the industry, with greater importance attached to external sources of research, and to the national research infrastructure, as firms have been seeking new ways (e.g. through alliances and external contracting) to maintain their product portfolios.

Structural change: mergers, focusing, outsourcing

The developments summarised above have led to two apparently contradictory tendencies in the pharmaceutical industry. On the one hand, there has been pursuit of scale, for economy of effort, cost reduction in common core functions and facilities, and market reach: mergers such as that between Ciba-Geigy and Sandoz, announced in March 1996, have typically been seen by the stock market as likely to offer substantial additional value through cost savings (Ciba shares soared by 30 per cent on the announcement, Sandoz by 20 per cent). The announcement on 30 January 1998 of the proposed merger between Glaxo-Wellcome and SmithKline Beecham elicited a similar reaction, adding $15.7 billion to their combined value on the first day of subsequent trading. On the other hand, there has been a surge of interest in "outsourcing" an ever wider range of functions and activities; Sir Richard Sykes, (then) Head of Glaxo-Wellcome, was quoted by *The Economist* (1997) as forecasting "the rise of 'virtual' pharmaceutical firms, which would contract out most scientific tasks and concentrate on marketing ".

Certainly the biotechnology start-up firms have in many cases been obliged for their survival, and to retain or attract the confidence of investors, to "focus", and to concentrate on core activities; a logic no less applicable to the surviving medium-size established firms, where even a turnover of one billion dollars is less than 1 per cent of the world market. Many medium-to-large firms have been acquired during the past three years: Wellcome, American Cyanamid, Boots, Marion Merrell Dow.

The question of the independent survival of such firms was addressed by Mads Ovlisen, president and CEO of Novo Nordisk, at a conference in April 1997; describing himself as "an endangered species: the CEO of a medium-sized research-based pharmaceutical company". Their strategy is to sharpen their focus onto a limited number of core areas; with outlicensing and alliances also playing a key role: "If new leads fall within one of our core areas, we will develop them and market them ourselves. If not, we will seek to maximise the value of the discovery by outlicensing it to other companies". He noted that in 1997, the group would spend 25 per cent of its discovery cost on external alliances; three years ago, this figure was less than 10 per cent (*Pharmaceutical Business News*, 23 April 1997). In the article on Merck cited above, *The Economist* notes that, "only 5 per cent or so of Merck's research spending ends up outside the firm's own laboratories; at other top firms the figure is often twice or four times that amount - and rising". Merck's counter-argument is quoted as being that "their rivals go shopping for ideas because they are not clever enough to come up with their own. To aim at being a virtual company, they argue, is suicidal: without first-class in-house talent, a drug firm cannot tell the biotech ideas worth buying from the duds." In fact, 5 per cent of Merck's $1.7 billion (expected, for 1997), would amount to some $85 million annually, a considerable scale of effort; and their scale contains a broader range of in-house strengths than in many smaller companies.

The logic of outsourcing is not new -- "never make what you can buy". There are service companies available for practically every function of a research-based pharmaceutical company, from lead discovery, through manufacturing and clinical trials and registration to marketing. However, the use of outsourcing within the pharmaceutical sector has increased greatly over the past decade; and in conjunction with the recent and ongoing wave of mergers, restructuring and downsizing to reduce costs, is reducing employment within the (statistically) recognised "pharmaceutical sector" (see Figure 2), presumably with at least a partially compensating increase in employment in supplier companies.

The use of outsourcing in biopharmaceutical companies has extended to their research activity: firstly because of the commercialisation of modern biotechnology, and the consequent proliferation of specialist biotechnology companies; and more recently because of the bioinformatics and genomics explosion of information. The *Economist* (survey of the pharmaceutical industry, 21 February 1998) reports outsourcing as a percentage of R&D expenditure rising from 8 per cent in 1990 to 17 per cent in 1996 (source: PhRMA, Lehman brothers).

Genomics in particular has become an area where the combination of highly developed specific expertise, in sequencing technology and in sophisticated software for analysing its significance, has given rise to a growing number of specialised companies. Millennium Pharmaceuticals, a genomics firm, has made four separate deals likely over the next 5-7 years to be worth over $250 million, and in October 1997 transferred their proprietary technologies in genomics, gene sequencing and bioinformatics to a new subsidiary formed by Monsanto for developing plant and agricultural products, in a deal giving them $118 million in advance, and an additional $100 million over the next five years if research objectives are realised. Human Genome Sciences (HGS) received $120 million from SmithKline Beecham for access to its sequence data, SB announcing that they envisage three out of five of their future drug targets to be derived from such information. That initial alliance has since been broadened to include also Merck, Synthelabo, Schering-Plough and Takeda. When SB suspended its use of the HGS database in February 1998, it was in part because having identified over 3 000 genes, the company needed to pause and study the targets already identified (and in part because of the increased availability in public domain of high quality sequence data) (Butler, 1998). Similarly Incyte Pharmaceuticals has established a high reputation for its sequencing skills, database and software: it collaborates with Hoechst Marion Roussel, Hoffmann-La Roche, Monsanto, Pfizer, Schering, BASF, Abbott Laboratories, Pharmacia & Upjohn, Johnson & Johnson, Novo Nordisk, Zeneca and others. Ernst & Young (Lee *et al*., 1996) quote it as having "committed fees of over $160 million". In September 1997, Incyte and SB announced a joint venture, creating diaDeXus, a diagnostics company focusing on "tests for disease detection, improved diagnostics, patient stratification in oncology and infectious disease, and pharmacogenomic tests to optimise treatment" (Marshall, 1997).

Measurement: the survey

It was against this background of rapid change, corporate restructuring and consolidation, and proliferating inter-corporate links, licenses, and agreements that the OECD initiated a micro-economic study of the impact of health-care biotechnologies on:

1. organisational change in the pharmaceutical and biotechnology sector, taking into account intra-firm, inter-firm and institutional change;
2. the impacts of change on work-force composition, and quantity and quality of labour demand;
3. labour mobility and turnover.

The OECD commissioned the Institute for Biotechnology Information (IBI), North Carolina (US), to undertake a questionnaire-based survey. For limitations of time and resources, the scope of the survey was restricted to US firms -- by all evidence, the most dynamic region of the global biopharmaceutical industry. The results are summarised below, and the details presented in the Annex. The difficulties encountered limited the precision and value of the results, but illustrated some of the problems indicated above, of trying to characterise and measure a sector in rapid growth, evolution, restructuration and transformation.

Summary

IBI mailed the OECD Pharmaceutical Biotechnology Survey to 324 biotechnology firms and pharmaceutical corporations in the United States. This survey included questions about biotechnology research programmes, research and development (R&D) staff and expenditures, and R&D collaborative research agreements and contracts. Seventy-one companies returned surveys. The small number of returned surveys did not allow for statistical comparisons of the different types of companies (e.g. of biotechnology firms vs. pharmaceutical companies, of large biotechnology firms vs. small biotechnology firms). Although no comparison of subsets of the data was made, summary statistics of several of the survey variables were calculated.

The background information section of the survey, which included questions about the total number of employees (220, 60), the total number of R&D employees (103, 44), and the total amount of R&D expenditure in 1995 ($23.4 million, $8.3 million), was well completed. The mean and median of these survey variables are reported in parentheses above (Mean, Median). Survey statistics for these variables agreed closely with industry-wide statistics from IBI's *U.S. Companies Database*. This agreement suggests that the 71 responding companies are a representative subset of US biotechnology firms. For most of the remaining questions on the survey, however, IBI was not able to use its databases to determine whether the survey data was representative of the industry because the detailed information requested on the survey is not contained in those databases.

Only 66 per cent of companies that returned surveys claimed to have an active research programme in new biotechnology. This result may be due, in part, to the narrow definition of biotechnology used on the survey (see Annex, below). More companies reported using new biotechnologies in basic research and development than in manufacturing, perhaps because several biotechnology companies have no manufacturing activities. Most of the responding companies (85 per cent) conducted new biotechnology research at only one site or facility.

The survey questions about internal and external R&D spending required respondents to distinguish between "pharmaceutical" and "new biotechnology" research. This distinction proved difficult for respondents, both in this and in all subsequent sections of the survey. The instructions asked respondents to report all new biotechnology R&D spending as a subset of their total pharmaceutical R&D spending. Some respondents followed the instructions, others did not; as a result, no reliable summary statistics about the details of internal and external R&D expenditures could be calculated from the survey data. Furthermore, several respondents would not provide details of R&D expenditure because they regarded that information as proprietary.

Although survey respondents had some difficulty answering questions about their R&D staff because of the "pharmaceutical/new biotechnology" distinction, summary statistics about R&D staff activities, educational degrees, and geographic location were calculated. The majority of R&D staff at US biotechnology companies work in basic research and discovery and hold upper-level educational degrees (see Tables 6, 7, 8, 9).

The respondents reported that most of their collaborations are with academic and private research labs in the United States. In the United States, responding companies were almost nine times more likely to collaborate with a research lab than with another company. The respondents had the next greatest number of collaborations with European research labs and companies. Respondents also reported collaborations in Japan, Canada, and Australia.

Survey respondents predicted increased R&D spending and staff for 1998-1999 in both new biotechnology and pharmaceutical research. Survey respondents also predicted an increase in the number of collaborative agreements with universities and companies.

As mentioned earlier, survey respondents had difficulty with the distinction between "pharmaceutical" and "new biotechnology" R&D, even given the survey definitions. This distinction is not recognised by some companies, and no two companies that recognise the distinction are likely to understand it in the same way. It would be much more productive to ask companies about their R&D efforts without asking them to make this distinction. This distinction introduced a great deal of confusion and complexity to the survey. The information sought from the survey was also quite detailed, and this fact may explain the low number of returned surveys. Some of the non-responding companies may have considered much of the information on the survey to be proprietary.

For these reasons, the results of the survey reported below need to be treated with considerable reserve. Nonetheless, even an unsuccessful experiment can be informative; and similarly the difficulties encountered in this survey may be worth recording as guidance to other research efforts.

ANNEX: SURVEY DETAILS AND RESULTS

Methods

IBI received a list of questions from the OECD Biotechnology Unit to include in the survey. IBI reformatted, rewrote, and condensed those questions based on the suggestions of the OECD and the input of experienced IBI staff. Several words and phrases on the survey were defined in order to standardize their interpretation on the survey. Survey definitions of research and development and R&D staff were obtained from the *Frascati Manual* (OECD, 1994).

IBI attempted to shorten and simplify the survey as much as possible while retaining the questions that were important to the OECD. IBI submitted several iterations of the survey to the OECD for approval. In the end, the OECD wanted information from the survey that was detailed, complex, and considered proprietary by many companies.

IBI mailed surveys to 324 companies: 290 biotechnology firms and 34 pharmaceutical companies, in the United States. Surveys were mailed on 14 June 1996 with a cover letter from Mark Cantley, Head of the Biotechnology Unit of the OECD, and a letter from Carl Feldbaum, President of the Biotechnology Industry Organization (BIO). Five weeks later (week of 22 July 1996), IBI faxed a letter reminding companies about the OECD survey and requesting that they complete and return the surveys to IBI.

IBI entered the data into a spreadsheet and computed basic, summary statistics. The data were entered exactly as reported, with no interpretation or correction. Where possible, IBI used its proprietary database, *U.S. Companies Database*, to determine whether the survey data was representative of the US biotechnology industry at large.

Survey design: definitions and structure

Several terms (new biotechnology research, pharmaceutical research, R&D, R&D staff) were defined to standardize their interpretation on the survey. The definitions provided were:

- *New biotechnology research* employs recombinant DNA techniques, hybridoma technology or other processes involving site-specific genetic manipulation techniques.

- *Pharmaceutical research* includes the new biotechnology techniques and older methods of drug discovery and development. In all tables below that request data for both pharmaceutical and new biotechnology R&D spending and staff, new biotechnology should be a subset of pharmaceutical.

- *R&D* (research and experimental development) comprise creative work undertaken systematically in order to increase the knowledge of a topic and to devise new applications for that knowledge.

– *R&D personnel* should include all persons directly employed in research and development, as well as persons providing direct services to researchers such as R&D managers, administrators, and clerical staff.

The final survey was divided into seven main parts:

I. Background information
II. Research programmes in new biotechnology
III. Organisational changes in the 1990s
IV. Internal and external R&D expenditure in 1995
V. Global R&D staff organisation in 1995
VI. Collaborative agreements and contracts in 1995
VII. R&D forecasts for 1998-1999

The first section included general questions about companies including company contact name, contact telephone number, total number of employees, total number of R&D employees, and total R&D spending in 1995.

The second section consisted of check box questions about the number and location of company research programmes and the use of new biotechnologies in basic research, product development, and manufacturing.

The third section consisted of questions about organisational changes in the 1990s and how the organisational changes had affected R&D spending and staff.

The fourth section included questions about internal and external R&D expenditures in 1995, about the types of R&D work that was contracted out by companies, and about the fraction of manufacturing activities that was contracted out.

The fifth section included questions about the number of R&D staff engaged in a variety of R&D activities, about the educational degrees held by R&D staff, about the geographic distribution of R&D staff, and about the turnover of R&D staff positions.

The sixth section consisted of questions about the number of collaborative agreements and contracts that companies had either with academic/government research labs or with other companies.

The seventh section consisted of forecasting questions about the level of R&D spending, the number of R&D staff, and the number of collaborative research agreements three years into the future.

Results

Survey returns

Seventy-one surveys were returned, and recorded in standard form on spreadsheets in Microsoft Excel Workbook format.

Of the 290 biotechnology companies that received surveys, 67 (23 per cent) returned surveys, and of the 34 pharmaceutical companies that received surveys, four (12 per cent) returned surveys (Table 1). Two companies declined to participate in the survey effort. Ethicon, Inc. (Johnson & Johnson) declined to complete a survey because “the methodologies that we employ, as well as the allocation of funds, [are]

seen as highly confidential". Immunotherapeutics (Fargo, ND) declined to return a survey citing a lack of time to complete it.

Table 1. **Companies (71) that returned surveys**

3-Dimensional Pharmaceuticals, Inc.	Human Genome Sciences, Inc.
Activated Cell Therapy	ICAgen, Inc.
Advance Biofactures Corp.	ICOS Corporation
Alexion Pharmaceuticals, Inc.	Immunex Corp.
Alteon Inc.	Incyte Pharmaceuticals, Inc.
Amgen, Inc.	Innovir Laboratories
Anergen, Inc.	Intercardia
*Aronex Pharmaceuticals, Inc.	Introgen Therapeutics, Inc.
Arris Pharmaceutical	Isis Pharmaceuticals, Inc.
AVID Therapeutics Corp.	La Jolla Pharmaceutical Co.
BioCryst Pharmaceuticals	Magainin Pharmaceuticals
*Bristol-Myers Squibb	Medarex
CellPro, Inc.	Mercator Genetics, Inc.
Centocor, Inc.	MetaMorphix
Cephalon, Inc.	*Microcide Pharmaceuticals
Connective Therapeutics	Mitotix, Inc.
Cortech, Inc.	Molecumetics Ltd.
Corvas International, Inc.	NeoRx Corporation
Creative Biomolecules	Neotherapeutics, Inc.
Cubist Pharmaceuticals, Inc.	Neurobiological Technologies, Inc.
Curative Health Services	Neurogen Corporation
Cytel Corporation	*Ontogen Corporation
Cytokine Sciences	Osiris Therapeutics, Inc.
Fibrogenex, Inc.	Prizm Pharmaceuticals
GalaGen	Progenitor, Inc.
GelTex Pharmaceuticals	Ribozyme Pharmaceuticals
GeneMedicine, Inc.	SciClone Pharmaceuticals
Genetics Institute	Scriptgen Pharmaceuticals
Genome Therapeutics Corp.	Targeted Genetics
Gensia, Inc.	Techniclone International, Inc.
Genzyme Corp.	Texas Biotechnology Corp.
Geron Corporation	Therapeutic Antibodies Inc.
Gilead Sciences	Therapeutic Discovery Corp.
Hawaii Biotechnology Group Inc.	Zonagen Inc.
Hitachi Chemical Research Center, Inc.	Zymogenetics Inc.
Houston Biotechnology	

* Pharmaceutical company.

Source: Author.

Several of the larger biotechnology companies (more than 300 employees) returned surveys: Amgen, Centocor, Cephalon, Genetics Institute, Gensia, Genzyme Corporation, and Immunex returned surveys. The mid-sized companies (50-300 employees) were represented by Arris, CellPro, Creative Biomolecules, Cytel, Genome Therapeutics, Gilead Sciences, Human Genome Sciences, Icos Corporation, Incyte, Isis Pharmaceuticals, La Jolla Pharmaceutical, Neurogen, Targeted Genetics, Zymogenetics, and others. As is true for the US biotechnology industry at large, small companies (less than 50 employees) comprised the largest group in the survey data set: Activated Cell Therapy, Alexion Pharmaceuticals, BioCryst, Connective Therapeutics, Innovoir Laboratories, Intercardia, Mitotix, Prizm Pharmaceuticals, and Zonagen are just a few of the companies in this group.

The four pharmaceutical companies that returned surveys are Aronex Pharmaceuticals, Bristol-Myers Squibb, Microcide Pharmaceuticals, and Ontogen Corporation. These companies are not classified by IBI as biotechnology companies because although they develop human therapeutics, they were not founded on a biotechnology. However, these companies were included with the biotechnology firms in the analysis because there were too few of them to analyse separately and because the data that they reported were not dissimilar to the data that biotechnology firms reported. Bristol-Myers Squibb reported only 270 total employees, a number that is equalled or surpassed by many of the larger biotechnology firms that returned surveys (e.g. Amgen, Centocor, Cephalon, Gensia, etc.). Aronex, Microcide, and Ontogen are relatively small pharmaceutical companies; they reported, 60, 80, and 38 total employees respectively. The numbers that Bristol-Myers Squibb reported must be so low because the numbers reflect the situation at the particular facility that received the survey and not the situation at the entire company.

Survey results

I. Background information (survey questions 1-6)

For the responding companies, the average number of employees was 220. The median number of employees was much lower, 60, because small companies (less than 50 employees) comprised the largest group in the survey data set (Table 2). Both of these survey statistics agree well with industry-wide statistics from IBI's *U.S. Companies Database*. As computed from the database, the average number of employees was 213 and the median was 58 (the *U.S. Companies* statistics are based on numbers provided by over 270 biotechnology companies).

Table 2. **Summary statistics for total number of employees, total number of R&D employees, and total R&D spending**

	Total number of employees	Total number of R&D employees	Percent of employees that are in R&D*	Total R&D spending (in $ millions)
Number of survey responses (sample size)	70	62	62	62
Average	220	103	70	23.4
Median	60	44	76	8.3
Minimum value	2	3	3	0.3
Maximum value	4 500	1 965	100	438.0

***** This column was not calculated from the first two columns in this table. Instead, for each responding company, IBI calculated the percent of total employees that were R&D employees and then calculated summary statistics.

Source: Author.

The average number of research and development (R&D) employees at responding firms was 103. Again the median number was much lower, 44 R&D employees, because small companies were the largest group in the data set.

For each responding company, IBI calculated the percent of total employees that were R&D employees and then summary statistics were computed for those percentages. On average, between 70 and 76 per cent of employees were engaged in research and development (Table 2).

For responding firms, the average total R&D expenditure in 1995 was $23.4 million. The median total R&D expenditure in 1995 was $8.3 million (Table 2). Both of these survey statistics agree well with industry-wide statistics from IBI's *U.S. Companies Database*. As computed from the database, the average total R&D expenditure in 1995 was $20.6 million and the median was $7.7 million.

II. Research programmes in biotechnology (survey questions 7-9)

Forty-seven of the 71 responding companies (66 per cent) claimed to have an active research programme in developing new biotechnology products (Table 3). Three of the responding companies that claimed not to have an active research programme in biotechnology products did have agreements with other institutions to develop biotechnology products.

Table 3. **Number of responding companies with active research programmes in developing new biotechnology products**

	Active research programme?
Number responding Yes	47
Percent responding Yes	66%
Number responding No	24
Percent responding No	34%

Source: Author.

One company, Therapeutic Antibodies, responded that its activity "is significant new biotechnological research, but does not meet [the survey's] overly narrow definition [of biotechnology]." Fibrogenex indicated that their research did not satisfy the definition on the survey either.

Several companies reported using biotechnology as an enabling technology in basic research, new product development, and manufacturing. Forty-nine companies reported using new biotechnologies in basic research, 50 companies reported using biotechnology in new product development, and 19 companies reported using new biotechnology in manufacturing. Fewer companies may have reported using new biotechnology in manufacturing (19) than in basic research and development (49-50), because fewer companies have reached the stage where they have any manufacturing.

The majority of responding companies did not conduct new biotechnology research in more than one geographic location. Fifty-seven of 67 responding companies (or 85 per cent) conduct research at only one site. This result is explained, in part, by the fact that small and mid-sized biotechnology companies, which are the largest groups in the survey data set, often do not have more than one research facility. Ten companies reported conducting new biotechnology research at more than one location. Of these ten, seven listed multiple sites in the United States, and three included European sites.

III. Organisational changes in the 1990s (survey questions 10-11)

Thirty-one of 69 responding companies (or 45 per cent) reported a significant organisational change in the 1990s. Nine companies reported a significant downsizing, but an almost equal number, eight, reported substantial growth in the 1990s. Four companies reported making an acquisition; four companies reported being part of a merger; and three companies reported being founded. One company, Genetics Institute, reported a 60 per cent acquisition by a major pharmaceutical company. One company, Curative Health Services, reported moving out of the biotechnology industry (Table 4).

Table 4. **Organisational changes in the 1990s**

Company	Date	Activity
Amgen, Inc.	December 1994	Acquisition of another US biotechnology firm (Synergen)
Aronex	September 1995	Three way merger of Argus, Triplex, Oncologix
Arris Pharmaceutical	December 1995	Acquisition of private biotechnology company
Avid Corp.	December 1993	Merger with parent company: Quality Biotech and Avid merged to form Avid Corporation
Bristol-Myers Squibb	Continuous changes	
Connective Therapeutics	1993	Company founded in 1993, has grown from zero to 42 employees in 30 months
Cortech, Inc.	1995	Downsizing (200 to 76)
Corvas International, Inc.	December 1994	Closed subsidiary in Europe
Creative Biomolecules	September 1994	Downsizing
Curative Health Services	April 1995	Moved out of biotechnology base
Cytel Corporation	June 1996	Downsizing
Cytokine Sciences	July 1996	Acquisition
GalaGen	May 1995	Eliminated transgenics programme
Genetics Institute	1992	60 per cent acquisition by major pharmaceutical company
Genome Therapeutics Corp.	April 1996	Increase in staff and R&D spending
Gensia, Inc.	February 1995	Failed clinical trial required reduction in clinical/data handling group
Genzyme Corp.	June 1996	Acquisition of DSP for $210 million
Houston Biotechnology	February 1995	Downsizing and cost control
Human Genome Sciences, Inc.		Increase in size
Icos Corporation		Growth from 65 to 188 full time employees
Immunex	June 1993	Merger
Intercardia	1994	Company founded
Introgen Therapeutics, Inc.	1996	Rapid growth to public company
Magainin Pharmaceuticals	January 1996	Added a genomics department of research
NeoRx Corporation	February 1990	Downsizing
Neotherapeutics, Inc.	September 1996	Public offering will enable hiring additional personnel and scale-up of R&D
Neurobiological Technologies, Inc.	February 1994	Company went public
Osiris Therapeutics, Inc.	January 1993	Company founded
Progenitor, Inc.	December 1994	Downsized due to relocation
Texas Biotechnology Corp.	June 1994	Merger with Immunotherapeutics, Inc.
Therapeutic Antibodies Inc.	1995 and 1996	Rapid growth

Source: Author.

Of the 31 companies reporting an organisational change in the 1990s, 20 reported that the use of new biotechnology had been a contributing reason for the organisational change. As a result of the organisational change, almost all respondents expected R&D staff and spending to increase in both pharmaceutical and new biotechnology research areas.

IV. Internal and external R&D expenditure in 1995 (survey questions 12-14)

On the survey, the respondents were asked to report a breakdown of their 1995 total R&D expenditure including: the fraction of spending that was internal versus external; the fraction of internal R&D expenditure that was salary and staff-related expenditure; the fraction of external R&D expenditure that went to external research institutes or other companies. Several respondents were reluctant to report the details of their 1995 R&D expenditure. Several respondents left this table blank or provided only a total figure for 1995 R&D expenditure.

For respondents that did complete the R&D expenditure table on the survey, the distinction made on the survey between "Pharmaceutical" expenditure and "New Biotechnology" expenditure was confusing. The survey instructed respondents to report all new biotechnology expenditure as a subset of pharmaceutical expenditure. However, few respondents followed these instructions. As a result, no reliable summary statistics about the breakdown of internal and external R&D expenditures can be calculated from the survey data.

A few generalisations can be made on the basis of the responses to the questions about internal and external R&D expenditure. Most responding companies reported that internal R&D expenditure was greater than external R&D expenditure. Ten companies reported that all of their 1995 R&D expenditure was internal. Most responding companies reported some external R&D expenditure: 30 companies reported some 1995 R&D expenditure at external research institutes, and 24 companies reported some R&D expenditure at other companies.

Survey respondents were asked to indicate what type of R&D activities their external expenditures supported (e.g. basic research, toxicology testing, clinical research, other activities). Again, respondents were asked to distinguish between "Pharmaceutical" R&D and "New Biotechnology" R&D, and the survey instructed respondents to report all new biotechnology activity as a subset of pharmaceutical activity. However, most respondents instead reported their data in *either* the "Pharmaceutical" or the "New Biotechnology" column. Twenty-two respondents reported their external R&D activities in the "New Biotechnology" column, and 21 respondents reported their external R&D activities in the "Pharmaceutical" column.

For the 22 respondents that classified their external R&D activity as "new biotechnology," the primary external R&D activity that was funded was basic research (Table 5). On average, 73 per cent of companies' external R&D expenditure was allocated to basic research. Clinical research received 13.2 per cent of external expenditures on average, and toxicology received 5.8 per cent of external expenditures on average (Table 5); as indicated by the zero median, for at least half the respondents, no external expenditure was allocated to clinical research or toxicology.

For the 21 respondents that classified their external R&D activity as "pharmaceutical," the primary external R&D activity that was funded was clinical research (Table 6). On average 44.5 per cent of these companies' external R&D expenditures was allocated to clinical research. Basic research received 35.4 per cent of external expenditures on average, and toxicology received 11.9 per cent of external expenditures on average (Table 6).

Table 5. **Average percent allocation of external R&D expenditure to R&D activity types**

Activity type	New biotechnology	Median	Sample size
Basic research	73.3	95.0	22
Toxicology	5.8	0.0	22
Clinical research	13.2	0.0	22
Other	7.7	0.0	22

Source: Author.

Table 6. **Average percent allocation of external R&D expenditure to R&D activity types**

Activity type	Pharmaceutical	Median	Sample size
Basic research	35.4	15.0	21
Toxicology	11.9	4.0	21
Clinical research	44.5	39.0	21
Other	8.2	0.0	21

Source: Author.

Respondents were also asked what percent of their 1995 new biotechnology manufacturing activities were contracted out. Eleven people answered this question. Six companies (Aronex Pharmaceuticals, Connective Therapeutics, GalaGen, Introgen, MetaMorphix, and Neurobiological Technologies) reported that 100 per cent of their new biotechnology manufacturing activities were contracted out. Most small and mid-sized US biotechnology firms do not have their own manufacturing facilities. Prizm Pharmaceuticals reported contracting out 80 per cent of its new biotechnology manufacturing activities; NeoRx reported contracting out 50 per cent, and Isis reported contracting out 10 per cent. Magainin Pharmaceuticals and Mercator Genetics reported contracting out none of their new biotechnology manufacturing activities. It is not clear whether these companies meant to indicate that they do all of their manufacturing activities in-house or that they have no manufacturing activities.

V. Global R&D staff organisation in 1995 (survey questions 15-18)

Activities of R&D staff

The first question about R&D staff organisation was about the number of R&D staff involved in different R&D activities such as, basic research and discovery, preclinical development, clinical development, regulatory affairs, post-marketing activities, and administrative support. Survey respondents were asked to indicate whether any R&D staff were included or counted in more than one activity category. Only 34 of the 71 survey respondents answered this question about double-counting, and only nine of those answered affirmatively. For the purpose of this summary, the nine respondents that double-counted some employees were included in the analysis with the others. For this reason, the following estimates should be interpreted as the number of positions at a company and not as the number of people actually employed at a company. (One person can fill more than one position.)

The questions about R&D staff activities required respondents to distinguish between "pharmaceutical" and "new biotechnology" staff. Survey respondents had trouble putting staff in one category or the other, and survey respondents did not interpret the instructions consistently; some survey respondents reported new biotechnology staff as a subset of all pharmaceutical staff, while other respondents did not. Nonetheless, the total number of staff reported by all survey respondents in each R&D activity category is a good indication of how staff are distributed among the different R&D activity categories in the biotechnology industry (Table 7).

Table 7. **The number of R&D staff in each R&D activity category. The sum of the numbers reported by all survey respondents is listed in the table**

R&D activity	Pharmaceutical	New biotechnology
Basic research and discovery	1 045	1 560
Preclinical development	284	643
Clinical development	373	267
Regulatory affairs	82	93
Post-marketing activities	7	23
Support (administrative, other)	243	261

Source: Author.

The number of R&D staff in basic research and discovery is higher than the number of R&D staff in all other activity categories combined. The number of R&D staff involved with preclinical development is roughly the same as the number of R&D staff involved with clinical development. The number of administrative and other support staff exceeds the number of staff in regulatory affairs and in post-marketing activities (Table 7). Only three survey respondents reported having any R&D staff in post-marketing positions.

Educational degrees of R&D staff

Due to all of the difficulties mentioned above, the distinction between "pharmaceutical" and "new biotechnology" R&D staff was ignored for the purpose of analysing educational degrees earned by R&D staff. On average, the percentage of R&D staff holding no college degree is 7 per cent, the percentage holding Bachelor's degrees is 30 per cent, the percentage holding Masters degrees is 18 per cent, the percentage holding PhDs is 40 per cent, and the percentage holding medical degrees (MDs) is 5 per cent (Table 8). Almost all PhDs and MDs are involved with basic or clinical research according to the survey respondents.

Table 8. **The percentage of R&D staff holding each degree type**

Degree	Percentage of employees holding degree (average)	Median
None	7	5
Bachelors	30	31
Masters	18	15
PhD	40	38
Medical degree (MD)	5	2

Note: Only the highest degree earned by an employee was reported. The percentages listed in this table are the average of the percentages reported by 62 responding companies.

Source: Author.

Regional allocation of R&D staff

For responding companies, R&D staff were located almost exclusively in the United States. Therapeutic Antibodies was the only company to report a majority of R&D staff in Europe: 95 per cent of its R&D staff are located in Europe. Only six other companies reported having any R&D staff in Europe. Neotherapeutics reported that all of its R&D staff is located in Canada. Genzyme Corporation was the only company to report any R&D staff in Japan: 1 per cent of Genzyme's R&D staff in Japan. No respondents reported R&D staff in Mexico or Australia.

Only two survey respondents reported that they had encountered geographic locations where new biotechnology R&D staff positions were difficult to fill. Medarex reported having difficulty when it was in New Hampshire (US), and Hawaii Biotechnology reported having difficulty in Hawaii (US).

Turnover of R&D staff

On the survey, respondents were asked to estimate the number of R&D employees that began or left employment at the company in 1995. The question was designed so that respondents had to distinguish between "pharmaceutical" and "new biotechnology" staff. This distinction was problematic; again, not all respondents reported new biotechnology R&D staff as a subset of pharmaceutical R&D staff. An analysis of the data reported does not indicate that "pharmaceutical" staff are leaving and being replaced by "new biotechnology" staff. Indeed, most responding companies could not even distinguish between "pharmaceutical" and "new biotechnology" staff for the purpose of completing the survey. R&D staff cannot be placed in one category or the other. R&D positions at these companies most likely require knowledge and practice of both new biotechnology techniques and more traditional pharmaceutical chemistry.

The distinction between pharmaceutical and new biotechnology staff was ignored in the analysis of these data. Numbers reported by survey respondents indicate that, in 1995, more R&D staff began employment than left employment -- the respondents' companies are growing.

VI. Collaborative agreements and contracts in 1995 (survey question 19)

All of the 27 respondents to this question ranked the United States first in 1995 expenditure on collaborative agreements. As a group, the responding companies made most of their collaborative agreements with US research labs (Table 9). In each country, collaborative agreements with research labs outnumbered collaborative agreements with other companies (Table 9).

Table 9. **The number of collaborative agreements or contracts in each category. The sum of the numbers reported by all survey respondents is listed in the table**

Collaborative agreements and contracts	With academic/ government/ private research labs	With other companies
United States	961	110
Europe	116	57
Japan	28	13
Canada	31	5
Mexico	0	0
Australia	24	4

Source: Author.

VII. R&D forecasts (survey question 20)

The final section of the survey asked respondents to make forecasts about the amount and number of R&D spending, staff, and agreements three years into the future. Almost all survey respondents expected R&D spending, R&D staff, and the number of collaborative R&D agreements to be increased by 1998-1999 (Table 10).

Table 10. **R&D forecasts for 1998-1999. Number of each response to forecasting questions**

	Increased	Decreased	No change
R&D spending, pharmaceutical	53	0	9
R&D spending, new biotechnology	53	2	8
R&D staff, pharmaceutical	51	0	11
R&D staff, new biotechnology	53	2	9
Collaborative agreements in new biotechnology with other companies	58	0	7
Collaborative agreements in new biotechnology with universities	48	2	13

Source: Author.

NOTES

1 This chapter reports on a survey conducted for OECD by the Institute for Biotechnology Information (IBI). The resulting report, which forms the second part of the chapter, was drafted by IBI President Dr. Mark Dibner. Supplementary material and commentary has been added in an introductory section prepared by Mark Cantley, drawing on other OECD work as cited.

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IMPLICATIONS OF RECENT CHANGES IN PHARMACEUTICAL PATENT LEGISLATION IN CANADA

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Preface

For almost two decades (between 1969 and 1987), patent protection of prescription drugs in Canada was weakened by allowing compulsory licensing of drug imports. Between 1969 and 1987, about 400 licences were granted, most of them to import active ingredients. Compulsory licensing facilitated the proliferation of cheaper generic substitutes for brand-name prescription drugs, and thus made possible substantial savings for consumers and for governments responsible for funding of drug costs (Eastman, 1985). It also contributed in a major way to the development of a strong, mostly Canadian-owned generic drug industry which, by 1995, accounted for 10 per cent of the dollar value of wholesale market and 21 per cent of unit volume of prescription drug sales (DFAIT, 1996).

The multinational drug companies objected to the weakening of their intellectual property rights since the enactment of the licensing provisions and publicised their reluctance to invest and conduct R&D in Canada. The pressure to repeal the legislation gained additional impetus when compulsory licensing became an obstacle to successful completion of the free trade agreement between Canada and the United States. In 1987, the government enacted Bill C-22, which provided for a period of protection from compulsory licensing for a period of seven years in the case of licence to manufacture, and ten years in the case of licence to import. Bill C-91, which was enacted in 1992, abolished compulsory licensing completely, in accordance with the provisions of GATT and the North American Free Trade Agreement.

This paper will evaluate the impact of the restoration of intellectual property rights on R&D and foreign investment in the Canadian Pharmaceutical and biotechnology industry.

The modifications of the Canadian patent legislation affect several aspects of the pharmaceutical industry performance, and among them, the prices of prescription drugs. The connection between changes in patent protection and drug prices is not dealt with here. The paper touches only selectively on those aspects of the patenting process which are repeatedly cited as a barrier to growth of biotechnology firms. A full analysis of the patenting process, including the intricacies of patentability of various life forms, is beyond the scope of the paper.

The paper is organised as follows: the first section provides an overview of the industry in Canada and briefly summarises the history of patent legislation with a view to establishing the most important benchmarks required for quantitative analysis. The second section focuses on the statistical analysis of

the impact of the 1987 changes in patent legislation on R&D spending in the Canadian pharmaceutical industry. Trends in pharmaceutical R&D spending are compared first with those in other Canadian industries, next with pharmaceutical R&D spending in other OECD Member countries, and finally with the trends in international distribution of R&D activity by US-based multinational drug companies. The impact of the abolition of compulsory licensing on the Canadian drug industry is briefly discussed, with emphasis on R&D spending.

The third section highlights selective key information about the Canadian biotechnology industry. Most of the available data on R&D spending and investment cover the period 1989-1993. However, a rigorous analysis of the impact of changes in patent legislation, comparable to that performed in the second section for the pharmaceutical industry, was not possible, since as discussed below, biotechnology is a pervasive presence in many sectors of the economy. The limitations of the available data are further compounded by the relatively recent origins of modern biotechnology, and rapid changes in the business structures within which biotechnology activity takes place. For these reasons, much of the statistical information in the paper deals with the pharmaceutical (or "biopharmaceutical") industry, as defined in the available data sources. In the fourth section, recent mergers in the multinational pharmaceutical industry are reviewed, together with their consequences for the industry in Canada. The fifth section concludes the paper.

Introduction

The Canadian pharmaceutical industry

According to the most recent Annual Report of the Patented Medicine Prices Review Board (PMPRB, 1995), the Canadian pharmaceutical industry represents less than 2 per cent of all shipments, employment, investments and value added in the Canadian manufacturing sector. It did, however, account for 10 per cent of manufacturing sector R&D in 1994. In 1993, the industry consisted of 119 manufacturing establishments, both brand-name and generic. The factory-gate sales of drug products in 1994 were $5.94 billion, consisting of $4.45 billion in shipments, plus $2.06 billion in imports, minus $0.57 billion in exports. In recent years, imports represented about 35 per cent of sales, and exports 11 per cent. In 1994, the manufacturing segment of the industry employed 19 300 people.

In 1994, patented drug products accounted for 40 per cent of all drug sales, but only 6 per cent of the total number of drug products approved for sale (22 054). The PMPRB had jurisdiction over the prices of 871 patented drug products, of the total of 1 219 registered patented drug products (not all of these were offered for sale).

In 1994, 73 companies, including 53 members of the Pharmaceutical Manufacturers Association of Canada (PMAC) representing brand-name companies, filed reports on R&D. Of the 73 companies, ten reported no eligible R&D expenditures. Statistics Canada listed 55 R&D performers in the SIC 3741 category: in that year, 62 companies reported eligible R&D expenditures to the PMPRB (PMPRB, 1995).

The brand-name sector of the industry is dominated by multinational companies, mostly headquartered in the United States and Europe. In 1994, the companies represented by the PMAC accounted for 78 per cent of prescription drug sales, 70 per cent of unit volumes, and approximately 80 per cent of industry assets. The generic sector accounted for 10 per cent of the dollar value of wholesale market and 21 per cent of unit volumes (DFAIT, 1996).

Brief history of the patent legislation

The Patent Act of 1923 provided for compulsory licensing of pharmaceuticals for purposes of manufacturing of active ingredients in Canada. However, between 1923 and 1969, only 22 compulsory licences were granted, primarily because manufacturing in Canada was not profitable, due to the small size of the market and thus, the absence of economies of scale.

Three commissions of inquiry during the 1960s concluded that drug prices in Canada were too high, both relative to production costs and relative to other countries. In 1969, amendments to the Patent Act allowed for compulsory licensing of imports of patented medicines or their active ingredients. From 1969 to 1987, there were 765 applications filed, mostly by (then) small Canadian-owned generic companies. About 400 licences were granted, almost all of them to import active ingredients (Heller, 1995). The licensees were required to pay a fixed royalty rate of 4 per cent of the net selling price of the drug in final dosage form. In an effort to reduce their health care bills, provincial governments passed amendments to their pharmacy acts, mandating substitution of a prescribed drug by the cheapest generic equivalent in the pharmacist's inventory.

The PMAC opposed the compulsory licensing legislation from its inception and continued to do so until the provision was repealed. In 1983, the government appointed a commission of inquiry (the Eastman Commission) to investigate the impact of compulsory licensing and suggest modifications. In its Report, the Commission compared a number of statistical series for the pharmaceutical and other industries during the period 1967-1983, both for Canada and the United States. It concluded that the industry in Canada had been growing fairly steadily and that "any negative impacts of the changes to the Patent Act in 1969 appear to have been more that offset by other factors like especially strong growth in demand" (Eastman, 1985).

Specifically, the Commission found it difficult to detect a major trend in R&D expenditures that could be associated with compulsory licensing. Similar conclusions apply to the ratio of exports to imports, and to growth of net fixed assets and total assets. The value of factory shipments grew from 1967 to the early 1970s, but then exhibited a downward trend until about 1979. This is as expected in a market where compulsory licensing led to a reduction in prices (Eastman, 1985). The Commission's recommendations included a four-year period of exclusivity from generic competition, a variable royalty rate determined by the world-wide R&D-to-sales ratio of the patent holder, removal of the Patent Act provision which limited pharmaceutical patents to processes, and a variety of improvements in the process of regulation, marketing and distribution of drugs.

The review of the compulsory licensing legislation, initiated by the Liberal government, was completed by the newly elected Conservative government of Prime Minister Mulroney, and culminated in the drafting of Bill C-22. Its passage was facilitated by a public commitment by the PMAC to raise the R&D-to-sales ratio of the member companies from the 1984 benchmark of 4.9 per cent to 8 per cent by 1991, and 10 per cent by 1996 (PMAC, 1993). Press reports of the day also alleged that the government of Canada was under pressure from the US government to modify the compulsory licensing provisions as a condition for a successful completion of the free trade agreement between Canada and the United States. This agreement (FTA) came into effect on 1 January 1989.

On 7 December 1987, amendments to the Patent Act contained in Bill C-22 came into effect. They provided for a period of exclusivity (protection from compulsory licensing) for patented medicine of ten years from the date of the first Notice of Compliance in the case of licence to import, and seven years in the case of licence to manufacture. If the medicine was invented and developed in Canada, no

compulsory licence for importation could be granted, and patent protection would extend for 20 years from the date of application.

Bill C-22 also established the Patented Medicine Prices Review Board (PMPRB) with two major mandates. The first was to review the prices of patented medicines and, if a price is found excessive, to direct the patentee to lower the price or permit a compulsory licence against the product in question or, under certain conditions, another product of the patentee. The second was to monitor the commitments made by the PMAC in respect to R&D spending. Further amendments affecting the Board's remedial powers and other matters came into force in February 1993 (PMPRB, 1995).

The board has exercised its powers, rolled back prices, and imposed penalties on offending companies. Recently, some pharmaceutical and biotechnology firms attempted to circumvent the jurisdiction of the board by dedicating Canadian patents to the public. The underlying premise is that the long lead time a potential competitor would need to enter the market would protect the original patent holder's sales and profits in the absence of patent protection. The board has, however, dealt with such attempts by extending its jurisdiction to products whose patents have been so dedicated. In other words, the definition of "patentee" includes a patentee in the post-dedication period (Heller, 1995).

Total abolition of the compulsory licensing provisions of the Patent Act was proposed in Bill C-91, tabled on 23 June 1992. While abolishing the compulsory licensing section of the Act, Bill C-91, which received Royal Assent on 4 February 1993, also abolished all compulsory licences issued on or after 20 December 1991, the date of release of GATT draft proposals on intellectual property, which included a ban on routine use of compulsory licensing.

The 1991 GATT provisions on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which required a 20-year patent protection for almost all inventions from the date of filing of the first complete application, were one of the factors responsible for the enactment of Bill C-91. Another factor was the treatment of intellectual property rights in the North American Free Trade Agreement (NAFTA), announced on 12 August 1992. Article 1703 requires equal treatment for drugs developed domestically and for those developed in the other member countries. Article 1709 includes, among other provisions, the requirement that each country extend the length of patent protection to 20 years from the date of filing. This term may be further extended to compensate for delays caused by the regulatory process.

In the opinion of some lawyers, the compulsory licensing provisions of the Patent Act could be accommodated under the "limited exception" provision of GATT and NAFTA. It allows for limited exceptions to the exclusive patent rights if they do not unreasonably conflict with a normal exploitation of the patent. The negotiating history of these treaties and the current position of the government of Canada do not, however, favour this interpretation (Heller, 1995).

An additional relevant recent revision of the Patent Act (not explicitly directed at pharmaceutical or biotechnological inventions) is contained in Bill C-115, in effect since 1 January 1994. It permits the Commissioner of Patents to authorise federal or provincial governments to use a patented invention to supply the domestic market for a limited period. Thus a government, but not a generic drug company, could obtain a compulsory licence to import, make or sell patented medicines, as an additional means to control the price of pharmaceuticals (Heller, 1995).

Bill C-22 mandated a cabinet review of the impact of the Patent Act amendments after four years, and a Parliamentary review after nine years (i.e. sometime in 1997). This review was completed in April 1997, and the government put forward corresponding changes in early 1998. The key questions to be answered relate to the benefit-cost analysis of the trade-off between higher prices of prescription drugs

(due to the abolition of compulsory licensing) and the contributions to the Canadian economy of increased R&D activity by multinational pharmaceutical companies. In addition, the implications of the abolition of compulsory licensing for the (predominantly Canadian-owned) generic industry are a sensitive policy issue.

Tax incentives for R&D

Canada's system of tax incentives for R&D has been evolving since 1944. Until 1983, the federal tax law measures consisted of three components: (1) deduction of eligible R&D expenditures, both current and capital; (2) an allowance for incremental R&D (50 per cent of the difference between R&D spending in the current year and the average of preceding three years); and (3) a 10 per cent tax credit for eligible R&D expenditures (the rates for R&D in Atlantic Canada were 20 per cent, and rates for R&D expenditures by small businesses were 25 per cent), up to a specified annual limit. In 1983, the annual limits on R&D tax credits were eliminated, limited refunds for unused investment tax credits were allowed, the existing carryforward period was extended to seven years, and a three-year carryback provision for R&D tax credits was introduced. The incremental allowance was eliminated, and the R&D tax credit rates were raised by 10 percentage points. The government also introduced a "scientific research tax credit" mechanism, allowing firms to transfer unused R&D tax credits to investors. However, the system was subject to abuse and fraud, and was terminated in 1985.

In 1985, the definition of eligible R&D activities was expanded to include experimental development. Payments by corporations for R&D performed on their behalf by approved organisations, such as the Medical Research Council, or the Natural Sciences and Engineering Research Council, became eligible for R&D tax incentives in 1986. The 1987 tax reform extended the carryforward period for R&D tax credit from seven to ten years. Additional changes in R&D tax incentives were introduced in 1988 (shorter turnaround time for processing of refund claims). In 1992, the treatment of tax credits for overhead R&D expenditures was simplified, eligibility for capital R&D expenditures was expanded, and improvements were made in the administration of R&D tax programmes (Clark et al., 1993; Iqbal, 1995).

Several Canadian and US studies published in the 1980s attempted to evaluate the impact of tax incentives on R&D spending. Based on data covering a cross-section of industries, they concluded that each dollar of tax abatement increased R&D expenditures by anywhere from 30 to 80 cents (Palda, 1993). All of the changes in R&D tax incentives discussed above applied to all Canadian industries, and there is no reason to believe that the benefits derived by the pharmaceutical industry differed from those derived by other research-intensive sectors of the economy. There is anecdotal evidence from press reports that some changes in the tax treatment of R&D encouraged firms to re-classify some of their activities so as to benefit from tax concessions. Survey data from Canada and Sweden put the amount of such re-classification at about 13 to 14 per cent of R&D expenditures (Palda, 1993). While it is plausible to assume that the extent of such re-classification varies from industry to industry, there is no evidence to indicate that the pharmaceutical industry benefited disproportionally.

Impact of legislative changes on R&D in pharmaceuticals

Three methodological approaches

One approach to assessing the consequences of increased patent protection is to observe the trends in pharmaceutical and biotechnology R&D spending and investment in Canada over time. This is pursued in the section below. The two critical dates are 1987 (the enactment of Bill C-22), and 1992 (the enactment

of Bill C-91). The testable hypothesis is that there exists a distinct (upward) change in the trend in R&D and investment at both of these dates. For all practical purposes, only the 1987 date is relevant, since not enough data has been accumulated since 1992. The timing of the effect is also likely to be confounded by leads and lags in the R&D budgeting process, and by the fact that some companies may have anticipated the passage of the legislation and modified their spending earlier. A more serious methodological problem is the possibility that the observed increase in R&D spending by the PMAC member companies in Canada is a part of some underlying change in the pattern of R&D spending, unrelated to modification of the patent legislation. For example, it could be a consequence of a paradigm change in pharmaceutical research, which took place in the 1980s. It is a shift from a largely empirical industrial research process (based on trials of many compounds) to a more rational search for innovation, grounded on more effective use of scientific knowledge and computerised research technologies (Gambardella, 1995).

Alternatively, it could be that changes in the Canadian pharmaceutical R&D spending are a part of a more general change in R&D spending behaviour that the industry has in common with other sectors of the Canadian economy. Finally, the increase in R&D spending of the PMAC member companies, most of which are subsidiaries of multinational corporations, could be due to a global trend toward decentralisation of R&D activities from corporate headquarters to subsidiaries (Grandstrand *et al*., 1993).

In what follows, various attempts are made to separate these and other factors, which may have influenced pharmaceutical R&D spending in Canada from the contribution made by patent protection change. Canadian pharmaceutical R&D spending is compared to R&D spending in other Canadian industries to control for factors affecting all sectors of the Canadian economy. There is also a review of the behaviour of R&D spending in the pharmaceutical industry in Canada in relation to other OECD Member countries, with the help of the OECD ANBERD database. An attempt is made here to determine whether the pharmaceutical industry in Canada merely follows a general trend or whether it has behaved differently, first in response to compulsory licensing and then in response to Bill C-22. The position of Canada over time as a location for foreign investment and R&D activity of US-owned multinationals is also examined.

Data availability dictates that the bulk of the quantitative analysis focus on R&D spending in pharmaceuticals. The assessment of the impact of patent changes on investment is based largely on anecdotal evidence, since no systematic database is available. As for biotechnology, the paper relies heavily on the extensive recent study by Heller (1995). However, its statistical information covers the period 1989-93, and therefore does not make it possible to make any solid quantitative inferences about the implications of changes in patent legislation.

Trends within the Canadian pharmaceutical industry

Two separate data sources are available to evaluate the impact of patent legislation on pharmaceutical R&D spending. One set of data, pertaining to patent-holding companies, is collected by the PMPRB and by the PMAC, and is discussed in this section. Another set of data, reported by Statistics Canada, covers the industry as a whole and is discussed in the next section.

While the PMAC has collected and reported data on R&D spending of its member companies for several decades, reliable time-series based on consistent definitions are available only since 1984. They are reported in Table 1 and show a marked acceleration in annual rates of growth of R&D spending for the years 1987, 1988 and 1989; starting in 1990, the growth rates, while still substantial, exhibit a more moderate pace.

Table 1. **Rate of growth of pharmaceutical R&D expenditures in Canada, 1984-1994**

Year	Current $ (million)	Rate of growth (1984=100)	Constant 1986 $ (million)	Rate of growth (1984=100)	Annual rate of growth (constant $)
1984	69	100.0	72	100.0	not available
1985	82	118.8	84	116.7	16.7
1986	93	134.8	93	129.2	10.7
1987	103	149.3	98	136.1	5.4
1988	166	240.6	151	209.7	54.1
1989	245	355.1	213	295.8	41.1
1990	305	442.0	257	356.9	20.7
1991	376	544.9	308	427.8	19.8
1992	412	597.1	334	463.9	8.4
1993	504	614.6	404	561.1	21.0
1994	561	813.0	447	620.8	10.6

Note: The GDP implicit price index, 1986=100 (Statistics Canada Cat. No 13-001 and 13-201), was used to calculate R&D spending in constant dollars.

Source: PMAC, 1995*b*.

The PMPRB collects data on R&D spending of companies with active Canadian patents pertaining to medicine sold in Canada. Its data series covers a shorter period than either the PMAC or Statistics Canada, but provides insight into the composition of R&D activity and includes the R&D-to-sales ratios for the two groups of patent-holding companies. Table 2 summarises the main aggregates monitored by the PMPRB. The R&D expenditures in current dollars increased by 238.6 per cent between 1988 and 1994; Statistics Canada data, reported in Table 5 in the next section, show an increase of 192.4 per cent over the same period, and a 202.5 per cent increase between 1988 and 1995. The coverage of the industry differs between the two sources; for example, for the year 1993, Statistics Canada data represented 119 establishments, while only 70 companies reported to the PMPRB.

Recent information material prepared by the PMAC (e.g. PMAC, 1992; PMAC, 1995a; PMAC, 1995b) describes the R&D spending data from Annual Reports of the PMPRB as "R&D spending by PMAC members". Strictly speaking, the definition R&D in the PMPRB reports refers to "patentees", regardless of membership in the PMAC, but the differences are minor. For example, for the year 1994, the PMAC reported that its patent-holding member companies spent $514 million on R&D. The PMPRB figure for the same year, reported in Table 2 below, is $561 million, implying that non-PMAC member companies selling patented medicines in that year spent $47 million. The PMAC member companies without patented medicines on the market in 1994 spent $70 million, bringing the PMAC total to $584 million (PMAC, 1995*b*).

Table 3 shows R&D spending by performer. The bulk of the R&D activity is performed by the patentees or by related companies. Heller (1995) believes that only research performed in the university/hospital sector is likely to give rise to Canadian intellectual property rights. Given that only between 23.6 per cent and 25.0 per cent of the total R&D spending during the 1988-94 period was in that sector, the long-term economic contribution of the increased pharmaceutical R&D spending to Canada, in Heller's view, may be limited. However, a long-standing tradition in Canadian literature on R&D and science policy decries the relatively low proportion of R&D activity performed in the private sector (for a

review, see e.g. Palda, 1993). The share of the private sector in the Canadian pharmaceutical industry, in this respect, is closer to the ratios observed in other countries.

Table 2. **Canada: Total R&D expenditures and R&D-to-sales ratios, pharmaceutical companies with Canadian patents pertaining to medicine sold in Canada**

Year	Number of companies reporting	Total R&D expenditures ($ million)	Sales revenues ($ million)	R&D-to-sales ratio (%)	
				All patentees	PMAC patentees
1988	66	165.7	2 718.0	6.1	6.5
1989	66	244.8	2 973.0	8.2	8.1
1990	65	305.5	3 298.8	9.3	9.2
1991	65	376.4	3 894.8	9.7	9.6
1992	71	412.4	4 164.4	9.9	9.8
1993	70	503.5	4 747.6	10.6	10.7
1994	73	561.1	4 957.4	11.3	11.6

Notes: Total R&D expenditures include current expenditures (95.6 per cent of the 1994 total), capital equipment expenditures (3.4 per cent) and allowable depreciation expenses (1 per cent). The reported expenditures are only those that would have been eligible for Investment Tax Credit for scientific research and experimental development under the provision of the Income Tax Act in effect on 1 December 1987.

As new patents are granted and others expire, the group of companies required to file R&D data may change from year to year.

Source: Patented Medicine Prices Review Board (PMPRB), 1995.

Table 3. **Canada: Current R&D expenditures by R&D performer. Companies with Canadian patent pertaining to medicine sold in Canada (percentages)**

R&D performer	1988	1989	1990	1991	1992	1993	1994
Patentees	60.4	58.6	53.1	56.6	62.7	59.0	59.2
Universities and hospitals	23.6	24.1	24.1	23.7	23.6	25.0	23.9
Other companies	16.0	9.6	16.4	13.5	7.0	8.3	7.9
Others		7.7	6.4	6.2	6.7	7.7	9.0
Total	100	100	100	100	100	100	100

Note: The category “others” includes individuals, organisations such as private clinics, and federal and provincial governments. For the year 1988, spending by “others” is reported together with spending by “other companies”.

Source: Patented Medicine Prices Review Board (PMPRB), *Annual Report*, 1989, 1991, 1993, and 1995.

As shown in Table 4, applied research continues to represent the largest share of R&D (62.7 per cent in 1994). In Canada, it comprises mostly clinical and pre-clinical trials. Expenditures for drug regulation submissions, bio-availability studies, and Phase IV clinical trials are reported in the “other R&D” category. Basic research as a share of total R&D reached its peak in 1990 and has been declining since. In 1994, it declined in absolute dollar terms as well (for the first time since PMPRB started reporting).

Table 4. **Canada: Composition of current R&D expenditures, companies with Canadian patents pertaining to a medicine sold in Canada (percentage of all current R&D expenditures)**

Type of research	1988	1989	1990	1991	1992	1993	1994
Basic research	**19.1**	**23.4**	**27.2**	**26.5**	**26.4**	**25.3**	**21.9**
• Chemical	10.0	11.9	14.0	12.2	12.3	10.9	9.2
• Biological	9.0	11.5	13.0	14.3	14.1	14.4	12.6
Applied research	**67.2**	**62.7**	**58.0**	**57.3**	**57.1**	**60.3**	**62.7**
• Manufacturing process	4.0	6.9	5.0	5.3	5.0	5.5	6.6
• Pre-clinical I	9.0	5.1	5.0	2.8	1.8	1.9	1.4
• Pre-clinical II	4.0	4.3	3.0	2.4	2.3	2.3	3.3
• Clinical I	3.0	2.7	2.0	4.3	3.0	3.6	4.0
• Clinical II	15.0	14.6	8.0	7.1	7.1	10.5	12.2
• Clinical III	33.0	28.9	38.0	35.3	37.8	36.5	35.2
Other R&D	**13.7**	**13.9**	**14.8**	**16.2**	**16.5**	**14.4**	**15.4**
Total	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Source: Patented Medicine Prices Review Board (PMPRB), *Annual Report*, 1989, 1990, 1991, 1992, 1993, 1994 and 1995.

These breakdowns are of immediate interest, since critics of Bill C-22 and Bill C-91 have argued that any increases in R&D spending in Canada by foreign-owned multinationals will most likely be heavily skewed toward the applied end of the spectrum. The perception, at least in some circles of the Canadian scientific community, is that the long-term benefits of basic research for Canadian science, and ultimately for the economy, are greater than those from equivalent amounts spent on applied research.

Pharmaceuticals vs. other Canadian industries

It is not *a priori* evident that the growth in pharmaceutical R&D spending in Canada in the 1988-1995 period should be attributed to tightening of patent protection. The question explored in this section is whether the growth observed above may be due to an improved general climate for R&D in Canada. If this is the case, other sectors of the Canadian economy should exhibit a similar R&D spending growth.

The trends in R&D expenditures of selected Canadian industries as reported by Statistics Canada are summarised in Table 5. It shows that the pharmaceutical R&D spending as a share of all manufacturing R&D spending rose from 4.5 per cent in 1975 to 9.4 per cent in 1995. There appears to be a clear discrete jump in this share around the year 1988; this would suggest that Bill C-22 had a positive effect. A similar change in trend is evident when pharmaceutical R&D is calculated as a percentage of R&D in all industries.

Table 5. **Canada: Total intramural R&D expenditures by industry (millions of current $)**

Year	Pharma and medicine	Manufacturing	All industries	Pharma R&D as a % of	
				Manufacturing	All industries
1975	25	561	700	4.5	3.6
1976	26	603	755	4.3	3.4
1977	25	669	857	3.7	2.9
1978	27	795	1 006	3.4	2.7
1979	33	1 000	1 266	3.3	2.6
1980	43	1 247	1 571	3.4	2.7
1981	52	1 700	2 124	3.1	2.4
1982	58	1 958	2 489	3.0	2.3
1983	66	2 021	2 585	3.3	2.5
1984	63	2 256	2 994	2.8	2.1
1985	81	2 601	3 605	3.1	2.2
1986	103	2 748	3 996	3.7	2.6
1987	107	2 932	4 312	3.6	2.5
1988	134	3 199	4 618	4.2	2.9
1989	177	3 225	4 783	5.5	3.7
1990	256	3 475	5 216	7.4	4.9
1991	261	3 576	5 439	7.3	4.8
1992	300	3 669	5 845	8.2	5.1
1993	366	3 971	6 374	9.2	5.7
1994[p]	392	4 144	6 743	9.5	5.8
1995[i]	405	4 326	6 999	9.4	5.8

Note: "i" describes "intentions", and "p" stands for "preliminary".

Source: Statistics Canada, *Industrial Research and Development,* Catalogue No. 88-202, 1982, 1983, 1984, 1987, 1989, 1992, 1993, 1995.

Pharmaceuticals in Canada vs. pharmaceuticals abroad

The analysis in the previous section suggests that pharmaceutical R&D grew disproportionately with the R&D in other sectors of the Canadian economy in the aftermath of Bill C-22. The possibility remains, however, that the faster growth is due to factors specific to the pharmaceutical industry, regardless of the country. For example, as mentioned in the section on methodological approaches, there could have been a paradigm shift in pharmaceutical research methodology, or a "cluster" of innovations could have caused an acceleration of pharmaceutical R&D spending. If this is the case, the share of pharmaceutical R&D in the total R&D in all sectors of the economy should be growing in other countries as well.

This hypothesis is explored in this section with the help of the ANBERD database compiled by the OECD. It provides figures on Business Expenditures on R&D (BERD), by industry, for 15 OECD Member countries (Australia, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Japan, the Netherlands, Norway, Spain, Sweden, United Kingdom, United States), for the period 1973-1992 (for some countries also 1993 and 1994). In order to ensure cross-country comparability, the development of

the ANBERD data required adjustments; therefore these figures do not necessarily concord with the R&D spending estimates reported in the various national statistical publications. For purposes of this section, the aggregate of these 15 countries is referred to as "the OECD". Whenever necessary, the ANBERD data, given in national currencies, were converted into US dollars using the purchasing power parity exchange rates, developed by the OECD.

For ease of interpretation, the results of this analysis are presented in the form of comparisons of plots of relevant time series. Figure 1, illustrating "Pharma R&D spending (Canada as percentage of OECD)", shows a relatively steady climb in Canada's share since 1987. Figure 2 compares the rate of growth of pharmaceutical R&D expenditures in Canada with the OECD growth. The two series track each other very closely until 1989; after that year, Canada's rate of growth surges ahead of that of the OECD. A similar pattern is observed in Figure 3, where Canada's growth is compared with that of the United States. It is reasonable to conclude from this analysis that the passage of Bill C-22 had a positive effect on the growth of R&D spending in Canada.

The ANBERD data is also used to control for the presence of factors common to the pharmaceutical industry in all OECD Member countries. In Figure 4, pharmaceutical R&D is calculated as a percentage of R&D in all industries. For the OECD as a whole, this ratio shows a steady rise during the whole period; for Canada, however, it declines until about 1987 and rises thereafter. When pharmaceutical R&D is calculated as a percentage of manufacturing (Figure 5), and chemical industry R&D (Figure 6), the rising trend in Canada begins as early as 1984. The same patterns are evident when these three ratios are compared between Canada and the United States (not shown here). In this case, it appears that the pharmaceutical R&D share in both Canada and the United States started rising as early as 1984. The rise in all three ratios for Canada, however, is faster than for the United States. Again, these patterns are consistent with the hypothesis that the enactment of Bill C-22 had a significant positive effect on pharmaceutical R&D spending in Canada.

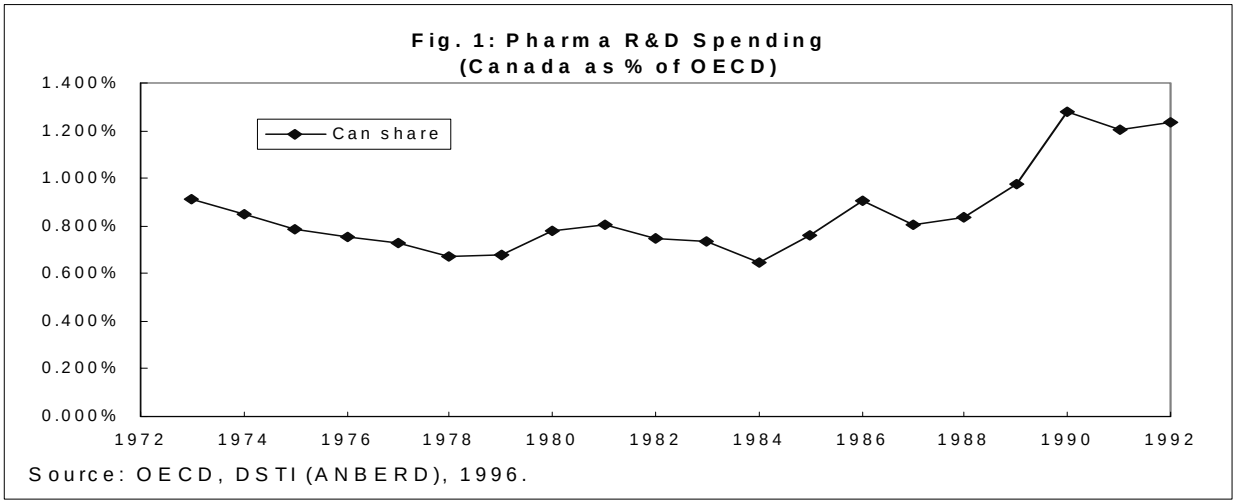
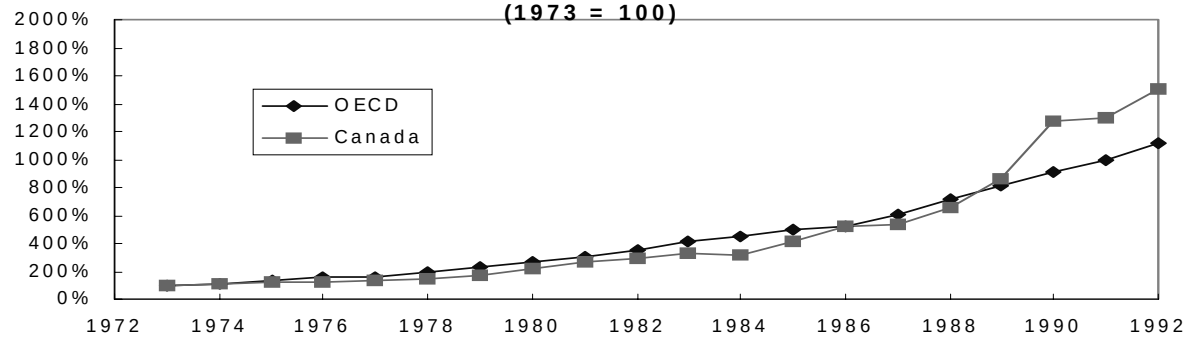
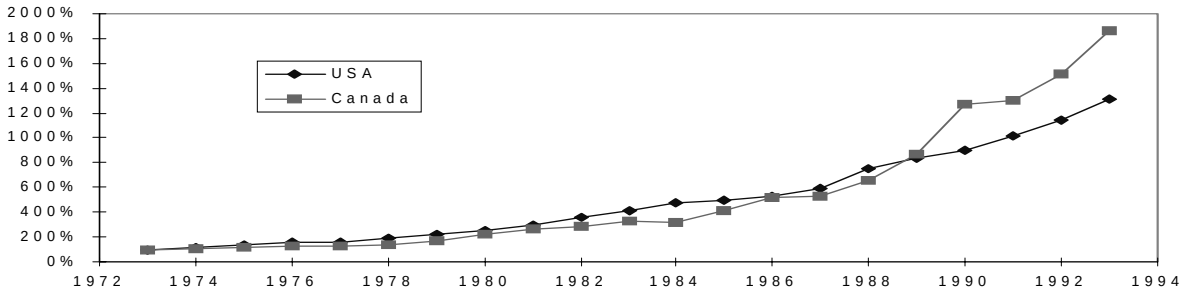


Fig. 2: Rate of Growth of Pharma R&D Expenditures (1973 = 100)



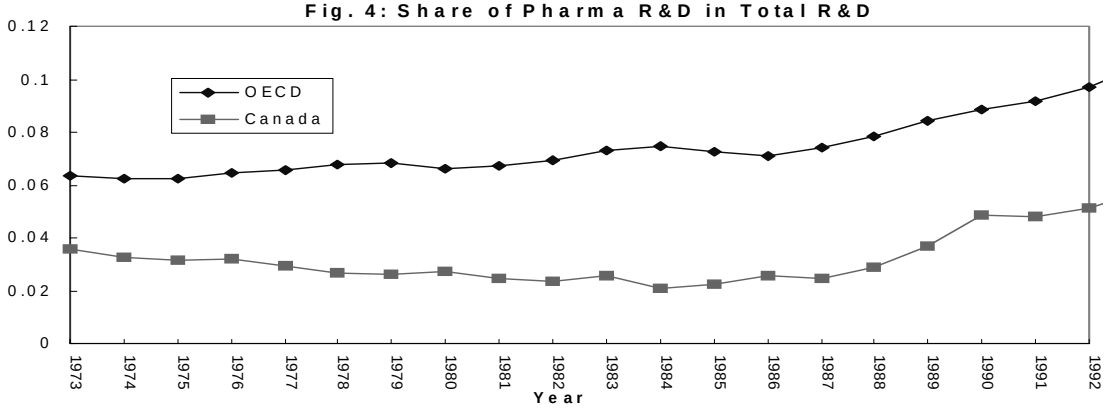
Source: OECD, DSTI(ANBERD), 1996.

Fig. 3: Rate of Growth of Pharma R&D Expenditures (1973 = 100)

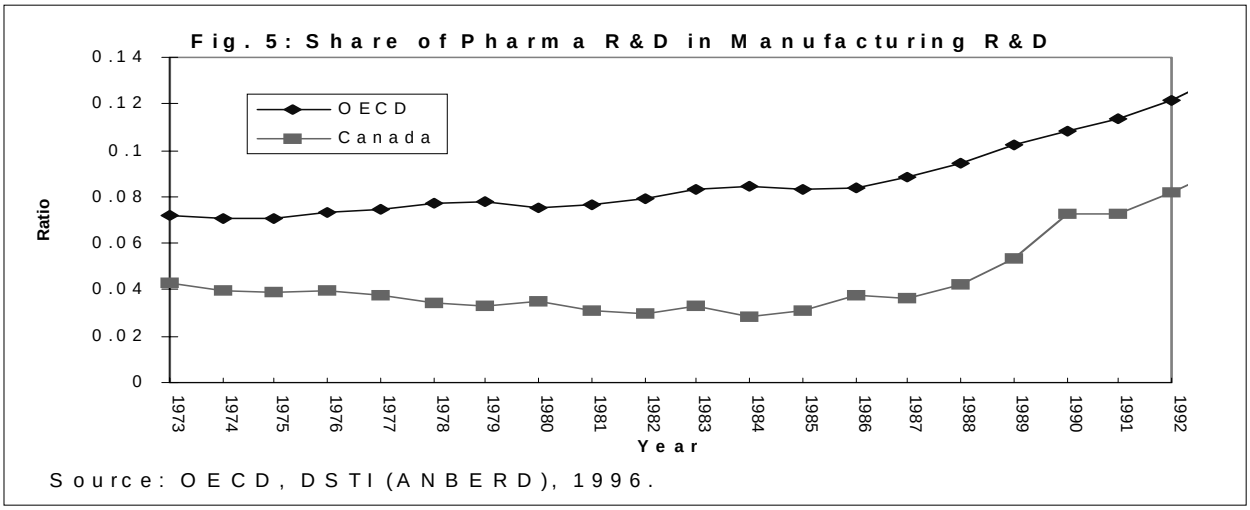


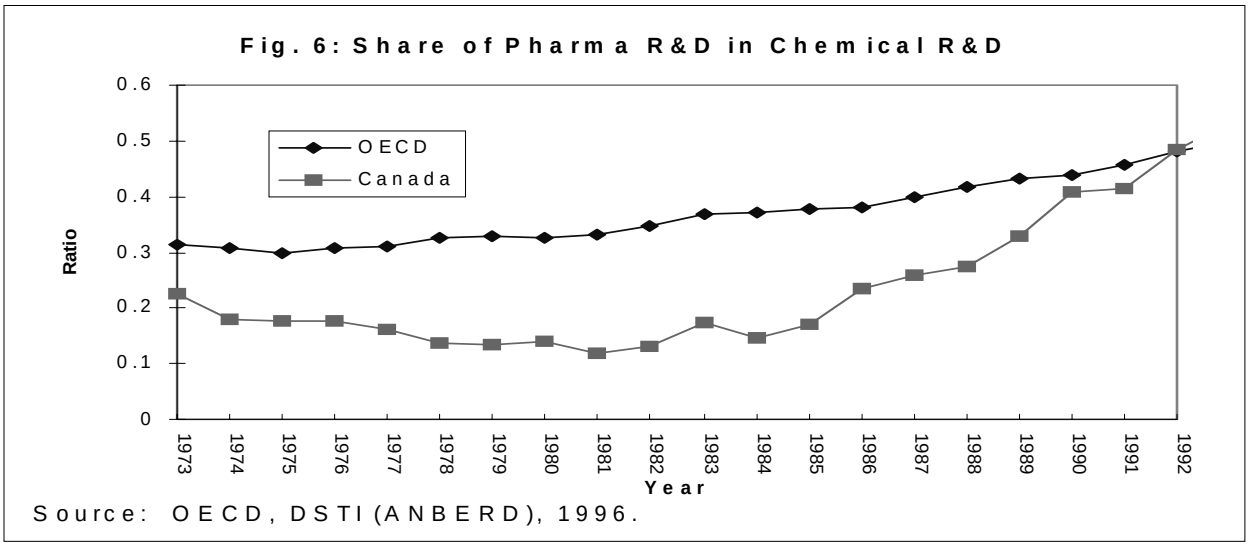
Source: OECD, DSTI(ANBERD), 1996.

Fig. 4: Share of Pharma R&D in Total R&D



Source: OECD, DSTI(ANBERD), 1996.





Location of R&D activity by multinational corporations

It is conceivable that the apparent increase in pharmaceutical R&D spending in Canada can be attributed to the growing attractiveness of Canada as a location for R&D in general, not just in the pharmaceutical industry. This hypothesis is explored with the help of information on the geographic distribution of R&D expenditures by foreign subsidiaries of US-owned corporations.

US multinational corporations are the dominant source of foreign direct investment in the Canadian economy. Historically, Canada was a primary foreign location both for investment and for R&D activities of US multinationals, given its proximity to the United States, common language, closely related business practices and cultural similarity. However, with the growing maturity of multinational corporations, other countries became attractive locations. The US Department of Commerce statistics, published in Survey of Current Business, show that in 1966, Canada represented over 30 per cent of US foreign direct investments in "all industries", and slightly higher shares in "manufacturing" and "chemicals and allied products". By 1994, this share dropped to less than 12 per cent in "all industries" and in "chemicals and allied products" and to just under 16 per cent in "manufacturing" (the data for "pharmaceuticals" are, unfortunately, not available).

The decline in Canada's share of R&D performed abroad by US-owned multinationals was even more dramatic, as shown in Table 6, based on the periodic "benchmark" surveys of US foreign direct investment conducted by the US Department of Commerce. The table shows a decline in Canada's share of pharmaceutical R&D from 8.6 per cent to 7.3 per cent between 1977 and 1982 (when compulsory licensing was in effect), while the other three industry aggregates showed an increase. In contrast, the pharmaceutical industry shows an increase in the post-compulsory licensing year 1989, while the other industry aggregates either declined, remained constant, or showed only a marginal increase.

Table 6. **Canada's share of foreign direct investment and foreign R&D spending by US-owned multinational corporations (Canada as a percentage of all countries)**

Year	All industries		Manufacturing		Chemicals		Pharmaceutical	
	Investment	R&D	Investment	R&D	Investment	R&D	Investment	R&D
1966	30.3	27.6	32.3	29.5	27.5	33.8	n.a.	n.a.
1977	23.5	12.3	25.3	10.7	17.6	13.0	n.a.	8.6
1982	20.9	14.9	22.5	12.3	22.9	10.6	n.a.	7.3
1989	16.7	13.0	20.4	13.3	16.5	10.7	n.a.	10.0

Notes: n.a. = not available.

Canada's shares of investment are calculated from "US direct investment position on a historical cost basis".

Data on R&D spending are for "majority-owned nonbank affiliates of nonbank US parents". For the years 1966 and 1977, they represent "R&D expenditures by affiliates" (for themselves and for others); for the years 1982 and 1989, they represent "R&D expenditures for affiliates" (by themselves and others).

Sources: Data on investment: US Department of Commerce, no date; US Department of Commerce: *Survey of Current Business*, 1978, 1983 and 1990.
Data on R&D: US Department of Commerce, 1970, 1981, 1985 and 1992.

The US Pharmaceutical Manufacturers Association (PMA) periodically reports data on R&D spending of its member companies, both in total, and the amount spend abroad. Both series cover the period 1979-1994 and show that the US pharmaceutical industry's spending abroad as a proportion of total company R&D spending grew from 8.4 per cent in 1970, to 21.6 per cent in 1980. It levelled off somewhat during the 1980s, registered 19.9 per cent in 1988, and was expected to reach 17.6 per cent in 1994.

The data for R&D spending by the PMA member companies in Canada as a percentage of R&D spending abroad is available (with some gaps) for the period 1977-1994. As shown in Table 7, Canada's share of the total spending abroad moved roughly between 4 per cent and 6 per cent during the late 1970s and early 1980s, and rose somewhat in the second half of the 1980s. The year 1989, i.e. two years after enactment of Bill C-22, registered the historically high share of 10.4 per cent, but it dropped to 7.1 per cent in 1992, rising again to 7.5 per cent in 1994. At the same time, spending abroad as a percentage of total R&D spending of PMA member companies changed only marginally since 1987, suggesting the absence of a significant trend toward decentralisation of R&D away from headquarters of US-owned multinational pharmaceutical corporations.

Table 7. **Trends in R&D spending of PMA member companies, ethical pharmaceuticals**

Year	Total R&D ($ million)	Domestic US R&D ($ million)	R&D abroad ($ million)	Abroad as % of total	Canada as % of abroad
1977	1 276.1	1 063.0	213.1	16.7	5.8
1978	1 404.0	1 166.1	237.9	16.9	5.1
1979	1 626.8	1 327.4	299.4	18.4	5.0
1980	1 976.7	1 549.2	427.5	21.6	4.0
1981	2 339.5	1 870.4	469.1	20.0	5.5
1982	2 773.7	2 268.7	505.0	18.2	6.1
1983	3 217.6	2 671.3	546.3	17.0	7.0
1984	3 578.8	2 982.4	596.4	16.7	not available
1985	4 077.6	3 378.7	698.9	17.1	7.3
1986	4 740.1	3 875.0	865.1	18.2	7.5
1987	5 502.2	4 504.1	998.1	18.1	7.6
1988	6 537.5	5 233.9	1 303.6	19.9	6.3
1989	7 330.0	6 021.4	1 308.6	17.8	10.4
1990	8 420.3	6 802.9	1 617.4	19.2	not available
1991	9 705.4	7 928.6	1 776.8	18.3	7.4
1992	11 467.9	9 312.1	2 155.8	18.8	7.1
1993	12 740.9	10 477.0	2 263.0	17.8	7.4
1994	13 449.4	11 101.4	2 348.0	17.4	7.5

Sources: Pharmaceutical Manufacturers Association, *Backgrounder: US Pharmaceutical R&D and Sales*, February 1994; Pharmaceutical Manufacturers Association, *Annual Survey Report*, 1983-85, 1985-86, 1986-87, 1987-89, 1989-91, 1990-93, 1993-96; personal communication (Canada 1977 -1981).

Any conclusions about the impact of legislative changes that may be drawn from these statistics are somewhat less clear-cut than those reported previously.

Trends in investment

Neither Statistics Canada nor the PMAC report data on assets or investments in the industry in sufficient detail and over a sufficiently long period of time to allow an analysis of the impact of modifications in the patent legislation. The information on "investment" resulting from Bill C-22 and Bill C-91, as reported by the PMAC, consists of various lists of new spending announced by individual member companies. It is a mixture of announced expansions of production capacity, increased intramural spending (both current and capital), and grants to and joint ventures with various Canadian universities, hospitals, and research institutes. The amounts and dates in different sources sometimes differ from each other; one reading of the total of the various spending announcements by different PMAC member companies is as follows: announcements from January 1992 to 8 June 1992 represented $320 million; those made from 23 June 1992 to 14 January 1993 represented $666.25 million, and those made between November 1994 and October 1995 represented $48.05 million (PMAC, 1993; PMAC, 1995b; DFAIT, 1996; Boards of Trade, 1996).

Impact of the abolition of compulsory licensing on the Canadian generic industry

The Canadian generic drug industry originally focused on manufacturing of products whose patents have expired, or on products manufactured under compulsory licence. Its sales have continued to grow, even after the abolition of compulsory licensing. For example, according to IMS Canada, the increase in 1994 over 1993 represented 38 per cent (DFAIT, 1996). Over the same period, sales of patented drugs declined by almost 1 per cent, while sales of all non-patented drugs (both generic and brand-name products no longer subject to patents) increased by 18 per cent (PMPRB, 1995). The continuing growth of sales of generic drugs can be attributed to the spread of provincial drug formularies, health care budget cuts, reference pricing systems, hospital policies favouring generic prescribing, and other factors.

Some Canadian generic firms have evolved into fully integrated pharmaceutical companies increasingly engaged in R&D (CDMA, 1995c). The two largest generic companies are Apotex, Inc. and Novopharm Ltd. According to a 1995 estimate (Yorkton, 1995), 20 per cent of all prescriptions dispensed in Canada are filled with products of these two companies. In 1994, Apotex (with an R&D-to-sales ratio of 16.2 per cent, up from 14.4 per cent in 1993), ranked 19th in absolute volume of R&D spending among all Canadian companies from all industries (up from 30th place in 1992), and third among Canadian pharmaceutical companies (after Merck Frosst and Connaught Laboratories). Novopharm (with an R&D-to-sales ratio of 7.9 per cent in 1994, down from 8.7 per cent in 1993) ranked 42nd overall, and tenth among Canadian pharmaceutical companies (Report on Business Magazine, 1994, 1995).

Neither company is listed on the stock exchange and information on their sales and profits is not available. Informed observers estimate the 1996 revenues for Apotex at $1 billion; Novopharm gives its 1995 revenues at $600 million, and its sales growth at 10 per cent a year. The profit margins for both companies are estimated to be in excess of 30 per cent (Globe and Mail, 1995).

According to the Canadian Drug Manufacturers Association, the average R&D-to-sales ratio for the generic companies in Canada in 1993 was 13 per cent, up from 7 per cent in 1988 (CDMA, 1994a). The Association does not provide time-series data for the dollar value of R&D expenditures, and their growth during the period 1988-93 cannot be compared with the growth of R&D spending by the brand-name companies. The rise in the R&D-to-sales ratio from 7 per cent to 13 per cent suggests, however, that the generic companies may be responding positively to the increased patent protection provided by Bill C-22. The response of their R&D to Bill C-91 cannot be assessed from the data presently available.

Canadian generic drug companies are also forming alliances with brand-name PMAC member companies. For example, Novopharm has such agreements with Marion Merrell Dow, with Merck Frosst, and with Rhône-Poulenc Rorer. The terms of such agreements may stipulate that the brand-name companies allow copying of their products six months before patent expiry, and, in exchange, benefit from the experience of their traditional adversaries in marketing of generic drugs (Nadeau, 1996).

Recent strategic alliances between Canadian generic firms and biotechnology firms include a purchase agreement between Cangene Corp. of Mississauga with Apotex Biotechnology Holdings (ABH), a subsidiary of the parent company which also owns Apotex Inc. (Nadeau, 1996). In July 1995, Novopharm Biotech (a division of Novopharm Ltd.) completed a merger with the San Diego biotechnology firm Hygeia. The new company is developing monoclonal antibody technology for the treatment of cancer (Yorkton, 1995). Both Cangene and Hygeia are listed on the stock exchanges, while Apotex and Novopharm are not. The take-overs will thus give both generic firms access to public financing through their new subsidiaries (Globe and Mail, 1995).

As discussed in a previous section, Bill C-91 contained a provision in which compulsory licences granted on or after 20 December 1991 would cease to have effect on the day the Bill came into force. This provision has been described by the opponents of the legislation as "retroactive", and has been a major cause for complaint from the generic segment of the drug industry, on the grounds that it did not allow the generic companies to adjust to the new rules, and made worthless the investment they already made in preparation for production under licence (CDMA, 1994b). More than 50 applications for compulsory licences were filed in 1991, approximately twice the number of applications filed in 1990. More than 120 additional applications were filed in the first half of 1992; none of these was, of course, granted (PMAC, 1992).

Another bone of contention is a provision of Section 55.2 of Bill C-91 which prevents the issuing of a Notice of Compliance to a generic drug manufacturer when there is a challenge over the patent rights. These "linkage" regulations were promulgated on 12 March 1993 and came into effect on 13 April 1993. They require a demonstration that all relevant patents have expired, or a court determination that sale of the second entry product would not infringe the patent. Before this regulation came into effect, the patentee was obliged to pursue patent infringers through the courts (CDMA, 1995*a*; PMAC, 1995*a*). In the view of the generic drug industry, this provision has opened a floodgate of "nuisance lawsuits" by patent-holding multinational corporations. Their purpose is to extend the effective protection against generic competition beyond the termination date of the patent, i.e. for as long as the lawsuit lasts (for a maximum of 30 months). More than 90 such cases were launched between 1993 and 20 May 1996 (Globe and Mail, 1996).

Bill C-91 also contains provisions prohibiting exports of drugs which are still protected by a Canadian patent, even though the patent protection in the importing countries has already expired. This may be due to differing regulatory delays in new product approval, or the fact that some countries define the patent term from the date of filing of patent application, and others from the date of patent grant. A study commissioned by the CDMA found that, for a sample of new drugs on the 1993 list published by the PMPRB, patents in Italy expired 17.5 months earlier than equivalent Canadian patents, for example. Patents in Japan expired 14 months earlier, in the United States 10.6 months earlier, and in Germany 21.9 months earlier (CDMA, 1994*c*). The generic industry draws attention to the negative implications of this restriction for the Canadian balance of trade.

Biotechnology

Definitions

Conceptually, the "biotechnology industry" is difficult to define for two main reasons (Heller, 1995): first, "biotechnology" includes two sets of technological activities: (a) recombinant DNA cell fusion and related technologies, and (b) advanced bioprocess engineering. Second, the molecular science applications of biotechnology are utilised in a number of different industries. Heller (1995) therefore uses the term "community", rather than industry, to include nine categories of organisations: (1) biotechnology firms; (2) university departments of microbiology and related disciplines; (3) research institutes; (4) established corporations in the chemical, pharmaceutical, agricultural and other industries with own biotechnology R&D operations or strategic alliances; (5) venture capital firms; (6) regulatory bodies; (7) industry associations; (8) scientific granting agencies; (9) suppliers of equipment and biological reagents.

Among the landmarks in the development of the Canadian biotechnology industry are the following (Heller, 1995; Ernst & Young, 1994): in 1981, two companies were founded: Allelix Inc. (as a joint

venture between the Canadian Development Corporation, John Labatt Ltd., and the Government of Ontario), and Quadra Logic Technologies (QLT). In 1983, the National Biotechnology Strategy was initiated; in 1984, Cangene was established; in 1985, Hemosol and Biomira; in 1986, Imutec Corp. and BioChem Pharma, and the Industrial Biotechnology Association of Canada were formed; and in 1987, the Biotechnology Research Institute and Plant Biotechnology Institute. In 1988, Boehringer Ingelheim acquired Bio-Mega Ltd., in 1989, Institut Mérieux of France purchased Cannaught Bioscience Inc.; also in 1989, Ag. West Biotech Inc. was founded. Allelix and Cangene filed their Initial Public Offering and were listed on the Toronto Stock Exchange. Hemosol did so in 1993. By the end of 1993, the publicly traded Canadian "new biotechnology firms" had market capitalisation of $2.7 billion.

Heller's survey of the industry

Developments in the Canadian biotechnology industry over the past two decades have been analysed in three reports produced by consulting company Ernst & Young, entitled Biotech 89, Biotech 92, and Biotech 94 (Ernst & Young, 1994). However, the most comprehensive and detailed source of information to date is a survey by Heller (1995). It is based on a stratified random sample of 175 firms from a universe of 538 firms comprising the 1993 Canadian biotechnology community. A total of 156 firms responded. The universe was defined as all Canadian biotechnology firms deploying second generation biotechnology, or having the potential to do so in the near future. Second generation biotechnology includes rDNA technologies and applications using process technology, chemistry, and classical engineering. Environmental firms whose activity fell within the scope of the draft Canadian environmental regulation for imported or manufactured biotechnology were also included.

As of the date of the survey (1993), most of the 538 firms (57 per cent) had no more than ten employees. Among final product manufacturers, 22 per cent were health care firms, 13 per cent environmental, 11 per cent resource and 10.5 per cent agri-food firms. Some 32 per cent were supplier firms, and 12 per cent were research institutes (Heller, 1995).

The share of biotechnology in Canada's GDP in 1993 was estimated at 0.17 per cent (up from 0.08 per cent from 1989, i.e. an average annual growth rate of 20 per cent). The biotechnology community's employment represented 0.19 per cent of aggregate employment in Canada in 1993 (up from 0.11 per cent in 1989). Its share in the value of shipments of manufactured goods rose from 0.29 per cent in 1989 to 0.68 per cent in 1993 (Heller, 1995).

The activities of many of the firms spanned several sectors of the economy. The respondents were therefore asked to allocate their R&D, production and sales activities into one or more of the ten following economic sectors into which biotechnology has diffused: agriculture, aquaculture, including fisheries; energy; environment; food and beverage, including fermentation; forestry; health care, including diagnostics, therapeutics and vaccines; horticulture; mining; and pulp and paper. In this breakdown, 48 per cent were in health care, 27 per cent in agri-food, 14 per cent in environment, and 11 per cent in the resource sectors (Heller, 1995). Respondents were also asked to divide their activities according to the type of life form (naturally occurring micro-organisms, or NOMs, and genetically engineered or modified micro-organisms, or GEMs). Some 73 per cent of firms were in the NOM business and 23 per cent in the GEM business (Heller, 1995).

The 1993 world-wide sales of biopharmaceutical products were estimated at $7.7 billion, and the Canadian health-care sector rDNA sales in that year (converted to US dollars) were about $300 million, i.e. 3.9 per cent of the world market. The market capitalisation of the 32 publicly traded Canadian biotechnology firms was $2.64 billion as of December 1993, which is about 6 per cent of the market

capitalisation of similar firms in the United States. The volume of sales by Canadian biotechnology companies in the same year represented less than 6 per cent of the US volume. Canada thus seems to be lagging behind the "expected" 10 per cent of the US magnitudes of both variables. In contrast, the count of Canadian biotechnology firms represent 11.6 per cent of the US number, perhaps indicating a greater share of proprietary technologies suitable for development (Heller, 1995). Ernst & Young, in its 1994 report on the industry, estimated that Canada lagged at least five years behind the United States in the industrial development of biotechnology. In the same survey, Ernst & Young introduced a distinction between "core" companies, whose primary business is research, development, and production of biotechnology products and processes on the one hand, and "broadly" defined biotechnology companies on the other. The survey identified 121 core companies with total employment of 6 500 in 1993, and 310 companies in the broader category (i.e. firms with some biotechnology activity). The average core Canadian biotechnology company in 1993 had revenues of about 22 per cent of an analogous US firm and spent approximately 51 per cent on R&D, compared to its US counterpart (Ernst & Young, 1994).

According to Heller (1995), about 64 per cent of Canadian biotechnology companies focus on therapeutic or diagnostic applications (globally, their proportion is twice the estimated global proportion of 10 per cent). Chemical industry and environmental applications amount to 12 per cent (only 8 per cent globally), and the remainder of the firms supply or licence services and instrumentation to other firms in the biotechnology, chemical and pharmaceutical industries.

Trends in investment and R&D

The Heller survey (1995) estimates that during the period 1989-1993, the annual investment in productive capacity grew on average by 16 per cent per year. The fastest growth was in the sectors of agriculture (31 per cent) and health care (18 per cent), while the food and beverage sector registered only a 5 per cent growth rate. Ernst & Young (1994) observed that, as of 1994, the biotechnology industry in Canada has not reached the level of "critical mass" necessary to attract the outsourcing of R&D taking place in the pharmaceutical industry. Heller (1995) concludes that strengthening of investor confidence in the Canadian biotechnology industry will require the deployment of multi-dimensional approaches to technology assessment of the value of the firm. Key dimensions are the strength of the intellectual property protection and the degree to which the firm's technologies are well characterised.

A recent detailed analysis of the sources of financing of biotechnology investment in Canada suggests that the volume of private sector investment is much higher than previously believed. Dr. Denys Cooper of the National Research Council of Canada drew upon a variety sources, including published company results, media reports, grant applications, and private contacts to estimate biotechnology investments in Canada for the period 1991-1995 (Re$earch Money, 1996). His estimates, reported in Table 8, exclude pharmaceutical companies (with the exception of QLT PhotoTherapeutics), but include most agrobiotechnology firms.

Cooper's forecast for the year 1996 is $400 million, i.e. the largest amount yet. Given the growth stage of the industry and the absence of a longer time-series of comparable data, it is difficult to evaluate to what extent the growth in investment can be attributed to the changes in patent legislation. The qualitative information from interviews reported by Heller, Cooper's opinions, as well as the views of industry representatives expressed elsewhere, all point to the conclusion that patent protection is an indispensable prerequisite for growth in biotechnology investment and R&D spending.

Table 8. **Biotechnology investments in Canada, 1991-1995 ($ million)**

Year	PP/VC	IPO	PO	Other	Total	Number of placements
1991	64.4	131.3	66.3	0.0	262.0	40
1992	51.9	19.6	22.9	0.0	94.4	18
1993	80.9	87.9	53.5	19.5	241.6	34
1994	53.2	19.2	96.3	0.0	168.7	26
1995	126.3	27.1	74.1	6.7	234.2	43
Total	376.7	285.0	313.1	26.2	1 000.9	161
No. of placements	108	24	22	7	161	

Notes: PP/VC = Private Placement/Venture Capital; IPO = Initial Public Offering; PO = Public Offering/Rights Offering

Source: Re$earch Money, 1996.

Total R&D expenditures of the "Canadian biotechnology community" for the period 1989-1993 are reported in Table 9, categorised by economic sector. The data show an annual rate of growth of R&D expenditures of 41 per cent, with the agri-food sector growing at 112 per cent per year, followed by health care at 77 per cent. The slowest annual growth rate (5 per cent) was recorded in the research sector, which represents federal government biotechnology expenditures. The R&D-to-sales ratio rose from 27.7 per cent in 1989 to 47.3 per cent in 1993. The breakdown between basic and applied research is available only for the year 1993. On average, basic research represented 31.5 per cent of total; the research firms had a ratio of basic to total research of 70.8 per cent, resource firms 45.1 per cent, supplier firms 43.3 per cent, the health care sector 27.4 per cent, agri-food 15.2 per cent and environment 14.5 per cent (Heller, 1995).

Table 9. **Canadian biotechnology R&D expenditures ($ million)**

Sector	1989	1990	1991	1992	1993
Health care	34.6	92.7	143.7	196.9	337.9
Agri-food	18.6	260.7	258.5	291.6	374.5
Environment	10.9	10.0	12.9	20.9	29.7
Supplier firms	21.6	24.6	30.2	42.8	53.7
Research firms	150.6	171.3	173.0	180.8	182.3
Resource	12.9	14.1	14.0	13.0	13.3
Total	249.2	573.4	632.3	745.9	991.3
Sales	899	1 085	1 298	1 667	2 095
R&D/sales ratio	0.28	0.53	0.49	0.45	0.47

Source: Heller, 1995.

The survey also makes it possible to analyse the R&D expenditures of Canadian rDNA product firms according to the three types of originating life form: (1) animal, or its products; (2) plant, or its products; and (3) micro-organisms, or their products. The results are reported in Table 10.

Table 10. **R&D activity of Canadian rDNA product firms by type of originating life form, 1989-1993 ($ million)**

Originating life form	1989	1990	1991	1992	1993
Animal					
R&D	113.2	118.7	121.4	123.7	131.8
Sales	74.6	87.2	102.1	116.0	222.7
R&D/sales ratio	1.52	1.36	1.19	1.07	0.59
Plant					
R&D	3.4	11.4	13.5	19.0	23.0
Sales	0.2	0.5	1.7	2.0	3.2
R&D/sales ratio	17.0	22.8	7.94	9.50	7.19
Micro-organisms					
R&D	99.2	115.6	118.5	128.2	177.3
Sales	10.0	15.5	45.4	87.5	235.3
R&D/sales ratio	9.92	7.46	2.61	1.46	0.75
Total					
R&D	215.8	245.7	253.4	270.9	332.1
Sales	84.8	103.2	149.2	205.5	465.2
R&D/sales ratio	2.54	2.38	1.70	1.32	0.71

Source: Based on Heller, 1995.

Most of the activity of the rDNA product firms in the survey period was concentrated in agriculture and health care, while the other sectors were relatively small. Table 11 illustrates this.

Table 11. **R&D activity in Canadian rDNA product firms by economic sector, 1989-1993 ($ million)**

Economic sector	1989	1990	1991	1992	1993
Agriculture					
R&D	38.6	44.9	53.4	55.0	57.5
Sales	53.1	59.0	63.7	64.6	59.5
R&D/sales ratio	0.73	0.76	0.84	0.85	0.97
Health care					
R&D	165.6	184.8	182.2	217.6	256.4
Sales	31.4	43.6	84.0	133.1	397.9
R&D/sales ratio	5.27	4.24	2.17	1.63	0.64
Total					
R&D	215.8	245.7	253.4	270.9	332.1
Sales	84.8	103.3	149.2	205.5	465.2
R&D/sales ratio	2.54	2.38	1.70	1.32	0.71

Source: Based on Heller, 1995.

The growth in R&D spending is impressive. However, once again, given the growth stage of the industry and the relatively short time-series, it is difficult to evaluate the extent to which R&D spending has been affected by the changes in patent legislation.

Intellectual property legislation

The importance of patents as a method of appropriating the results of business R&D varies from industry to industry (see e.g. Levin *et al.*, 1987). The pharmaceutical industry is typically classified among those in which patent protection is crucial, and the propensity to patent is very high. Similarly, the Heller survey (1995) shows that, over a five-year period, 57 per cent of Canadian biotechnology firms used patents, 52 per cent used trade secrets, 37 per cent used trademarks, 14 per cent copyrights, and 11 per cent used industrial design as a method of protecting their technology. Only the small and very small firms used trade secrets more than patents.

Protection of intellectual property in Canada was, perhaps surprisingly, not listed among the factors important in commercialisation of biotechnology inventions. Heller (1995) reports that the industry respondents ranked the importance of the Canadian market behind the United States, European and Japanese markets. It is therefore the case, especially for health care biotechnology firms, that product approval and intellectual property protection in those markets are more important than product approval and patent protection in Canada. The majority of Canadian biotechnology firms typically seek patent protection in the United States first, and then in Canada.

As is the case in most Canadian industries, the vast majority of applicants for Canadian patents are foreign inventors. For example, 96.9 per cent of Canadian biotechnology patent applications during 1989-92 came from abroad. Based on this data, Heller (1995) concludes that the strengthening of intellectual property protection in Canada may contribute to the growth in Canada's trade deficit in biotechnology products.

The ability of biotechnology firms to protect their intellectual property is adversely affected by inadequate access to capital, since substantial cash flow is required to obtain and maintain patent protection. At the same time, provision of investment capital by financial institutions is contingent on the ownership of or access to patentable technology. Thus, a firm cannot raise capital, either through private or public market placements, or through a licence, joint venture, or strategic alliances, in the absence of patentable technology, or with poorly characterised patents (Heller, 1995). After adjustment for the relative size of the two economies, US companies filed three times as many applications for biotechnology patents during the 1989-92 period than their Canadian counterparts. Heller (1995) hypothesises that this discrepancy may be due to the better capitalisation of the US firms, or to a more advanced stage of their development.

The problem of financial resources required to file for and maintain a patent is especially acute for universities and research institutes. It is further aggravated by the lack of "entrepreneurial culture" among academics, and by their propensity to publish their findings before a patent application is filed. An invention cannot be patented if it was disclosed publicly before patent application was filed (Canada, United States, Japan and a few other countries have a grace period between publication and filing for patent). As a consequence, some of the results of university research are ignored by industry (Heller, 1995).

The Heller survey (1995) found that many Canadian and multinational biotechnology firms have chosen not to commercialise their products in Canada because of the high cost of obtaining and defending patent protection relative to the small size of the market. Other firms choose to file a patent application, but defer examination. The firm thus can claim the date of first filing, and the existence of such an application creates uncertainty for potential competitors, while minimising the risk of potential loss of sales if the patent application if rejected. Some firms also seek broad blocking patents. A broad blocking

Canadian patent, when obtained by a multinational corporation, prevents Canadian firms from manufacturing, using, or selling the product or process in Canada. A broad blocking US patent affects Canadian firms in the same negative fashion. Even if a broad blocking patent is invalid, the small size of the Canadian market does not justify the cost of litigation.

Regulatory delays reduce the effective patent term. Heller (1995), however, believes that this factor has not been critical to the development of Canadian biotechnology firms, even though patent term extension for reasons of regulatory delay is not available under the Canadian Patent Act. In addition, Heller (1995) reports that some practitioners and industry representatives considered the Canadian system of protection of intellectual property a barrier to global commercial prospects for Canadian biotechnology firms. Delays at the Canadian Intellectual Property Office in prosecuting patent applications are one reason for this. Other factors are the uncertainty about the scope of patent protection and the global cost of obtaining a patent.

In most countries, medical treatment is not patentable; it follows, therefore, that a new therapeutic use of known compounds cannot be patented. Canada is an exception, together with the United States, and a few other countries, since new therapeutic uses have been granted protection by the patent office (Heller, 1995).

Biotechnology regulatory framework

US analysts cite federal government support for biomedical R&D, technology transfer policies, and strong protection of intellectual property among the most important factors in the discovery and commercialisation of new products and therapies. Additional factors include the rationalisation of the regulatory process and the growth of health insurance for prescription drugs.

A special feature of biotechnology drugs is that a small variation in the method of producing them can lead to unexpected changes in the product. For this reason, the FDA will require clinical testing of generic copies of biotechnology products even after patents on the original product have expired. This will significantly raise the costs of entry and will have significant implications both for the US and Canadian generic drug industry (Heller, 1995).

A comprehensive recent comparative analysis of the US and Canadian biotechnology regulatory frameworks found their basic premises to be remarkably similar. The Canadian system was found to be more flexible and less complex, featuring fewer pieces of legislation, smaller and better linked regulatory agencies, and a more collegial attitude. Its flexibility could be especially beneficial to the agri-food biotechnology sector. The Canadian system does, however, require more data to support a product submission; this could mean a competitive disadvantage in the costs of obtaining a product approval, and could mean that less support of commercialisation is offered by the Canadian than by the US system (KPMG, 1995).

There are also differences in the evolution of the regulatory framework. For example, Canada has not experienced the type of visible scientific debate or public review of research which took place in the United States, and does not have court rulings supporting the patentability of life forms. In addition, the biotechnology industry associations have not yet developed a cohesive voice or a supportive public constituency (KPMG, 1995). This assessment is shared by the Ernst & Young (1994) survey which observes that the various Canadian biotechnology groups and organisations send conflicting signals about the industry to the public and trading partners. It also reports (1994) that in the respondents' assessment

of the impediments to commercialisation of biotechnology, the complexities of the regulatory environment ranked number one in 1993, while this distinction was previously held by insufficient capital.

Supporting and related industries

With the help of questionnaire responses and personal interviews with managers, the Heller survey attempted to establish the negative and positive influences on international competitiveness of Canadian biotechnology firms. Eight such factors were listed, and the responses were categorised by the economic sector of the responding firm's operations. The most important findings are as follows (Heller, 1995).

Availability of raw materials was rated as Canada's advantage by 66 per cent of respondents, and as a disadvantage by 30 per cent. All of the environmental firms and about two-thirds of supplier and research firms, however, saw Canada at a disadvantage in this regard.

Average wage rates were overwhelmingly (by 74 per cent of respondents) viewed as a disadvantage; this opinion was held across all sectors.

Quality of education, availability of trained personnel, and sources of training were investigated through three separate questions dealing with staffing needs of biotechnology firms. The quality of Canadian education was considered as an advantage by 57 per cent of respondents, with higher percentages in the health, supplier, and research firms. About two-thirds of the agricultural firms and almost half of the environmental firms viewed this factor negatively. The opinion on the other two questions was roughly evenly divided. About two-thirds of the agricultural and resource firms viewed Canada at a disadvantage in the availability of trained personnel, and two-thirds of the environmental and supplier firms rated the sources of training as contributing to Canada's disadvantage.

Current exchange rates were seen to put Canada at a competitive disadvantage (58 per cent of responses), especially so in the research and agricultural sectors. Research centres contributed to Canada's competitive advantage in the view of 56 per cent of respondents; their support was especially valued by firms in the agricultural and health sectors (well over two-thirds of respondents valued their contribution).

The regulatory environment was viewed as a disadvantage by almost two-thirds of respondents; the degree of dissatisfaction was the lowest in the health sector (53 per cent) and the highest in the research sector (76 per cent).

Industry structure and competitiveness

The results of the Heller survey (1995) suggest that the major reason for market entry (cited by 49 per cent of respondents) is a "market opportunity or demand", followed by "in-house expertise" (24 per cent of respondents), and "access to proprietary knowledge" (12 per cent of respondents). In the health sector, "access to research facilities" was prominent (21 per cent of respondents). Each of several other factors, including spin-off opportunities, the regulatory environment, government incentives, financing, access to raw materials, and availability of production facilities received less that 10 per cent of responses.

"Lack of financing" was cited by 31 per cent of respondents as the major barrier to entry; it was especially significant in the research, resources and health sectors (around 40 per cent of respondents).

The second most important barrier was "lack of market acceptance", cited by 21 per cent of respondents (with the environmental sector reporting 35 per cent). "Canadian regulatory barriers" (13 per cent of all respondents from all sectors combined, with agriculture reporting 24 per cent) followed, along with labour availability (12 per cent of respondents).

As of 1995, there were about 40 private Canadian health care biotechnology firms pursuing recombinant product development. Given the fact that access to capital is the most important barrier to entry into the industry, the competition for limited capital resources will likely result in mergers, buyouts, and some failures. Further complications arise from health care spending cuts and the increasing sensitivity of drug purchasers to the costs of new therapies. For the next ten years, Heller (1995) forecasts an annual rate of growth for the Canadian health care biotechnology sector within the 5-15 per cent range (the most likely estimate is 10 per cent). The agricultural biotechnology sector is expected to grow within the 10-30 per cent range (the most likely estimate is 20 per cent), and the environmental and resource sectors within the 25-50 per cent range (the most likely estimate is 40 per cent).

Restructuring of the multinational pharmaceutical and biotechnology industry

Impact of recent mergers

R&D spending and investment in the Canadian pharmaceutical and biotechnology industry has undoubtedly been affected by the large number of mergers and acquisitions which took place on the global scene since 1988. A partial list includes the following (CDMA, 1995b): acquisition of Sterling Drugs Inc. by Eastman Kodak Co. in February 1988; acquisition of SmithKline Beckman by Beecham Group PLC in July 1989; acquisition of Squibb Corp. by Bristol Myers Co. in October 1989; acquisition of Marion Laboratories Inc. by Dow Chemical Co. and of Merrell Dow Pharmaceuticals by Marion in December 1989; purchase of 60 per cent of Genentech Inc. by Roche Holding Ltd. in February 1990; acquisition of Rorer Group Inc. by Rhône-Poulenc SA in March 1990; acquisition of Medco Containment Service Inc. by Merck & Co. in July 1993; acquisition of Syntex Corp. by Roche Holding Ltd. in May 1994; acquisition of Diversified Pharmaceutical Services Inc. by SmithKline Beecham in May 1994; acquisition of Gerber Products Co. by Sandoz Ltd. in May 1994; purchase by Elf Sanofi SA of the prescription drug business of Sterling Winthrop Inc. from Eastman Kodak Co. in June 1994; purchase by Eli Lilly and Co. of PCS Health Systems Inc. from McKesson Corp. in July 1994; acquisition of American Cyanamid Co. by American Home Products Corp. in August 1994; purchase of Wellcome PLC by Glaxo PLC in January 1995; acquisition of Marion Merrell Dow Inc. by Hoechst AG in May 1995; merger between Upjohn Co. and Pharmacia AB in August 1995.

Some of these mergers and acquisitions led to consolidations of Canadian operations and job losses. A list compiled by the CDMA from reports in Canadian media (CDMA, 1995b) suggests that some 720 jobs were lost during the period 1988-1992. An additional 1 800 jobs were lost as a result of mergers and acquisitions since the passage of Bill C-91 in 1993. A publication co-sponsored by the PMAC reports that restructuring in the global pharmaceutical industry resulted in a reduction of employment in the PMAC member companies in Canada from 17 261 in 1993 to 16 646 in 1994, i.e. a loss of 615 jobs in one year (Boards of Trade, 1996). The available data does not make it possible to determine how many of the job losses have been in R&D, or how R&D spending in Canada has been affected. It seems reasonable to assume, however, that the observed positive impact of changes in patent legislation on R&D discussed above would have been even greater in the absence of the countervailing effect of consolidations in the global pharmaceutical industry, resulting from mergers and acquisitions.

Alliances and joint ventures

During the 1980s, equity investment by venture capitalists was the primary source of funding for biotechnology start-ups. More recently, new biotechnology firms (NBFs) have increasingly resorted to financing their R&D by establishing various forms of arrangements with "established firms" with commercial interests in biotechnology (Heller, 1995). These include joint ventures and agreements in R&D, licensing, manufacturing, and product development. Typically, the established firm funds the development costs in exchange for an exclusive licence to market the product, while the NBF is the general partner and bears the liability, and the limited partners provide funds in return for equity in a product or product line.

Examples of recent alliances affecting Canadian biotechnology firms include the following: the partnership between the German firm Fresnius A.G. Oberusel and Hemosol Inc. to develop a red blood-cell substitute; partnership between Hoechst-Roussel and Allelix Biopharmaceuticals to accelerate the development of drugs for psychiatric disorders; and Warner Lambert's partnership with BioChem Pharma in anti-thrombosis research (DFAIT, 1996).

Most respondents to the Heller survey (73 per cent) entered into at least one agreement; the majority of them (58 per cent) with universities (75 per cent of research firms, 72 per cent of health care firms, and 63 per cent of agricultural firms had such agreements), 35 per cent with another biotechnology firm, and 21 per cent with an investment capital firm. Access to technology (70 per cent of all firms), to research facilities (45 per cent), and to production facilities (29 per cent) were cited as the most important benefits, followed by access to financing (45 per cent) and to production facilities (29 per cent). The existing Canadian patent protection was considered "helpful" by 37 per cent of respondents in facilitating such agreements, and a "hindrance" by 18 per cent of respondents.

Heller (1995) speculates that the extension of patent protection by Bill C-91 was the "helpful" element, since 62 per cent of the health sector firms responded in this fashion. The negative view was most widespread from respondents in the resource sector (43 per cent) and in the agricultural sector (26 per cent). These responses are difficult to interpret, although Heller believes that the perceived inadequacy of the breeders' rights legislation may have been a factor.

Conclusions

In 1969, Canada amended its Patent Act to allow for compulsory licensing of imports of prescription drugs. Between 1969 and 1987, about 400 licences were granted, almost all of them to import active ingredients. Compulsory licensing contributed in a major way to the development of a strong, mostly Canadian-owned, generic drug industry which, by 1995, accounted for 10 per cent of the dollar value of wholesale market and 21 per cent of unit volumes of prescription drug sales (DFAIT, 1996). The patent-holding multinational brand-name companies were negatively affected in different degrees, depending on the importance of the licensed product(s) in their respective product portfolios. A commission of inquiry which examined the aggregate performance of the industry concluded in its 1985 report that any negative impacts were more than offset by positive factors, like a strong growth in demand (Eastman, 1985).

The multinational drug companies objected to the licensing provision since its enactment, and publicised their reluctance to invest and conduct R&D in Canada. The pressure to modify the legislation gained additional impetus when compulsory licensing became an obstacle to successful completion of the

free trade agreement between Canada and the United States. In 1987, the government enacted Bill C-22, which provided for protection from compulsory licensing, for a period of seven years in the case of licence to manufacture, and ten years in the case of licence to import. Bill C-91, which was enacted in 1992, abolished compulsory licensing completely, in accordance with the provisions of GATT and the North-American Free Trade Agreement.

A number of indicators of pharmaceutical R&D spending in Canada presented in a previous section of this paper show an increase in R&D activity starting around the year 1987 (the time of enactment of Bill C-22 and of the Investment Tax Credit). One indicator is a dramatic increase in the annual rate of growth of R&D expenditures, reported in Table 1. While the annual rates of growth of R&D spending (in real terms) during the period 1984-1987 ranged from the high of 16.7 per cent to the low of 5.4 per cent, during the year 1988 alone, R&D spending increased by 54.1 per cent, and rose by an additional 41.1 per cent in 1989. The annual rate of growth retracted to around 20 per cent in 1990 and 1991, and to 8.4 per cent in 1992, etc. The R&D-to-sales ratio rose from 5 per cent in 1984 to over 11 per cent in 1994, as shown in Table 2.

This paper examines the question of whether the observed increase in R&D spending can be attributed to the enactment of Bill C-22 (not enough data has accumulated to evaluate the impact of Bill C-91).

One hypothesis tested here is that the observed growth in pharmaceutical R&D spending is due to a general improvement in the R&D and investment climate in Canada. If this were the case, similar growth patterns would be observed in other industries as well. However, data from Statistics Canada suggest that this hypothesis should be rejected. As shown in Table 5, R&D spending in the pharmaceutical industry, which represented from 2.8 to 4.5 per cent of Canada's manufacturing R&D during the period 1975-1987, rose to 5.5 per cent in 1989, and reached 9.5 per cent in 1994, indicating a distinctly different pattern of growth for the pharmaceutical industry since 1987.

Another hypothesis is that the observed increase in R&D spending, while unique to the pharmaceutical industry, cannot be attributed to Bill C-22, but to such factors as a shift in the pharmaceutical research paradigm, or the appearance of a cluster of inventions which required increased R&D resources. If this were the case, a similar change would be observed in the pharmaceutical industry of other countries as well. The analysis draws on the ANBERD database developed by the OECD and concludes that the pharmaceutical industry in Canada behaved differently from its counterparts in other countries.

As shown in Figure 1, Canadian pharmaceutical R&D spending as a share of the total pharmaceutical R&D spending of 15 OECD Member countries for which comparable data is available declined moderately between 1972 and 1984. It started rising in 1984 and grew especially rapidly during the 1988-1990 period. A comparison of the rate of growth of pharmaceutical R&D expenditures in Canada with the rate of growth in the remaining 14 OECD Member countries, and separately with the United States, is presented in Figures 2 and 3. Again, it shows a change in the pattern of growth in Canada starting in about 1988. In Figures 4, 5, and 6, the pharmaceutical R&D is plotted separately for Canada and for the remaining 14 OECD Member countries; first, as a percentage of R&D in all industries, second, as a percentage of R&D in manufacturing, and, third, as a percentage of R&D in the chemical industry. Once again, the ratios for Canada indicate a changing pattern in relation to the rest of the OECD Member countries, starting approximately in 1987.

The third hypothesis proposed here is that the growth of Canadian pharmaceutical R&D spending is due to the decentralisation of R&D activities of multinational drug companies. Data on US-owned

multinational corporations shows that spending abroad as a percentage of total R&D spending of the member companies of the (US) Pharmaceutical Manufacturers Association changed only marginally since 1987, suggesting the absence of a significant trend toward decentralisation of R&D away from headquarters. Canada's share of the total spending abroad moved roughly between 4 and 6 per cent during the late 1970s and early 1980s, and rose somewhat in the second half of the 1980s. The year 1989 registered the historically high share of 10.4 per cent, but it dropped to 7.4 per cent in 1991 (the last year for which data are available). The hypothesis that the surge in R&D spending in Canada is due to a general decentralisation of R&D activities of multinational corporations does not appear to be supported by the data.

It would be difficult to explain the dramatic increase in R&D activity in the Canadian pharmaceutical industry exclusively in terms of the economics of patent protection. It should be noted that the PMAC member companies made a commitment during the debate on the merits of Bill C-22 to double the ratio of R&D to sales from less than 5 per cent in 1984 to 8 per cent in 1991 and 10 per cent in 1996 (PMAC, 1992). This commitment was made in a highly charged national debate and was extensively publicised. It is unlikely that the economic benefits of increased patent protection alone would cause such an increase. In other words, this effect is not easily generalisable, i.e. it does not follow that an increase in patent protection in another industry or in another country would lead to a result of this magnitude.

Information on R&D spending and investment in biotechnology industries in Canada is analysed in the section entitled "Biotechnology". Most of the available time-series cover the period 1989-1993, although some data series continue for an additional two years. A survey of institutions belonging to the "Canadian biotechnology community" (Heller, 1995) reported an average annual rate of growth of R&D expenditures of 41 per cent during the period 1989-1993, with the agri-food sector growing at 112 per cent per year, followed by the health care sector at 77 per cent. The slowest growth (5 per cent per year) was recorded in the research sector, representing federal government biotechnology expenditures affected by government spending restrictions. Given the absence of longer time-series, it is difficult to evaluate to what extent the growth in R&D spending can be attributed to changes in the patent legislation. This difficulty is further compounded by the fact that the biotechnology industry is still in its growth stage.

Qualitative information from surveys, interviews, and industry publications suggests a two-way relationship between protection of intellectual property and the ability of biotechnology firms to gain access to capital. On the one hand, financial institutions make provision of investment capital contingent on the existence of well characterised patents or patentable technology. On the other hand, the ability of biotechnology firms to protect their intellectual property depends on adequate access to capital, since substantial cash flow is required to obtain and maintain patent protection. This problem is especially acute for universities and research institutes, and is further aggravated by the lack of "entrepreneurial culture" among academics and their propensity to publish their findings before a patent application is filed. For this reason, some of the results of university research are ignored by industry (Heller, 1995).

Given the small size of the Canadian market, the cost of obtaining patent protection is especially onerous, relative to the profit potential. The majority of Canadian biotechnology firms therefore typically seek patent protection in the United States first, and then in Canada. Given the better capitalisation and more advanced stage of development of foreign (especially US) biotechnology firms, the vast majority of applicants for Canadian patents (96.6 per cent during the period 1989-1992) are foreign firms. Heller (1995) thus hypothesises that the strengthening of intellectual property protection in Canada may contribute to the growth in Canada's trade deficit in biotechnology products.

Heller (1995) also found that many Canadian and multinational biotechnology firms have chosen not to commercialise their products in Canada because of the high cost of obtaining and defending patent

protection relative to the small size of the market. In addition, the Canadian regulatory system requires more data to support a product submission than the US system, and thus further increases the competitive disadvantage of commercialisation in Canada (KPMG, 1995).

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SECTION II: REGULATION, RATIONALE AND REFINEMENT

EFFECTS OF US REGULATORY POLICIES ON THE RESEARCH, DEVELOPMENT, AND APPROVAL OF NEW BIOTECHNOLOGY DERIVED BIOPHARMACEUTICALS: POINTS TO CONSIDER FOR OECD MEMBER COUNTRIES

by

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Introduction

Over the past decade, policy-makers in many countries have focused attention on biotechnology as a key element in future economic growth. Although the United States has been considered to be an early leader in the commercialisation of biotechnology, other nations are adjusting their industrial policies to encourage expansion of their biotech sectors. At the same time, many companies now investing in biotechnology are multinational, making the industry an active player in the global economy (OTA, 1991). In 1995, there were 485 biotech companies in Europe and over 1 100 in the United States (Lee and Burrill, 1995). The growth of this industry has generated interesting debates on economic, ethical, regulatory, and legal issues.

Biotechnology has revolutionised the manner in which research and product development occur. Through genetic manipulation of plants, animals, and cells, experimental testing of hypotheses that two decades ago were merely theories can now be realised. Applications of our technical advancements to product development have changed the way in which individuals live their daily lives. Examples of biotechnology's influence include bioremediation in the form of cleaning toxic oil spills, contaminated waste sites, and other pollutants posing a threat to the balance of the ecosystem; enhancement of food processing and textile manufacturing; improvement of nutritional value, flavour, and yield of many agricultural products; and finally, development of biopharmaceuticals, recombinant vaccines, and biologic-based diagnostic kits for human therapeutic use (BIO, 1995).

Since 1980, the US biotech industry has been developing biopharmaceutical products for human therapeutic use. The rapid expansion of this sector of the biotech industry has caught the attention of the pharmaceutical industry, government, the investment community, and academic groups. This interest has been sustained by the growing numbers of biopharmaceutical products that have entered human clinical trials. In the last 15 years, the number of investigational new drug applications (INDs) filed annually at the FDA for the start of human clinical trials in the United States has grown from four in 1980 to 79 in 1995 (Tufts CSDD Biotech Database, 1996).

Not only has the industry produced growing numbers of biopharmaceutical products, but the technical applications have broadened. The cornerstone of biotechnology, recombinant DNA technology, has been applied to generate recombinant human therapeutic proteins and recombinant vaccines. Indirectly, this technology has laid the foundation for the discovery and development of new cellular therapies, hybridoma technology to generate monoclonal antibodies, gene therapy vectors, small peptide molecules, the design and high throughput screening of small molecules, anti-sense oligonucleotides, and small molecules. In total, more than 600 diverse biologic products have entered human clinical testing in the United States since 1980. Forty-eight per cent of the products are in early Phase I/Phase II clinical development, and 15 per cent are in Phase III or under regulatory review. Thirty-three per cent have entered clinical testing for malignant diseases, 23 per cent for infectious diseases, 11 per cent for endocrine disorders, and 10 per cent for conditions of the immune system. From these products, there have been 49 approvals, 29 of which are first version approvals, or new biologic entities (Gosse and Manocchia, 1996).

The application of molecular biological techniques to the development of these products has spurred a revolution in drug development. In 1995 alone, traditional pharmaceutical companies invested more than three billion dollars in 165 newly established agreements with smaller biotech companies (BioWorld, 1996). This is over and above annual investments made prior to 1995 by traditional pharmaceutical houses.

Since many of these biopharmaceutical products have altered traditional drug development by targeting innovative methods to create therapies or to treat the genetic basis of disease, the policies and regulations mandated by the Center for Biologics Evaluation and Research (CBER) at the US Food and Drug Administration (FDA) have had to be modified. The regulations, some dating from 1902, have not kept pace with the changing technology (Korwek, 1995). Proposals for regulatory reform have been advocated by federal, industrial, and academic groups. These regulatory reforms must strike an even balance between the interests of industry in speeding their products to market, and those of patients in having access to safe and innovative treatments.

Recent US regulatory initiatives governing emerging biotechnologies have established guidelines for biopharmaceutical development programmes. In this chapter, we examine the impact of these guidelines and regulations on biologic product development in the United States and some of their equivalents in other countries. This chapter has four sections. The first section describes current and proposed regulations aimed at expediting drug development and review, strengthening intellectual property protection, and reforming the FDA process. The second section discusses the economic implications of these US policies governing biopharmaceutical development and approval that deal with efforts to reduce time to market and enhance biopharmaceutical innovation. The third section reviews international regulatory policies and proposals. The final section reviews the proposed or established guidelines governing biologic therapeutic product development of some emerging technologies. The extent to which US industrial policies, laws, and regulations are transferable to other countries is beyond the scope of this chapter. However, the following sections will provide a blueprint for OECD Member countries to consider as they take steps to foster biopharmaceutical development.

Current and proposed policy changes in the US development and approval process that affect biopharmaceutical products

The biotechnology industry in the United States currently employs 108 000 persons, up from 40 000 a decade earlier (Lee and Burrill, 1995). It has been described as “the most research intensive industry in the civilian manufacturing sector”, spending $68 000 per employee on research, “more than nine times the US corporate average of $7 500” (Ludlum, 1995). Numerous factors affect the economic vitality of the industry and its ability to maintain this level of investment and ultimately to realise a meaningful return. Chief among them is the body of laws and regulations that govern the business of the biotech industry at every stage of product development.

Over the past decade, both the individual states and the federal government have adopted measures designed to ease the financial and regulatory burden on the biotech sector, to take account of the circumstances unique to the early stages of this industry, and to respond to public health concerns that innovative products be made available to patients as quickly as possible. The following discussion examines several existing and proposed federal initiatives that have implications for the biotechnology industry. Not all the initiatives presented here pertain exclusively to biopharmaceutical development; however, aspects of the initiatives may be of particular benefit to start-up biotech firms. The measures reviewed here include the following: optional clinical development pathways that permit the broad distribution of a drug prior to marketing approval; fast-track approval processes that have expanded the boundaries of traditional drug regulation in the United States; benefits available to the industry under the *Prescription Drug User Fee Act of 1992* (Public Law No. 102-571) and the *Orphan Drug Act* (Public Law No. 97-414); long sought-after changes in the intellectual property and export arenas that benefit biotech firms; and proposals for change to the current *Federal Food, Drug, and Cosmetic Act* (Public Law No. 75-717), that potentially could alter the regulatory framework for drug development in the United States.

Current process

Early access to investigational therapies

Treatment INDs

Through informal procedures and agency regulations, the FDA may authorise the distribution of investigational new drugs for treatment purposes outside of clinical trial protocols. The practice dates back to the mid-1970s when "compassionate-use INDs" were used to distribute experimental drugs under treatment protocols to patients whose life-threatening conditions proved unresponsive to existing therapies, or for which an FDA-approved drug was unavailable. FDA regulations also allow for an "emergency IND" procedure under which the agency may authorise shipment of a drug for a specified use in advance of IND submission (21 *CFR* 312.36). These "compassionate" and "emergency" release programmes were the precursors to two more recent early access programmes intended to reach larger numbers of patients. The new initiatives were, in large part, a response by the US drug regulatory system to the AIDS epidemic.

The first, introduced in 1987, extended beyond AIDS therapies to target "promising" investigational drugs intended to treat serious and life-threatening conditions for which satisfactory alternate therapies are lacking. The treatment IND regulations (21 *CFR* 312.34) allow access to experimental compounds outside of, but concurrent with, ongoing clinical trials. Sponsors are required to exercise ongoing due diligence in the pursuit of marketing approval. The intent of the treatment IND initiative is two-fold: to facilitate the availability of promising investigational new drugs to desperately ill patients as early in the drug development process as possible, and to obtain additional data on the drugs' safety and effectiveness. Contrary to the general regulatory requirement that sponsors absorb, as a normal cost of doing business, the costs associated with the use and distribution of investigational drugs, the treatment IND regulations permit sponsors to impose a charge for the drug, when they can establish that clinical trial enrolment is adequate and that no efforts will be made to commercialise the treatment IND. Sponsors electing to impose a charge must do so on a cost-recovery basis, and the charge is not to exceed manufacturing, research and development, and distribution costs.

For the period from June 1987 through December 1995, the FDA reported 41 treatment IND designations involving eight biologics and 33 chemical compounds (Tufts CSDD Early Access and Accelerated Approvals Database, 1996). The drugs were indicated for a variety of disease categories; however, cancer, AIDS, and HIV-related conditions accounted for almost two-thirds of the designations. With the exception of Videx (didanosine) for the treatment of AIDS, which was released under a treatment protocol at the end of Phase I, the compounds were in Phase II or III at the time of designation; in a number of instances, the treatment IND was used to bridge the gap between the date of NDA/PLA submission and the date of FDA marketing approval.

Thirty per cent of the drugs distributed under a treatment IND have had a charge associated with their distribution. More companies may elect to do so in the future, given a new level of leniency that recently has become apparent in the reimbursement practices of both public and private third party payers in the United States (*The Pink Sheet*, 1996; Shrine, 1995). Coverage for treatment INDs is still far from standard practice; however, there has been sufficient indication that payers are prepared, in certain circumstances, to bend the customary rule of denying coverage for treatment INDs, and any associated care, on the basis of exclusionary clauses governing experimental therapies. Over time, increased

certainty of third party coverage may also encourage more companies to consider a treatment IND distribution.

There are a number of reasons why a company may want to consider a treatment IND designation as part of its product development strategy. There is some evidence that original and supplemental applications for treatment INDs were reviewed more quickly when compared to similar non-treatment IND compounds, even though the treatment IND regulations promise no specific benefit in terms of speedier FDA review (Shulman and Brown, 1995). On average, the new chemical entities (NCEs) designated as treatment INDs (n=20) approved between 1987 and 1994 had a mean FDA review time 13 months shorter than that for non-treatment IND NCEs (n=21) with a similar therapeutic rating and approved during the same period. This difference was substantially maintained when the "fast-track" approvals among the treatment INDs were removed from the sample (1.5 years versus 2.3 years). The mean FDA review time for the four treatment IND supplemental applications involving new indications or new formulations for already-approved drugs (three of which involved AIDS or an AIDS-related condition) was just over one year (Shulman and Brown, 1995). In comparison, for the period 1989 to 1994, the mean FDA review phase was 2.4 years for all supplemental indications approved by the FDA's antiviral division (n=14), and two years for the anti-infective division (n=27) (DiMasi *et al*., 1996).

Among other potential benefits of a treatment IND distribution are the following:

- It can offer the opportunity to establish a market niche for the product among physicians and patients and to generate a degree of good will by responding to patients' needs for new therapies.
- When the treatment IND involves a new indication for an already-approved drug, the sponsor has a limited opportunity to advertise the off-label use, a practice otherwise prohibited by regulation.
- Distribution under a treatment IND also provides the opportunity to gather substantial safety data that can be used to augment and facilitate a marketing application.
- Having elected to distribute a drug under a treatment IND, a sponsor may exercise the option to charge for the drug, generating a cost-recovery revenue flow prior to full-scale marketing.

Parallel track

The parallel track programme, the second early access initiative implemented in response to the demands of AIDS advocates seeking access to new therapies, was introduced in a Public Health Service policy guideline in December 1992 (*57 FR*:13250, 1992). A parallel track designation is available only to drugs for the treatment of AIDS and HIV-related conditions. It extends the treatment IND concept to an earlier stage of clinical development, permitting distribution at the end of Phase I. However, in contrast to the treatment IND regulations, no charge may be imposed for parallel track drugs. Three AIDS therapies have been distributed under a parallel track protocol, two (Videx and Hivid) prior to the publication of the final policy, and one (Zerit) following publication (Shulman and Brown, 1995). All three drugs were distributed to thousands of patients at no charge. Although the initiative was not intended to provide research data, both the FDA and the participating sponsors have acknowledged that a volume of safety data was generated for all three drugs, ultimately facilitating FDA approval under the accelerated approval regulations, details of which are discussed below (Feigel, 1994; Carter, 1995).

The cost of a broad distribution would be prohibitive to a start-up biotech company since there is no discretion to charge for the drug under a parallel track protocol; however, it may be possible to circumscribe distribution to a limited number of patients, thereby controlling costs and still creating a

source of additional safety data. Several companies in the United States have adopted a model for a more limited "open-label" early access programme using a lottery system to equitably distribute limited supplies of drugs for the treatment of AIDS (*The Pink Sheet,* 1995*a*; *The Pink Sheet,* 1995*b*).

Fast-track development and approval

Two FDA regulatory initiatives have been designed and implemented since 1988 with the goal of compressing the clinical development and FDA review periods, thereby moving drugs intended to treat life-threatening and seriously debilitating illnesses to market with greater speed and efficiency. Both initiatives depart to varying degrees from traditional standards of drug development and approval by invoking a more sensitive and uncertain balancing of risks and benefits. They were intended to inject broad flexibility into the clinical development process. As with the early access programmes, the so-called fast-track regulations were part of the FDA's response to AIDS patients' desire not only to have access to new therapies, but to have access to FDA-approved therapies. Although access to the same drugs may have been possible through the treatment IND or parallel track mechanisms, negative reimbursement decisions by third-party payers often made access difficult and inequitable. It is important to note that the benefits of the fast-track approval pathways are not restricted to AIDS therapies, but are available to any drug intended for the treatment of critical conditions for which satisfactory treatment is lacking. Since biotech firms often target drugs for diseases that fit these criteria, the fast-track regulatory options may appropriately be considered as these firms map out their development strategies. Several important new biopharmaceuticals received their first approval under one of the two fast-track mechanisms. Of the 29 new biologic entities (NBEs) approved by the FDA between 1980 and 1994, four (Ceredase, Cerezyme, Betaseron, and Pulmozyme) were designated as fast-track approvals by the FDA (Gosse and Manocchia, 1996).

Expedited Subpart E procedures

The first fast-track pathway, adopted in regulations in 1988, is referred to as the Subpart E expedited procedures (21 *CFR* 312.80). The regulations adopt the model established during the development and approval of AZT (zidovudine), the first drug authorised for the treatment of AIDS (Kaitin, 1991). The FDA has described the framework as one in which the drug development process is viewed as a "coherent whole", with interventions at one stage designed to lead to efficiencies in the next (53 *FR*:41516, 1989). Early and ongoing collaboration between the FDA and the industry sponsor is the core concept underlying the Subpart E model. The main features of the regulations are the following:

- pre-IND meetings between the FDA and the sponsor early enough in the drug development process to review and reach agreement on the design of animal studies, on the presentation and formatting of data in the IND, and on the scope and design of Phase I testing; outside scientific consultants or FDA advisory board members may be involved in these meetings;

- an end-of-Phase I meeting between the sponsor and FDA-reviewing officials to review and reach agreement on the design of Phase II controlled clinical trials;

- phase II testing sufficiently adequate in scope and design to provide a quantity of safety and effectiveness data to support a marketing decision at the end of Phase II;

- active FDA monitoring of the progress and conduct of the clinical trials;

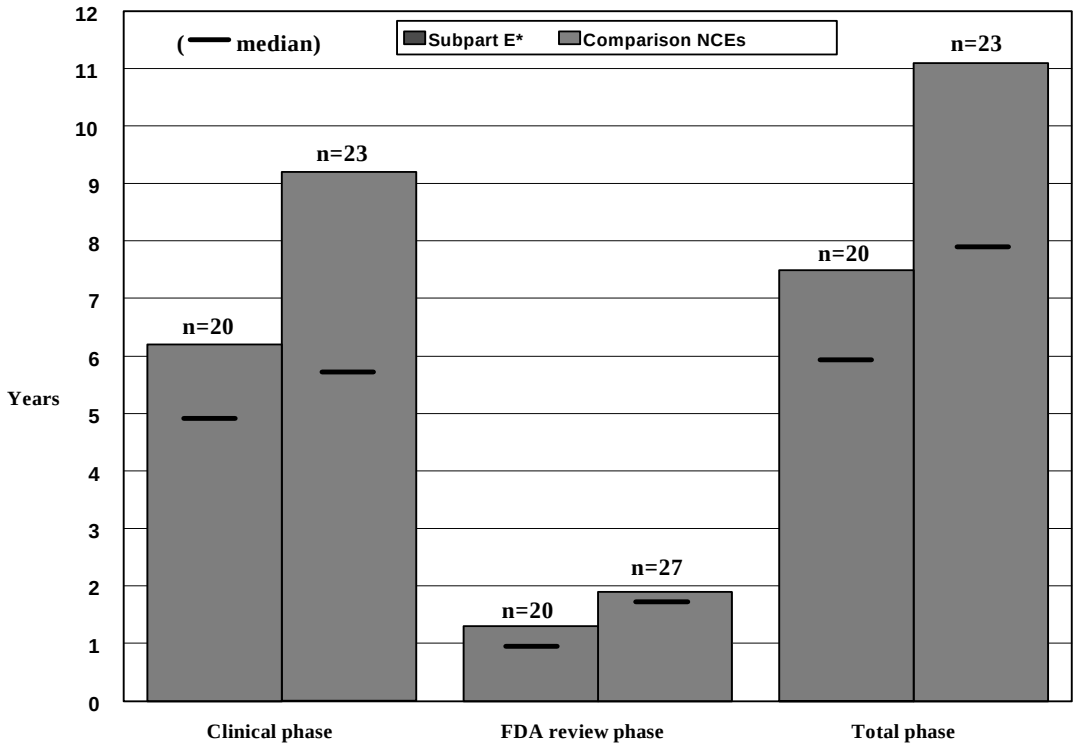
- FDA involvement in seeking a treatment IND to cover the balance of the clinical and the FDA review phases, if the results of preliminary Phase II data analyses are promising;

- application by the FDA of a "medical" risk-benefit standard when making the decision on approvability; in accepting this standard, the agency has acknowledged that patients with life-threatening or severely debilitating illnesses are willing to accept a higher level of risk; disease severity and the lack of satisfactory alternative therapies are among the specific factors to be considered during the review process;

- phase IV or post-approval clinical studies may be required as a condition of approval.

Between October 1988 and December 1994, the FDA reported 28 Subpart E approvals, (three biologics and 25 chemical compounds), almost two-thirds of which were for the treatment of cancer and AIDS or other HIV-related conditions. On average, the total time from IND submission to FDA approval was 3.3 years less for the 20 Subpart E NCEs[1] than for similarly rated non-Subpart E NCEs approved during the same period (Shulman and Brown, 1995). Although a difference was observed in both the clinical and FDA review phases, the greater disparity was evident in the clinical phase, which was 2.7 years shorter for the Subpart E approvals; the mean FDA review phase was 6.3 months shorter (Figure 1). These results suggest that the Subpart E procedures may hold promise for a substantial decrease in clinical development times and a lesser, although not unimportant, decrease in FDA review times. The hallmark of the procedures is early and sustained FDA/sponsor collaboration, a joint investment in the development process that may be a key factor in moving drugs to market more quickly.

Figure 1. **Mean and median clinical, FDA review, and total phase lengths for subpart E[1] and comparison NCE approvals: 1987-1993**



1. Excludes new formulations and supplemental approvals.
Source: Shulman and Brown, 1995.

Accelerated approval regulations

Implemented in late 1992, the accelerated approval rule represents the most significant departure from traditional FDA drug approval standards (21 *CFR* 314.500; 21 *CFR* 601.40). The major point of departure in the regulations is the ability to grant accelerated or "conditional" approval on the basis of a drug's effect on a surrogate endpoint. The link between the change in the surrogate endpoint and actual clinical benefit need not be validated at the time of approval. Approval is granted with the sponsor's agreement that the legitimacy of the surrogate marker, in terms of establishing a correlation between the surrogate and slower disease progression, longer survival, or fewer opportunistic infections, will be determined in post-approval confirmatory studies. Given the potentially high level of uncertainty inherent in this process, the FDA has built additional safeguards into the regulations:

- conditions of approval may restrict the distribution and use of the drug to a specific health care facility or group of physicians, or may require that a specific test or procedure be linked to the administration of the drug;

- promotional materials intended for distribution within 120 days of product approval must be submitted to the FDA during NDA/PLA review; thereafter, submission is required 30 days prior to intended use;

- a streamlined withdrawal procedure provides a rapid mechanism for the FDA to remove the drug from the market in any of the following six circumstances: anticipated clinical benefit is not confirmed in post-approval studies; the sponsor fails to exercise due diligence in the conduct of post-approval studies; restrictions on use and distribution of the drug prove insufficient to ensure safe usage; the sponsor fails to adhere to restrictions on usage and distribution; promotional materials prove to be false or misleading; or, other evidence indicates that the drug is not safe or effective under its conditions of use.

The FDA reported twelve accelerated approvals between January 1993 and December 1995 (seven NCEs, two new biopharmaceuticals, and three supplemental applications for already-approved drugs) (Tufts CSDD Early Access and Accelerated Approval Database, 1996; Shulman and Brown, 1995). Eight approvals were for AIDS or HIV-related indications; approval for these compounds was based on observed changes in the CD4 count, viral load, and P24 antigen levels. The remaining four approvals involved drugs for the treatment of multiple sclerosis, cystic fibrosis, pancreatic cancer, and cardioprotection from doxorubicin toxicity in breast cancer patients.

Clinical development and FDA review phase lengths for the accelerated approvals indicate that the FDA is meeting its initial goal of moving selected drugs to market more quickly using the accelerated approval process. On average, the clinical development time for the nine new compounds was five years; the mean FDA review time was nine months. The three supplemental applications were reviewed in 10.3 months. At this point in the evolution of the programme, however, the focus of both the FDA and patient groups has shifted somewhat. Currently, the emphasis is less on speeding the availability of new compounds than on establishing therapeutic value. This followed some early disappointment with the reliability of the CD4 cell count, in particular, as a predictor of the clinical benefits to be gained from several AIDS therapies. Concerns were expressed that the agency had failed to articulate sufficiently clear guidelines for the selection of surrogate markers, and that the FDA had been less than rigorous in its monitoring of Phase IV studies, raising doubts about access to long-term data on actual clinical benefit. (Link, 1994). The FDA has indicated that some reevaluation of the accelerated approval process is underway (Kessler, 1994); however, this has not prevented the FDA from advocating more extensive use of the accelerated approval regulations.

Expanded access and accelerated approval for cancer drugs

A new initiative to improve patients' access to cancer drugs was announced by the Clinton Administration and the FDA in March 1996 (Clinton and Gore, 1996). The new policy is intended to facilitate research on oncologic therapies and to shorten the time for first and subsequent marketing approvals for cancer drugs. The initiative includes a combination of early access under a pre-approval distribution using either a treatment or compassionate IND or an open-label protocol, followed by review under the accelerated approval regulations. Although the accelerated approval mechanism was formerly available to sponsors of cancer therapies, it has been under-utilised for drugs in this therapeutic area. In large part, this has been attributed to the lack of agreement on reasonable surrogate endpoints[2] (Clinton and Gore, 1996).

Under the programme, the FDA will encourage companies that have cancer therapies approved abroad, and that are pursuing FDA marketing authorisation for those compounds, to consider an expanded access protocol in the United States. In a departure from traditional requirements that a sponsor demonstrate improvements in survival time or quality of life, approval will be possible on the basis of changes in a surrogate marker. For example, measurable but incomplete tumour shrinkage will be an acceptable basis for marketing approval. All the safety provisions in the accelerated approval regulations will apply as they would to any other compound approved under the accelerated procedures. As part of the cancer drug initiative, the FDA will also encourage the submission of supplemental applications for new uses of FDA-approved cancer therapies under the accelerated approval mechanism.

Other changes under the new procedures provide for the inclusion on the FDA Oncologic Drugs Advisory Committee of an *ad hoc* member who has personal experience with the illness targeted by the drug under review. The agency also announced that it will not require the filing of an IND by physicians wishing to study new uses in already approved cancer therapies where there is no intention to commercialise the drug for that use.

The first approval under the new procedure was announced on 16 May 1996. Taxotere, approved on the basis of evidence that it effectively reduces tumour size, is indicated for the treatment of breast cancer in patients who fail to respond to standard treatment. Survival time and quality of life will be evaluated in post-approval studies.

Prescription Drug User Fee Act of 1992

Since 1993, under the authority of the *Prescription Drug User Fee Act of 1992* (Public Law No. 102-571), the FDA has collected user fees from applicants seeking FDA approval for certain new drug applications (NDAs), product license applications (PLAs), and supplemental applications. The legislation, signed into law by President Bush on 29 October 1992, signalled the start of an unprecedented phase in the history of the FDA (Shulman and Kaitin, 1996). The Act established a five-year programme for the payment of user fees, which generated $36 million (US) in the first fiscal year. Fee revenues increased to $56 284 200 in FY94, $77 415 000 in FY95, and $79 981 200 in FY96 (58 *FR*:65184, 1993*a*; 59 *FR*:63808, 1994; 60 *FR*:61702, 1995*a*). The fees fall into three categories: application, product and establishment. Until the required amount of fee is paid, a new application is considered incomplete and is therefore not acceptable for filing by the FDA.

The pharmaceutical and biotechnology industries' expectations for speedier FDA review of applications for new drugs and biologics have figured prominently in the implementation of the user fee

programme. Time consumed by regulatory review is a key variable in the economics of drug development. A crucial component of the programme is a series of performance goals designed to achieve specific incremental improvements in the speed and efficiency of the drug review process. The agency is required to submit an annual report to Congress outlining its progress toward meeting the performance goals. For example, the backlogs of applications at CBER and CDER were eliminated by the specified date, allowing FDA resources to focus on new PLAs, NDAs, and supplemental applications. The agency has met the performance goal requirements that defined proportions of new standard applications filed with CBER and CDER in each fiscal year covered by the legislation be reviewed and "acted on" within 12 months of submission (Food and Drug Administration, 1995). Starting in fiscal year 1997, almost all priority applications are to be reviewed and "acted on" within six months of submission. An "action" for the purposes of the Act constitutes one of three responses by the FDA: the issuance of an approvable letter, an approval letter, or a non-approvable letter.

Fee waivers and reductions

Industry support for the user fee programme was strengthened by the inclusion of provisions that took account of potential economic hardship and issues of equity (Shulman and Kaitin, 1996). These provisions were of particular importance to biotech and other start-up firms with a limited source of capital. The legislation authorises the FDA to waive or reduce one or more of the scheduled fees under any of the following four circumstances: the fees either present a financial barrier to a firm's ability to develop a drug deemed important to the protection of the public health or are a barrier to the continued pursuit of innovative technology; the amount of the fees exceeds the costs to the FDA of reviewing the submission; the drug is the same as or similar to a generic drug for which no user fees were payable; or the application was withdrawn after filing but before any substantial work could be done on the application.

In addition, although orphan drug status (i.e. drugs intended to treat conditions affecting small populations, defined as ones that affect less than 200 000 persons in the United States) is not a specific ground for granting a waiver or reduction, the FDA has acknowledged that certain orphan drugs that are innovative and provide public health benefits may qualify even though they have been developed by other than start-up or small companies (Food and Drug Administration, 1993).

A report outlining user fee waiver actions for the period 16 July 1993 to 28 April 1995 has been released by the FDA (Waivers and Reductions, 1995). During that period, 94 fee waivers representing a total of $3.8 million in potential user fee revenues were granted. Thirty-five per cent of that amount was attributable specifically to orphan drugs. Among the firms applying for relief from application fees, the most financially onerous of the three user fee categories, more than one-third were orphan sponsors. Overall for the approximately 22-month period, orphan drugs were the subject of 50 waiver requests, 31 of which were granted.

The small business exception

This provision in the user fee legislation, in combination with the potential for fee waivers, was key to enlisting the support of the biotechnology industry (Skaletsky, 1992). Companies with fewer than 500 employees, including those in affiliates, and with no marketed prescription drug product are eligible for the small business exception, which provides a one-year deferral and a 50 per cent reduction in the application fee. This is a two-step process. First a determination is made on the deferral. This requires confirmation of small business status by the US Small Business Administration. The decision on whether

to grant the 50 per cent reduction in the application fee is made one year later when the FDA confirms that the company still meets the requirements for the exception. Through 28 April 1995, the FDA reported 19 deferrals and seven fee reductions for qualifying small businesses.

The FDA's report does not indicate how many biotechnology firms received waivers or reductions. However, given the emerging nature of the industry, its uncertain financial status, and the highly innovative nature of its products, biotech firms are likely to be well-represented among the recipients of both waivers and small business exceptions.

Orphan drug tax credit

The *Orphan Drug Act* of 1983 (Public Law No. 97-414) established four incentives for the development of orphan drugs. The incentives include grants to support research on orphan drugs, assistance with clinical trial protocols, a seven-year period of marketing exclusivity for the drug and the approved orphan indication, and a tax credit for "qualified clinical testing expenses".

The orphan drug scheme has been a key factor in the early growth of the biotechnology industry. During the 13 years since the implementation of the *Orphan Drug Act*, almost one third of the 315 orphan drug sponsors have been from the biotech sector, and more than one third of all orphan designations were attributable to those firms (Shulman and Manocchia, 1996). Of the 102 orphan drugs that have received marketing approval, 28 were biologics, including 12 recombinant protein products and one therapeutic monoclonal antibody. Over the period 1980-1994, 29 new biologic entities (NBEs) were approved by the FDA; 16 of these products were orphan drugs (Gosse and Manocchia, 1996). The critical incentive for the biotech sector has been the award of marketing exclusivity that effectively has bolstered a traditionally weak or unfavourable patent position for biotech products.

Recently, however, the importance of the orphan drug tax credit to the biotechnology industry has become increasingly apparent. As it is currently written, the terms of the 50 per cent tax credit, found at section 28 of the *Internal Revenue Code of 1986* (Public Law No. 99-499), is available only for expenses related to human clinical testing involving the orphan drug for the specific orphan indication. Preclinical costs, clinical trial expenses prior to the date of orphan designation, and those incurred after FDA approval currently do not qualify for inclusion in the credit. A further limitation requires that the credit be used in the taxable year in which the expenses were incurred. The credit is therefore meaningless to the many biotech firms that have no current tax liability against which to apply the credit. In addition, the credit was designed to be time-limited. The original Internal Revenue Code provisions called for termination of the tax credit on 30 June 1992; subsequent amendments extend the date to 31 December 1994, and more recently to 31 December 1997.

The biotech sector has called for a restructuring of the tax credit. There has been strong industry support for a bill currently before Congress (S.1052) that would make the terms of the credit more relevant to the needs of the biotech industry. If enacted, the bill would make the tax credit permanent and would allow qualified expenses to be carried forward to a year in which a tax liability is incurred. It would also make the credit retroactive to 1 January 1995, to cover clinical testing expenses incurred after the termination date of 31 December 1994 and before re-enactment of the credit. The industry is seeking to have additional provisions included in the bill that would extend the credit to include expenses related to preclinical research and to clinical trial expenses incurred up to one year following FDA marketing approval.

Intellectual property issues

Biotechnology Patent Protection Act

This legislation corrected a long-standing deficiency in the US patent system that has had a disproportionate impact on the biotechnology industry. Prior to enactment of the legislation in November 1995, the US Patent and Trademark Office (PTO) was guided in its determinations on the issuance of process patents by a 1985 decision of the US Court of Appeals for the Federal Circuit (*In re: Durden*, 1985). In that decision, the court stipulated that a process is not patentable if its steps are obvious, even if the process involves the use of a novel starting material or produces a novel product. Only if the results of the process were entirely unexpected could a process patent be issued. Since the techniques used by the biotechnology industry to make a drug are often ones that are known, well-established, and therefore obvious, process patents were difficult to obtain. This compounded an already difficult patent environment for the industry. The end product often was not patentable due to prior scientific publication referencing the compound, or because the compound had already been patented. Without an enforceable process or product patent, companies had little protection for their inventions. Although a patent could be obtained on a novel starting material, it was of little benefit since US patent law does not give starting material patents the same enforcement rights as those that accrue to other kinds of patents. A competitor may use a US-patented starting material in another country and import the end product without consequence (*Amgen v. International Trade Commission*, 1990; *Amgen v. Genetics Institute and Chugai Pharmaceutical*, 1991).

The 1995 legislation amends the Patent Act to provide that a recognised biotechnology process can be considered novel, and therefore patentable, if it uses or produces a novel or non-obvious material or substance. This change puts the United States in conformity with Europe and Japan on this issue. The amendment strengthens the industry's position considerably, since importation of a product manufactured in a foreign country is now prohibited if a US-patented process has been used in its manufacture.

Other issues related to patenting biotechnology inventions remain unresolved. For example, the patent term in the United States was recently changed from 17 years from the date of patent issuance to 20 years from the date of filing. The shift was included in the 1994 US legislation implementing the General Agreement on Tariffs and Trade. Since the PTO often has taken longer than three years to issue biotech patents, the industry is concerned that, in cases where such a delay occurs, the patent term for those products will be eroded to less than the original 17 years. In anticipation of this occurrence, the Biotechnology Industry Organisation (BIO) has proposed legislative amendments that would lengthen a patent term when the delay is caused by an interference proceeding, appeal of a patent denial, or other circumstances beyond the control of the applicant (Bernstein, 1996*b*).

Elimination of utility data requirement

Two separate developments have decreased the time and uncertainty associated with obtaining patents for biotechnology and some pharmaceutical inventions. The biotech industry has long argued that the PTO has held biotech patents to a higher standard of usefulness than is required for other types of inventions.

A 1995 decision of the Court of Appeals for the Federal Circuit (*In re: Brana*, 1995) held that the results of human clinical trials are not an essential component of a drug product patent application. The Court first confirmed that the PTO must carry the initial burden of establishing that an invention lacks

utility. Second, the Court found that the PTO's requirement that applicants submit the results of human clinical trials to establish utility exceeded the requirements of the patent law. The decision clearly restricts the discretion of the PTO to deny drug patents on the basis of an alleged lack of utility (Bastian and Storella, 1995).

In July 1995, the Commissioner of Patents published the final version of "The Utility Examination Guidelines" to be used by PTO examiners in making determinations on the utility requirement (60 *FR*:36263, 1995*b*). Results from *in vitro* assays or animal models that are reasonably predictive of utility in humans should be sufficient to establish an asserted utility (Bastian and Storella, 1995). Unless the supporting logic is "seriously flawed", a specific utility (i.e. treatment of a particular condition) asserted in the application must be considered credible. The Commissioner also indicated that when an applicant has initiated Phase I clinical trials, this alone should establish that the asserted utility is sufficiently credible for the purposes of the patent application.

Establishment License Application (ELA) elimination

Until recently, firms engaged in the development of all new biologic drugs, vaccines, and diagnostics that were to be reviewed for marketing approval by the FDA's CBER were required to submit an establishment license application (ELA) to CBER for the manufacturing facility in which their products are produced. The application, which requires review and approval by the FDA, is separate from the application on which product marketing approval is based [a product license application (PLA)]. The PLA includes information on the biological product's safety, efficacy, potency, and purity standards. ELAs contain detailed information on the manufacturing facility's physical design, equipment, utilities, methods of production and testing, personnel organisational charts with associated credentialing information about key personnel, and other key characteristics of the production process. Each manufacturing facility is to have either a separate ELA or an amendment to an ELA filed and approved by the FDA. This dual application process for biologicals can be contrasted with regulation of chemical compounds reviewed at FDA's CDER, where a separate application relating to production of the product is not required.

In a proposed rule issued on 29 January 1996 (*60 FR*:63048, 1995*c*), the FDA altered its policy on ELAs and no longer required that ELAs be submitted for "well-characterised biologics." The FDA also provided an interim definition of a well-characterised biologic. This definition was to be subject to further refinement in a final rule. The proposed rule allowed the license holder to assume responsibility for all establishments engaged in significant production steps.

After reviewing comments sent to the agency on its proposed rule, the FDA published a final rule on 14 May 1996 (61 *FR*:24227, 1996*a*), effective as of 24 May 1996. The final rule differs notably from the proposed rule, in that it indicates that the FDA has abandoned its attempt to define a "well-characterised biologic" for the purpose of determining whether an ELA should be submitted. The FDA concluded that it might not be possible to define the term "well-characterised" clearly enough to provide sufficient guidance to potential applicants. Instead the FDA has issued a list of specific product categories that would be subject to an exemption from ELA requirements. The product categories are DNA plasmid products, therapeutic synthetic peptide products of 40 or fewer amino acids, monoclonal antibody products for *in vivo* use, and therapeutic recombinant DNA-derived products.

As described in a Federal Register notice (61 *FR*:2739, 1996*b*), the FDA has also eliminated lot-by-lot release requirements for well-characterised products. Until recently, the regulations reflected the view that there is inherent variability in the production of biologics coming from living tissues.

Therefore, each individual lot had been subjected to evaluation and testing at the FDA's CBER. The lot release programme required manufacturers of licensed products to submit product samples, protocols, and test results of individual lots for review by the FDA prior to distribution of the lot. Under the new terms, once a company has established an ability to consistently produce acceptable lots for these biologics and has a procedure in place to prevent release of lots that do not meet specifications, it will not be necessary for the FDA to formally release the lots of well-characterised biologics.

Export of unapproved drug products

Legislative proposals to open foreign markets to investigational compounds for commercial purposes were first considered by the US Congress in 1976. Increasing concerns related to US international competitiveness, a declining US pharmaceutical balance of trade, the growing strength of the pharmaceutical industry in Europe and Japan, and the fear that the early US lead in biotechnology would be jeopardised resulted in enactment of the *Drug Export Amendments Act of 1986* (Swanson, 1985). A restrictive US trade policy had barred access to markets and revenue sources, and was blamed for the loss of jobs and investment capital. The burden was viewed as falling primarily on the biotechnology industry, in part because many of the small firms characteristic of the industry lacked the financial base to locate separate facilities abroad, and were forced either to seek joint ventures or licensing agreements, or to transfer proprietary technology abroad, denying the full profits of the endeavour to the innovator. The benefits of the 1986 amended export policy thus were expected to accrue principally to the biotech sector (Hatch, 1985).

The *Drug Export Amendments Act of 1986* (Public Law No. 99-660) allowed the export of unapproved human and animal drugs, unlicensed biologics, and partially processed biologics (PPBs) to any of 21 countries listed in the Act. The drugs were required to be under active investigation for marketing in the United States and approved for marketing in the receiving country. The Act also contained specific conditions for the export of unapproved drugs intended for the treatment of tropical diseases. Sponsors wishing to export products in any of the categories covered by the Act had to obtain FDA export authorisation.

A review of how the Act was implemented during the first five years following enactment suggested that the FDA assumed broad authority under the Act (Shulman *et al.*, 1994). For example, the agency required export approval for modifications in dosage, strength, formulation, packaging, or the US manufacturing site for drugs already approved in the United States. The agency also required that PPBs be exported in a form that required a major manufacturing step in the receiving country. Formulation into a final dosage form was not deemed significant to meet this requirement. This restriction was viewed as severely limiting the number of export approvals for PPBs. For these reasons and others, the broad range of benefits expected to flow to the biotech industry did not materialise.

It was not surprising, therefore, that the biotechnology industry, as part of its broader FDA reform effort (details of which are discussed later in this chapter), sought material changes to the export legislation. The proposed amendments had sufficient support that they were put forward as a separate package and enacted as part of the 1996 budget legislation that was signed into law in late April 1996 [the *FDA Export Reform and Enhancement Act of 1996* (Public Law No. 104-134)]. The amendments simplify the process of exporting PPBs, unapproved drugs, biologics, and medical devices, and limit FDA's authority to regulate this sphere of export activity.

FDA now has a new statutory obligation to provide companies with an export certificate within 20 days of request. The number of countries to which unapproved products may be exported has also

been increased. The amendments permit export to any country, assuming the product is in compliance with the laws of that country and has valid marketing authorisation in Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, the European Union (EU), or a country in the European Economic Area (the countries of the EU and the European Free Trade Association). The Secretary of Health and Human Services may designate additional countries that meet certain statutory requirements. The changes in the statute have opened up untapped markets for products still under investigation in the United States.

Proposed revisions

FDA reform proposals in the United States

A number of more or less comprehensive US FDA reform packages have been offered and discussed in recent months. These include proposals by the industry trade associations [Biotechnology Industry Organisation (BIO) and Pharmaceutical Research and Manufacturers of America (PhRMA)] and federal legislators (e.g. Senator Kassebaum and Congressman Burr).

Recently, BIO has proposed that ELAs be eliminated for all biopharmaceuticals and biotechnology-derived diagnostics. It asserts that pre-approval inspections are sufficient to assess the adequacy of the facility and the manufacturing and process controls. The trade association also argues that manufacturers should be able to make some process changes without prior approval. An appropriate definition of a well-characterised biologic, they maintained, would assist the FDA in determining a tiered system for assessing the kinds of manufacturing changes that can be made without prior approval. BIO suggested that the definition of a well-characterised biologic be expanded to include such products as proteins, peptides, polysaccharides, and polynucleotides isolated from natural sources or produced using recombinant DNA or monoclonal antibody technologies, or by chemical synthesis. The product categories included would be therapeutics, vaccines, and diagnostics. The organisation has also suggested that manufacturing issues be incorporated in a chemistry, manufacturing, and controls (CMC) section of a PLA. Under the association's proposals, the ELA requirement would remain only for a small subclass of products best regulated by process controls (e.g. certain cell and tissue therapies where a PLA is neither practical nor needed).

In a proposal circulated in June 1995, PhRMA, the trade association representing traditional pharmaceutical manufacturers, asserted that except for whole cell vaccine products, the ELA and PLA should be merged into a single licensing application. It further proposed that batch certification be required only if the license holder's batch release procedures have been found to be inadequate to assure the safety and effectiveness of the product.

Some of the concerns regarding regulation of biopharmaceuticals have been addressed in some fashion in the Clinton Administration's "Reinventing Government" (Gore, 1993) initiatives and in Senate and House bills. Senator Kassebaum's FDA reform bill (S.1477) has been revised by the Labor and Human Resource Committee. Congressman Burr has sponsored a bill (H.R.3199) in the House of Representatives that some House members expect to be altered somewhat and brought to the House floor in June 1996.

S.1477 seeks to harmonize the regulatory treatment of drugs and biologics, but the statute governing regulation of biologics, the *Public Health Service Act* (Public Law No. 78-410), would remain in effect. If, as in a previous draft of S. 1477, the regulation of well characterised biologics were governed by the drug provisions of the US *Federal Food, Drug, and Cosmetic Act* (Public Law No. 75-717) then the provisions of the 1984 US *Drug Price Competition and Patent Restoration Act* (Waxman/Hatch Act) (Public Law No. 98-417) regarding approval of generic products would apply to these biologics. The

House bill would subject biologics to the *Federal Food, Drug, and Cosmetic Act* (Public Law No. 75-717), but expressly states that the Waxman/Hatch Act generic drug provisions would not apply to biologics.

Both S.1477 and H.R.3199 codify Administration initiatives by eliminating batch certification for insulin and certain antibiotics. Both bills maintain provisions for the export of these products. S.1477 eliminates the ELA requirement as proposed by the FDA. H.R.3199 also codifies other Administration proposals, such as allowing minor manufacturing changes without prior FDA approval, and allowing development of biologics to proceed until approval with the products manufactured in pilot plants (unless the FDA can demonstrate that a full-scale facility is needed to establish safety and efficacy). Changes in the manufacturing facility or personnel may be made at any time and only reported annually for biologics that are not the subject of a monograph and cannot be adequately characterised. Other changes would require a study demonstrating equivalence, and can be made at any time, but they must be reported at the time of the change. Additionally, the House bill requires the FDA to establish requirements for tissue products, including which products derived from tissue must be regulated. Human tissues would be regulated only if the FDA demonstrated that "voluntary regulation under generally accepted scientific standards is inadequate to protect the public health".

The Senate and House bills contain numerous other provisions that can have a general effect on how quickly new drugs and biologics are developed and reviewed. Some of the salient provisions are those that pertain to authorisation to conduct clinical trials; timetables for handling clinical holds; collaboration between the FDA and sponsors on clinical trial design; a streamlined fast-track approval process for drugs indicated for life-threatening or serious diseases; directives for the FDA to work with other countries on international harmonization of relevant regulations; elimination of the RAC's role in approving gene therapy protocols; the use of historical data as the basis for approval of supplemental indications; the structure of agency oversight; and the use of external or third-party reviews. Currently, no bill provides a basis for automatic approval of drugs, as desired by PhRMA, that have already been approved in the United Kingdom or Europe (subject to a decision with accompanying justification by the FDA not to approve the drug within a short period of time after an application is submitted to the FDA).

Economic implications of US policies on the development and approval of new biopharmaceuticals: factors to consider to enhance biopharmaceutical development in OECD Member countries

The effects of reduced time to market in the drug development process on the cost of innovation

Developing new biopharmaceuticals and getting them approved for marketing is a lengthy, uncertain, and costly process. In general, the quicker, the less uncertain, and the cheaper the process is made, the more attractive investment in biopharmaceutical R&D will become. Many of the intended effects of the policies and proposals noted above relate to reducing out-of-pocket costs, making the process more predictable, and moving effective and safe products to market faster. If realised, any of these effects will increase incentives for firms to engage in and for investors to invest in biopharmaceutical R&D.

The evidence to date indicates that the development process for biopharmaceuticals has been shorter than that for traditional chemical compounds, but still lengthy. The time from the initiation of clinical testing in the United States to submission of a PLA with the FDA, and to approval of the PLA by the FDA, averaged 3.9 and 5.7 years, respectively, for new biopharmaceuticals approved in the United States from 1990 to 1994 (Gosse and Mannochia, 1996). Policies that can reduce these times will lower the effective cost of bringing new biopharmaceuticals to market and increase the returns that may be expected from successful product introductions.

Although new drug development costs can change significantly over time, the relative contributions of various components of the development and regulatory review processes are likely to be much more stable. Thus, it is worthwhile to examine what is known about R&D costs to obtain a reasonable sense of the extent to which shortening various development and review phases will effect overall costs.

DiMasi *et al*. (1991) estimated R&D costs for a sample of new drugs that first entered clinical testing anywhere in the world from 1970 to 1982. The drugs from this period that were successful were generally approved in the 1980s, although some were approved in the 1970s and others were approved in the 1990s. The mean out-of-pocket and capitalised clinical phase costs for the approved drugs in that sample are shown in Table 1. Out-of-pocket costs are the direct costs that firms incur in the course of development. Capitalised costs are the sum of out-of-pocket costs and time costs. Time costs are measured as the return that could have been earned on R&D expenditures from the time that they are incurred to the date of marketing approval if the funds spent on R&D had instead been invested in a financial instrument of similar risk. For individual development projects, the results in Table 1 show that clinical trial costs are much greater in Phase III than in earlier phases.

Table 1. **Mean clinical phase costs for approved new drugs (1995 US$ millions)**

Clinical phase	Mean out-of-pocket cost	Mean capitalised cost
Phase I	3.2	5.1
Phase II	7.3	11.0
Phase III	25.9	33.2

Note: Based on a sample of 21 marketed new chemical entities that first entered clinical testing during 1970 to 1982.

Source: DiMasi *et al.*, 1991.

When the costs of research failures and preclinical expenditures are included in cost estimations, DiMasi *et al*. (1991) found that time costs account for more than half of total costs. Thus, reductions in the amount of time spent in development or regulatory review can significantly reduce costs. Table 2 shows the percentage declines in cost per approved new drug (failures included) that can be achieved from one year reductions in clinical trial and regulatory review phase lengths. The cost savings indicated in the table are determined by assuming that out-of-pocket costs remain the same. That is, they represent reductions in time costs only. If the reductions in time to market are also associated with lower out-of-pocket expenditures, then the cost savings from shortening the process will be even larger. Additionally, faster times to market will mean longer effective patent lifetimes and so higher net returns to the investment in R&D. Lower costs and higher returns translate into greater incentives to pursue new drug development. The benefits to speedier development and regulatory review are particularly important for start-up biotech firms, which generally have high burn rates relative to available capital (Lee and Burrill, 1994).

Table 2. **Percentage declines in cost per approved new drug from one-year reductions in average phase length**[1]

One-year reduction in phase	Percentage decline in time cost	Percentage decline in total cost
Phase I	11.1	5.6
Phase II	13.7	6.9
Phase III	15.4	7.8
NDA Review	16.2	8.2

1. Based on a sample of 93 investigational new chemical entities that first entered clinical testing during 1970 to 1982.

Source: DiMasi *et al.*, 1991.

Current and proposed regulatory reforms that may enhance biopharmaceutical innovation

The policies and proposals described in this chapter have economic implications for firms already engaged in the development of biotechnology-derived drugs and for firms that might form to take advantage of promising opportunities in this area. The precise impact of these myriad factors cannot de determined at this time. However, it is reasonable to conjecture about the direction of effect and the ways in which individual policies would work to provide greater incentives or disincentives for biopharmaceutical innovation. The lists shown below portray regulatory reforms and policies that should lower the expense or improve the efficiency of some aspect of the drug development process. These factors should therefore encourage development of new biopharmaceuticals by both start-up and established biotechnology and pharmaceutical firms.

Many of the reforms listed below, some of which are discussed in this chapter, can affect the viability of both traditional chemical and biopharmaceutical drug development. Of particular relevance to biotechnology firms, though, are the elimination of ELAs for some product categories, the lifting of lot-by-lot release requirements, and the ability to use small-scale pilot plants instead of fully functioning commercial facilities during late stage clinical development. The requirement to use commercial scale facilities placed extraordinary economic burdens on small start-up companies. Firms that desired to proceed to late stage clinical development on their own had to raise enough capital to cover the costs of both 1) building a manufacturing facility to meet the requirements of an ELA, and 2) funding large scale Phase III clinical trials. Many biotech companies have had to seek investments or establish agreements with larger pharmaceutical companies to utilise established manufacturing facilities or fund clinical trials. For example, 72 per cent of the first US-approved recombinant proteins or monoclonal antibodies during the period 1980-1994 (Tufts CSDD Biotech Database, 1996) shared or entirely gave up marketing or commercial rights to large pharmaceutical companies.

Other policies that have been of special economic significance to biotechnology firms are the *Orphan Drug Act* (Public Law No. 97-414), the *FDA Export Reform and Enhancement Act of 1996* (Public Law No. 104-134), the *Biotechnology Patent Protection Act* (Public Law No. 104-141), and the elimination of the need to provide clinical data to establish utility in a patent application. As noted above, biotechnology products and biotechnology firms are disproportionately affected by these legislative acts and rulings. Their positive impact on biopharmaceutical development is further compounded by the fact that start-up biotechnology firms are not as well financed as traditional pharmaceutical firms. Thus, even relatively

modest economic benefits resulting from new policies and regulations can mean the difference between survival and failure for some of these firms.

Reduced capital expenditures, production costs and administrative costs

- Use of small-scale pilot plants for Phase III supplies
- Elimination of lot-by-lot release review and approval
- Elimination of ELAs

Reduced clinical trial expenditures

- Elimination of costly Phase III trials (Subpart E regulations)
- Utilisation of surrogate markers for product approval (Accelerated Approval regulations)
- Grants for clinical trials under the Orphan Drug Act

Faster time to market

- Elimination of lot-by-lot release review and approval
- Elimination of ELAs
- No prior approval needed for some manufacturing changes
- Eliminating the RAC's regulatory role
- International harmonization of regulations
- Increased collaboration between sponsors and regulators (meetings on clinical trial design and other development and regulatory issues)
- Third party regulatory reviews
- Streamlined fast-track approval process for drugs to treat life-threatening or serious illnesses
- Encouraged use of paper SNDAs (supplemental new drug applications)
- User fee resources and performance goals
- Use of Institutional Review Boards to grant approval to begin clinical testing of investigational drugs
- Timelines for handling clinical holds

Increased net returns to development

- Biotechnology Process Patent Protection Act (easier patenting)
- US Patent & Trademark guidelines for determining the utility of biotechnology products (earlier patenting)
- FDA Export Reform and Enhancement Act of 1996 (sale of US investigational drugs manufactured in the United States for sale in some markets where approved)
- US Research Tax Credit (proposals to make it permanent)
- Orphan Drug Tax Credit (proposals to make it permanent, carry it forward, and expand coverage to preclinical research)

An international comparison: current regulatory policies affecting biopharmaceutical development in OECD Member countries

The role of government in biopharmaceutical development

As policy-makers world-wide debate mechanisms for speeding access to important new therapeutic products, the role of government is increasingly being questioned. To what extent can regulatory policies either facilitate or impede the development of new drugs and biologics? Does society benefit from having stringent regulatory standards which, on the one hand, may prevent hazardous and ineffective products from reaching the market, but on the other, may delay patient access to potentially beneficial compounds and serve as a disincentive to new product development? These questions cannot be answered easily.

In the United States, some have argued that excessive government regulation and stringent product review processes have slowed the rate and increased the costs of pharmaceutical and biopharmaceutical innovation. In the area of biotechnology, studies by the Tufts Center for the Study of Drug Development have shown that whereas most biopharmaceutical products introduced world-wide originate and begin clinical testing in the United States, they are usually first marketed in Europe (Bienz-Tadmor, 1993). Longer clinical development and regulatory review times in the United States compared with Europe are cited as possible reasons for this phenomenon. On the other hand, proposed and recently implemented changes in product application requirements for biotechnology sponsors (discussed in another section of this chapter) are certain to have an impact on biopharmaceutical development and review processes.

The US government has played a crucial role in encouraging and nurturing research on biotechnology and has supported the growth of a young biotechnology industry. According to Greenwood and Levinson (1996), federal funding of basic research was critical to the development of the field of biotechnology. Moreover, the Clinton Administration's current objective is to continue to promote policies that help the biotechnology industry grow. These policies include fostering partnerships between federal laboratories and the private sector and authorising tax incentives to stimulate investment in biotechnology firms.

This section of the Tufts Center's chapter examines how current regulatory policies affect biopharmaceutical development in OECD Member countries. In contrasting the regulatory policies of the United States with those of OECD Member countries, it is important to keep in mind that all major European countries, unlike the United States, regulate not just the safety, efficacy, and quality of new products, but also drug prices and, in the United Kingdom, pharmaceutical industry profits. Although evidence suggests that these policies may have a considerable impact on pharmaceutical innovation in individual countries (Redwood, 1993)[3] , their effect on biopharmaceutical development will not be considered here.

Regulatory policies and biopharmaceutical development in Europe

With a population of approximately 370 million, the European Union (EU) represents the largest pharmaceutical market in the world, a market that is about 30 per cent larger than that of the United States. To facilitate the establishment of a single European market for pharmaceuticals, the EU modified existing product approval procedures and created the European Medicines Evaluation Agency (EMEA). These efforts were intended to provide a faster and more efficient process for the review and approval of pharmaceutical and biopharmaceutical products, while ensuring that approved products meet the highest standards of safety, efficacy, and quality.

Enacted in 1993, the European Union's new product approval procedures established two new processes for attaining product approvals recognised within the EU: a centralised procedure, leading to a single marketing authorisation valid throughout the EU, and a decentralised procedure, based upon the principle of mutual recognition of national authorisations and covering the member countries identified by the sponsor.

Pharmaceutical companies seeking marketing approval of certain biotechnology products[4] must use the centralised procedure, whereas for other high-technology and innovative products[5], companies may choose either the centralised or decentralised procedures. Product approval under the centralised procedure allows a pharmaceutical company to market its product in all 15 member states without having to obtain separate approvals from each state.

The EU's centralised drug registration system was implemented on 26 January 1995. In January 1996, in his review of 1995's highlights, the EMEA's Executive Director, Fernand Sauer, declared the centralised procedure a success (EMEA, 1996). The agency granted the first "Community Marketing Authorisation" on 20 October 1995, for Gonal-F (follitropin-alpha), produced by the Italian-Swiss company Ares-Serono. In November 1995, Community Marketing Authorisations were granted for Taxotere (docetaxel) by Rhone-Poulenc Rorer and Betaferon (interferon beta-1b) by Schering. As of March 1996, three more products have received marketing authorisation: Schering Plough's Fareston (toremifene); Roche's CellCept (mycophenolate mofetil); and Novo Nordisk's NovoSeven (Factor VIIa) (*World Pharmaceuticals Report*, 1996; Tufts CSDD Biotech Database, 1996).

The advantages to biopharmaceutical manufacturers of receiving community-wide registration approval are obvious. Firms can expect demonstrable savings in time and cost by preparing and submitting a single registration document that permits marketing in all EU member countries. Industry's recognition of these advantages is evidenced by the fact that over two-thirds of the 30 new applications for human medicinal products received or announced in the second half of 1995 were voluntary applications, which could have used alternative routes for authorisation (EMEA, 1996).

In addition to the community-wide registration approval, manufacturers may benefit from another EMEA initiative -- companies may now ask the EMEA, through its committees, for scientific advice long before they prepare and submit their applications (EMEA, 1996). Shulman and Brown (1995) and DiMasi and Manocchia (1996) have recently documented the advantages to manufacturers of collaboration with regulatory agencies. US-approved drug products that were the subject of fast-track development and review and that had FDA/sponsor conferences at the early stages of R&D tended to have shorter clinical development, as well as shorter regulatory review phases.

International harmonization efforts

The European Union, in addition to its efforts to facilitate product development through its EMEA initiatives, has participated in many meetings designed to enhance international harmonization of regulatory policies and procedures through the International Conference on Harmonization (ICH). The ICH was organised to provide an opportunity for harmonization among the United States, Japan, and the European Union. The ICH has been concerned with harmonization of technical requirements for the registration of pharmaceutical and biopharmaceutical products in the three markets.

Initiatives and guidelines have been developed with input from representatives of regulatory agencies (i.e. the FDA, the Japanese Ministry of Health, and the European Commission) as well as major pharmaceutical industry organisations [PhRMA in the United States, the Japanese Pharmaceutical

Manufacturers Association, and the European Federation of Pharmaceutical Industries Associations (EFPIA)].

In the last few years, Europe, the United States, and Japan have made considerable progress in at least agreeing in principle on various technical requirements and biotechnology-specific guidelines, including general toxicity testing, reproductive toxicology, clinical safety, good clinical practices, and dose-response trial designs. These trends suggest that biopharmaceutical manufacturers may benefit not only by the elimination of needlessly extensive and prolonged animal toxicity testing, but from the acceptance by different countries of the same filing format for product registration applications (Lasagna, 1996). The ICH has clearly moved closer towards achieving its goal of identifying and then reducing differences in technical requirements for drug development among the various regulatory agencies.

Current and proposed changes in US policies governing biopharmaceutical products in development: a focus on maintenance of safety and efforts to streamline the regulatory process

Emerging technologies

In previous sections we have discussed current US regulatory policies and proposed changes to those policies that could affect the development and approval process for biopharmaceutical products. In these discussions the focus was on well-established technologies. In this section, we describe current regulatory policies for emerging technologies. In developing regulatory guidelines for new technologies, policy-makers are challenged to strike a balance between public concern over unknown technological risks and guidelines that foster, not impede, research on promising new treatments. We have chosen five areas as examples of the difficulties and complexities that the US regulatory authorities have faced. The five are human gene therapy, xenotransplantation, cellular therapy, transgenic animals, and AIDS vaccines.

Human gene therapy

Many genes responsible for specific diseases have been identified and isolated, and the exact nature of the defect has been characterised, i.e. deletions, insertions, or single base substitutions. Among this group are genes for adenosine deaminase (ADA) deficiency, many of the clotting factors and hemoglobins involved in blood disorders (hemophilia, sickle cell anemia, thalassemia), cystic fibrosis transmembrane conductance regulator (CFTR, cystic fibrosis), insulin (diabetes), many other circulating peptide hormones, and enzymes involved in intracellular metabolism, such as tyrosine hydroxylase (Parkinson's disease). In certain disease states the defective gene product (protein) can be supplemented or replaced. Examples are glucocerebrosidase, a protein supplementation for the treatment of Gaucher's disease, and insulin for the treatment of diabetes mellitus.

In contrast to protein replacement therapy, gene therapy involves introducing the wild type (normal) gene into the affected tissues or cells, which constitutively produce the protein product. The primary goal is to introduce the normal gene in a stable and long-lasting form and to generate levels similar to normal gene expression in the native cells. Clearly, irreversible pathological manifestations of any given genetic disease will, by definition, not be altered by such therapy.

Current methodologies utilise an expression vector vehicle harbouring the gene to direct DNA transfer to the recipient cell. After the cell has taken up the genetic material, the gene is then incorporated into the existing nuclear compartment. To be an effective treatment, the expression rate of the newly incorporated gene must be similar to the rate and extent of normal tissues. The newly introduced gene is

transcribed, and the now normal protein is able to re-establish normal physiological activity within the cell. To date, all human gene therapy protocols involve somatic cells, not germ line cells.

The first clinical trial of human gene therapy occurred in 1990 at the National Institutes of Health (NIH) in Bethesda, Maryland (Culver, 1994; Anderson *et al*., 1990). Since that landmark study, well over 100 clinical trials testing human gene therapy vectors have commenced. Products from 17 different companies have entered 63 human clinical trials in the United States since 1991 (Tufts CSDD Biotech Database, 1996). Ninety-five per cent of these products are in Phase I/II trials. Sixty-three per cent are aimed at attenuating malignant disease, 11 per cent are for cystic fibrosis, 11 per cent are for the therapeutic management of HIV-1 infection or autoimmune deficiency syndrome (AIDS), 11 per cent are targeting congenital genetic defects, and 4 per cent are in trials for other categories of genetic diseases.

Five US biotech companies developing human gene therapy vectors have products in clinical trials outside of the United States. There are five such clinical trials, and they are being conducted in Canada, China, Germany, and the Netherlands; all are for the treatment of cancer.

US regulation of human gene therapy protocols

The US regulatory process for human gene therapy protocols has changed dramatically over the last year and a half. In the early 1990s, two federal regulatory agencies had oversight responsibilities for human gene therapy clinical trial proposals, the Recombinant DNA Advisory Committee (RAC) from the Office of Recombinant DNA Activities (ORDA) of the National Institute of Health (NIH) and the FDA.

The RAC committee was founded in 1974 to advise the Secretary of Health and Human Services, the Assistant Secretary of Health, and the Director of the NIH on "the current state of knowledge and technology regarding DNA recombinants and to recommend guidelines to be followed by investigators with recombinant DNA" (*The Blue Sheet*, 1994).

Over the years, RAC has proved useful in addressing sensitive issues of medical ethics in a public forum and proposing guidelines for recombinant DNA technology, generation of transgenic animals, and, more recently, human gene therapy protocols. The RAC meets quarterly to review these protocols to ensure that proposals fall within the guidelines delineated in a NIH points-to-consider document (NIH Guidelines, 1996). Prior to mid-1995, all gene therapy protocols arising from federally-funded research had to be submitted for RAC review. The RAC proceeded to make specific recommendations, ensured that safety precautions were addressed, and reviewed the scientific basis of the proposal. The time needed to obtain RAC approval of a protocol was affected by the limited meeting schedule. The Director of the NIH awarded final NIH approval.

The second federal government mechanism to approve a human gene therapy trial is via the standard investigational new drug application (IND) submitted to the FDA. A new FDA division at CBER was created to regulate human cellular and gene therapies. A recently amended points-to-consider document for human somatic cell and human gene therapy underscores the changes in the federal review of human gene therapy protocol proposals (Points to Consider, addendum, 1996).

The seemingly redundant process of protocol review by the NIH and the FDA increased time to commencement of human clinical trials and drew criticism from industry, academia, and AIDS activists. The ORDA and the FDA worked closely together over an 18 month period to agree on a single, accelerated, review format for investigational human gene therapy protocol review (NIH Guidelines, 1996; Points to Consider, addendum, 1996). RAC reserved the right to review all protocols that involved

novel approaches to standard gene therapy protocols. However, these reforms were still perceived as insufficient and may have prompted the director of NIH to further consider the role of the RAC (Marshall, 1996), announcing his intention in early 1996 to terminate RAC review of all gene therapy clinical protocols (Usdin, 1996). Immediately following the formal decision to exclude protocols from RAC review, two subsequent RAC meetings were cancelled due to an insufficient number of items on their agendas. An upturn in this 22 year old committee's fortunes came in November 1996, when following public outcries, RAC was reprieved. A smaller team with new terms of reference presided over a full agenda in December 1996.

Review of human gene therapy trials in the United Kingdom

The US RAC set a precedent for review of human gene therapy trials. In 1989, the government of the United Kingdom established the Committee on the Ethics of Gene Therapy, under the chairmanship of Sir Cecil Clothier. Based upon the recommendations of the Clothier Committee, the UK Gene Therapy Advisory Committee (GTAC) was established in 1992 to review the proposals for the genetic therapy of human disease. The GTAC has prepared a booklet "GTAC Guidance on Making Proposals to Conduct Gene Therapy Research on Human Subjects", for the preparation of human gene therapy proposals in the United Kingdom (GTAC, 1994). GTAC serves to complement local research ethics committees (LREC) and will not consider proposals for germ cell gene therapy. Outside of the United States, GTAC is the closest equivalent to the RAC. GTAC review of a human gene therapy protocol is similar to the initial US RAC/FDA separate and parallel review. The proposal can be submitted simultaneously to both GTAC and the Medicines Control Agency (MCA, the British FDA counterpart). Representatives from the MCA are always present during GTAC review. GTAC evaluations and recommendations are then communicated to the LREC and the principal applicant. Although the GTAC is similar to the RAC, GTAC does not have a history of public debate and access. It is a smaller group, and thus is more likely to seek external *ad hoc* reviewers. Subsequent to approval, the name of the research institution and a description of the research are made publicly available in the GTAC Annual Report.

Xenotransplantation

Xenotransplantation, organ transplantation from one species to another, is a technological area of pursuit by some biotechnology companies for two reasons. First is the growing number of organ transplant cases, representing a lucrative potential market. In the United States alone, the number of kidney transplants (allografts) during 1994 exceeded 10 000, with over 29 000 patients on a waiting list (Taylor, 1995). The number of other vascularized organ transplants (heart, liver, lung) were lower than that for kidneys, but were substantial. These numbers reflect the advancement of sophisticated transplantation surgical techniques (Wight and Cohen, 1996), as well as the availability of new therapies to manage graft vs. host disease. The availability of human organs and tissue type matching (histocompatibility) is limiting, so that supply will probably never meet the ever growing demand. Primates and pigs, in contrast, represent an unlimited potential organ donor source.

The second reason biotech companies are developing products for use in xenotransplantation is the advancement of knowledge of the underlying mechanisms of rejection of a xenograft by the host immune system. The applications of molecular biological techniques to thwart the rejection of the xenograft are currently being tested in preclinical animal models. Medications approved to suppress the recipient's immune system have proven useful in allogeneic transplantation. In the case of xenotransplantation, however, the underlying mechanism of initial rejection has only recently been addressed. In the following

section, safety and ethical issues to be considered by both public and industrial sectors, and the proposed advisory committee oversight of xenotransplantation trials in the United Kingdom are reviewed.

Safety issues related to xenotransplantation. Proposals to limit xenosis in xenotransplantation

Regardless of the technology or mechanism of the proposed products currently being developed, there are safety factors that must be considered. The safety issues were recently addressed for simian-human transplantation.

Suggestions for ways to prevent the transmission of potential xenogeneic pathogens are listed below (Chapman *et al*., 1995; Allan, 1996):

1. A ban on all simian species transplantation should be in place world-wide until further study and regulatory mechanisms can be established. Protocols should be limited to include only swine donors for future protocols.

2. A federal regulatory structure, as exists for human gene therapy, should be put in place for the oversight of the xenotransplantation experiments:

   a) Xenotic infections should be preventable and identifiable. This may be achieved by controlling quality of animals, quarantining animals, and procuring tissues under aseptic technique. Specific guidelines should be established to ensure that operation, facilities, licensing, and medical standards are maintained.

   b) Only pathogen-free (gnotobiotic) animals and the establishment of specific pathogen-free (SPF) colonies should be considered. Standardized screening criteria for all known animal viruses and rigorous quality control standards should be established to ensure that no infected animal is used for organ donation.

   c) Bacterial, parasitic, or other known infections are to be treated prior to tissue collection.

3. Surveillance procedures should include monitoring individuals, as well as populations of transplant recipients, to determine unexplained illness or cluster events. These procedures may better assess the risk to the general population and provide a mechanism for prompt suspension of a clinical protocol.

4. A national registry documenting exposure to xenogeneic tissue should be developed.

5. A multidisciplinary task force should be established to ensure that a review of the promise of benefits of xenotransplantation for specific patients is accompanied by risk management to assess the potential of harm to the wider community.

Proposed advisory committee oversight of xenotransplantation human clinical trials: the UK model

In the United States, guidelines for human xenotransplantation are not yet publicly available (should be updated, if further discussed in terms of impacts). Within the United Kingdom, a recent report outlined a proposed mechanism at the national level to oversee the regulation of human xenotransplantation trials. The Nuffield Council on Bioethics (1996) has recommended the establishment of an Advisory Committee on xenotransplantation. Members of this committee would bring both medical and scientific expertise to

examine protocols, bearing in mind the broader issues of safety and bioethics of the new technological advances applied in xenotransplantation protocols. This committee would function publicly and thus would be held accountable for its actions. The tasks of this committee would be the following:

1. To gather and assess information pertinent to risks of xenosis and to make specific recommendations to limit xenotic transmission.

2. To establish a regulatory mechanism to ensure that gnobiotic animals are used.

3. To establish guidelines to monitor future xenograft recipients as well as manage a xenograft patient registry.

4. To review and approve human xenotransplantation clinical protocols as well as the centres involved in such protocols.

5. To review and address issues of consent and conscientious objection.

6. To provide a public forum for debate of current and future issues related to xenotransplantation.

This report further suggests that a moratorium be placed on human xenotransplantation trials until such an advisory committee is instituted. This proposed advisory committee appears to be modelled after the Gene Therapy Advisory Committee (GTAC) (Moran, 1996) which is further reminiscent of the Recombinant DNA Advisory Committee in the United States (see section above on human gene therapy). Although usually any additional measure of government regulation of clinical trial protocols is met with industry resistance, in the case of xenotransplantation, clearly many risks are acknowledged by all. The research director of a leading UK biotech company, Imutran, Inc., has said "We want to be regulated.... The last thing we need is a load of cowboys doing xenotransplants and giving it a bad name" (Moran, 1996). As of December 1996, no new animal to human transplantation clinical trials have commenced in the United States or the United Kingdom.

Cellular therapies

Somatic cellular therapies include autologous, allogeneic, and xenogeneic cells that have been propagated, expanded, selected, or pharmacologically treated for administration into humans for the prevention, treatment, or mitigation of disease or injuries (58 *FR*:53248, 1993*b*). These cellular therapies do not include human vascularized organ transplants, semen, human milk, or bone marrow. There are a growing number of cellular therapies developed by biotech companies that have entered US clinical trials since 1992 (Tufts CSDD Biotech Database, 1996). These products (n=13) are primarily for the treatment of malignant diseases (31 per cent), rheumatoid arthritis (16 per cent), and neurodegenerative diseases (16 per cent). FDA's Center for Biologies and Evaluation Research (CBER) has recently proposed draft regulations that would govern the development of these therapies (58 *FR*:53248, 1993*b*; Draft Document, 1996; Draft Document, 1995). The most recent of these draft regulations addresses allogeneic hematopoietic progenitor cell transplants (Draft Document, 1996; Draft Document, 1995). In this brief review, we focus on these innovative cellular transplantation therapies.

US regulation of hematopoietic stem cell for allogeneic transplantation

Peripheral blood stem cells (PBSC) from human donors and from human umbilical cord blood are currently being included in allogeneic and autologous transplant protocols to aid the recipient's myelopoietic and immunologic reconstitution processes. PBSC are biologic products used for the treatment of malignant or genetic diseases, and are thus regulated by CBER at the FDA. The current draft documents concerning PBSC products for human therapeutic use reflect the FDA's regulatory responsibilities under the *Public Health Service Act* (Public Law No. 78-410) and the *Federal Food, Drug, and Cosmetic Act* (Public Law No. 75-717). Thus, both PBSC and umbilical cord stem cells are subject to premarket approval, labelling provisions, manufacturing establishment registration, and other regulations governing interstate commerce mandated by these Acts. Because some of the hematopoietic progenitor cells are typically subjected to purification and/or expansion *in vitro* prior to injection to the recipient, the final product may be described as a combination of a device, biologic, or a drug. Under these circumstances, the FDA has established procedures to co-ordinate review by CBER, the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiologic Health (CDRH). These FDA centres have additional interceptor agreements in order to conduct a joint product review. Since no cellular therapies have been approved by the FDA, it remains to be determined how these working agreements will affect approval times.

Human umbilical cord blood is a rich source of pluripotent hematopoietic stem cells. These cells provide a treatment alternative to those individuals who are unable to receive stem cells from allogeneic donors. Transplantation of PBSC obtained from human umbilical cord blood as a method to reconstitute immune function and myelopoiesis (in malignant or genetic diseases) have raised additional safety, efficacy, and medical concerns (Draft Document, 1996). Three main obstacles are listed below:

1. The availability of umbilical cord hematopoietic stem cells is limited.

2. The safety and efficacy of umbilical cord stem cells transplants have yet to be determined and verified.

3. Autologous or allogeneic umbilical stem cells transplants represent complex medical issues:

   a) banking of tissues for possible future transplantation;

   b) cord blood is obtained from new-borns without established medical histories;

   c) quality control, quality assurance, safety, purity, potency, and efficacy are factors that must be considered and applied to umbilical cord blood.

Hematopoietic progenitor cells, regardless of the source, can be either manipulated or nonmanipulated PBSC. Manipulated PBSC for use in human transplantation protocols may be subjected to *ex vivo* techniques, e.g. using devices, monoclonal antibodies, or other biologics in combination with devices, to purge certain cell types or enrich others in the population. Manipulated PBSC require final product licensing by the FDA. The manipulated PBSC are subject to IND regulations during clinical development and as final biologic products. Current examples of manipulated PBSC may be one or a combination of the following:

1. peripheral blood-derived mononuclear cells enriched for CD34+ cells;
2. peripheral blood-derived mononuclear cells depleted of tumor cells;

3. peripheral blood-derived mononuclear cells depleted of T lymphocytes.

Generally speaking, nonmanipulated PBSC are not regulated by the FDA. These progenitor cells typically are subjected to procedures that expand, enrich, functionally alter, or purge cell types from the population that are not regulated by the FDA. Such techniques might include centrifugation, density gradient separation, lysis of contaminating erythrocytes, addition of medium for cyropreservation, transfer to collection devices and to storage containers, or storage in a liquid or frozen state. If nonmanipulated PBSC are intended for future manufacture, these cell products then require review and licensing by the FDA.

In addition to *ex vivo* techniques to alter the composition of the PBSC population for allogenic or autologous transplantation, there are ancillary products that are currently used in PBSC transplantation protocols and which are regulated by the FDA. Depending on whether the ancillary product ultimately becomes part of the final product, the ancillary product is regulated as either a device or a biologic drug. Some of these ancillary products may have received FDA approval for the indicated use. In the cases of unapproved usage, the FDA proposes that cross-referencing or submission of a complete description of manufacturing, process, specifications, qualifications, and acceptance criteria of the ancillary product be performed. These cross-references should be in the form of an investigational new drug application (IND) or a master file format.

In the cases where the ancillary product becomes a part of the final product, the FDA may consider it to be a combination product. These products' components will then have to become a part of the cross-referencing documentation or already have approval for this intended use. Some ancillary products may be directly administered to the patient. Current examples of ancillary products administered to the recipient are:

1. investigational agents administered to PBSC to mobilise populations before collection of the product; these may be unlicensed for their intended use or unlicensed products;

2. anticoagulants added to collection containers and infused with the product into the patient;

3. storage media and cryoprotective agents added to the stored product and infused with products into the patient.

Ancillary products that do not become a part of the final product are usually devices that act to alter the stem cell population and are not intended for human use. These devices are regulated solely by the CDRH at the FDA. Current examples of these ancillary products that do not become a part of the final product are apheresis machines, equipment for purging or selecting stem cells populations, growth factors for *in vitro* stimulation or expansion, and lastly collection and storage containers.

Transgenic animals

Transgenic animals result from the introduction of foreign DNA into animal cells. Insertion of the desired DNA into a recipient animal's nuclear compartment and subsequent expression in the animal is designed in such a way as to create: 1) heterozygous gain of function, or 2) homologous loss function. In the first design, non-heritable somatic cell DNA insertion occurs. The foreign DNA may consist of a vector that only enters somatic cells and thus constitutes gene therapy techniques (see section on human gene therapy above). In the second design, heritable germ line DNA insertion occurs. In this case, the foreign DNA may consist of a vector that contains a specific DNA sequence that, hypothetically, will

allow specific site introduction to a region or genetic sequence of the recipient's cell genomic DNA. The aim of specific foreign DNA insertion is to attenuate gene expression of a gene or a gene cluster. Alternatively, the foreign DNA may be constructed so that random insertion into the recipient's genomic DNA occurs.

Regulation of the production of transgenic animals for the production of recombinant proteins for human therapeutic use

In the United States, both the transgenic animals used for the production of recombinant proteins for human therapeutic use, and the resulting recombinant protein product (biologic) are regulated by FDA's CBER (Points to Consider, 1995). Depending on the product produced in the transgenic animal, the therapeutic product may be additionally regulated by the CDER (non-biologic) or the CDRH (devices). Further, the Center for Veterinary Medicine (CVM), the Center for Food Safety and Applied Nutrition, and the United States Department of Agriculture have additional regulatory responsibilities for veterinary and food safety issues associated with final products and the use of transgenic animals. A recent points-to-consider document produced by CBER includes guidelines for the following seven aspects of transgenic animal production and biologic products resulting from transgenic technology for use in human therapy (Points to Consider, 1995):

1. generation and characterisation of transgene constructs
2. creation and characterisation of the transgenic founder (Go) animal
3. establishment of a reliable and continuous source of transgenic animals (founder strain)
4. generation and selection of production of herds
5. maintenance of transgenic animals
6. purification of the product from transgenic animals
7. preclinical safety evaluation.

Research conducted in the United States and its territories that is funded by the NIH and that results in the production of transgenic animals is additionally regulated by the ORDA at the NIH. Transgenic animal research, including research at the NIH must be conducted following established guidelines (NIH Guidelines, 1996). A principal investigator or other individuals who receive NIH support for research involving recombinant DNA technology must be associated with or sponsored by an institution that assumes the responsibilities described in the NIH guidelines.

The guidelines contain a cautionary statement; the experiments involving recombinant DNA in the production of transgenic animals may result in creation of a novel mechanism or undesirable trait in the host (recipient animals). Thus, under certain conditions, constant evaluation of containment procedures must be considered for transgenic animal experiments.

The guidelines further describe what gene and what gene product may be introduced and under what type of laboratory safety conditions. The guidelines suggest that there may be involvement of the Institutional Biosafety Committee in the proposed experiments and protocol management.

AIDS vaccine development

In many countries, both developed and developing, a safe, effective vaccine may be one of the few cost-effective methods to prevent transmission and to control the pathological consequences of HIV infection and transmission (OAR, 1996). Development of an HIV-1/AIDS vaccine, therefore, must be

considered a high priority on the agenda for combating this disease. To achieve maximum benefit, an HIV-1/AIDS vaccine must have the following qualities: the vaccine must prevent the initial infection and target already infected cells; it must be safe and effective while inducing a broad reactive and durable immune response to the virus; it must provide protection from mucosal surface entry and direct transmission through the blood stream; and finally, it must be easily administered, transportable, and stable in storage (NIAID, 1996; AIDS Agenda, 1996).

Since 1987, 16 HIV-1/AIDS recombinant vaccine products have entered human clinical testing in the United States (Tufts CSDD Biotech Database, 1996). Seventy-five per cent (12 of 16) of these products entered trials prior to 1992 and 25 per cent (4 of 16) entered after 1994. The current status of these 16 products paints an unsuccessful clinical picture; 38 per cent (6 of 16) have been discontinued. Furthermore, one of the vaccine products recently was shown in large scale clinical trials to elicit no greater immune response than placebo (McCarthy, 1996; Kaiser, 1996). Thus, the number of HIV/AIDS vaccine products entering clinical trials has tapered off in the last three years, and for those products in trials, the results are not overwhelmingly positive. This, coupled with bleak results from other biomedical and epidemiological studies, has prompted the government, working with the AIDS community at large, to re-examine policies and programmes supporting HIV-1/AIDS research and development programmes (OAR, 1996; NIAID, 1996; AIDS Agenda, 1996; Santiago, 1996). The information generated from this analysis can be divided into 1) identification of the scientific, organisational, and societal delays; and 2) proposed solutions to address the identified problems.

Problems and issues facing HIV-1/AIDS vaccine development

Identification of the scientific, organisational, and societal delays

a) Fundamental basic mechanisms of virus biology and human immunological response have made research and development difficult. Viral mutation rate, evasion and detection of cellular immune responses, coupled with silent or latent infection, are examples.

b) There is no clear correlate of immune protection identified in either animal models, or for humans at risk for HIV infection. The measured immune response (either blood-borne vs. mucosal viral infection protection, or antibody vs. cellular immune component response) has remained controversial. Other vaccines have been developed without these clinical correlates, but HIV-1 vaccine development programmes are locked into this scientific/technical controversy.

c) A candidate vaccine must have a broader, immune response than that demonstrated in animal models. Many have suggested that an effective HIV-1 vaccine must elicit both the humoral immune response (generation of antiviral antibodies to reduce the circulation of free virus) and a cellular mediated immune response (activation of cytotoxic T lymphocytes to attack infected cells).

d) Individuals at risk for HIV infection are typically exposed multiple times over a period of years to HIV genetic variants. An effective vaccine should not succumb to this virus's ability to circumvent vaccine-mediated immunity.

e) There is unusually high concern that HIV-1/AIDS vaccines may create a false sense of security, or in some cases increase risk-taking behaviour among trial subjects. Additionally, social and ethical factors suggest that efficacy trials will be difficult to plan and execute.

f) Market forces do not necessarily foster a desirable level of private sector activity in vaccine R&D programmes.

A government/industry plan for the development of an HIV-1/AIDS vaccine programme is needed to overcome the disadvantages of vaccine development (OAR, 1996; NIAID, 1996; Santiago, 1996). More specifically, a strategic programme must address all the factors arising from basic biomedical science, society and industry. The plan must also have provisions for enhanced industry/government/community partnerships for the development of vaccine products. Recent proposals have delineated government research and development activities that may address the difficulties of HIV-1/AIDS vaccine development.

Proposed solutions to jump-start HIV-1/AIDS vaccine development

a) Increase government funding of fundamental research on human immunology and vaccine biology programmes to address our lack of understanding of the basic mechanisms of human immunity.

b) Foster free exchange or provision of viral stocks, reagents, and access to animal models within the research community.

c) Further support for a global basic and clinical research network to include specimen repositories, viral characterisation labs, and communication among multidisciplinary clinical research sites.

d) Expand support for the National Institute of Allergy and Infectious Diseases (NIAID) HIV Vaccine Efficacy Trials Network. This organisation has gathered and maintained data on seronegative, high risk for HIV transmission individuals grouped into cohorts for baseline epidemiological studies. Further, data have been gathered on risk, incidence of HIV infection, and willingness to participate in future vaccine trials. This organisation also evaluates consent procedures for vaccine trial development. In the absence of a testable vaccine product, these data have thus been applied to biochemical non-vaccine product clinical trials, as well as other non-pharmaceutical behaviour-modifying measures aimed at prevention of infection. This network therefore must be composed of behavioural, social, epidemiological, preventive, pathogenetic, treatment research, and vaccine research expertise.

e) Enhance the involvement of the AIDS community in trial design, implementation, and data analysis. To address concerns that trial subjects will have perceived notions of presumed vaccine product protection, the term and concept of sterilising immunity must be changed to prevention of infection (preventive trials vs vaccine trials) to limit risk taking behaviour patterns. In addition, preventive measures in the form of behavioural modification and education about physical or chemical barriers to viral infection should be routinely included in trial protocols.

f) Renew commitment of government/industry research collaboration and AIDS community partnering in the execution of vaccine clinical trials.

g) Renew commitment to remain open to alternative clinical trial designs to expedite “proof of concept” efficacy vaccine trials.

h) Develop and implement strategies to identify and prepare promising candidate vaccines for human clinical trials, as well as to accelerate proven products into full-scale efficacy trials. Specific goals and criteria for the advancement of a product through the clinical trial process must be made clear

to all interested groups. Each preclinical and clinical stage must have clearly identifiable milestones and goals within the context of general product design allowing for product individuality.

i) Establish an AIDS Vaccine Research Committee. This committee should be led by a distinguished non-government scientist who would oversee the NIH's progress with its intramural and extramural programmes for HIV-1 and/or other AIDS-related opportunistic infections (OAR, 1996).

j) Establish a National AIDS Vaccine Task force. This group would work out of the White House Office of National AIDS Policy to integrate all government funded HIV-1 and AIDS-related opportunistic infection vaccine development programmes. Further, this task force would establish and foster communication of specific technical and other issues and policies to industry organisations, private agencies, similar groups from other nations, and international organisations.

Despite the urgent need for an HIV-1 vaccine, NIAID in June 1994, following the advice of an NIH advisory committee, decided not to proceed with funding of large scale testing of two HIV-1 envelope protein (gp120) recombinant vaccines. The argument against funding was based in part on data indicating these vaccine products could neutralise laboratory isolates of HIV-1 but could not neutralise primary isolates from infected individuals (Santiago, 1996). There has been some controversy surrounding the validity of the test to measure neutralisation, but nonetheless the NIAID decided to cease funding. The two companies whose products were in later stages of clinical development have responded very differently (Bernstein, 1996*a*). In one case, the gp120 vaccine product design has undergone revision, whereas development of the other gp120 vaccine has been terminated until funding for the original large scale trial can be secured. These responses were driven, in part, by how funding is to be garnered for the future Phase III trials for these two product versions.

In the first case, Chiron Biocine chose to accept and work with the government plan. This company established a collaboration with Pasteur Mérieux-Connaught. Together they altered their vaccine development programme to a more acceptable product design by a government appointed panel. The product, ALVAC (Santiago, 1996), has a prime-plus booster design. The canary pox virus has been genetically modified to express HIV-1 specific genes which will "prime" the immune response by eliciting a cytotoxic T lymphocyte response. The booster portion is the Chiron Biocine gp120 recombinant vaccine which has proven able to elicit a strong humoral (antibody generating) response. The prime-plus booster vaccine product is scheduled to enter Phase II human clinical testing in 1996 and will be the first test of the federal government's commitment and willingness to foster development of vaccines for HIV-1 infection and transmission.

The other corporate sponsor to react to the lack of government support for its recombinant gp120 vaccine is Genentech (Bernstein, 1996*a*). This company has invested one million dollars as seed money to form a new company, Genenvax, which is seeking an additional $18 million to fund a Phase III trial of the recombinant vaccine product that has been proven to elicit an antibody (humoral) response to HIV-1 (Bernstein, 1996). Genentech, the parent company of this start-up company, will invest an additional one million dollars once external funding is secured, leaving Genentech with a 25 per cent equity position in the spin-off company.

Summary

Biotechnology, as applied to the development of human therapeutic products, has provided and will continue to provide innovative technologies to aid the discovery of new disease mechanisms, the genetic

basis of human diseases, and novel therapies. Governments must realise the potential in this technology and create policies to foster innovation through regulatory practices, economic incentives, investment in research and development, and an expressed commitment to provide for its citizens the benefit of these technological advances. Concise regulatory practices must be aimed specifically at protection of the population from potentially harmful or ineffective products while allowing innovative research and development to flourish.

In this chapter, we have outlined some policies and regulations governing biopharmaceutical development in the United States. We have discussed US regulation of some emerging technologies, those for which a product has not been approved for human therapeutic use, and initiatives that provide early access mechanisms to ensure that novel treatments for life-threatening diseases are available sooner for patients who might benefit from them. We have delineated economic incentives that might provide a reduction in the costs of drug development. Regulatory measures, either proposed or realised, enabling a reduction in the development times and expediting regulatory review times for biopharmaceutical products are described in this chapter. Finally, we discussed the progress of and the prospect for further international regulatory standardization and its effect on world-wide biopharmaceutical development.

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GLOSSARY

Acted-on: To meet the requirements of the FDA's user fees goals, the FDA must issue one of the following letters, within prescribed time limits, to firms that filed an NDA, PLA, or supplemental application: an approval letter, an approvable letter, or a non-approval letter.

Adeno-associated virus (AAV) vectors: A DNA construct composed of adenoviral sequences that aid in the introduction of foreign DNA into the accepting host cell. AAV mediated gene delivery can result in targeted integration of the foreign DNA into the host cell's chromosome 19.

Adenovirus (AV) vectors: A DNA construct composed of adenoviral sequences that aid in the introduction of foreign DNA to the accepting host cell. AV vectors can infect both dividing and nondividing cells and the viral DNA does not integrate into the host cell's genome.

AIDS: Acquired immunodeficiency syndrome.

Allogeneic transplantation: Transplantation of living cells or tissues from a donor to a recipient of the same species.

Allografts: Transplantation of donor living tissue to a recipient whose species is the same as the donor.

ALVAC: A potential HIV-1 vaccine product having a "prime-plus" booster design. A vaccine consisting of a canary pox virus containing HIV-1 genes may specifically stimulate cytotoxic T lymphocytes (prime portion). The booster portion is a gp120 recombinant vaccine that may stimulate the production of antibodies (humoral response) to that protein component of HIV-1. It is the combination of these two immunogens that may generate an efficacious vaccine product.

Antigenic epitope: The portion of a protein or a molecule that is specifically recognised by antibodies.

Autologous transplantation: A transplantation protocol in which donor cells or tissues are removed from a patient and after some manipulation are replaced into the same patient.

BIO: Biotechnology Industry Organisation.

Burn rate: Company expenditures per unit of time.

CBER: Center for Biologics and Evaluation Research at the FDA.

CD34+ cells: Cells that have the CD34 protein marker expressed on their plasma membrane.

CD59 and CD54: Proteins located on the plasma membrane of living tissue that can be recognised by circulating antibodies. CD59 and CD54 are proteins that prevent complement proteins from attacking the body's cells. Thus, in protocols with the aim to limit the complement cascade of xenograft rejection, the same species CD59 and CD54 may be introduced by transgenic technology to potential organ donor

animals. In protocols limiting the complement cascade of xenograft rejection, the same species CD59 and CD54 may be introduced by transgenic technology to potential organ donor animals.
CDER: Center for Drug Evaluation and Research at the FDA.

CDRH: Center for Devices and Radiologic Health at the FDA.

Centralized Procedure: A procedure of review and approval whereby applicants are allowed to market their products in all 15 EU member states without having to obtain separate approval in each state. The centralized procedure is required for firms seeking approval of certain biotechnology products, and is optional for those seeking approval of other high-technology and innovative products.

CFSAN: Center for Food Safety and Applied Nutrition at the FDA.

Clinical Development Phase: The time from the date of IND filing to the date of NDA/PLA submission.

CMC: Chemistry, manufacturing, and controls.

Community Marketing Authorisation: Permission granted by the EMEA to market a product in all 15 EU member states.

Complement cascade: A series of protein interactions that result in enzymatic cleavages and activation of the inflammatory process. The complement cascade ablates foreign organism infection and is responsible for initial transplant rejection reactions.

CVM: Center for Veterinary Medicine at the FDA.

Decay accelerating factor (DAF): A protein located on living tissue that regulates the complement cascade. DAF is the protein that prevents complement proteins from attacking the body's cells. Thus, in protocols with the aim to limit the complement cascade of xenograft rejection, the same species DAF may be introduced by transgenic technology to potential organ donor animals.

Decentralized Procedure: A procedure based upon the principle of mutual recognition of national authorisation and covering the member countries identified by the sponsor.

Delayed response: The second stage of the xenograft rejection continuum. This stage occurs within days of the xenotransplant and is mediated by inflammatory cytokines and histamine as well as a contribution from the type I endothelial cells.

Effective patent lifetime: The time from marketing approval of a new drug to the expiration of the patent.

ELA: Establishment Licence Application (US FDA).

European Medicines Evaluation Agency (EMEA): The agency created by the European Union in 1993 to provide a faster and more efficient process for the review and approval of pharmaceutical and biopharmaceutical products and to facilitate the recognition of a single marketing authorisation throughout the European Union.

Fast-Track: Refers to two FDA regulatory pathways designed to move important new drugs for serious and life-threatening diseases to market more quickly and efficiently by compressing clinical development and FDA review times.

FDA: The United States Food and Drug Administration.

FDA Review Phase: The time from the date of New Drug Application/Product License Application submission to the date of FDA marketing approval.

Final stage of xenograft rejection: This stage occurs within days of the xenograft. It is a process mediated by activated cytotoxic T-lymphocytes and type II endothelial cells. This stage usually results in loss of graft organ or tissue function and is associated with fatality.

Founder strain: The establishment of a transgenic animal that is able to reproduce, and its offspring have the foreign gene intact in their genome.

Gnotobiotic animals: Animals free of all known pathogens.

gp120: Glycoprotein 120 (a protein having a molecular weight of 120 kilodaltons) found on the envelope portion of HIV-1.

GTAC: Gene Therapy Advisory Committee (UK).

Hematopoietic progenitor cells: Cells that form the foundation of the bone marrow and the immune system.

Hematopoietic chimerism: This is a model whereby the recipient of a xenograft is first exposed to donor marrow cells. In these protocols, the recipient hypothetically re-establishes an immune system so that self and donor's tissues are not differentially recognised.

Histocompatibility: Immunologic similarity or identity of tissues sufficient to permit successful allograft transplantation.

HIV-1: Human immunodeficiency virus type-1.

Hyperacute stage: The initial stage of xenograft rejection occurring within minutes after xenotransplantation.

IND: Investigational New Drug Application (US).

International Conference on Harmonization (ICH): An international effort concerned with the harmonization of technical requirements for the registration of pharmaceutical and biopharmaceutical products in the European Union, the United States, and Japan.

LREC: Local Research Ethics Committees in the United Kingdom.

Membrane cofactor protein (MCP): A protein located on living tissue that regulates the complement cascade. MCP is the protein that prevents complement proteins from attacking the body's cells. Thus, in

protocols with the aim to limit the complement cascade of xenograft rejection, the same species MCP may be introduced by transgenic technology to potential organ donor animals.

NCE: New chemical entity.

NIAID: National Institute of Allergy and Infectious Diseases of the NIH.

NIH: National Institutes of Health (US).

ORDA: Office of Recombinant DNA Activities of the NIH.

Open-label protocol: An uncontrolled clinical study that may be used, with the approval of the FDA, to examine the safety of an investigational drug in extremely ill patients for whom no therapy exists, or who do not qualify for more formal clinical trials. A drug may be studied under an open-label before the requirements of a treatment IND have been met.

Orphan Drug: A drug intended for the treatment of a disease affecting less than 200 000 persons in the United States.

Peripheral blood stem cells (PBSC): Cells found in the peripheral circulation that are myelopoietic progenitor cells that form the foundation of the bone marrow and the immune system.

Phase IV Studies: Clinical trials conducted in the period following FDA-marketing approval, frequently as condition of approval agreed to by the sponsor.

PhRMA: Pharmaceutical Research and Manufacturers of America.

PLA: Product Licence Application (US).

Plasmid Construct: A DNA construct composed of plasmid sequences that aid in the introduction of foreign DNA into an accepting cell. The plasmid DNA is not integrated into the host cell's genome.

PPBs: Partially-processed biologics.

PTO: US Patent and Trademark Office.

RAC: Recombinant DNA Advisory Committee of the ORDA at the NIH.

R&D: Research and development.

R&D capitalised cost: Sum of R&D out-of-pocket and time costs for a new drug.

R&D out-of-pocket cost: Direct costs incurred by drug developers to research and develop new drugs.

R&D time cost: Return that could have been earned on out-of-pocket R&D expenditures if the funds had instead been invested in a financial instrument of similar risk.

Retroviral-based vector: DNA construct composed of retroviral sequences (Moloney murine leukemia virus) that aid the introduction of foreign DNA to the accepting host cell. The viral infection occurs only in dividing cells and integration of the viral DNA occurs within the host cell's genome.

SPF colonies: Specific pathogen free colonies.

Surrogate Marker: A laboratory measurement or physical sign that is used as a substitute for a clinically meaningful endpoint and that is expected to predict the effect of a particular therapy.

Transgenic animals: Animals in which the germline, heritable, cells have been manipulated to contain foreign DNA. Introduction of DNA into the animals genome results in either gain of protein expression (gain of function) or loss of gene expression (loss of function).

USDA: United States Department of Agriculture.

Xenogeneic transplantation: Transplantation of living cells or tissues from a donor to a recipient of a different species.

Xenograft: Transplantation of donor living tissue to a recipient whose species is different from the donor.

Xenoreactive antibodies: Naturally occurring antibodies found in the circulation that recognise foreign tissue. These antibodies establish the hyperacute stage of xenotransplant rejection.

Xenosis: Infections resulting from transmission of pathogens from one species to another.

Xenotransplantation: Transplantation of donor living tissue to a recipient whose species differs from that of the donor.

Zoonosis: Disease or infection that is transmitted under natural conditions from one animal species to another.

NOTES

1 Three biologics are included in the "NCE" sample. Ceredase (alglucerase), Cerezyme (imiglucerase) and Survanta (beractant) were all reviewed by the FDA's Center for Drug Evaluation and Review (CDER).

2 See Chapter 1, "Biotechnology in the changing health-care environment: methods for economic evaluation of innovative technology", by Drummond and Mason, of *Part I: Biotechnology and medical innovation: socio-economic assessment of the technology, the potential and the products*, for an in-depth discussion on endpoints in health economic evaluations.

3 In a study of over 400 new molecular and biological entities marketed or in the post-clinical, preregistration phase in at least four of the world's seven leading markets (United States, Japan, Germany, France, Italy, United Kingdom, and Spain) during 1970-1992, Redwood (1993) observed that the United States had a clear lead in discovering major, medically innovative, globally competitive new drugs. He concluded that "higher prices and pricing freedom in the USA have acted as potent incentives for pioneering efforts in pharmaceutical research and development". Price regulation, in contrast, "tends to undermine the resolve to conduct serious long-term R&D in scientifically difficult therapeutic areas where the risk of failure is exceptionally high".

4 EU regulations define biotechnology products as those derived from recombinant DNA technology, from controlled expression of genes coding for biologically active proteins in prokaryote or eukaryote cells, and from hybridoma technology (monoclonal antibodies).

5 EU regulations define other high-technology and innovative products as new delivery systems, new indications, new manufacturing processes that represent significant innovations, and new active substances not previously approved for human use in the EU.

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INTERNATIONAL REGULATORY REVIEW TIMES[1]

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Summary

1) At a time when both companies and regulatory authorities are evaluating their strategies to increase efficiency, it is important to have comparative data on overall development times. Therefore, as the period a new therapeutic candidate spends in regulatory review contributes to the overall development time, it is of value to have information on review times within different authorities.

2) A study has been initiated to collect data on application and approval dates in nine of the major pharmaceutical markets (the United States, Canada, Japan, Australia, the United Kingdom, France, Germany, Italy and Spain). Preliminary analyses show differences in review times between authorities, even for the same compounds submitted within a similar time frame.

3) The reasons for differences in review times should be questioned, as all authorities have the same basic tenets, to protect and promote the public health and to review dossiers based on quality, safety and efficacy. In order to understand the reasons behind these differences, other factors need to be assessed, such as the quality of dossiers, companies' response time to authorities' questions and the ability of authorities to manage the review effectively and efficiently.

Introduction

Regulatory review is the last major development hurdle that must be passed by a new chemical entity (NCE) before it reaches the market. This occurs at the end of a lengthy research and development process, which takes on average 9.5 years from synthesis to first application for a product licence. The total development time to launch in the first market will also include the review process which, in the early 1990s, was between one and three years for the major markets (MacInnes *et al.*, 1995).

Pharmaceutical companies realise that it is necessary to reduce the long development times, both to the first market and to the international market, in order to remain competitive in the future. Although regulatory review is the one step in the process that is not within industry control, companies can influence the duration by submitting a good quality scientific dossier and responding in a timely manner to any questions raised by the reviewer.

Over the last five years the regulatory arena has seen a number of changes which have the potential to have a major impact on both review times and the relationship between industry and regulatory

authorities (Table 1). This has led to optimism regarding the possibility of improving the review process. At a time when both pharmaceutical companies and regulatory authorities are evaluating their strategies in order to increase efficiency, there is a need for data on review times within different authorities. However, with the exception of a few authorities that publish annual statistics, accurate information is not available. Furthermore, it is difficult to draw comparisons between authorities based on published data, as different definitions are used with regard to what is included in the review time.

Table 1. **Factors which may impact on review times in the future**

• Harmonisation of technical requirements
• Increase in dialogue between industry and authorities
• New European procedures
• Restructuring and reorganisation of authorities
• Introduction by authorities of fees and target review times

Source: Author.

The measurement of total regulatory review times (i.e. time from date of application to date of approval, including any company down time) is one gross way of evaluating the time compounds spend in the review process. A study has therefore been initiated to obtain this information for the major authorities. The objectives are to:

- obtain data on regulatory review times from 1990 to 1995 in the United States, Canada, Japan, Australia, the United Kingdom, France, Germany, Italy and Spain;

- investigate trends in review times over the last decade;

- provide data to establish a baseline with which to evaluate authorities and changes that may occur in the future.

Methodology

New chemical entities marketed in the countries of interest between 1990 and 1995 have been identified using the CMR international marketed medicines database (MacInnes *et al.*, 1994). An NCE is defined as any new active substance which has not been available previously for therapeutic use in man and is to be made available as a "Prescription Only Medicine" for the cure, alleviation, prevention or *in vivo* diagnosis of diseases in man. New salts, prodrugs, esters of existing compounds, combination products (unless one of the active constituents has never been marketed previously), vaccines, antigens and veterinary medicines are not included. To date, 46 companies responsible for marketing 275 NCEs between 1990 and 1995 have been asked to provide application and approval dates in the countries of interest, for marketed NCEs and any others which have been approved but not yet marketed. The regulatory authorities in Japan, France, Australia, Canada and Germany have also been asked to identify all approvals during the 1990s and to provide application and approval dates, where possible.

To date, 32 pharmaceutical companies in Japan, the United States and Europe have provided data on 213 compounds. Information has also been received from the authorities in Canada, Germany and Australia, and application and approval dates in the United States have been obtained from the public

domain (PMA, 1990, 1991, 1992, 1993; PhRMA, 1994). Missing information on compounds known to have been approved in the 1990s is being pursued.

This paper presents preliminary analyses, as full data are not yet available for every country. An indication of the completeness of each data set for each year of approval is provided with the analyses, based on:

$$\frac{\text{Number of compounds with full data}}{\text{Number of compounds known to have been approved in that year} + \text{Compounds known to have been marketed in that year, but for which approval dates are not known}} \times 100$$

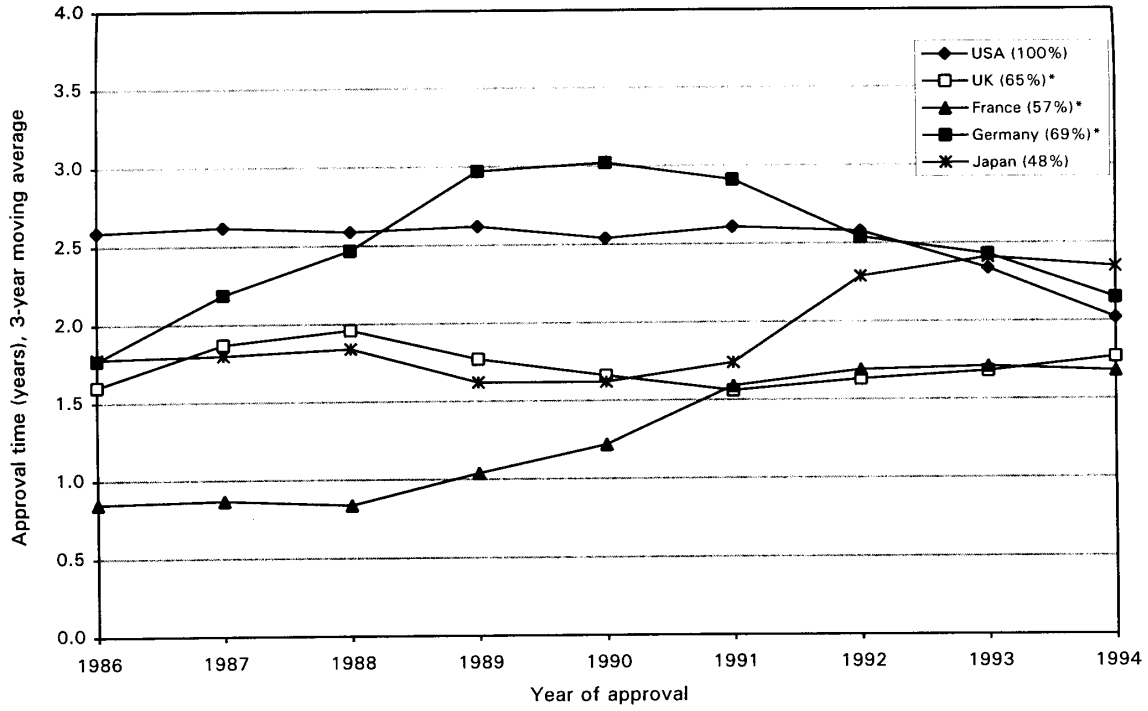
Trends in total regulatory review times over the last decade

The mean total review times are shown as three-year moving averages for the United States, Japan, Germany, France, the United Kingdom (Figure 1), Canada, Australia, Spain and Italy (Figure 2). Although still incomplete, these data suggest that compounds may have spent, on average, between 0.75 years (France) and 3.75 years (Spain) in the review process, over the last decade. However, it appears that average review times in five of the major markets are converging on two years in the 1990s (Figure 1), with the United Kingdom and France being the fastest authorities. Improvements have also been seen in the remaining countries, but review times remain at 2.5 years or greater in these markets (Figure 2).

Total regulatory review times in the 1990s

Although the mean provides the average for all approvals, it can be influenced upwards or downwards by outliers. The median may therefore be more representative of the actual time compounds are spending in the approval process. Data for median review times in the 1990s show a decrease over time in the United States, Germany, Australia and Spain, and an increase in the United Kingdom, France, Japan and Italy (Figure 3). In 1994-95, median review times were very similar -- between 1.3 and 1.5 years -- in France, Spain, the United Kingdom, the United States and Germany.

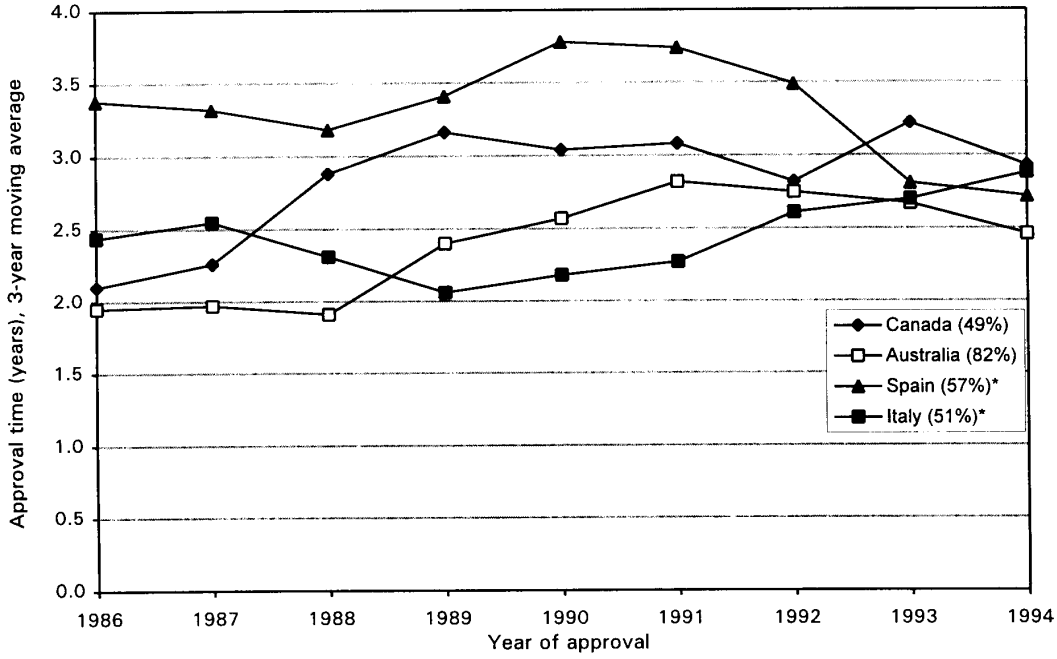
Figure 1. **Mean regulatory approval times in five countries (1985-1995). Preliminary data**



Note: Three authorisations through the European centralised procedure in 1995 have been excluded. ( ) = % of data available.

Source: Author.

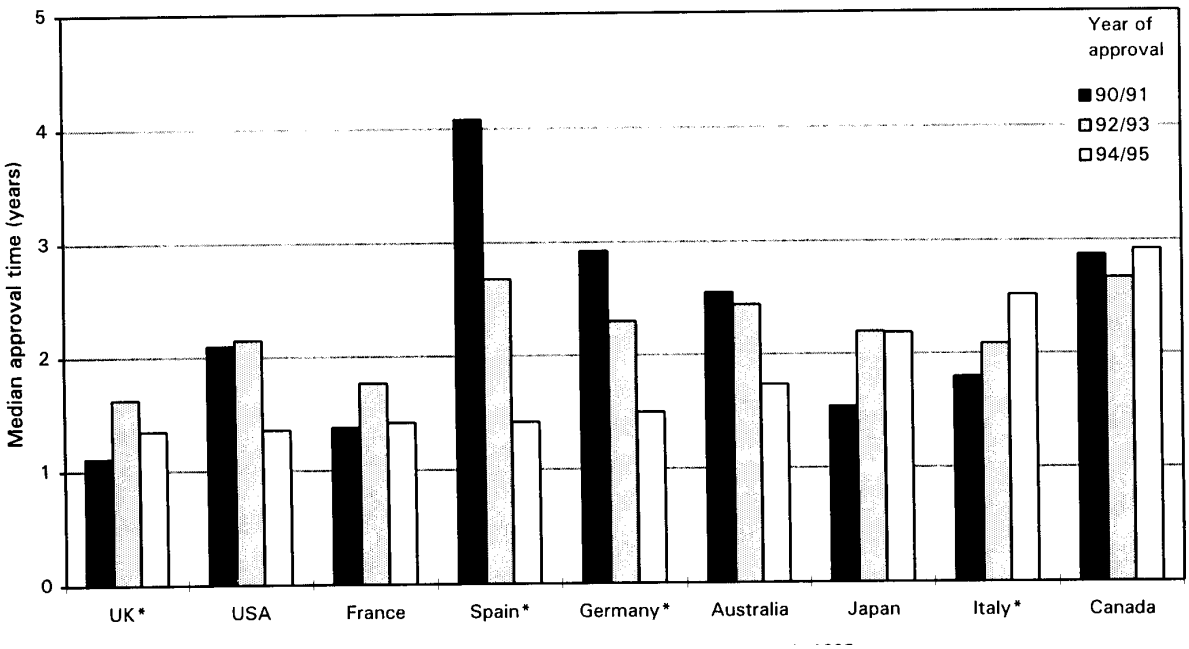
Figure 2. **Mean regulatory approval times in four countries (1985-1995). Preliminary data**



Note: Three authorisations through the European centralised procedure in 1995 have been excluded. ( ) = % of data available.

Source: Author.

Figure 3. **Median regulatory approval times 1990-1995. Preliminary data**



Note: Three authorisations through the European centralised procedure in 1995 have been excluded.

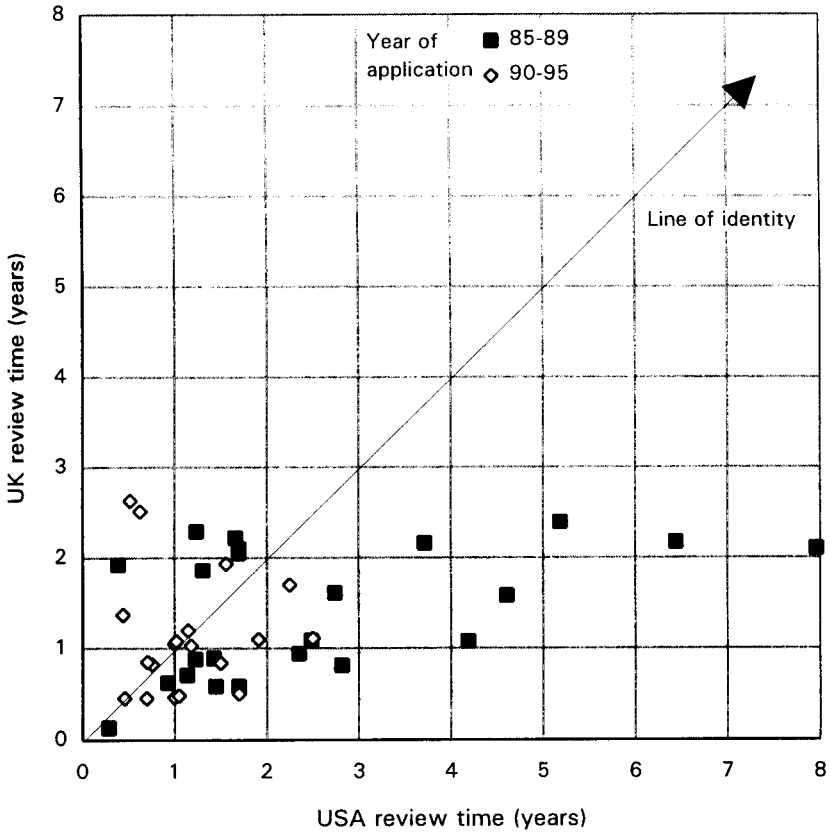
Source: Author.

Comparison of the United Kingdom and the United States

There are limitations to the conclusions that can be drawn from mean or median approval times, particularly as the same compounds were not necessarily submitted or reviewed at the same time in each country. True comparisons can be drawn between authorities only by assessing a cohort of compounds submitted within a similar time frame.

The examination of a group of compounds submitted to both the United Kingdom and the United States, within a six-month period, still shows considerable differences between the total review times (Figure 4). Within the latter half of the 1980s, the United Kingdom was consistently quicker than the United States at reviewing the same compounds. Over this period, the United States took longer than the United Kingdom to review 17/23 of the compounds in this cohort, with the difference being more than one year for 11 compounds. In contrast, the United Kingdom took longer to review six compounds. The situation has changed in the 1990s, with 6/19 compounds submitted to both authorities being reviewed in virtually the same time. Although the United States took longer than the United Kingdom to review nine compounds in the 1990s, the difference was more than one year for only two of these.

Figure 4. **Comparison of review times for compounds submitted to the United States and the United Kingdom within six months**



Source: Author.

Discussion

This preliminary analysis of total review times in nine major markets shows that companies can expect their compounds to spend on average between 1.5 and 3 years in the review process, depending on the authority. Although considerable differences have existed between authorities in the past, it appears that review times are converging at around two years in at least five countries -- the United States, the United Kingdom, Japan, France and Germany. Similar review times in European countries may be partially explained by the use of the concertation or multistate procedures. Indeed, in the future, the approval times for all authorities in Europe should be even more uniform as the new European licensing procedures, which have defined timelines (CEC, 1994), are used. The idea of defining the timelines for the assessment of NCEs is becoming more widespread amongst the major regulatory authorities, as user fees are introduced, with the United States, Canada and Australia also having target review times for the assessment of NCEs.

Care must be taken when drawing conclusions based on average total review times, as the same compounds are not being compared across countries. This should become less of a problem in the future, as pharmaceutical companies aim to submit a marketing application in all major markets simultaneously (Donnelly *et al.*, 1996). Thus, in future it may become increasingly difficult to justify differences in review times between agencies, as they will be assessing the same dossier at the same time.

It is apparent that review times vary for the same compounds, even when they are submitted to different authorities within a similar time frame. The reasons for this could be questioned, as all authorities have the same basic tenets, to protect and promote the public health and to review dossiers in terms of quality, safety and efficacy. This suggests that differences in review times between the competent authorities may be related to the way in which the review is managed. Certainly, the approaches vary; for example, more reliance is placed on industry opinion, summaries and expert reports in Europe than in the United States (Barrowcliffe, 1994).

Conclusion

There are differences between the major authorities in total regulatory review times in the 1990s. In order to understand the reasons behind these differences other factors need to be assessed, such as the quality of the dossiers, companies' response time to authorities' questions and the ability of authorities to manage the review effectively and efficiently. Future CMR studies will address these issues.

NOTES

1 This article appeared in *Improving the Regulatory Review Process: Industry and Regulatory Initiatives*, Proceedings of a CMR Workshop held at Nutfield Priory, Nutfield, United Kingdom, September 1995, and is published here with the permission of Kluwer Academic Publishers.

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THE ORPHANS OF THE HEALTH CARE SYSTEM[1]

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Although certain drugs are effective in treating rare diseases, no pharmaceutical company develops them because it would not be profitable to do so. In the United States, since 1983 these "orphan drugs" have benefited from highly favourable legislation that gives them a special status. As a result, US pharmaceutical firms have taken an interest, and most of the orphan drugs on the market today are of US origin. In Europe, however, there is no consistent policy either at the national or the Community level. Nevertheless, there is a growing awareness of the problem, and the time seems ripe for change. On the eve of the French presidency of the European Union, William Gunnarson, CEO of Orphan Europe, a consultancy firm for the development of orphan drugs in Europe, summed up the situation as follows: "The world's largest market has neither an official definition of orphan drugs nor any legislation in this field". But what are orphan drugs exactly?

Orphan drugs or orphan indications?

In the health care field, the term "orphan" was initially used in the United States to refer to those categories of patients who have serious diseases for which treatment either does not exist or is not available. In most cases, the lack of a suitable treatment is due to the rarity of the disease. Given this situation, what is the position of the pharmaceutical industry and the various health care actors? Who are these orphans of the health care system?

An orphan drug can be defined as a product that is recognised as being effective in treating a disease, but that no company develops because it would not be profitable. Usually this is because the disease is too rare for the sales of the drug to cover R&D costs, as in the case of Huntington's chorea or numerous enzyme deficiencies. The orphan concept can also be applied to products that are indispensable for certain indications, but are withdrawn from the market for economic reasons -- a sale price that is too low or a drop in consumption -- or because of a risk involved in their use. For example, thalidomide, introduced as an hypnotic in 1956 and withdrawn from the market because of its teratogenic properties, can be considered as an orphan drug for Hansen's disease (leprous erythema nodosum) and graft-versus-host disease. Its inflammatory properties provided a major therapy for these diseases, for which no other treatment is available. Sometimes the term orphan drugs refers to products that have not been developed either because they are difficult to patent because of their biological origin, such as carnitine (a substance that some people lack), or because they concern large but unprofitable markets, such as developing countries. In fact, it would be more accurate to speak of orphan indications, since a product may well be marketed for a common disease, but not developed for a rare indication. Such is the case of pimozide, a neuroleptic marketed for productive psychotic symptoms (paranoid delirium, hallucinations, etc.), but which is an "orphan" for Gilles de la Tourette syndrome.

Neglected diseases

Another problem is the lack of knowledge of most rare pathologies because there is little incentive to carry out related basic research. But the fact remains that there are people who suffer from these diseases, and they feel they have been abandoned. The only way to improve their treatment would be to introduce a policy combining support for basic research with regulatory provisions promoting the development of orphan drugs, whether by the public or private sector.

However, promoting the development of therapies for rare diseases does not mean bypassing the usual testing and monitoring. One thing the pharmaceutical industry, government and physicians all agree on is that these products should be subject to the same standards of authorisation as other drugs before they are placed on the market. This being the case, how can the costs of clinical tests be covered? There are two possibilities for government action: the public sector can develop these drugs, or incentives can be introduced to guarantee that pharmaceutical industries will cover their costs. In either case, it is essential to define orphan drugs accurately. The first country to do so was the United States.

Compensating for unprofitability: the US solution

It is difficult to pinpoint exactly when the US system was established, but the thalidomide scandal in 1962, after which firms were required to prove that drugs were safe, led to a greater awareness of the R&D costs of some pharmaceutical products. The first official measure taken was the creation of the Inter-Agency Committee on Drugs of Limited Value in 1974. In May 1982, the Under-Secretary of Health established the Orphan Products Board responsible for co-ordinating federal programmes in this field. Later the FDA (Food and Drug Administration) set up an Office of Orphan Products Development. In the same year, Abbey Meyers, a mother of three children suffering from Gilles de la Tourette syndrome, became the head of the National Organization for Rare Disorders (NORD), which brought together the various associations of patients suffering from rare diseases in Ann Arbor for the first conference on orphan drugs (there are more than 5 000 rare disorders that, taken together, affect approximately 20 million Americans). The following year, largely due to pressure exerted by patients' associations, pharmaceutical industries and the government, the FDA was able to implement the Orphan Drug Act, which defined the status of orphan drugs as "drugs or biological products intended for the diagnosis, treatment or prevention of rare diseases, whose estimated sales in the United States would not make it possible to recover R&D or distribution costs." The concept of a rare disease was only determined two years later, when an orphan disease was defined as one affecting less than one person out of 1 000, or less than 200 000 people in the United States[2]. Along with this definition, the statutory standard for orphan designation was changed from profitability to prevalence and the requirement that a potential sponsor establish a lack of commercial viability was deleted from the Act. However, the legislation has remained relatively flexible since it allows the FDA to grant orphan status to a product intended for a disease affecting over 200 000 people if it considers that the profits from sales in the United States do not cover the costs of clinical tests. The manufacturer must provide proof that this is the case, but thus far no one has used this clause.

In 1985 the Act was amended again to make orphan status accessible to patentable as well as unpatentable drugs.

Exclusive rights

Orphan drug status is granted on a permanent basis and entitles manufacturers to technical and financial aid. They can receive scientific assistance with test protocols, for instance. Furthermore, under the open protocol procedure a product can be marketed before completing clinical tests if it is intended to treat a fatal disease for which no other therapy exists. This measure does not apply specifically to rare diseases, but it is primarily used for products that have orphan drug status. In this regard, we should mention that the Orphan Drug Act explicitly establishes a link between open protocols and orphan drugs.

Until recently, the financial incentives also included tax credits that amounted to half the costs of clinical tests, and research grants from the Orphan Products Grants Program[3]. Grants can also be provided for "medicinal food" and medical equipment. However, the most important measure from the standpoint of manufacturers is the guarantee of seven years of exclusive rights to produce an orphan drug, provided, of course, that national needs are met.

Overly profitable orphans

Pharmaceutical companies soon realised the potential of the Act, and since 1983, 149 ODs have been approved for marketing in the United States, of which 28 are biotechnology products (see Table 1). At present, virtually all orphan drugs available world-wide are of US origin. Since sale prices are not set by the government and the market is small and free from competition, manufacturers have, in several cases, charged high prices, which the legislation did not intend. This happened with the development of zidovudine (AZT) for the treatment of HIV infection, and with erythropoietin for the treatment of anaemia due to renal insufficiency. This was also the case with the growth hormone used to treat pituitary dwarfism, which can easily cost as much as $10 000 a year for a single patient.

Under pressure from patients' associations, especially NORD, amendments that would limit such excessive prices are under discussion. A number of proposals were made, such as introducing a ceiling on total sales ($200 million of accumulated sales) beyond which exclusive rights would be withdrawn, reducing the period of exclusive rights or taxing profits above a certain threshold. These proposals have met with strong opposition from manufacturers' associations, such as ABC (Association of Biotechnology Companies) or IBA (Industrial Biotechnology Association), which are opposed to restricting orphan drug status in any way. So far they have succeeded in blocking these amendments. At this point it should be emphasized that sales figures are not a conclusive argument. Commercial viability depends on costs as well as revenues. Production, R&D, distribution and marketing costs all need to be considered in evaluating profitability. Furthermore, an appropriate evaluation of R&D costs should include the fixed costs of discovery research and of compounds that fail in testing, as well as income foregone from having funds tied up and not earning a return during the development process[4]. It is maybe, not by chance that four out of the ten orphan drugs with the greatest sales in the first year of marketing are biotechnology products. Nonetheless, prevalence, as the sole determinant of orphan drug status, if that status is intended to reflect also diminished commercial viability, is not completely reliable and there may be some purpose in amending the statutory terms "orphan drug" and "rare disease condition".

Orphans in Japan

The US example has not gone unnoticed, and other countries have modelled legislation of their own on the Orphan Drug Act. Japan was the first to follow in 1993, but its legislation provided for a stricter

monitoring procedure than in the United States in order to prevent companies from making unfair profits. The Ministry of Health and Welfare is the supervisory authority. In Japan, drugs that concern fewer than 50 000 people qualify for orphan status. Orphan drugs benefit from scientific assistance in clinical testing and are given priority in authorisation examinations. Tax relief is granted for research costs and research subsidies are provided out of a special fund. Manufacturers have exclusive rights to products for a ten-year period. In return, they must pay 3 per cent of their profits into a special fund. Unlike the United States, in Japan orphan status can be withdrawn if circumstances change (for example, if the number of people with the disease increases, as happened for zidovudine in the United States, where the manufacturer finally gave up its exclusive rights voluntarily). However, this provision is used judiciously so as to take into account the social impact of a withdrawal of orphan status. Lastly, the development and marketing of the product are monitored very closely and may cease only if the manufacturer has notified the authorities one year in advance. At present, about 29 drugs have been granted orphan status in Japan, five of which were produced by genetic engineering[5]. Canada is also looking into the problem of rare diseases, but has not yet taken concrete steps. In Europe an orphan drug directive is planned for the 1996/1997 legislative programme. Existing European legislation through Directives 75/318, 91/507 and 93/41 (as discussed in the following sections) lay down already some of the relevant groundwork.

France: the public or the private sector?

France is one of the countries that has shown the greatest interest in this problem, but no specific legislation in this field currently exists. According to article L 601-2 of the Act of 8 December 1992 amending the public health code with regard to pharmaceutical and medicinal products, the Medicinal Products Agency can authorise, for a limited period, the use of a drug that has not been officially approved -- known as a temporary authorisation of use -- if no other therapy is available and if there are valid reasons for believing that it will be effective in treating serious pathologies or rare diseases. This was the first time the concept of rare diseases was used in French legislation, but no definition or thresholds were provided. Physicians may also take the responsibility of requesting that a product sold abroad be imported for a specific patient. These exceptional and limited authorisations may involve orphan drugs, but are not specifically intended for them. Similarly, enterprises that engage in research can receive a tax credit under article 224 B of the general tax code, although once again this measure does not specifically concern orphan drugs.

The Central Pharmacy of Hospitals, which is part of the system of Public Health and Welfare-Hospitals of Paris (AP-HP), manufactures products that the pharmaceutical industry fails to develop for limited or undeveloped markets. These hospital preparations, whether they are mass produced for AP-HP or developed individually at the request of doctors, may not be sold on the open market. This practice is a first step by the public sector towards taking responsibility in this field, which could be complemented by research conducted in the Inserm, the national medical research institute. However, a government decree of July 1994 which states that only pharmaceutical companies may manufacture or import drugs, even on an exceptional basis, may place hospital initiatives in a difficult situation. Thus, the French legal system allows some ad hoc solutions, but it does not encourage pharmaceutical laboratories to develop orphan products.

Currently the debate is focused on whether orphan drugs should be developed by the public sector or by private industry. But the fact is that French pharmaceutical companies simply do not have the financial capabilities of their American counterparts, and the national market is too small for orphan products to be developed profitably, even with favourable legislation.

Europe: scattered solutions

Europe could be the answer. In this profitable market that is even bigger than the US market, pharmaceutical industries will be able to recover their investments. However, legislative changes will be necessary to make this possible. Since 1975, the European Union has sought to harmonise the conditions under which pharmaceutical products are placed on the market in the Member States. Some provisions can be interpreted as being favourable to orphan drugs. For example, Directives 75/318 and 91/507[6] make it possible to grant, under certain circumstances, an authorisation to market a product for which sufficient data has not yet been gathered for valid reasons. The reasons considered to be valid are: insufficient scientific knowledge, ethical problems raised by collecting data or the rarity of the disease. These exceptional authorisations also entail restrictions, for the pharmaceutical company must submit a programme of studies that will prove, over time, that the benefits outweigh the risks, the product must be given only by prescription (or in a hospital), and the information and packaging must alert the prescribing doctor that some data may be inadequate.

Directive 93/41 on high technology medicinal products[7] lays down the same conditions of exceptional authorisation, as well as a period of exclusive sales for a ten-year period, above and beyond patent rights. Since, if we refer to US data, approximately one orphan drug out of five was developed using biotechnology, it is very likely that this directive will help promote orphan drugs (see Table 1).

Lastly, new opportunities may open up with the legislative changes introduced in 1993 that led to the creation of the European Agency for the Evaluation of Medicinal Products. Based in London, this Agency has been in operation since 1 January 1995. Since that date, there has been a centralised procedure of European authorisation to market medicinal products[8]. There is also a decentralised procedure of mutual recognition of national authorisations.

Orphan drugs will stand to benefit from some of these general provisions, but these drugs are not defined *per se* and there is no specific legislation regarding their status, co-ordinated research programmes, tax incentives or exclusive rights. Oddly, the term “orphan drugs” does appear in a proposal to lower the registration fees charged for these products by the European Agency. In any case, a definition will no doubt become a necessity in the near future.

A lack of information and knowledge

Economic arguments alone cannot explain the failure of pharmaceutical firms to become involved in the field of rare diseases. Manufacturers, physicians and patients all emphasise the lack of information about these diseases and the inadequate level of basic research. Physicians sometimes do not know what to do when they observe totally unfamiliar symptoms and are unable to diagnose the disease rapidly. They also may not know that an effective remedy has been marketed or is undergoing clinical testing and could be available with special authorisation. As for manufacturers, they may already be holding, among the chemical formulas they have developed, some that would be effective in treating rare indications, but are unaware of this fact. All too often, this information is simply not available because no research has been done on the subject.

Table 1. **List of biotech orphan products approved in the United States through June 1997**

Name **Generic name** **TN = Trade Name**	**Indication designated**	**Sponsor and address** **DD = Date Designated** **MA = Marketing Approval**	**Prevalence**
Aldesleukin TN = Proleukin	Treatment of metastatic renal cell carcinoma	Chiron Corporation 4560 Horton Street Emeryville, CA 94608 DD = 14/09/88; MA = 05/05/92	75 000
Antihemophilic factor (recombinant) TN = Kogenate	Prophylaxis and treatment of bleeding in individuals with hemophilia A or for prophylaxis when surgery is required in individuals with hemophilia A	Bayer Corporation Pharmaceutical Division, Biological Products 400 Morgan Lane New Haven, CT 06516 DD = 25/09/89; MA = 25/02/93	16 000
Coagulation Factor IX (recombinant) TN = BeneFix	Treatment of hemophilia B	Genetics Institute, Inc. 87 Cambridge Park Drive Cambridge, MA 02140 DD = 03/10/94; MA = 11/02/97	6 000
Digoxin immune FAB (ovine) TN = Digibind	Treatment of potentially life threatening digitalis intoxication in patients who are refractory to management by conventional therapy	Glaxo Wellcome Inc. 5 Moore Road Research Triangle Park, NC 27709 DD = 01/11/84; MA = 21/03/86	4 000
Domase alfa TN = Pulmozyme	To reduce mucous viscosity and enable the clearance of airway secretions in patients with cystic fibrosis	Genentech, Inc. 460 Point San Bruno Boulevard South San Francisco, CA 94080 DD = 16/01/91; MA = 30/12/93	30 000
Epoetin alfa TN = Epogen	Treatment of anemia associated with end stage renal disease	Amgen, Inc. 1840 Dehavilland Drive Thousand Oaks, CA 91320 DD = 10/04/86; MA = 01/06/89	78 000
Epoetin alfa TN = Epogen	Treatment of anemia associated with HIV infection or HIV treatment	Amgen, Inc. 1840 Dehavilland Drive Thousand Oaks, CA 91320 DD = 01/07/91; MA = 31/12/90	28 000
Filgrastim TN = Neupogen	Treatment of patients with severe chronic neutropenia (absolute neutrophil count less than 500/mm^3)	Amgen, Inc. 1840 Dehavilland Drive Thousand Oaks, CA 91320 DD = 07/11/90; MA = 19/12/94	5 000
Filgrastim TN = Neupogen	Treatment of neutropenia associated with bone marrow transplants	Amgen, Inc. 1840 Dehavilland Drive Thousand Oaks, CA 91320 DD = 01/10/90; MA = 15/06/94	2 100
Filgrastim TN = Neupogen	For use in the mobilisation of peripheral blood progenitor cells for collection in patients who will receive myeloablative or myelosuppressive chemotherapy	Amgen, Inc. 1840 Dehavilland Drive Thousand Oaks, CA 91320 DD = 17/07/95; MA = 28/12/95	11 300
Imiglucerase TN = Cerezyme	For replacement therapy in patients with types I, II, and III Gaucher's disease	Genzyme Corporation One Kendall Square Cambridge, MA 02139 DD = 05/11/91; MA = 23/05/94	5 000

Table 1. **List of biotech orphan products approved in the United States through June 1997 (cont'd.)**

Name **Generic name** **TN = Trade Name**	**Indication designated**	**Sponsor and address** **DD = Date Designated** **MA = Marketing Approval**	**Prevalence**
Interferon alfa-2a TN = Roferon A	Treatment of chronic myelogenous leukemia	Hoffmann-La Roche, Inc. 340 Kingsland Street Nutley, NJ 07110 DD = 06/06/89; MA = 19/10/95	10 000
Interferon alfa-2a (recombinant) TN = Roferon A	Treatment of AIDS-related Kaposi's sarcoma	Hoffmann-La Roche, Inc. 340 Kingsland Street Nutley, NJ 07110 DD = 14/12/87; MA = 21/11/88	10 000
Interferon alfa-2b (recombinant) TN = Intron A	Treatment of AIDS-related Kaposi's sarcoma	Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033 DD = 24/06/87; MA = 21/11/88	10 000
Interferon beta-1a TN = Avonex	Treatment of multiple sclerosis	Biogen, Inc. 14 Cambridge Center Cambridge, MA 02142 DD = 16/12/91; MA = 17/05/96	150 000
Interferon beta-1b TN = Betaseron	Treatment of multiple sclerosis	Chiron Corp. and Berlex Laboratories 4560 Horton Street Emeryville, CA 94608 DD = 17/11/88; MA = 23/07/93	145 000
Interferon gamma-1b TN = Actimmune	Treatment of chronic granulomatous disease	Genentech, Inc. 460 Point San Bruno Boulevard South San Francisco, CA 94080 DD = 30/09/88; MA = 20/12/90	300
Pegademase bovine TN = Adagen	For enzyme replacement therapy for ADA deficiency in patients with severe combined immunodeficiency	Enzon, Inc. 20 Kingsbridge Road Piscataway, NY 08854 DD = 29/05/84; MA = 21/03/90	40
Sargramostim TN = Leukine	Treatment of neutropenia associated with bone marrow transplant, for the treatment of graft failure and delay of engraftment, and for the promotion of early engraftment	Immunex Corporation 51 University Street Seattle, WA 98101 DD = 03/05/90; MA = 05/03/91	3 000
Sargramostim TN = Leukine	To reduce neutropenia and leukopenia and decrease the incidence of death due to infection in patients with acute myelogenous leukemia	Immunex Corporation 51 University Street Seattle, WA 98101 DD = 06/03/95; MA = 15/09/95	50 000
Satumomab pendetide TN = Oncoscint CR/OV	Detection of ovarian carcinoma	Cytogen Corporation 600 College Road East Princeton, NJ 08540 DD = 25/09/89; MA = 29/12/92	65 000
Somatrem for injection TN = Protropin	For long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion	Genentech, Inc. 460 Point San Bruno Boulevard South San Francisco, CA 94080 DD = 09/12/85; MA = 17/10/85	15 000

Table 1. **List of biotech orphan products approved in the United States through June 1997 (cont'd.)**

Name **Generic name** **TN = Trade Name**	**Indication designated**	**Sponsor and address** **DD = Date Designated** **MA = Marketing Approval**	**Prevalence**
Somatropin TN = Nutropin	For long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion	Genentech, Inc. 460 Point San Bruno Boulevard South San Francisco, CA 94080 DD = 06/03/87; MA = 17/10/85	15 000
Somatropin TN = Humatrope	Treatment of short stature associated with Turner syndrome	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 DD = 08/05/90; MA = 30/12/96	16 000
Somatropin for injection TN = Humatrope	For the long-term treatment of children who have growth failure due to inadequate secretion of normal endogenous growth hormone	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 DD = 12/06/86; MA = 08/03/87	10 000
Somatropin for injection TN = Nutropin	Treatment of short stature associated with Turner's syndrome	Genentech, Inc. 460 Point San Bruno Boulevard South San Francisco, CA 94080 DD = 23/03/89; MA = 30/12/96	8 250
Somatropin for injection TN = Nutropin	Treatment of growth retardation associated with chronic renal failure	Genentech, Inc. 460 Point San Bruno Boulevard South San Francisco, CA 94080 DD = 04/08/89; MA = 17/11/93	3 600
Somatropin for injection TN = Serostim	Treatment of AIDS-associated catabolism/weight loss	Serono Laboratories, Inc. 100 Longwater Circle Norwell, MA 02061 DD = 15/11/91; MA = 23/08/96	182 834

Source: Office of Orphan Products Development, Food and Drug Administration, 1997.

A goal-directed US system ...

In the United States, the NIH (National Institutes of Health) carries out its own programme of basic and clinical research on orphan diseases and their treatment. Government bodies such as the Orphan Products Board and the National Commission on Orphan Diseases co-ordinate this public research and evaluate which diseases should be given orphan status. They are continuously in touch with scientific, medical and industrial organisations to keep abreast of the latest progress and to encourage producers to develop orphan drugs. The FDA publishes and continuously updates a list of recognised orphan products -- most of which have not been developed -- that so far comprises some 500 indications. It also funds the National Information Center on Orphan Drugs and Rare Diseases (NICODARD), which provides telephone information on products or ongoing research. Manufacturers' associations have established organisations such as the Commission on Drugs for Rare Diseases of the PMA (Pharmaceuticals Medical Association) or the Institute for Orphan Drugs of the Generic Pharmaceutical Industry Association, which both identify orphan drugs. As for NORD, it has established the Rare Disease Database, which includes the description, aetiology, symptoms, statistical data, bibliography and the treatment available or currently being tested for some one thousand rare diseases. Maintaining this database is for this organisation a priority task.

... disarray in Europe

In Europe, information and research on orphan diseases are at best rudimentary. BIOMED, the biomedical segment of the fourth Framework Programme for Community Research provides ways of obtaining some non-specific financial aid. This programme also provides for the collection of statistical and epidemiological data on certain diseases. This could include orphan pathologies. Lastly, the European Agency for the Evaluation of Medical Products may well establish a database on orphan diseases, although it does not seem indispensable to repeat work already carried out by the United States. This problem of orphan pathologies is only specifically dealt with in two centres, the Centre for Clinical Studies on Orphan Diseases opened by the Mario Negri Institute at Villa Camozzi, near Bergamo, and the Frambu Healthcare Centre, a Norwegian Foundation.

Furthermore, there is no European equivalent of NORD. However, there is an essential need for a strong association that represents all those suffering from rare diseases to act as a pressure group, to disseminate information, and even to help laboratories find enough volunteers with rare diseases to conduct clinical tests. Instead, there are innumerable specialised national associations devoted to a single disease. They do important work at their own level, but in the view of William Gunnarsson, "They would do well to join forces so as better to defend their interests. The fact that Europe is divided into a number of countries makes it difficult to establish a single supranational association. A first stage might be to set up a general association in each country by grouping together specialised associations, and then to set up a European confederation".

Towards a European orphan status

Should orphan drugs be given a special status in Europe or not? The question is under discussion. The representatives of the French Medicinal Products Agency argue that European legislation already allows for conditional authorisations to market products and mentions rare pathologies. In their view, then, the problem is not administrative but merely financial. What is needed is a fund to finance clinical or toxicological studies and provisions that guarantee exclusive rights, tax credit and technical assistance. However, they do not think that a specific status is indispensable, and Europe is not sufficiently integrated to implement a comprehensive policy. Manufacturers, on the other hand, support the concept of a special status based on the US Orphan Drug Act. For them, the situation is clear-cut. They simply cannot increase their capacity to invest in research and development. As a result, they tend to use these funds to develop products that are certain to be profitable. According to William Gunnarsson, "The main problem is the lack of definition and legislation. Directives 75/318 and 91/507 open up possibilities, but they do nothing to encourage the development of these products. No one is going to develop them under the present circumstances." This is how the debate currently stands. France is one of the European countries where the debate on the subject is hottest, and a broad movement that includes physicians, the pharmaceutical industry, patients' associations, government authorities and even policy-makers is emerging in support of orphan drugs. The National Union of the Pharmaceutical Industry has drafted a text of recommendations. For reasons of its own it currently refuses to make it public, but there is every reason to believe that it is asking for a definition of orphan drugs, financial incentives, scientific assistance and a guarantee of exclusive rights. Furthermore, an official report on orphan drugs was submitted to the Minister in November 1994, although its contents are also confidential. It is likely that it recommends measures along the lines of the US system.

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ORPHAN DISEASES

According to Jean-Michel Alexandre, of the Medicinal Products Agency, "most new drugs submitted to the Agency can be considered as orphan products. And many of pathologies affect less than 1 per cent of the population". Antiviral products, drugs used to treat AIDS and many cancers can be included in this category, as can the antidotes to infrequent types of poisoning (plutonium, digitaline, etc.) or the drugs used to treat diseases of the very elderly. One can also find on the FDA list products as diverse as lung surfactants (for premature infants), monoclonal antibodies (for tests) and interferon α (for Kaposi's sarcoma linked to AIDS).

However, most very rare diseases are genetic in origin. They occur because an individual lacks an enzyme, a hormone or some other functional substance. The treatments mostly involve replacement products that are either extracts or are produced through recombinant biotechnology, such as PEC-adenosine deaminase for treating an ADA deficit. Paediatricians are concerned in particular, for these diseases appear in childhood. However, the small size of the market and the problems involved in clinical tests with children make it difficult to develop paediatric products. It is impossible to determine the total number of people suffering from rare diseases in Europe, since there is neither a database nor a single patients' organisation. However, it is estimated that some 20 million people in the United States suffer from one of the more than 5 000 rare diseases that are now known to exist. Extrapolated to the size of Europe, these figure indicate a potential market of over 30 million people.

Some diseases will always be greater "orphans" than others. Rarity is not the only criterion. Diseases that are rare, but attract the attention of the media and concern a profitable market, such as Alzheimer's disease, migraines or myopathy, do not remain orphans for long. Manufacturers will take risks for these diseases that can be potentially profitable or that have a useful symbolic value. Meanwhile, tropical diseases that affect millions of people go untreated. Allopurinol, an effective remedy for Chagas's disease, does not interest any pharmaceutical firm. This is why some exponents of orphan drugs support the concept of a public service mission and in the United States measures have been taken to assist products intended for the Third World. However, the World Health Organization does not seem to be considering any initiative along these lines.

NOTES

1 This article appeared in *Biofutur*, January 1995, and has been translated and prepared for publication with the permission of *Biofutur*.

2 Though Congress defined a patient limit of 200 000 for orphan disorders, most of these conditions occur at well below this statutory ceiling. In 1992, 47 per cent of designated orphan diseases affected an estimated 25 000 or fewer people. Some disorders, such as infant botulism and severe combined immunodeficiency syndrome have populations less than 100.

3 Initially the law provided a 50 per cent credit of the sponsor's expenses for human clinical trials against current income taxes (a $1 million expenditure was rewarded with a tax credit of the current year's taxes up to $500 000). These conditions, however, rarely applied to biotechnology companies, which, in general, incur several years of losses before they can generate any revenue. To remedy this situation, the US Congress amended the tax credit to provide that the amount could be carried back for three years or forward for 15 years from the year in which it was earned. However, the entire tax credit authorization expired on 31 May 1997. The expectation is now that it will be reauthorized and made retroactive.

4 Cited from: Implementation of the Orphan Drug Act: 1983-1991. Sheila R. Shulman *et al*. in *Food and Drug Law Journal* Vol.47, Number 4, 1992.

5 Factor VII and somatotropine developed by the Danish company Novo Nordisk, interferon ß 1b developed jointly by Schering AG (Germany) and Chiron (United States) for the treatment of multiple sclerosis, somatomedine made by the Japanese producer Sumitomo Pharmaceuticals and TGF (transforming growth factor) ß 2 produced by Santen Pharmaceutical.

6 Council Directive of May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (Official Journal of the European Communities L147 of 9 June 1975) and Directive 91/507 repealing Directive 75/318 (OJEC of 26 September 1991).

7 Council Directive 93/L41 repealing Directive 87/22 of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology (OJEC L214 of 24 August 1993).

8 In accordance with European Regulation 93/2309 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products.

GLOSSARY OF TERMS*

Allele	One of several alternative forms of a gene encoding alternative forms of a single trait.
Allelic diversity	Within populations, the presence of different alleles at a gene locus.
Amino acid	The building blocks of proteins. In vertebrates, there are 20 amino acids. In a gene, each sequence of 3 nucleotides (codon) encodes for only one amino acid and instructs the cell to insert that amino acid in a specific position as the protein is assembled.
Attributable risk	The proportion of people with a specific risk factor, for instance, a genetic predisposition, who would not manifest a disease were it not for the presence of the risk factor.
Biological sample	Any material part of a body or of discharge known to contain DNA, including but not limited to tissue specimen, blood or urine.
Biotechnology	The application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services.
Carrier	(1) A person of either gender who has inherited an allele from one parent which, when inherited from both parents, results in an autosomal recessive disease. (2) A female who possesses an allele on one of her X chromosomes which results in disease in males.
Chromosome	The nucleoproteins along which the genes are arrayed in the nucleus. In human somatic cells, the chromosomes consist of 22 pairs of autosomes and, in females, two X chromosomes and, in males an X chromosome and a Y chromosome. Normally, therefore, each cell contains 46 chromosomes.
Clinical endpoint	A term to indicate any endpoint which physicians conducting a study consider an appropriate measurement of a trial.
Clinical practice guidelines	The Institute of Medicine defines clinical practice guidelines as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." However, guidelines can also be developed with additional goals explicitly in mind, such as cost containment.

Clinical trial	The systematic investigation of the effects of materials or methods (e.g. a medical technology) on humans in a clinical setting. Clinical trials can be either non-randomised (e.g. a small trial to test a drug for major side-effects) or randomised.
Cost-benefit analysis	A study design which is used when both the inputs and consequences of different interventions are expressed in monetary units so that they compare directly and across programmes even outside health care.
Cost-effectiveness analysis	A study design which is used when consequences of different interventions may vary but can be measured in identical natural units and inputs are costed. Competing interventions are compared in terms of cost per unit of consequence.
Cost-minimisation analysis	A study design which is used when consequences of different interventions do not vary and inputs are costed. Competing interventions are compared in terms of cost.
Cost-utility analysis	A study design which is used when interventions which we compare produce different consequences in terms of both quantity and quality of life and these are expressed in utilities. These are measures which comprise both length of life and subjective levels of well-being. In this case, competing interventions are compared in terms of cost per unit of utility gained (for example, cost-per-QALY).
DNA	Deoxyribonucleic acid. Comprised of sequences of deoxyribonucleotides (nucleotides for short). Each nucleotide contains either adenine, thymine, guanine or cytosine. In a gene, the sequence of these nucleotides over several hundred or thousands of nucleotides, determines the function of the gene, for instance, the synthesis of a protein and the amino acid sequence of the protein.
Direct medical costs	Fixed and variable costs associated directly with a health care intervention (e.g. physician salaries).
Direct non-medical costs	A non-medical cost associated with provision of medical services (e.g. transportation of a patient to a hospital).
Discounting	A procedure used in economic analysis (e.g. cost-effectiveness analysis) to express as "present values" those costs and benefits that will occur in future years. Discounting is based on two premises: (i) individuals prefer to receive benefits today rather than in the future; and (ii) resources invested today in alternative programmes could earn a return over time.
Economic endpoint	A measure of cost-effectiveness suitable for establishing the economic value of a health-care technology.
Economic evaluation	A collective term for cost-effectiveness analyses, cost-benefit analyses, cost-utility analyses, etc.

Effectiveness	The probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under average or actual conditions of use. Compare with *efficacy*.
Effectiveness research	The category of research efforts aimed at broadly identifying effective technologies and practices, and developing and refining methods to support the identification of effective care.
Efficacy	The probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use. Efficacy is generally evaluated in controlled trials of an experimental therapy and a control condition. Compare with *effectiveness*.
Equity	Fairness in the allocation of resources or treatments among different individuals or groups.
Enzyme	A protein with a catalytic function; that is, one that accelerates a chemical reaction reaching equilibrium.
Gene	According to the current molecular definition, a gene consists of all the DNA sequences necessary to produce a functional polypeptide or RNA product. In biological terms, a gene is an heritable function detected by observing the effect of a mutation.
Gene expression	The multi-step process in which a gene sequence is converted into a functional protein, thus a phenotype. The main molecular steps in this process are transcription of a DNA sequence into RNA and translation of RNA into protein.
Gene product	The mRNA or protein encoded by a specific gene, or more properly, alleles of the gene.
Gene heterogeneity	(1) The presence of different alleles at a gene locus. (2) The ability of more than one allele to cause the same trait, for instance, a disease depending on the absence of a metabolite, the formation of which involves several enzymes. Alleles at different gene loci (locus heterogeneity), as well as those at the same locus (allelic heterogeneity), may each be expressed as the same trait.
Genetic information	The information that may derive from an individual or a family member about genes, gene products or inherited characteristics.
Genetic locus	The position on a chromosome at which the gene for a particular trait resides; locus may be occupied by any one of the alleles for the gene.

Genetic predisposition	The presence of a variation in the composition of the genes of an individual or an individual's family member which is scientifically or medically identifiable and which is determined to be associated with an increased statistical risk of being expressed as either a physical or mental disease or disability in the individual or having offspring with a genetically influenced disease, but which has not resulted in any symptoms of such disease or disorder.
Genetic test	Any laboratory test of human DNA, chromosomes, genes or gene products to diagnose the presence of a genetic variation linked to a predisposition to a genetic disease or disability in the individual or the individual's offspring; such term shall also include DNA profile analysis. "Genetic test" shall not be deemed to include any test of blood or other medically prescribed test in routine use that has been or may be hereafter found to be associated with a genetic variation, unless conducted purposely to identify such genetic variation.
Genome	The entire array of genes of an organism or species.
Genotype	The particular pair of alleles that an individual possesses at a gene locus. One of these alleles is inherited from the mother, the other from the father.
Germline	Sperm and egg cells, which have only a single set of chromosomes, and the cells from which they arise.
Health maintenance organisation (HMO)	A health-care organisation that, in return for prospective per capita (capitation) payments, acts as both insurer and provider of comprehensive but specified health-care services. A defined set of physicians (and, often, other health-care providers such as physician assistants and nurse midwives) provide services to a voluntarily enrolled population. Prepaid group practices and individual practice associations, as well as staff models, are types of HMOs.
Health technologies	Drugs, devices, procedures, and the organisational and support systems within with health care is delivered.
Health technology assessment	A structured analysis of a health technology, a set of related technologies or a technology-related issue that is performed for the purpose of providing input to a policy decision.
Heterozygote	A person who has inherited two different alleles (one from each parent) at a gene locus.
Homozygote	A person who has inherited identical alleles (one from each parent) at a gene locus.
Indirect cost	The cost of reduced productivity resulting from illness or treatment (may be estimated by loss of wages and other means).
Intangible cost	The cost of pain and suffering occurring as a result of illness or treatment.

Informed consent In strictly legal terms, is used to delimit the process that involves the exchange of information between a consumer and a health-care provider about a test, treatment, or research study. In general, a statement signed by a person who will be subjected to a test or to a new kind of therapeutic of prophylactic intervention, whereby he/she declares his/her understanding of risks, possible failures, etc., and states his/her agreement, including duties, right to withdraw, right to privacy.

Karyotype The array of chromosomes in a cell.

mRNA The ribonucleic acid (RNA) transcribed from the DNA of a gene in the cell nucleus. mRNA serves as a template for protein synthesis; that is, dictates the amino acid sequence of the polypeptide encoded originally by the gene.

Metabolite Usually a compound that is either used or produced by an enzyme-catalysed reaction. If the enzyme is dysfunctional, a metabolite used by the reaction it catalyses will accumulate, whereas a metabolite formed as a result of the reaction will be absent or reduced in concentration.

Morbidity A measure of the extent to which an illness or abnormality occurs within a given population.

Mortality The death rate, reflecting the number of deaths within a given population.

Mutation Any change in the nucleotide sequence of DNA.

Nonsense mutation A change in the nucleotide sequence that replaces a codon for an amino acid with one that does not encode for any amino acid and results in premature termination of the protein chain when it is being synthesised.

Nucleotide The basic unit of DNA and RNA, consisting of a purine or pyrimidine bases, ribose sugar (deoxyribose in the case of DNA) and phosphate.

Outcome Any result that stems from exposure to a causal factor, or from preventive or therapeutic interventions.

Outcomes research A term originally used to describe a particular line of health services research that focused on identifying variations in medical procedures and associated health outcomes. The term has since been applied to a wide variety of vaguely associated activities and no longer has a clearly identifiable meaning. See *effectiveness research*.

Payer An entity that pays for health-care services (e.g. individuals, health insurers, government programmes). Third-party payers are payers other than the individuals receiving the services, usually health insurers.

Penetrance The proportion of cases in which organisms with a given genotype express the corresponding phenotype. If the gene is expressed in all cases, it is completely penetrant; if not, it is incompletely penetrant. It also signifies the probability that an individual with a given genotype will develop the disease.

Phenotype	The expression of a genotype. The same genotype may be expressed differently from one individual to the next due to differences at other gene loci or in the environment.
Placebo	A drug or procedure with no intrinsic therapeutic value. In a randomised controlled trial, a placebo is given to patients in control groups as a means to blind investigators and patients as to whether an individual is receiving the experimental or the control treatment.
Polymorphism	Occurrence in the same population of two or more alleles at a locus, with at least one allele having a frequency exceeding 1 per cent.
Positive predictive value	The probability that a person with a positive test result has, or will develop, a disease.
Predisposition testing	A test for a genetic predisposition. Not all people with a positive test result will manifest the disease.
Presymptomatic testing	A test for a single-gene, late-onset disease in a healthy or apparently healthy person. If the test has high specificity and is performed reliably, a person with a positive test result will almost always manifest the disease.
Protein	String of amino acids linked by peptide bonds. Some proteins have more than one polypeptide chain. Each chain is encoded by a different gene.
Provider	A person or organisation that provides health-care services (e.g. physician, optometrist, hospital, home health agency).
Quality of care	Evaluation of the performance of medical providers according to the degree to which the process of care increases the probability of outcomes desired by patients and reduces the probability of undesired outcomes, given the state of medical knowledge. Which elements of patient outcomes predominate depends on the patient condition.
Quality of life	In the context of *effectiveness research* and *cost-effectiveness analysis*, health-related quality of life is "the value assigned to duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy".
Quality-adjusted life year (QALY)	Years of life saved by a technology or service, adjusted according to the quality of those lives (as determined by some valuation process). The QALY is the most commonly used unit to express the results of cost-utility analyses.
Recombinant DNA techniques	The ability to excise exact segments of DNA and insert them into DNA of other organisms, which can then replicate the segment millions of times.
Relative risk	The ratio of the probability that an event (e.g. disease) will occur in a person with a given factor to the probability that the event will occur in a person without the factor.

Reliability	The reproducibility of a measure. A measure is reliable if it yields similar results each time it is used on similar samples.
RNA	Ribonucleic acid. Comprised of sequences of ribonucleotides. Each nucleotide contains either adenine, uridine, guanine, or cytosine. See also *mRNA.*
Single-gene disorder	The presence of an allele in either single dose (dominant disorders in males or females, X-linked disorders in males), or double dose (recessive disorders), accounts for the presence of disease.
Specificity	*Analytical*: The probability that a test will be negative when an analyte is absent from a biological sample. *Clinical*: The probability that a test will be negative in a person free of a disease, and who will not develop the disease.
Systematic review	The application of explicit methods to systematically identify, locate, retrieve and analyse published data on a topic in order to diminish bias and generalise conclusions.
Toxicity	The quality of being poisonous or the degree to which a substance is poisonous. Referring to medical treatments, the degree to which they produce unwanted, adverse effects.
Willingness to pay	The maximum amount that a person is willing to pay: (i) to achieve a particular good health state or outcome, or to increase its probability of occurrence, or (ii) to avoid a particular bad health state or outcome, or to decrease its probability.

* Definitions included in this glossary are drawn from chapters in this report as well as from the following sources:

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