The Global Pharmaceutical Market

International Trade and Competition in High Technology
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INTRODUCTION

We are currently in what the historians call the "Golden Age of Medicine." In the past 100 years, the number of drugs invented for improving health and extending life has increased significantly. Pharmaceutical manufacturers have been investing higher and higher percentages of their revenues into R&D. Currently, there are over 1000 drugs under development, including more than 100 for AIDS, more than 350 for cancer, 122 for heart disease and stroke, 26 for Alzheimer's disease, 25 for diabetes, and more than 200 for the specific needs of children.[1]

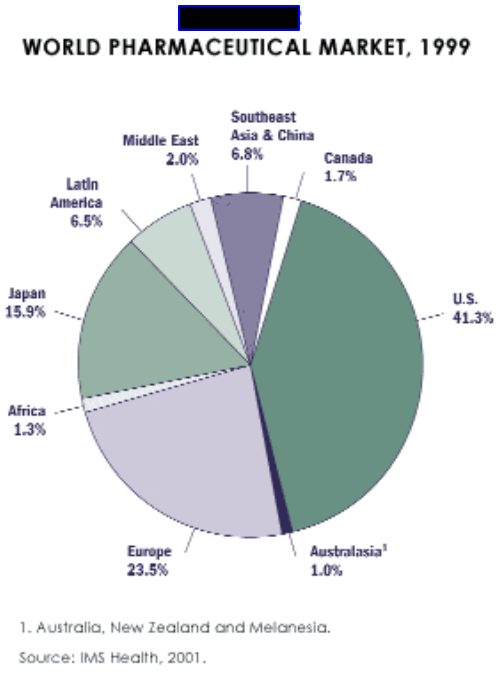
In this paper, we will give an overview of the global pharmaceutical industry, with an emphasis on the two largest global players – the US and Europe[2]. The paper is divided as follows: the first section gives the background of the global pharmaceutical industry. The second section reviews the development of the global pharmaceutical industry since 1945 and the emergence of molecular biology and biotechnology in US. The third section studies the environment in Europe and the US that shape the competitive landscape, including institutional organizations, regulatory authorities, financial institutions, governments, and heath care systems. The fourth section provides a comparative analysis of the US and European pharmaceutical industries.

SECTION 1: BACKGROUND

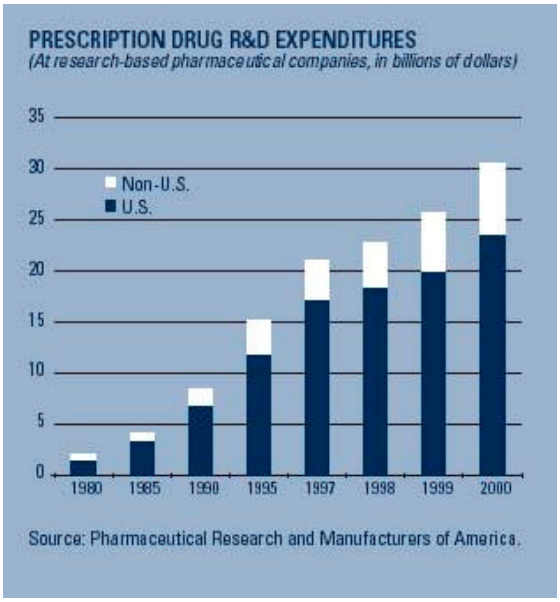
[1] PhRMA: *Pharmaceutical Industry Primer 2001*

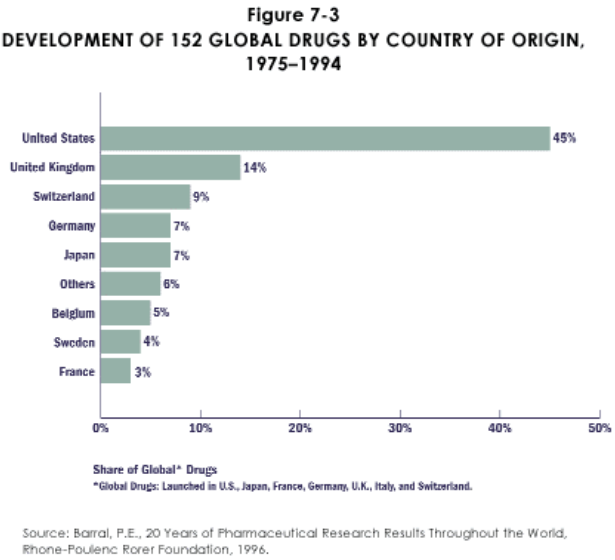
[2] In our work, the European industry includes the countries belonging to the European Community (EC) as well as the United Kingdom (UK) and Switzerland.

The pharmaceuticals industry, which includes the discovery, development, and distribution of drugs, is characterized by its large size, high growth, globalization, and high investment in R&D. The US leads global pharmaceutical sales with over one-third of global market, following by Europe (23.5%) and Japan (15.9%). Worldwide retail sales of prescription drugs in leading markets were expected to rise 10% to about US$350 billion in 2001, following a 10% advance in 2000, based on data provided by IMS Health Inc., a Connecticut-based market research firm specializing in pharmaceuticals.



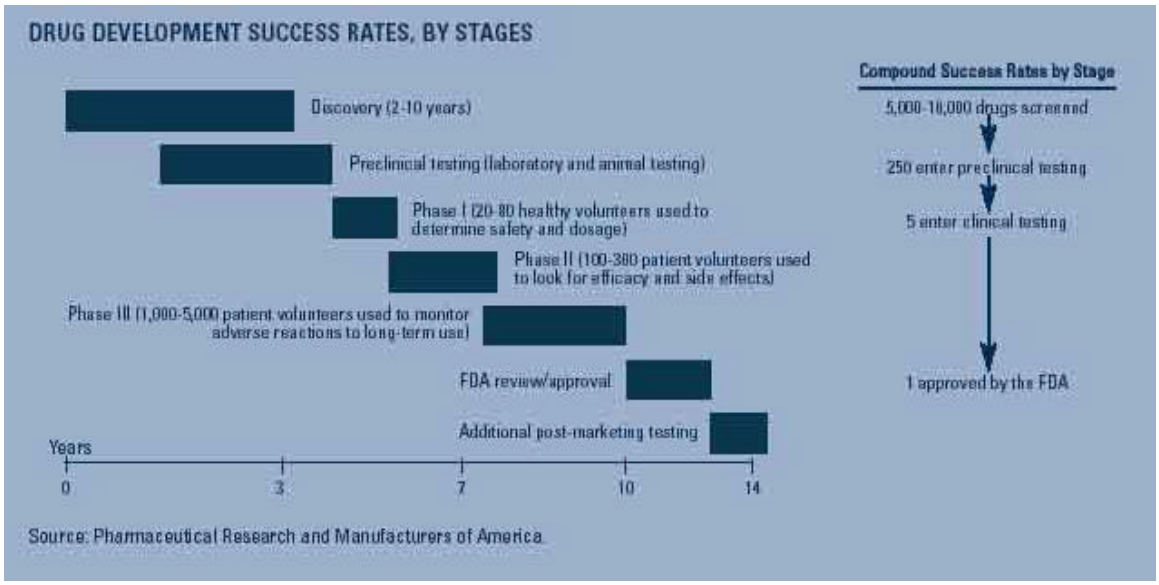
In addition to being the largest consumer of drugs, the U.S. also leads global pharmaceutical R&D, accounting for 36% of global research, as well as global drug development, accounting for 45% of major global drugs developed between 1975 and 1994.



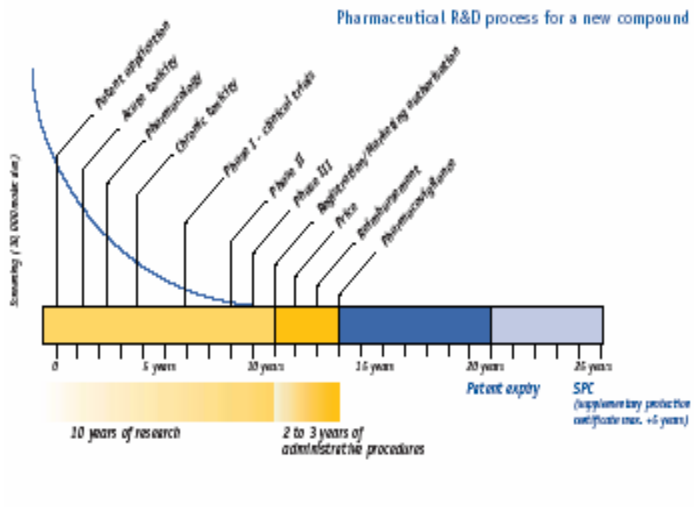


The Drug-Discovery to Commercialization Process.

The process from discovery to commercialization of a new drug is a long, costly and highly regulated process. To give just few figures, it requires an average of 12 years for a medicine to reach pharmacy shelves from discovery. Only one out of 5000 to 10000 promising substances survives the extensive testing in the R&D phase to become approved as a marketable product, with an average of $800 million in R&D cost (EFPIA Report 1, 2001). The drug discovery/approval process is extremely complex and involves a very diverse set of players at different stages of a drug lifecycle. The following figures show this process for the US as well as for Europe. The key differences are in the approval, pricing, and marketing phases. For a detailed description of the drug development process, refer to Appendix 2.



US Drug Development Stages



Europe Drug Development Process

Universities and public and private labs are mainly involved in the early stages of the discovery of new promising substances and the creation of seminal technology. Specialized firms, such as the New Biotechnology Firms (NBFs), bioinformatic companies, and general-purpose technology firms, operate mostly in the pre-clinical drug

R&D phase, developing new screening technology and tools. The practice of contracting out some of the more routine aspects of R&D activities in the pre-clinical and clinical trials to contract research organizations (CROs) has also been growing. Smaller national pharmaceutical firms, which are specialized in the sales, marketing and distribution of drugs, conduct mainly manufacturing and commercialization activities by licensing drugs from the global pharmaceutical firms. They do not invest in R&D, but rather leverage their knowledge of national regulatory environment and health care system. Large global pharmaceutical enterprises are present throughout the entire discovery-to-production process. National agencies, such as the FDA, and regional agencies, such as EMEA, are responsible for evaluating drug safety and effectiveness and for granting market authorization. Finally, a diverse set of institutions are involved in the price-setting phase. These institutions range from governmental agencies (Italy and France), which set price control policies based on public budget requirements, to heath management organizations (HMOs in US, the NHS in UK), which contract drug price directly with pharmaceutical firms.

Major Sectors of the Pharmaceutical Market.

The pharmaceutical market consists of three major sectors: Central Nervous System (CNS) drugs, Cardiovascular drugs, and Gastrointestinal/Metabolism drugs.

Central Nervous System (CNS) drugs include various narcotic and non-narcotic analgesics, sedatives, anti-anxiety agents, antidepressants, anti-epileptics, and nonsteroidal anti-inflammatory drugs (NSAIDs, which are prescribed mainly for arthritis). They also include drugs for Alzheimer's disease, Parkinson's disease, and

related neurological disorders. They are one of the industry's fastest growing sectors and the largest single ethical drug segment in the United States.

- **Selective serotonin reuptake inhibitors (SSRIs).** These drugs comprise the vast majority of antidepressant sales. Total U.S. new retail prescriptions written for SSRIs in September 2001 were about 7% ahead of comparable year-earlier levels. Greater acceptance of depression as a drug-treatable illness, several successful new products, and expanded insurance reimbursement have all contributed to move widespread use of SSRIs in recent years. The leading products in this class are Pfizer Inc. 's Zoloft (15.6% of the market as of late October 2001) and GlaxoSmithKline plc's Paxil (14.2%).
- **Antipsychotics.** One of the strongest CNS segments in recent years has been antipsychotics. Treatment costs, including inpatient and outpatient services and medications, have been estimated at over $30 billion a year. The leading product in this class is Johnson & Johnson's Risperdal (with 33.8% of new U.S. antipsychotic prescriptions as of late October 2001), followed by Zyprexa from Eli Lilly (with a 31.6% share of new scripts at the end of October).
- **Migraine treatments.** The prescription migraine market has remained fairly flat to date in 2001, as increased usage of over-the-counter (OTC) analgesics has cut into prescription growth. In past years, makers of leading OTC pain relievers were banned from claiming that their products could treat migraine. That changed a few years ago after Bristol-Myers Squibb successfully

completed studies demonstrating the efficacy of its Excedrin analgesic in treating migraine, winning FDA clearance to promote the medicine for that purpose. The leading prescription migraine drug is GlaxoSmithKline's Imitrex, with about 46% of the market in October 2001.

- **Anti-arthritics.** These drugs used primarily to treat osteoarthritis, a painful inflammatory condition affecting close to 20 million Americans, are nonsteroidal anti-inflammatory drugs (NSAIDs). A more severe form of arthritis called rheumatoid arthritis is treated mainly by powerful injectable drugs. Leading products are Pharmacia Corp.'s Celebrex, with a 23.1% market share in October 2001, followed by Merck's Vioxx, with 21.3%.

Cardiovascular drugs represent a high priority for many leading drug companies. The fact that patients remain on the medication for life means a steady and long-term market. Cardiovascular or heart drugs comprise the second largest therapeutic segment. This broad-based group includes treatments for heart attacks, hypertension, angina, arrhythmia, and elevated cholesterol levels. Cardiovascular drugs market has shown decent growth, with sales for the 12 months through August 2001 up 11% from the preceding 12-month period.

- **Cholesterol Drugs.** The cholesterol-lowering market is expected to exhibit vigorous growth in the years ahead, as people become more aware of the dangers of elevated blood cholesterol. This market is dominated by a class of cholesterol-lowering drugs known as "statins". They are highly effective in lowering LDL cholesterol and are associated with relatively minimal negative side effects. The lead statin is Pfizer's Lipitor. In October 2001, Lipitor

accounted for about 48% of all prescriptions for cholesterol reducers, followed by Merck's Zocor (21% of the market).

- **Antihypertensives.** Hypertension or high blood pressure is generally an asymptomatic condition that if left uncreated can lead to stroke, aneurysm, heart attack, and kidney failure. A large number of drugs with different mechanisms of action (ways of working in the body) are available to treat hypertension. The largest-selling categories include calcium channel blockers, led by Pfizer's Norvasc (sales of US$3.4 billion in 2000), and angiotensin converting enzyme (ACE) inhibitors, of which Merck's Prinivil/Prinizide (sales of US$1.1 billion) is a leading product. Older groups include products such as beta blockers, diuretics, vasodilators, and others.

The gastrointestinal/metabolism drugs have been the industry's third largest therapeutic sector in the 12 months through August 2001. They account for 15% of all drugs sales with sales approaching US$14 billion. The group includes a wide range of drugs, including antiulcer drugs, diabetes drugs, antiobesity drugs, and oral contraceptives. While the volume growth for most of the drugs in this class has slow down to single digit due to market maturity and the increasing percentage of cheap generics in the market, certain drugs such as diabetes treatments are showing above-average growth.

- **Antiulcer Drugs.** Antiulcer drugs form the largest segment in the gastrointestinal/metabolism drugs sector. Its retail prescriptions were 11% higher in October 2001 than the year earlier. This market comprises older H2

antagonists Zantac and Tagamet, as well as proton pump inhibitors such as AstraZeneca's Prilosec, the largest-selling prescription drug in the world.

- **Diabetes Drugs.** Fueled by a growing patient population and new breakthrough treatments, the diabetes drug market is expected to triple during the next several years. The estimated U.S. sales in 2000 were US$3.8 billion. Most of the growth reflects rapid expansion in sales of new drugs for Type 2, or adult-onset, non-insulin-dependent, diseases. Type 2 diabetes accounts for about 90% of all diabetes cases. Typically affecting persons who are over 40 or clinically obese, this condition is characterized by the body's inability to produce enough insulin or to use it properly. The number of patients suffering from Type 2 diabetes has increased significantly in recent years. The industry leader in the Type 2 market is Bristol-Myers Squibb's Glucophage line, which accounted for about 39% of the market in late October 2001.

Major Trends.

The pharmaceutical industry is dynamic, as evident from its ability to reinvent itself in the face of changing market structures and government regulations. Major trends include:

Aging Population Increases Demand for Drugs. Aging baby boomers and the lengthening of average life span are two key demographic trends that should generate powerful demand for pharmaceuticals over the next few decades. Globally, the over-60 crowd is expected to rise from about 66 million in 2000 to close to two billion by 2050,

based on data provided by the World Health Organization (WHO). As a result, medications targeting conditions that are common among the elderly – such as heart disease, stroke, arthritis, cancer, depression, impotence, and Alzheimer's Disease – should show the strongest growth.

Big Pharma steps up R&D Spending. The Pharmaceutical Research and Manufacturers of America (PhRMA) expects U.S. pharmaceutical companies to invest $30.5 billion in R&D in 2001, up 19% from 2000. This is a marked increase from the 11% average annual growth in industry R&D from 1995-2000. Major R&D expenditures in 2000 were in products acting on Central Nervous System (26%), cancers, endocrine system and metabolic diseases (21%), and cardiovascular system (18%). The recent step-up in research spending reflects drug companies scrambling to find new medicines in the face of a record number of patent expirations on popular products, as well as major scientific advances that have opened up new pathways in the treatment of infectious, chronic, and genetic diseases. The discovery of new research techniques in biochemistry, molecular biology, genetics, and information technology have also streamlined the overall R&D process and improved efficiency. According to PhRMA, all present drugs are based on about 500 distinct targets.

Mergers and Acquisitions Reshape the Industry. In 1990, the world's top 10 players accounted for just 28% of the global market. Ten years later, the proportion is more than 45% and still gaining. Even with consolidation, however, no individual player has a world market share more than 8%. Six of the top 10 companies are based in the United

States, and in general, leading U.S.-based companies raised their market share, whether they merged or not, reflecting the unparalleled growth of the U.S. market in the 1990s.

Biotech Firms Gain Clout in Partnerships with Big Pharma. While partnerships between pharmaceutical and biotech companies are nothing new, recent discoveries in molecular biology and genomics have triggered a burst in new strategic alliances between major pharmaceutical manufacturers and biotechnology companies in recent years. Historically, pharmaceutical companies have relied on biotech companies to perform early-stage drug development. Biotech companies received conventional milestone payments for their work. What has changed in recent years is the clout and the cash biotech companies have earned. Investors have increasingly latched onto the promise of biotech companies, as genomics may hold the key to new drug discoveries combating a range of illnesses from diabetes to Alzheimer's to AIDS.

Direct-to-Customer Push Proliferate in the US. Since FDA relaxed its rules governing direct-to-consumer (DTC) advertising in 1997, U.S. consumers have been bombarded with television and print media advertisements for a variety of prescription drug products. In 2000, drugmakers spent an estimated US$2.27 billion on advertising. Television accounted for about 62% of all DTC advertising, while print media attracted 36%. Whether the industry got its money's worth is a matter of debate. The concept behind DTC advertising for prescription drugs is to encourage patients to ask their doctors to prescribe a specific drug. However, different studies have shown that only between 4% and 10% of consumers asked their doctor about a drug based on DTC advertising. While some reports show that drug companies found these numbers disappointing, drugmakers

are expected to continue to make extensive use of DTC marketing. As with any other product, advertising has the obvious effect of promoting brand recognition.

Internet Emerges as Key Marketing Tool. Although the pharmaceutical industry was slow to embrace the Internet as a marketing tool, today virtually every major drugmaker has a product information website, and a number have e-business divisions. With the Internet, a form of indirect marketing, drugmakers create information content rather than straightforward advertisements. Often they do so through partnerships with third-party websites such as DrKoop.com, where consumers can find information on diseases and medical conditions. The sales pitch almost always consists of a link to a Web site promoting the drug company's product. Pharmaceutical companies also use the Internet to promote their brands directly to physicians. They have developed sites that collect market intelligence from prescribing physicians, tracking which drugs doctors are prescribing, patient population, and patient profiles.

New Role for Drugmakers: Defense. In the coming years, the U.S. government will probably invest billions of dollars in the U.S. drug industry, seeking new diagnostic and therapeutic agents to fight a multitude of biological threats. Many drugmakers may evolve into new types of government defense contractors, operating on large volumes but with reduced profitability.

SECTION 2: DEVELOPMENT SINCE 1945

1945-1970s: from the golden age to the crisis

Up until to the WWII the pharmaceutical industry was dominated by German and Swiss chemical firms, which acquired strong competencies during the war by developing efficient processes for mass production of penicillin. Driven by the emergence of socialized medicine and a period of economic growth, these companies synthesized a large number of anti-bacterial drugs and other compounds creating a prosperous market.

The success of these firms was the result of several factors: growing expenditure for drugs in a free market, loose regulation regarding drug safety, patent protection in their country of origin, capital access and chemical process know-how from chemical business. Moreover, the absence of almost *any* drug before WWII facilitates the success of random screening drug discovery tools leaving the real competitive advantage in chemical process expertise for mass production.

By the end of the 60's and beginning of 70's the industry begin to experience the crisis because of increasing R&D costs coupled with decreasing revenues. There are two main factors behind the increase in costs. One was the introduction with stricter regulation affecting drug safety, which resulted in both an increase in the cost and in the lengthening of clinical trials leading to longer time-to-market, thus patent cover during commercialization. The second factor was the decrease of ROI in R&D as all obvious routes to new drugs on the basis of the chemical synthetic paradigm had been exploited.

To aggravate the situation, pure pharmaceutical US and UK firms started eroding the dominance of the Swiss-German firms' duopoly and many European countries introduced price control measures.

1970s-1980s: the emergence of biotech in US

At about the same time, outside the industry two new technological paradigms were beginning to emerge: biotechnology and bioinformatics (see Appendix 3 for more details). Bioinformatics focused on improving *random* techniques for testing new compounds by using High Throughput Screening tools, such as biochips, and Combinatorial Chemistry. Since then, these two techniques have allowed a 7-fold increase in the number of compounds tested per year (Ramirez 1999). Biotechnology, instead, focused on the *rational drug design* by applying engineering and scientific principles to the processing of materials by biological agents. Albeit biotechnology and bioinformatics seem different in spirit, they were used synergistically: biotechnology helped searching promising families of compounds within the immense space of compounds that accounts of hundred of thousands of molecular entities; bioinformatics speeded up the testing of compounds of those families against a diverse number of diseases.

Despite the fact that both American and European pharmaceuticals were desperately trying to increase drug throughput into the market and these new paradigms promised a revolutionary shift, none of those firms took part in the initial development and commercialization of biotechnology. There were two reasons behind this choice: one economic and the other structural. The economic reason was the large amount of capital investments necessary to develop biotechnology and bioinformatics in a period of cost containment for large pharmaceuticals. The structural reason was the revolutionary change in expertise involved with embracing biotechnology. In fact, one major aspect of biotechnology is its multidisciplinary character that draws on a new number of scientific disciplines including biology, biochemistry, genetics, microbiology, biochemical

engineering and separation processing (Ramirez 1999). For a large vertically integrated pharmaceutical firm, whose competence and success relied on developing and processing chemicals, this was simply an unthinkable organizational revolution.

The development of biotechnology in US rather than in Europe was the consequence of a set of regional advantages combined with governmental policies:

- Huge commitment by the US government of federal funds to heath and biotechnology research just at the time when the major breakthroughs in genetic engineering were being made. The US National Institute of Heath (NHI), for example, invested in *basic research* at much higher level than European governments. Figures (Ramirez 1999) indicate that in 70s and 80s the expenditure for health-related research of UK, France and Canada combined together was around 12-15% of the US level over the same period.
- The *Bayh-Dole Act in 1980* weakened ownership rights of public institutions, such as universities and national labs, over the research developed within their structure. This facilitated the private appropriation and commercialization of publicly funded research and encouraged the transfer of high profile human capital into entrepreneurial entities.
- A set of new legislative decisions, such as the biotech patent (1983), which reinforced and expanded *property rights* for biotech products, and the Orphan Drug Act (1984), which subsidized the research for rare diseases, created the premises for the creation of Dedicated Biotechnology Firms (DBFs). In fact these companies could rely on royalties from patens as a secure source of income.

- The strong *US venture capital market*, stimulated by this new legislative environment, provided the necessary capital for these new DBFs. Also very important, venture capitalists provided the managerial and business expertise, which many of these pure research-oriented companies were lacking, by nominating some of their representatives onto the companies' boards.
- The well-developed *secondary stock markets* in the US, offered an additional resource of capital for growing company. Besides, stock options were a very strong incentive for attracting human capital from universities or national labs.

All these factors worked synergistically in the US, and by the mid 80's, biotechnology was an established sector in the pharmaceutical industry.

By the early 80's large pharmaceutical firms, which deliberately did not invest in biotech in the 70's, recognized that this new technology was sufficiently mature and would be essential for future product innovation. However, these companies pursued different strategies and moved at different speed to embrace biotechnology. Some companies decided to build new competencies through the acquisition of DBFs, others through merger with US counterparts, some others through external linkages with US and/or European DBFs. For example, Wellcome, Glaxo and Bayer chose as their main strategy to link up directly with their corporate US laboratories; ICI (later Zeneca) opted for reinforcing its link with the UK science; Hoechst, Ciba Geigy and Hoffmann LaRoche placed more emphasis on research alliances with DBFs. Bayer, Montedison and other German and Italian firms embraced biotechnology later, probably because their natural tendency to rely on chemicals as their core competencies.

At the same time, large firms increased the practice of contracting out some of the more routine aspects of R&D activities in the pre-clinical and clinical trials to contract research organizations (CROs).[3] While the emergence of DBFs and CROs did not weakened in any significant way the power of the large established firms, they started changing the internal organization of large pharmaceuticals and shifting the competitive advantage from large vertically integrated firms to large flexible and interconnected firms.

1990s: The growth of US pharma

In the 90s, the US pharmaceutical market has grown from being roughly equal to the European market to almost twice as much, representing today 40% the total world sales. Even more shocking is that the US market alone accounts for 60% of total worldwide company profits.[4] This dramatic change forced European companies to increase competitiveness on North American market rather than in their own market in order to benefit of larger profits. This competitiveness was pursued via a process of decentralization, mergers, acquisitions, and specialization. First, many large European chemical conglomerates, such as the German Hoechst and the Swiss ICI, de-merged their pharmaceutical subsidiaries from their bulk chemical activities, realizing that at this point was more a burden than an advantage. Secondly, many large firms merged to increase penetration in US and to leverage economy of scale on R&D: Glaxo and Wellcome merged in 1995; Sandoz and Ciba-Geigy formed Novartis in 1996; Astra and Zeneca merged in 1998; Hoechst and Rhone-Poulenc formed Aventis in 1999. Finally, many of

[3] The Economist, 02/21/98.
[4] Financial Times, 03/15/98.

these firms started specializing on a particular area of pharmaceutical research, such as cardio-vascular or neural-system drugs, and developed strong collaboration in world regions that excel in that area.

The results of this historical excursus can be summarized in three points:

- The emergence of biotechnology firms in US was not the result of direct intervention of large pharmaceutical firms, but the synergistic consequence of governmental policies and the entrepreneurial nature of US market
- Biotechnology has not displaced the power of large pharmaceutical firms, as many like to think, but it has changed their internal organization in a revolutionary way. The industry is shifting from large vertically integrated pharmaceutical firms, to horizontally specialized DBFs and CROs coordinated by large flexible pharmaceutical firms.
- The strategies adopted by the European pharmaceutical firms, i.e. moving R&D to US and M&A, are dictated by the necessity to compete with US firms on the North American market and exploit DBFs drug discovery and development expertise as well as knowledge spillovers.

SECTION 3: ENVIRONMENT

In order to understand the differentiated patterns of evolution of the pharmaceutical industry across countries, it is necessary to analyze the different institutional and financial environments within which they developed. In particular, we

want to highlight some of the reasons why biotechnology flourished in US and not in Europe, and why profit margins are higher in US than Europe.

Public support for heath-related research

Nearly every government in the developed world support publicly funded health related research, but there are significant differences across countries in both the level of support and in the ways it is distributed. In the US, most of the federal funding for heath related research is administered by the NIH and is now the second larger item in the federal research budget after defense ($20 billion in 2000). Public funding of biomedical research also increased dramatically in Europe, although total spending did not even approach American level, which was 4-6 times larger.[5]

In Europe, funding for basic research has tended to be administered at the national level with wide differences across countries, although recently the European Community (EC) created additional funds that can be accessed by any of its members. This structure is likely to have diluted excessively the resources. Moreover, in Continental Europe there is a tendency to separate patient care and medical practices from medical research, thus considering them as two separated entities. Finally, in Europe the technology and human transfer between academy and industry has always been hampered not only by bureaucratic burdens but also cultural prejudices, unlike in the US where the passage of the Bayh-Dole Act promoted it. An example for all, in 1996 Daniel Cohen, chief scientist at Genset, a French biotech company, created a public furor when he quit his directorship of a public research institute and took with him a team of 26 people.

[5] Malerba, 2001.

Intellectual Property Protection

Pharmaceuticals has been one of the few industries where patents provide solid protection against imitation, since small variants in a molecule's structure can drastically alter its pharmacological properties. A basic patent grants a 20-year long exclusive use since the date of application (not approval) of the patent. However, the scope and efficacy of patent protection has varied significantly across countries. In the US, the Bayh-Dole Act in 1980 and the Biotech Patent in 1983 granted very broad claims on patents. Moreover, the Patent Term Restoration (PTR) Act in 1984 allowed the extension of patent for an additional 5 years, as a means to account of long approval time during the FDA process. In Europe, in constrast, the scope for broad claims is greatly reduced and usually process rather than product patents are granted. Only recently, with the approval of the Biotechnology Patent law in 2000 and the Supplementary Protection Certificate (the equivalent of PRT for US patents) in 1994, Europe is aligning with US in terms of IP rights.

U.S.' recent need for Cipro antibiotics to combat Anthrax caused serious debates about the issue of intellectual property. The public's need for large quantities of medicines to be manufactured rapidly in times of national emergency has come into conflict with the drugmakers' desire to preserve patent rights. However, the U.S. government, by respecting the Cipro patent, has to some extent stopped accusations of hypocrisy by African and Latin American countries. These countries have contrasted the U.S. posture on Anthrax drugs to its earlier insistence that third world nations respect patent rights on AIDS drugs.

It is widely accepted that clearly-defined patent rights played a major role in making possible the explosion of DBFs funding in the US, since the new firms had few complementary assets that would have enabled them to appropriate returns from the new science in the absence of strong patent rights (Teece 1986).

Procedures for Drug Approval: FDA and EMEA

Procedures for approval have a profound impact on development time and cost for drugs. Until 1995, every European country had its own national institution responsible for granting market approval for a drug. Therefore, a pharmaceutical firm who wanted to commercialize a drug had to send a different application for every country. For example, in France, Germany and Italy, drug approval requirements had been much less demanding than that of the US and UK, thus allowing the survival of small national firms specialized in the approval and commercialization of domestic products. In contrast, the US, with the Kefauver-Harris Amendment Act in 1962, and the UK, with the Medicine Act in 1971, increased the stringency of their approval process by requiring proof-of-efficacy besides proof-of-non-toxicity. Initially, these amendments reduced worldwide competitiveness of American and British firms, since the amendments increased R&D costs, but in the long term this helped create an isolating mechanism for innovative rents. This is consistent with the appearance of innovative British firms in the early 80s, such as Glaxo and Smith-Kline, within the first top 15 pharmaceutical firms, the crisis of German firms during the same years, and the absence of Italian and French global firms.

In 1995, the European Community (EC) established the European Medicine Evaluation Agency (EMEA), a centralized agency that has the power of granting a single

drug approval for the whole trans-national EC market (Tufnell 2001). The role and the regulatory procedures adopted by EMEA mimic very closely its US counterpart, the FDA. The creation of the EMEA is a major step forward within the EU and represents the culmination of more than 20 years of effort to consolidate resources and improve efficiency among regulatory authorities. Today, the mean approval time of new drugs (NMCs), including biotechnology, in Europe is 18 months, which is virtually identical to that of US, although wide disparities exist within individual product review times (Impact Report 1999).

The Structure of Heath Care System and Systems of Reimbursement

Perhaps the biggest difference in institutional environments across countries is in the heath care systems. In Europe, unlike the drug approval procedure that is being centralized and uniformed under the EMEA, these differences are still present today in the different countries, creating strong frictions between the different EC members. In most of European countries, and up till 1996 in Germany too, the price of drugs is either directly set or heavily controlled by government and regulatory authorities. The criteria used to set prices differs between countries: for example in Italy the price is based on direct production costs whilst in France the price is determined by an assessment of the R&D effort, the therapeutic advantage offered and the novelty of new drugs. Even in countries that rely on free or semi-free prices set by competition, like UK and Germany, the industry faces a monopolistic market with one or few purchasing bodies in the form of regional or national public heath authorities, which can strongly reduce the pharmaceutical firms power in the price setting.

The different price control policies enforced by national authorities have two deleterious effects: the first effect is the delay between approval and presence of the drug on pharmacies' shelves, which can take between six months to three years, because of price and reimbursement negotiations (EFPIA homepage); the second effect is the price differential of the same drug on different European countries, which promotes parallel trade and erodes the pharmaceutical sales in lucrative markets. Today, parallel trade in Europe accounts for 5% of the total pharmaceutical market (Economist, 05/11/2002). Moreover, in many European countries, distribution margins for wholesalers and pharmacists are still fixed by law, in general as a fraction of final price (**Figure 17**). As a consequence, there is no incentive for introduction of cost-effective ways for drug dispensing or negotiation procedures between pharmaceutical firms and distributors.

Unlike in Europe, in US the delivery of the health care is administered by the private sector in the forms of multiple Health Managed Organizations (HMOs), which create a more competitive environment. However, many factors affect the pricing of new pharmaceuticals. These include efficiency of the drug, market size, competitive landscape, and cost of development. Although most drugs are priced near other established drugs in their class, prices for breakthrough therapies treating life-threatening conditions are usually set well above those for existing products.

Drug pricing also varies widely among specific markets. Large-scale buyers such as hospital chains usually pay below list price, as a result of heavy discounting and negotiated arrangements. On the other hand, drugs sold to wholesale distributors and pharmacy chains are priced at the higher end of the scale. Drugmakers have historically raised prices to private customers to compensate for the discounts they grant to large-

scale buyers. This practice is called "cost shifting". In recent years, several pharmacy chains and pharmacy trade associations have sued leading drug manufacturers, charging illegal price fixing and restraint of trade.

Recently, the Medicare debate in the U.S. could become a significant factor in price setting for prescription drugs. Medicare is the nation's principal healthcare subsidy program for the elderly, serving about 40 million elderly people. However, Medicare does not currently cover prescription drugs used outside of professional healthcare facilities. Congressional members from both parties had planned to promote their respective Medicare drug benefit programs. Republicans favor a Medicare drug plan run by the private sector, with the government's role limited to helping low-income seniors pay for supplemental drug coverage provided through managed care channels. Democrats generally favor a more comprehensive program, which would provide drug benefits to all seniors and would be administered by the federal government. Such a plan would make the federal government the nation's largest purchaser of prescription drugs. Drugmakers oppose Democrats' proposal, fearing that it would result in a 30% to 40% price discounting.[6] Therefore, although the U.S. faces a free market where price is determined by competition between a number of players, the power of the potential reforms in Medicare could shift the market to dependence on one key giant customer.

The different nature of US market and European countries is best highlighted in **Figure 10**, which reproduces market shares evolution of pharmaceutical firms during patent expiration in different countries. In US there is sharp transition from a pure monopolistic market during patent enforcement to a pure competitive market with multiple sellers and buyers soon after the patent has expired. Before patent expiration, the

[6] PhRMA: *Pharmaceutical Industry Profile 2002*

patent owner controls more than 80% of the market and can charge premium prices, after patent expiration competition increases, prices drop and the original drug maker market share declines to 30%. On the contrary, in Italy and in France, where prices are controlled and IP enforcement is weaker, the owner of the patent cannot profit from a monopolistic market before the patent expire, but at the same time he does not even experience such a high competition after its expiration, so that it maintains a constant share of 50-60%. Germany and UK, instead, represent an intermediate scenario where competition and market shares experience more mobility than Italy and France but not as much as US.

The market dynamic in US has two major consequences: it allow large pharmaceutical firms to obtain large profit margins during patent enforcement necessary to recoup R&D development costs, and at the same time it reduces the presence of inefficient firms and imitators in the off-patent periods. These two phenomena are highly reduced in Europe.

Financial markets and access to capital

The structure of financial market in the US played a key role in facilitating the creation of DBFs. Venture capital market in US has a long history and it was already well developed by the mid 70s when biotechnology appeared, while it was at his infancy in Europe. While in US the venture capital market encourages the creation of firms whose ownership is financial in structure and rooted in large secondary stock markets (e.g. NASDAQ), in Europe the venture capital market is mainly the result of public intervention. Several public policies at the beginning of the 80s tried to support the creation of new biotechnology firms: the establishment of the Business Expansion

Scheme (BSE) and the Unlisted Securities Market in UK; the establishment of a number of venture capital funds and secondary stock market in France; the European Venture Capital (EVC) association launched in 1983 by the EC; the creation of matching funds up to a fifty percent basis for virtually all private venture or bank-based capital for biotechnology activity in Germany (Ramirez 1999). However, despites its recent advances, venture capital markets, in particular for biotechnology, are still not as developed and large as in US (see **Figure 11**). In the case of the UK and France, for example, venture capital has acted more like a continuing fund once a certain level of performance could be demonstrated by DBFs rather than a source or start-up funds (Ramirez 1999).

SECTION 4: MISCONCEPTIONS OF THE EUROPEAN PHARMA INDUSTRY

There is a series of misconceptions about the European pharmaceutical industry based on two widely accepted beliefs. The first belief is that the global European pharmaceutical firms are losing sales and market share worldwide. The second is that biotechnology and bioinformatics, in which the US market is the undoubted leader, are the Pandora box for drug discovery. These beliefs seem to be contradicted by the following findings:

1. The number of European pharmaceutical firms among the top 15 players in terms of worldwide sales has remain roughly constant in the past 30 years (**Figure 3**)
2. The concentration of the pharmaceutical industry is low in all industrialized countries: rarely top firms account for more than 5-8% market share in any specific country. Despite the increasing process of M&A in the past 20 years, the

percentage of market share of the top corporate groups has remained almost constant worldwide (**Figure 4**).

3. The top European pharmaceutical firms have increased market share both worldwide and in North America, while maintaining the same share in Europe. American pharmaceutical firms, instead, lost 4% share in their own market since 1985 (**Figure 5**).
4. The net European trade balance of pharmaceutical products has been relatively constant and positive the past 15 years, exporting twice as much as importing. US trade balance, instead, has decreased over the years and currently US is importing more pharmaceutical goods than exporting (**Figure 6**).
5. The European top pharmaceutical firms invest in R&D at least as much as their American counterparts as percentage of sales (**Figure 7**).
6. Europe has a whole still introduces more New Molecular Entities (NMCs) than US, although this trend is reversing. On the other hand, US has just maintained then same performance over the past 25 years, even after the emergence of biotechnology (**Figure 8**).
7. The number of truly biotechnology entities introduced in the market is still very limited. Of all the 440 NMCs introduced in the past 10 year only 61 (14%) are biotech products. Moreover, the number of biotech NMCs introduced in the past 10 years does not show an increasing trend (**Figure 8**).
8. The biotech market is overall a non-profitable. Although biotechnology can be tracked back 30 years, only 11 biotech companies (9 in US and 2 in Europe), out of almost 2000 that populate the market, are profitable today (**Figure 9**).

9. The average development time for drugs (the period from isolation or synthesis of a new molecule to marketing) is still between 10 to 12 years, the same as the mid-80s when biotech was not fully exploited. This is despite the streamlining of clinical trials and shortening of regulatory approval. Both in US (FDA) and Europe (EMEA) approval times for a new drug dropped from 3 years to 18 months (Impact report 1999).

SECTION 5: COMPARATIVE ANALYSIS OF THE EUROPEAN AND US PHARMACEUTICAL INDUSTRIES

In this section, we analyze some important figures of performance, comparing the European and US pharmaceutical markets with particular focus on the top firms. The major findings are summarized below.

1. As already pointed out, the US pharmaceutical market has grown from being roughly equal to the European market at the beginning of the 90s to almost twice as much in very recent years, accounting for more than 40% of worldwide sales (**Figure 1**). The fact that US companies still hold 60% of the US market (Financial Times 05/13/98), explains why American companies has increased their share in worldwide sales more than European companies and why US is becoming an importer of pharmaceutical products mentioned in a previous paragraph.

2. While the top US companies sustained their internal growth by increasing sales mainly in the US market, European companies had to go through a significant merger and acquisition to remain in the top 15 (**Figure 3**).
3. Despites the fact that number of new drugs (NMCs) introduced by European multinationals is larger than that of US multinationals (**Figure 8**), the sales of the major innovative products by the US multinationals have increased more significantly than those of the European. This indicates that only few compounds are truly innovative and have significant therapeutic value, and that US companies are the owners of these blockbusters (**Figure 12**).
4. The portfolio of products held by European multinationals tends to be older than that of the US firms, which suggests that there are differences in research productivity in recent years (**Figure 13**).
5. US pharmaceutical firms have a tendency to collaborate more with DBFs and public research institutions than European firms. In fact, between 1990-1999 only 27% of all R&D projects in US pharmaceutical firms were developed in-house, while the others were either licensed in or out. On the contrary, European firms keep in house between 26 to 40% of total R&D projects. The licensed projects show a higher probability of success than in-house projects in all phases of clinical trial and for both European and US firms. However, US companies show a higher success rate for in-house projects than European companies (**Figure 14**). This indicates that "participation to division of innovative labor and to markets for technology can allow companies to get access to external knowledge and to increase productivity of their research" (Gambardella 2000).

6. European multinationals are gradually moving their R&D spending to US to leverage regional expertise, in particular in biotechnology (**Figure 15**). Novartis, one of the largest European pharmaceutical companies, announced it would move its research headquarters in Cambridge, Massachusetts and would open a new $250 million facility (Economist, 05/11/2002). This indicated that European firms are aware of importance of US biotechnology for future product innovation.
7. The European employment in the pharmaceutical industry has been roughly twice higher than the US during 1985-1997, although the European market has become smaller than the US one. In fact, the share of personnel costs on the total production value in Europe is almost twice higher than US (23% versus 14%) (**Figure 16**). This suggests "the presence in Europe of a relatively larger share of fringe companies that are specialized in low value added activities, like manufacturing and commercialization of product licensed from other companies, or simply of low value added medical or medical-like substances" (Gambardella 2000).

CONCLUSION

This paper presented an overview of the global pharmaceutical industry, the history of its development, and the role of environments in shaping the European and US pharmaceutical industries. We also presented some of the most relevant measures to compare competitiveness between European and US multinationals. All these elements suggest the following conclusions:

1. *Healthcare Environment*: In the 1990s the US industry has grown more than twice the European industry as a result of the restructuring of health care system and of the unregulated nature of the US drug price market. Mainly the top US firms, which account for more than 60% of US market versus only 32% for the top European firms, benefited from this new environment. By contrast, European market growth has been hampered because of restrictive price control policies for drugs, a rigid economic environment marked by fragmented legislation, and a weak protection of IP rights. As a consequence, European firms find themselves in a disadvantageous position relative to their US counterparts.
2. *Globalization*: Protection on local market diminishes and penetration of foreign companies increases. Market share of small domestic corporation falls everywhere in domestic markets: US top firms market share has increased in Europe from 19% in 1985 to 26% in 1999, European top firms market share has increased in US from 27% in 1985 to 32% in 1999. Nonetheless, none of these companies accounts for more than 8% in a single market.
3. *European firms M&A*: The strategy adopted by many European multinationals to sustain growth via merger and/or acquisition with other European multinationals, was dictated by the necessity to reduce R&D costs and to compete more effectively with US multinationals on the North American market.
4. *Blockbusters*: Albeit the number of new drugs (NMCs) lunched and the expenditure on R&D as a percentage of the total sales of European companies are at least as large as those of US companies, the sales of the major innovative products by the US companies have increased more significantly in the 90s and

they account for a large percentage of the total sales. This indicates that fewer truly new therapeutic drugs are being introduced despites larger R&D efforts, and that US companies are taking the lead.

5. *Biotechnology*: The emergence and the commercialization of biotechnology during the 70s and 80s in US was the result of the unique legislative and financial environment in which it developed, rather than an active intervention of large multinationals. A series reasons created the premises for the creation and sustention of new Dedicated Biotechnology Firms (DBFs) in US: a large monetary commitment of the US government to basic research in biotechnology, a legislative revolution that guaranteed strong IP protection, a mature venture capital market that provided funding and managerial expertise, legal and financial incentives for human capital and technology transfer from public universities and public labs into entrepreneurial entities. These factors were absent or still immature in Europe at that time, and only in the past years European governments have tried to recreate the same positive environment.
6. *DBFs, CROs and Multinationals*: Despite the fact that only few drugs available today on the market have been obtained using biotechnology and that only few companies in this area are profitable, DBFs have slowly but irreversibly being changing the internal organization of large multinationals. R&D collaborations between DBFs and multinationals have increased creating a symbiotic system that benefits both groups. The vertical specialization created in most of the sectors of the drug industry by DBFs, and to a certain extent CROs, shifted the paradigm of competitiveness among large multinationals: from large integrated vertical firms

during the 70s-80s to flexible and interdisciplinary firms within a networked system.

7. *Regional advantage and multinational R&D relocation*: Albeit most of biotechnology R&D is located in US, the increasing globalization of the pharmaceutical industry would suggest that European firms could easily tap the need for innovation by outsourcing technology from the US. To a certain extent, this is confirmed by the finding that the success rate of R&D projects developed in collaboration with DBFs and universities is approximately the same for European and US firms. However, the finding that R&D projects developed in-house have an higher probability of success in US firms, suggests that the presence of a local industry of research-based firms and technology suppliers is critical because of the knowledge transfer, which is notoriously difficult to codify. European multinationals seem to be aware of this regional advantage and they are relocating their R&D spending and resources in US.
8. *European market fragmentation and employment*: A major index of diversity between Europe and US is the employment in the pharmaceutical market that in Europe accounts for twice as many people than in US. The large differences between European countries in terms of legislation and policies for drug approval, price setting and reimbursement, have nurtured a large number of small national firms specialized in dealing with the national authorities and marketing, rather than R&D. These companies are highly labor intensive and eat out sales to more innovative firms, thus increasing inefficiency in the industry as a whole. This is the major issue for the EC at present to increase competitiveness and efficiency in

the pharmaceutical market, but it is unlikely to be solved soon because health care it is still managed at national level.

Appendix 1: U.S. Pharmaceuticals

The top five manufacturing companies dominate the U.S. pharmaceutical market with 87% of total sales.[7] Merck and Company, Inc. leads the industry with 24% share of total market value. This is primarily attributed to the company's strengths in AIDS protease inhibitor operations and cholesterol reducing drugs. Bristol-Myers Squibb Company and Glaxo Wellcome plc are second and third ranked, both with equal 18% shares. Bristol-Meyers' success is attributed to its popular anti-cancer drugs such as Platino, Taxo, and Paraplatin. The success of its Zantac and Zovirax drugs are partially responsible for Glaxo Wellcome's achievement. Pfizer and American Home Products Corp. follow behind with a respective 15% and 12% of the market share. Pfizer, in particular, enjoyed a 3% increase of its market share over 2000. Below we will briefly discuss the performances and corporate strategies of each of these five companies.

TABLE 5 CORPORATE OVERVIEW 2000

Companies (brands)	avg. sales growth	market share
Merck and Co	20.7	24.0
Glaxo Wellcome plc	0.0	18.0
Bristol-Myers Squibb Company	4.2	18.0
Pfizer Inc	32.3	15.0
American Home Products Corporation	-1.2	12.0

Source: Euromonitor

Merck and Company, Inc.

Merck's products are divided into 10 operating segments, some of which include Merck-Medco, elevated cholesterol, hypertension/heart failure, and antiulcerants. The Merck-Medco segment, which involves pharmacy benefits management, was the largest during the 5-year period. The company's popular drug, Pepcid, a gastrointestinal drug, achieved sales turnover of US$569 million in 2000.

[7] Euromonitor: *Pharmaceuticals In the USA*, June 2001

Merck & Co experienced a healthy 23.4% increase in revenues in 2000 to a value of US$40.4 billion. The company's net income increased 15.8% from 1999 to a value of US6.8 billion. This is the eighth consecutive annual increase in the company's net profits. Part of this success is attributed to the company's established products and new products such as VIOXX.

Even though the company has been avoiding the merger and acquisition trends over the last few years, in July 2001 Merck & Co. signed an agreement to acquire Rosetta Inpharmatics. The transaction was valued to US$620 million. E Merck also acquired the rights to two anti-cancer vaccines being developed by Biomira. The deal gave E Merck a product in its final stage of clinical trials. Unfortunately, Merck has finally lost patent protection in the USA and faces stiff competition in the following years.

GlaxoSmithKline Plc

Glaxo Wellcome's net revenue grew 4.2% from 1999 to a value of US$14.3 billion in 2000, marking the company's fourth consecutive increase. Glaxo Wellcome and SmithKline Beecham finished their merger after the US Federal Trade Commission and the UK High Court cleared the deal. The company posted a net loss of US$7.8 billion in 2000 due to costs associated with the merger.

The company is well known for its research in diverse areas such as new treatments for cancer, HIV, and asthma, as well, research for dermatological, gastrointestinal and respiratory conditions.

GlaxoSmithKline, Glaxo Wellcome's parent company, is in the process of restructuring its manufacturing operations. The company is closing 20 manufacturing plants, as well as is in the process of evaluating its business and research operations. The restructuring is

expected to save US$200 million. Also, Glaxo Research and Development Ltd. And Diversa Corp. entered a drug-discovery collaboration. The collaboration calls for the identification of pharmaceuticals derived from Diversa's Pathway Libraries.

Bristol-Meyers Squibb Company

Bristol-Meyers Squibb's net revenue decreased by 9.9% in 2000 with a value of US$18.2 billion. Net profit, however, increased by 13.1% over the last year reflecting net profits of US$4.7 billion. The company divides its operation into four business sectors: medicines, nutritionals, beauty care, and medical devices.

Bristol-Meyers Squibb is most well known products are Clairol and Excerdrin. However, the company is planning to sell its non-healthcare businesses because of its sharper focus on medicines and related businesses. Moreover, most of the company's sales come from pharmaceuticals. The company is also considering a possible merger in order to expand its drug pipeline and R&D efforts, as well as strengthen its marketing.

Pfizer Inc.

Pfizer's net revenue increased a dramatic 82.5% from 1999 to a value of US$29.6 billion in 2000, due to the strength of the company's pharmaceutical operations. The company's net income also increased 17.2% from 1999 to a value of US$3.7 billion in 2000. Pfizer's merge with its former competitor Warner-Lambert solidified the company's status as one of the top-five industry leaders.

The company is best known for drugs like the cardiovascular Norvasc, the impotence treatment drug Viagra, as well as general consumer products like Listerine, BenGay, Visine and Zantac. It also introduced an antipsychotic medication, Geodon, tapping into

the US$4 billion market for antipsychotic drugs. Geodon will compete with the market leader among antipsychotics, Lilly's Zyprexa, and J&J's Risperdal. The two later drugs control 47% and 32.8% of the antipsychotic market respectively.

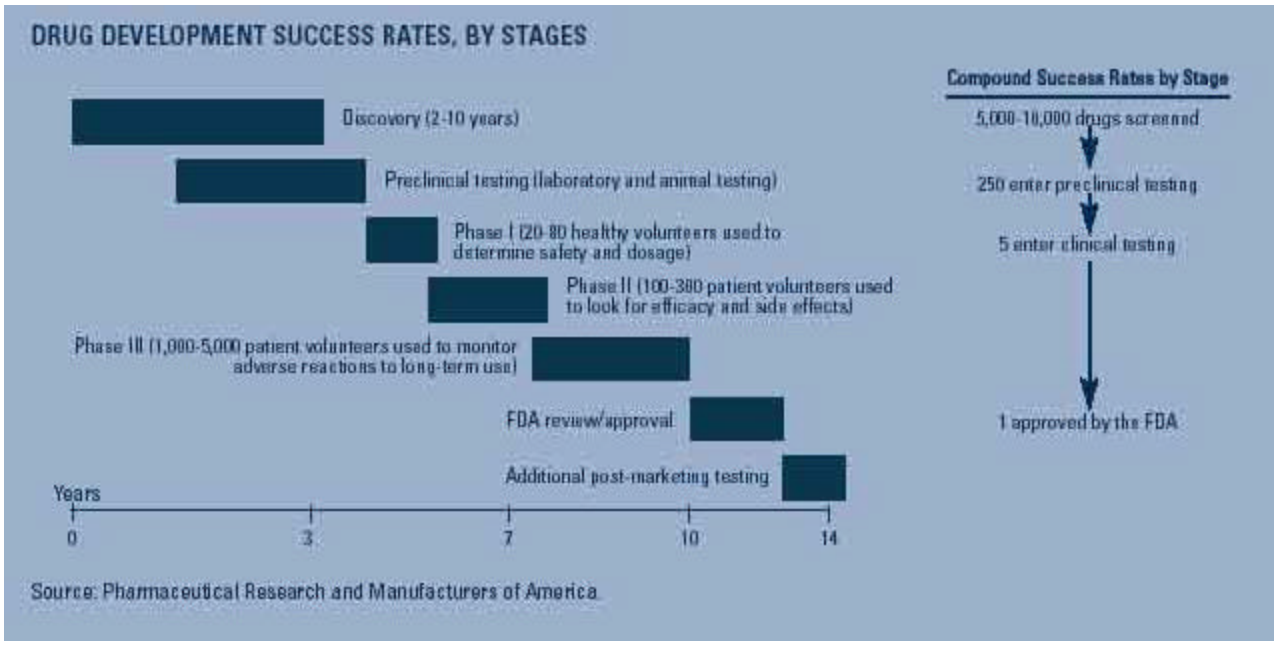
American Home Products Corporation

AHP Corporation's net revenue decreased by 2.1% in 2000 to a value of US$13.3 billion. This is primarily due to intense competition from generic products. It was expected to boost its profit by about 18% in 2001.

The company is effectively evolving into a research driven developer of vaccines and pharmaceuticals. Over the last two years, AHP has introduced nine new pharmaceuticals and has 60 new drugs in development. AHP's research and development expenditures are expected to reach approximately US$2 billion in 2001, an increase of approximately 18% from 2000.

The company's operations are divided into four business segments: agricultural products, consumer health care, corporate/other, and pharmaceuticals. The pharmaceutical segment was the largest in 1999. New drugs that have had significant sales for the company were the childhood disease vaccine Prevnar, the hormone treatment Premarin, and the anti-depressant Effexor.

Appendix 2: The Drug Development Process



THE DRUG DEVELOPMENT PROCESS

The effort to discover and develop new therapeutics generally consists of several distinct steps: early discovery and preclinical development (which includes target identification, target validation, assay development, primary screening, secondary screening, lead optimization, and preclinical studies), clinical trials, and regulatory filing and review.

Early discovery and preclinical development

According to a study by Joseph A. DiMasi of the Tufts Center for the Study of Drug Development, preclinical work is estimated to consume about 43% of the time it takes to

bring a new compound to market. PhRMA estimates that preclinical research represents 36% of R&D expenditures by research-based pharmaceutical firms.

Contemporary research tools and techniques developed through molecular biology, chemistry, and other related disciplines are now being applied to discovery and early development activities. New capabilities in research and development improve the chances of discovering more effective medications, while reducing the overall time and cost of the process. Key steps in the R&D process of biological drugs are described below.

- **Target identification.** During target identification, researchers focus on identifying genes and their respective products thought to be responsible for causing a particular disease. For infectious diseases, microorganisms need to be characterized. The ultimate goal in this step is to find and isolate potential areas for therapeutic intervention.

- **Target validation.** Once a prospective disease target is uncovered, its role in the disease in question must be determined. Researchers use various methods, such as differential gene expression, tissue distribution analysis, and protein pathway studies, to verify the target's significance in the illness.

- **Assay development.** An assay, or drug candidate screening process, must be constructed to detect the activity that potential treatments have on the target. Ideally, a drug development screen should be cost-effective, fast, accurate, easy to perform, quantitative, and amenable to automation. Some screens can be reused

for other drug development studies, while many others must be tailored for the specific target and set of therapeutic compounds that will be tested.

- **Primary screening.** Once the assay is ready for use, the drug developer will conduct tests with a library of chemical compounds in an attempt to modulate a validated target. Researchers look for a predefined minimum level of activity against the target. Compounds that meet or exceed this criterion are termed “hits” and will be included in subsequent screens.

- **Secondary screening.** This procedure is focused on confirming the activity, measuring the potency, and assessing the selectivity of hits from the primary screen. In doing so, a drug developer identifies the most promising drug candidates in terms of their pharmacological characteristics. Most secondary screens are done manually and therefore consume significant resources.

- **Lead optimization.** By rescreening compounds several times through the secondary screen, researchers attempt to zero in on candidates with the best chance of safety and therapeutic efficacy. New libraries of compounds that possess superior structure-activity relationships (SARs) are generated. The optimization process can include up to 10 or more iterations on previously optimized groups of compounds.

- **Preclinical studies.** Prospective compounds that exhibit the greatest activity with the least chance of toxicity are called leads. Leads move on to a set of FDA-mandated tests, which are necessary before human clinical trials can be initiated. The tests primarily involve animal studies that must prove a compound’s safety in

terms of potential carcinogenicity and other toxic consequences. Additionally, drug developers use preclinical testing to assess preliminary effectiveness and other pharmacological properties of a compound. A sponsoring drug company must submit the results to the FDA as part of an Investigational New Drug Application (INDA), which is a formal request for permission to begin human clinical testing.

Clinical trials: putting new drugs to the test

The clinical testing period in humans usually consists of three phases. During *Phase I,* the manufacturer gives the drug to a relatively small number of healthy people in order to test its safety. Small doses of the drug are administered first. If this initial test appears successful, the dosage is slowly increased to determine its safety at higher levels.

During *Phase II,* the drug is administered to patients suffering from the disease or condition the drug is intended to treat. This second round of tests is designed to evaluate the drug's effectiveness and safety, and generally includes a larger population of subjects and a lengthier test period than Phase I.

Drugs that pass the first two hurdles then undergo *Phase III,* in which the most complex and rigorous tests are performed on still larger groups of ill patients to verify the drug's safety, effectiveness, and optimum dosage regimens. Physicians closely monitor patients to determine efficacy and identify adverse reactions.

Regulatory filing and review

When clinical testing and research on a drug has been completed, the manufacturer analyzes all the data and, if the data successfully demonstrate safety and efficacy, submits an application for federal approval. The application is a compilation of the research completed during the three phases, and it includes full details of the product's formula, production, labeling, and intended use. On average, about 18 months elapse between the time a manufacturer submits an application and the time the government approves the drug.

Appendix 3: Advanced Technology Trends

Drug discovery and the overall R&D process have become more rational and systematic through the use of sophisticated technology and the recent sequencing of the human genome. Companies are finding it necessary to integrate genomics, proteomics, and other technologies to improve target identification, approval speeds, and shift to a more focused target population. There are approximately 500 known biological targets that are available for the development of human therapeutics and 10,000 new drug targets are expected by mid-decade.[8]

Genomics

Genomics refers to a new scientific discipline of mapping, sequencing, and analyzing genomes. Genome analysis can be divided into structural genomics and functional genomics. Structural genomics represents an initial phase of genome analysis with the goal of constructing high resolution genetic, physical, and transcript maps of an organism, its complete DNA sequence. Functional genomics refers to the development and application of global experimental approaches to assess gene functions by making use of information obtained through structural genomics. [9] Genomics is expected to significantly increase the number of targets identified and validated. Another potential trend is in Pharmocogenomics, which is the development of customized drugs for specific gene types. The figure below describes the typical business models along with recent key players.

[8] *High Performance Drug Discovery*, Accenture, 2001
[9] *The Genomic Era: A Primer*, Morgan Stanley Dean Witter, 2000

Genomics Business Models

GENOMIC TECHNOLOGY	STRUCTURAL GENOMICS	FUNCTIONAL GENOMICS	GENOMIC DRUGS
Focus:			
• Research tools, chips, hardware • Gene sequencing, expression	• Sequence/gene data • Polymorphism data • Personalized medicine • Clinical outcomes	• Associate genes with disease • Drug target discovery, validation • Pharmacogenomics	• Drug development
Business Model:			
• Hardware, reagent sales to research • Diagnostics	• Database Subscriptions • Internet Advertising • Patent asset	• Pharma genomics service providers • Patent asset • Budding product discovery programs	• Drug revenues • Patent asset
Customer Base:			
• Industrial/academic research	• Industrial/academic research • Physicians, general public	• Pharmaceutical industry	• Traditional Therapeutic Markets
Key Challenge:			
• Avoid commoditization	• Proprietary data, ease of use • Access to capital	• Quantity/quality of new discoveries • Access to capital	• Success in clinical trials
Examples:			
• PE Biosystems (PEB) • Nycomed Amersham (NYE) • Affymetrix (AFFX) • Nanogen (NGEN) • Hyseq (HYSQ) • Caliper (CALP)	• Celera (CRA) • Incyte (INCY) • deCODE (private) • Kiva Genetics (private) • Orchid (private) • Scientia (private)	• CuraGen (CRGN) ⇨ • Tularik (TLRK) • Myriad (MYGN) ⇨ • Genset (GENX) • GeneLogic (GLGC)	• Millennium (MLNM) • Human Genome Sciences (HGSI)

Source: Morgan Stanley Dean Witter Research

Proteomics

The term proteome refers to all the proteins expressed by a genome, and thus proteomics involves the identification of proteins in the body and the determination of their role in physiological and pathophysiological functions. The ~30,000 genes defined by the Human Genome Project translate into 300,000 to 1 million proteins when alternate splicing and post-translational modifications are considered. While a genome remains unchanged to a large extent, the proteins in any particular cell change dramatically as genes are turned on and off in response to its environment.[10]

[10] *Proteomics Conference Recap*, Morgan Stanley Dean Witter, 2001

It is believed that through proteomics new disease markers and drug targets can be identified that will help design products to prevent, diagnose and treat disease. Proteins provide structural and functional framework for cellular life. Genetic information is static while the protein complement of a cell is dynamic. Genomics and proteomics are complementary fields, with proteomics extending functional analysis.

Bioinformatics

Bioinformatics is an emerging industry with few large companies and many small players. Established players include Celera Genomics, Incyte Genomics, and Rosetta Inphamatics (owned by Merck & Co.).

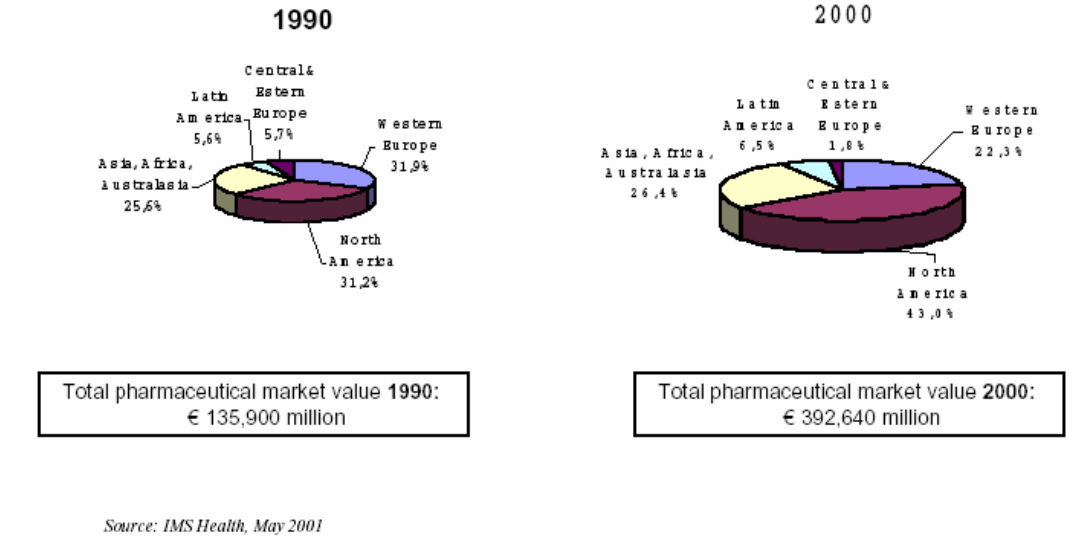
The current bioinformatics market is marked by collaborations among major pharmaceutical companies and drug-discovery companies. Another trend, although not yet common, is the acquisition of bioinformatics companies by big pharma, spear-headed by Merck's acquisition of Rosetta in July 2001. By gaining sole access to Rosetta's DNA microarray and gene-expression analysis technologies and knowledgeable staff, Merck positioned itself as a key player in gene-expression analysis. Despite Merck's acquisition, Drug and Market Development Inc. predicts that big pharma will continue to outsource drug discovery to smaller companies instead of acquiring them, since partnerships are more flexible as technology continually changes.[11]

The market for bioinformatics is estimated to expand to $1.90 billion by 2005.[12] The future of bioinformatics is in drug discovery. Thus far, genomics has not yet produced more effective drugs on the market, thus bioinformatics will take off once the

[11] Drug and Market Development Inc. (www.drugandmarket.com)
[12] Front Line Strategic Management Consulting Inc.

first drugs discovered through genomics is approved and on the market. The next generation of bioinformatic products will shift from sequence analysis to model a protein's structure and function, design drug targets, and further accelerate R&D.

Figure 1



Source: IMS Health, May 2001

Key figures (European Union, Applicant countries, OECD)

	Population (million)	Total GDP ($ billion)	GDP per capita ($)	Pharmaceutical market ($ billion)
Belgium	10	228	22,546	2,70
Denmark	5	173	33,185	1,10
Germany	81	1,835	22,539	21,80
Greece	11	100	9,576	1,20
Spain	39	559	14,264	7,60
France	58	1,538	26,462	25,30
Ireland	4	52	14,576	0,40
Italy	58	1,018	17,797	12,10
Luxembourg	0,5	11	27,053	0,10
Netherlands	15	395	25,591	4,20
Austria	8	233	28,844	2,10
Portugal	10	83	8,368	1,30
Finland	5	126	24,651	1,00
Sweden	9	229	25,779	2,80
United Kingdom	59	1,104	18,848	8,40
Bulgaria	8	10	1,127	0,20
Czech Republic	10	46	4,402	1,00
Estonia	2	2	1,132	0,03
Hungary	10	41	4,033	0,60
Latvia	3	4	1,767	0,05
Lithuania	4	6	1,495	0,10
Poland	39	93	2,402	1,40
Romania	23	30	1,324	0,20
Slovak Republic	5	17	3,220	0,10
Slovenia	2	14	7,024	0,10
United States	263	7,246	27,538	84,00
Japan	125	4,591	36,739	53,20
Switzerland	7	304	42,989	2,90

Source : EPISCOM Data

Figure 1 (Cont'd)

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Sweden	9	229	25,779	2,80
United Kingdom	59	1,104	18,848	8,40
Bulgaria	8	10	1,127	0,20
Czech Republic	10	46	4,402	1,00
Estonia	2	2	1,132	0,03
Hungary	10	41	4,033	0,60
Latvia	3	4	1,767	0,05
Lithuania	4	6	1,495	0,10
Poland	39	93	2,402	1,40
Romania	23	30	1,324	0,20
Slovak Republic	5	17	3,220	0,10
Slovenia	2	14	7,024	0,10
United States	263	7,246	27,538	84,00
Japan	125	4,591	36,739	53,20
Switzerland	7	304	42,989	2,90

Source : EPISCOM Data

Sources: Figure: EFPIA website
Tables: (Gambardella 2000)

Figure 2

Health expenditure and pharmaceutical expenditure (as % of GDP)

	Health expenditure (% of GDP)	Pharmaceutical expenditure (% of GDP)	Pharmaceutical expenditure (% health exp.)	Pharmaceutical expenditure ($ per capita)
Belgium	7,6 %	1,4 %	13 %	267
Denmark	7,7 %	0,7 %	12 %	215
Germany	10,4 %	1,3 %	11 %	269
Greece	7,1 %	1,8 %	25 %	118
Spain	7,4 %	1,5 %	16 %	193
France	9,9 %	1,7 %	17 %	435
Ireland	7,0 %	0,7 %	10 %	111
Italy	7,6 %	1,4 %	14 %	209
Luxembourg	7,1 %	0,8 %	12 %	260
Netherlands	8,5 %	0,9 %	13 %	272
Austria	7,9 %	1,1 %	10 %	260
Portugal	8,2 %	2,2 %	18 %	127
Finland	7,3 %	1,1 %	11 %	192
Sweden	8,6 %	1,1 %	16 %	315
United Kingdom	6,7 %	1,2 %	10 %	143
Bulgaria	n.a.	n.a.	35 %	25
Czech Republic	n.a.	n.a.	28 %	94
Estonia	n.a.	n.a.	28 %	20
Hungary	n.a.	n.a.	30 %	63
Latvia	n.a.	n.a.	29 %	19
Lithuania	n.a.	n.a.	25 %	19
Poland	n.a.	n.a.	19 %	36
Romania	n.a.	n.a.	23 %	10
Slovak Republic	n.a.	n.a.	17 %	23
Slovenia	n.a.	n.a.	13 %	52
United States	14,0 %	1,1 %	7 %	319
Japan	n.a.	n.a.	20 %	425
Switzerland	10,2 %	0,8 %	11 %	396

Data : 1997 - Source : OECD Health Data 98 + EPISCOM Data

Source: Gambardella 2000

Figure 3

RANK	1976	1987	1997	2000
1	Hoechst (DE)	Merck (US)	Merck (US)	Pfizer (US)
2	Merck (US)	Hoechst (DE)	Glaxo Wellcome (UK)	Glaxo-SKB (UK)
3	Roche (CH)	Ciba-Geigy (CH)	Novartis (CH)	Merck (US)
4	AHP (US)	Bayer (DE)	BMS (US)	AstraZeneca (SE/UK)
5	Ciba-Geigy (CH)	AHP (US)	Hoechst (DE)	BMS (US)
6	Bristol-Myers (US)	Glaxo (UK)	Pfizer (US)	Novartis (CH)
7	Pfizer (US)	Pfizer (US)	AHP (US)	J&J (US)
8	Warner-Lambert (US)	Sandoz (CH)	J&J (US)	Aventis (DE/FR)
9	Bayer (DE)	Eli Lilly(US)	SKB (UK)	Pharmacia (US)
10	Sandoz (CH)	Abbott (US)	Roche (CH)	Abbott (US)
11	Eli Lilly (US)	Warner-Lambert (US)	Eli Lilly (US)	AHP (US)
12	Boehringer (DE)	Takeda (JP)	Abbott (US)	Roche (CH)
13	Upjohn (US)	Bristol-Myers (US)	Astra (SWE)	Eli Lilly (US)
14	Rhone (FR)	Smith-Kline (UK)	Takeda (JP)	Schering (US)
15	Takeda (JP)	Upjohn (US)	Pharmacia (US)	Bayer (DE)

Source: (Ramirez 1999), (EFPIA report 2 2001)

Figure 4

Market Concentration in Selected Countries, Corporate Groups

	Corporate Groups			
	Top 10		Top 25	
	1994	1999	1994	1999
UNITED STATES *	52.82	47.87	81.50	84.51
JAPAN	38.38	37.25	64.18	63.65
SWITZERLAND *	49.90	51.57	71.62	75.58
AUSTRIA *	43.09	44.89	72.95	73.29
BELGIUM *	43.54	48.36	75.82	78.86
CZECH REPUBLIC *	48.79	44.64	69.46	69.09
DENMARK	58.01	53.22	85.33	84
FINLAND *	69.15	62.49	88.70	85.13
FRANCE	47.88	52.2	76.38	77.99
GERMANY *	34.97	38.35	61.79	64.9
GREECE	45.71	47.62	75.01	78.91
HUNGARY	65.34	58.91	86.83	86.48
IRELAND	48.82	50.17	77.01	77.62
ITALY *	44.18	44.68	70.06	73.19
LUXEMBOURG	44.04	51.15	73.14	76.46
NORWAY *	66.19	58.95	90.83	85.3
POLAND *	39.82	36.72	68.77	63.27
PORTUGAL	40.30	41.85	70.26	72.56
SLOVAK REPUBLIC *	55.86	49.45	76.65	75.24
SLOVENIA	81.35	72.6	94.23	92.05
SPAIN	39.47	40.27	67.12	69.8
SWEDEN *	68.02	56.87	88.22	82.49
UNITED KINGDOM *	48.04	49.13	71.53	71.39

Source: IMS International. * Including hospital sales

Source: (Gambardella 2000)

Figure 5

Shares of Top100 Corporate Groups, by Nationality of Corporation, Major Markets

	Nationality of Corporation*											
Market	USA	Japan	Switzerland	EU-15	Germany	UK	France	Italy	Sweden	Denmark	Netherlands	Belgium
1985												
World	34.2	13.1	7.7	24.8	9.6	9.2	2.8	1.3	0.6	0.2	0.5	0.6
North America	64.3	0.0	8.8	18.6	4.3	12.9	0.2	0.6	0.1	0.0	0.2	0.3
Europe	19.9	0.0	8.5	44.5	18.1	10.6	7.9	3.5	1.5	0.5	1.1	1.3
A/A/A	11.4	49.3	4.8	10.7	5.8	3.7	0.5	0.1	0.1	0.0	0.3	0.2
Latin America	34.4	0.0	11.1	22.9	14.8	4.5	2.2	0.5	0.1	0.0	0.6	0.2
1989												
World	31.2	15.7	10.1	24.7	9.6	7.4	3.2	2.1	1	0.4	0.5	0.5
North America	62	0.1	5.2	24.7	14	8.8	0.2	0.5	0.5	0.2	0.2	0.3
Europe	20.3	0.2	17.3	38.0	11.3	8.3	8.1	5.2	2.4	0.7	1	1
A/A/A	11.1	51.7	6.6	10.2	4	4.4	0.7	0.2	0.4	0.1	0.3	0.1
Latin America	30.9	0	15.9	22.8	5.7	12	3.3	1	0.2	0	0.6	0
1998												
World	36.0	11.0	8.0	28.8	10.0	9.0	4.4	0.6	2.8	0.7	0.6	0.6
North America	58.5	1.5	7.9	24.8	6.8	11.6	1.8	0.0	3.5	0.2	0.4	0.5
Europe	25.4	0.9	9.6	45.3	15.3	10.2	9.8	1.8	3.7	1.7	0.9	1.5
A/A/A	12.3	46.1	5.1	14.3	6.3	4.1	1.7	0.0	0.9	0.8	0.3	0.2
Latin America	28.6	0.2	11.9	27.8	16.1	5.8	4.1	0.1	0.7	0.0	1.0	0.0
1999												
World	39.0	11.1	7.7	27.8	7.3	11.9	6.1	0.5	-	0.7	0.6	0.6
North America	60.2	1.9	7.6	24.0	4.8	14.9	3.0	0	-	0.3	0.5	0.5
Europe	26.1	1.3	9.5	45.7	12.3	13.8	13.0	2.1	-	1.7	0.9	1.5
A/A/A	14.4	45.8	5.1	15.4	4.6	5.5	3.8	0	-	0.9	0.4	0.2
Latin America	29.6	0.2	11.7	26.7	12.1	6.6	6.7	0.2	-	0.1	0.9	0.1

*Location of Headquarters. Source: IMS International

Source: (Gambardella 2000)

Figure 6

International trade of pharmaceutical products (US $ million)

	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
EXPORTS FROM EU-15 to:														
Intra-EU-15	4458	6106	7687	8991	9530	12000	13511	16643	16376	19043	23679	25700	26329	30726
Switzerland & Norway	579	826	973	1069	1140	1498	1675	2082	2420	2471	3262	3263	3492	3935
Japan	407	640	889	1167	1177	1254	1449	1843	1906	2125	2227	2035	2009	1702
US	668	827	1006	1125	1246	1395	1710	2191	2291	2767	3636	4002	5282	7815
Rest of the world	3458	4190	4735	5228	5524	7201	7811	8875	9756	11016	13551	14725	16156	17175
Total world exports	9570	12589	15290	17580	18617	23347	26157	31634	32749	37421	46355	49725	53268	61353
Total extra-EU-15 exports	5112	6483	7603	8589	9087	11348	12646	14991	16373	18378	22676	24025	26939	30627
IMPORTS TO EU-15 from:														
Intra-EU-15	4517	6254	7806	9209	9989	12965	14928	17722	17121	20023	25307	26351	27127	31490
Extra-EU-15	2197	2916	3513	4031	4434	5663	6400	7706	8059	8719	10961	12344	12472	14426
Total world imports	6714	9170	11319	13240	14423	18628	21328	25428	25180	28742	36268	38695	39599	45916
PHARMAC. TRADE BALANCE														
Extra EU-15	2915	3567	4090	4558	4653	5685	6246	7285	8314	9659	11715	11681	14467	16201
Extra-EU-15 Export/Import ratio	2.33	2.22	2.16	2.13	2.05	2.00	1.98	1.94	2.03	2.11	2.07	1.95	2.16	2.12
EXPORTS FROM US to:														
EU-15	1162	1448	1459	1855	1686	1858	2070	2441	2508	2564	2811	3300	3819	4635
Switzerland & Norway	78	92	100	145	81	96	94	150	185	400	230	186	187	437
Japan	571	634	686	793	785	764	810	817	849	836	933	846	852	881
Rest of the world	979	1039	1103	1297	1108	1385	1635	1949	2204	2292	2459	2828	3179	3708
Total world exports	2790	3214	3348	4089	3660	4103	4609	5357	5747	6092	6433	7160	8037	9661
IMPORTS TO THE US														
Total world import	1718	2084	2498	3235	2117	2540	3092	3861	4198	4755	5605	7150	8737	10982
PHARMAC. TRADE BALANCE														
Trade balance	1072	1130	850	854	1543	1563	1517	1496	1549	1337	828	10	-700	-1321
Export/import ratio	1.62	1.54	1.34	1.26	1.73	1.62	1.49	1.39	1.37	1.28	1.15	1.00	0.92	0.88
EXPORTS FROM JAPAN to:														
EU 15	114	158	191	237	258	316	394	562	572	562	721	732	737	678
Switzerland & Norway	8	7	8	11	9	10	17	10	20	14	19	23	33	47
US	98	134	146	165	202	197	248	313	372	454	503	547	605	685
Rest of the world	171	215	244	303	299	354	431	485	514	525	602	587	577	505
Total world exports	391	513	589	717	768	877	1089	1370	1478	1556	1845	1889	1952	1915
IMPORTS TO JAPAN														
Total world import	1292	1724	2110	265+9	2732	2849	3313	3681	3947	4243	4917	4501	4242	3751
PHARMAC. TRADE BALANCE														
Trade balance	-901	-1211	-1521	-1942	-1964	-1972	-2224	-2311	-2469	-2687	-3072	-2612	-2290	-1836
Export/import ratio	0.30	0.30	0.28	0.27	0.28	0.31	0.33	0.37	0.37	0.37	0.38	0.42	0.46	0.51

Source: OECD World Trade Statistics, various issues. Note: Europe is EU-15 plus Switzerland and Norway.

Source: (Gambardella 2000)

Figure 7

Pharmaceutical R&D Expenditures, Top 10 Pharmaceutical Corporations, 1999

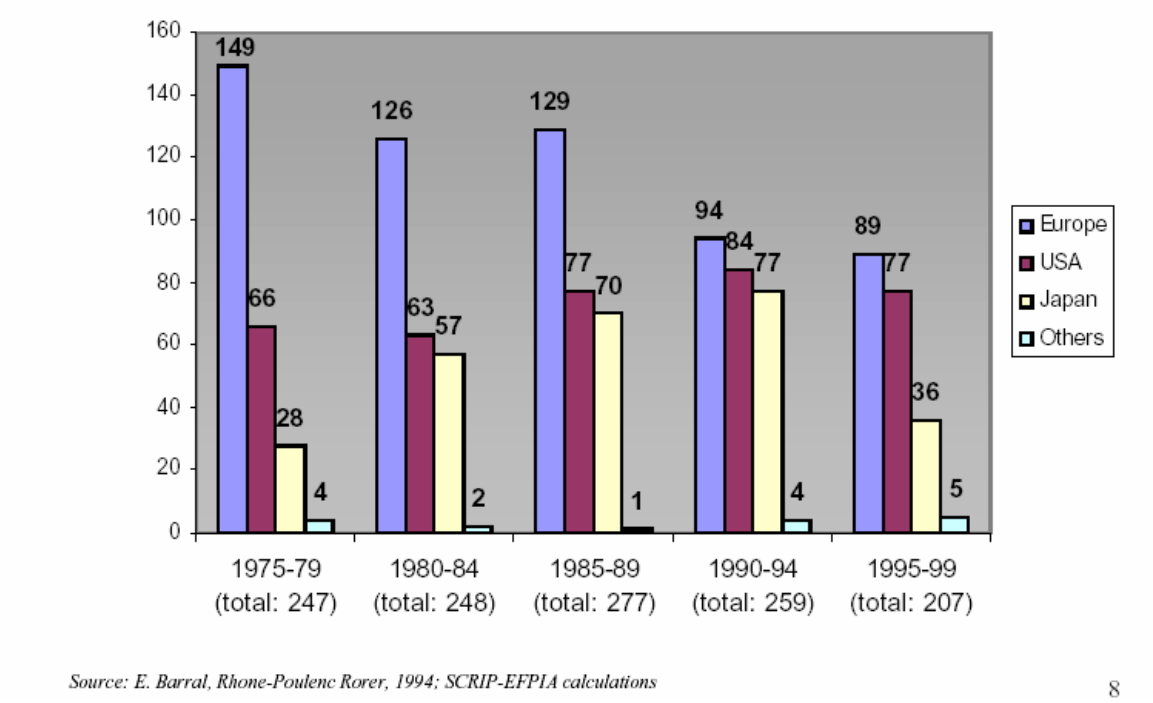
World Ranking 1999	Company	Nationality*	Pharma R&D Expenditures (US$m)	R&D as % of Sales
1	Merck&Co.	USA	1,821.1	11.9%
2	AstraZeneca	UK	2,183	17.1%
3	GlaxoWellcome	UK	1,927.5	14.6%
4	Pfizer	USA	NA	NA
5	Bristol Myers Squibb	USA	1,559	12.4%
6	Novartis	SWI	1,801.3	16.1%
7	Aventis	FRA	NA	NA
8	Johnson&Johnson	USA	1,400	16.4%
8	American Home Products	USA	1,389.9	15.6%
10	Roche	SWI	1,893.1	19.1%

* Location of Headquarters. Source: Scrip League Tables.

Source: (Gambardella 2000)

Figure 8

Total number of new molecular entities (NMCs) lunched from 1975 to 1999



Source: (EFPIA Report 2)

Figure 9

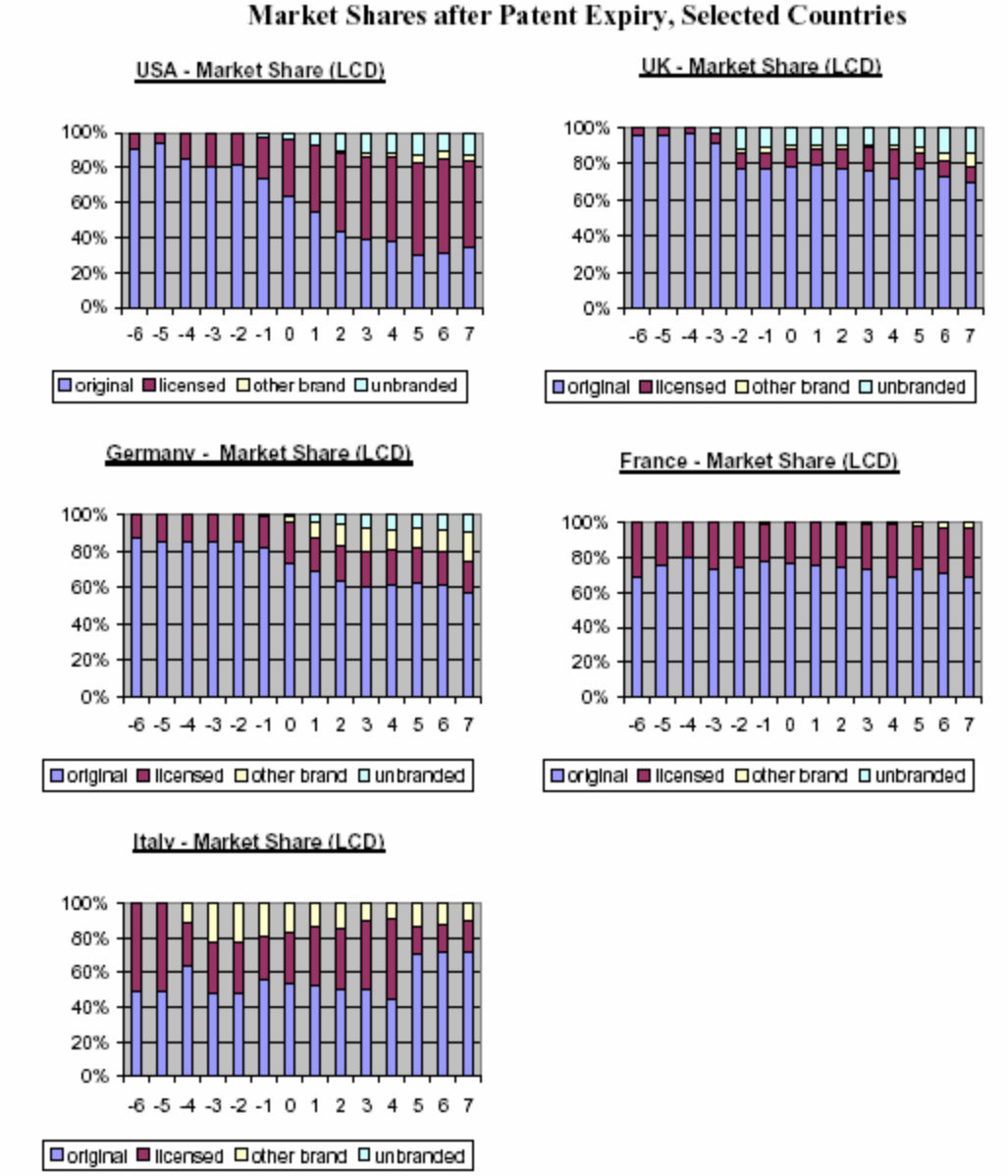
Biotech industry: Europe versus USA (2000)

Indicators	Europe	USA
Turnover (Euro million)	8,679	23,750
R&D expenditure (Euro million)	4,977	11,400
Number of companies (units)	1,570	1,273
Profitable companies (units)	9	2
Number of employees (units)	61,104	162,000
Net loss (Euro million)	1,570	5,960

Profitable companies: Amgen, Genentech, Biotech, IDEC, Immunex, BioChem Pharma, Medimmune, Chiron, Genzyme (US); Serono, Celltech (Europe)

Source: (EFPIA Report2001)

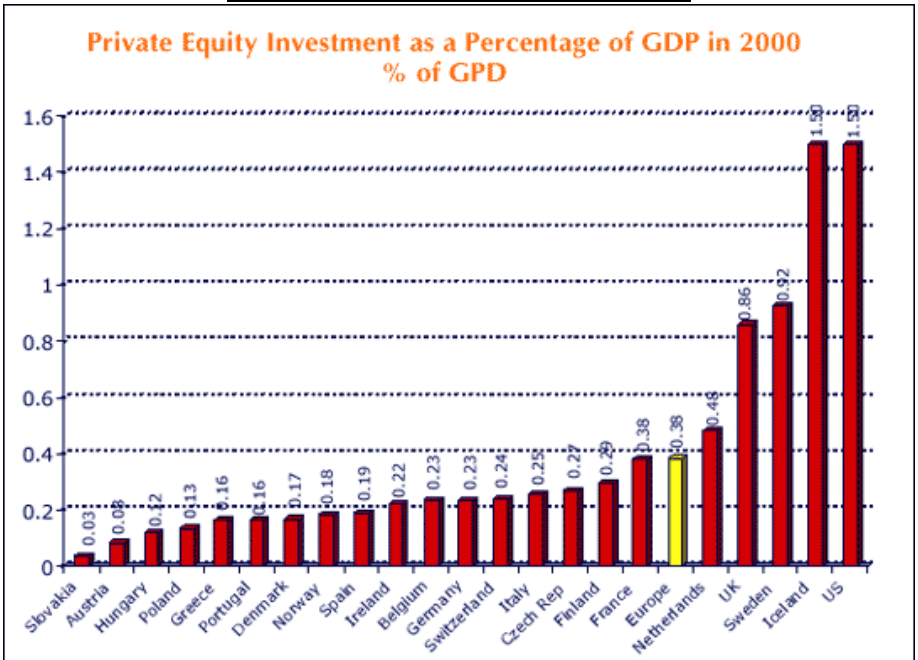
Figure 10



Source: (Gambardella 2000)

Figure 11

Venture capital market in Europe



Sectorial Distribution of Investments 1999-2000

(€ x 1,000)

	1999	2000
Communications	2,915,035	4,818,126
Computer related	2,717,792	4,660,342
Other electronics related	518,493	1,356,319
Biotechnology	643,838	1,017,185
Medical / Health related	1,006,227	2,767,514
Energy	201,855	248,426
Consumer related	4,727,333	6,463,101
Industrial products and services	2,915,425	3,494,188
Chemicals and materials	1,341,717	1,023,394
Industrial automation	218,972	720,860
Other manufacturing	2,275,999	3,264,158
Transportation	841,809	413,755
Financial services	452,744	642,879
Other services	2,048,723	1,963,850
Agriculture	94,513	85,916
Construction	639,335	625,185
Other	1,555,885	1,420,553
Total	**25,115,694**	**34,985,752**
High-Tech Investment	**6,418,215**	**10,976,494**

Source: European Venture Capital homepage

Figure 12

World Top 15 Drugs, by Origin of Main Producer Corporation

Nationality of the Main Producer Corporation*	Total sales, $ million, 1989	%	Total sales, $ million, 1999	%
US	1697	47.94	11227	82.06
Japan	1173	33.14	460	3.36
Switzerland	0	-	835	6.10
EU-15	670	18.93	557	4.07
UK	243	6.86	557	4.07
Germany	427	12.06	0	-
France	0	-	0	-
Sweden	0	-	0	-
Other EU	0	-	0	-
Other non EU	0	-	0	-
Total	3540	100	13682	100

* Location of Headquarters. Source: IMS

Source: (Gambardella 2000)

Figure 13

Recent Products' Contribution to Total Sales: Top 100 Global Corporations*, 1997

	% of Total 1997 sales from NCEs launched since 1988
USA	32
Japan	29
Switzerland	14
EU-15	16

* Location of Headquarters. Source: IMS

Source: IMS

Source: (Gambardella 2000)

Figure 14

Success and Failure Rates of Licensed vs. In-House Drug Compounds (*)

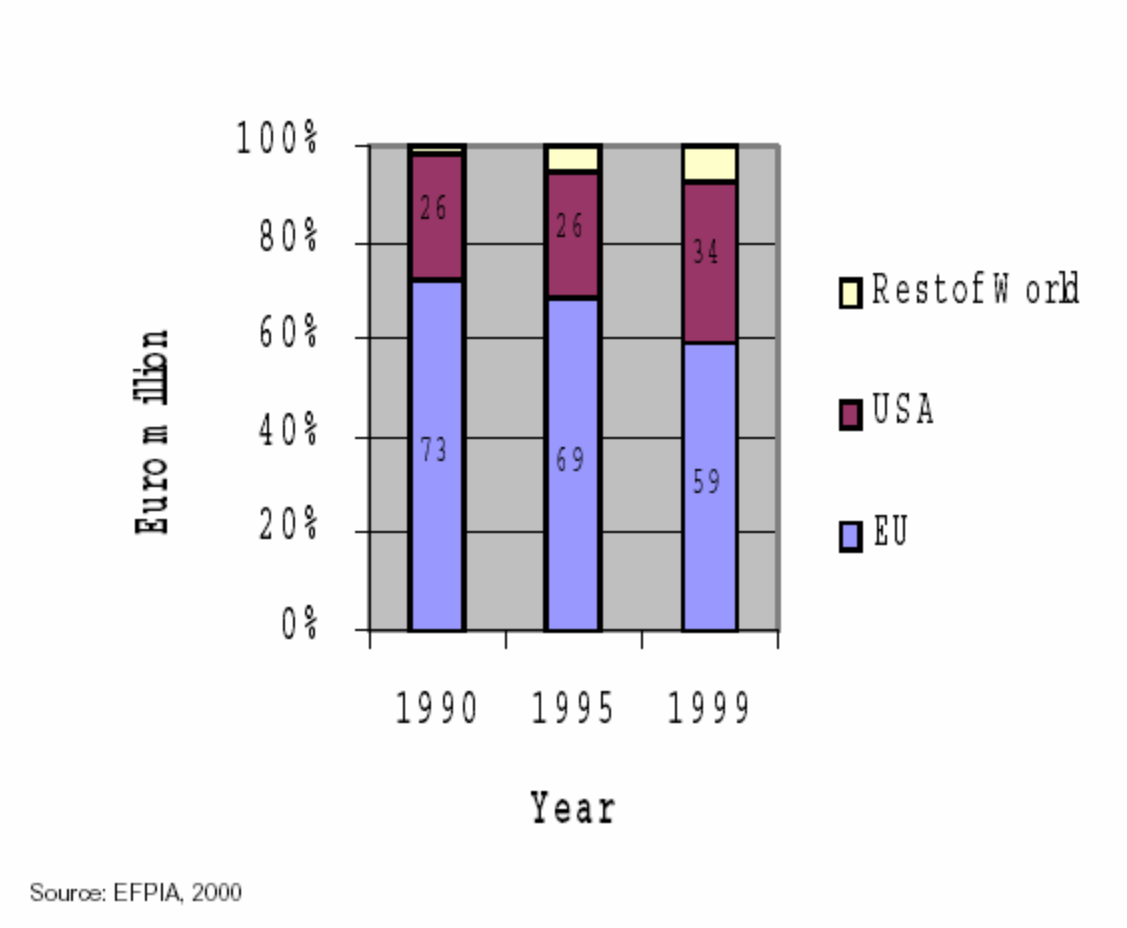
	Preclinical/Clinical I			Clinical I/II			Clinical II/III		
	Failure	Success	Total	Failure	Success	Total	Failure	Success	Total
Total									
In-House	2038 (58.1)	1470 (41.9)	3508 (100)	355 (20.6)	1268 (79.4)	1623 (100)	428 (38.0)	698 (62.0)	1126 (100)
Licensed	192 (38.2)	311 (61.8)	503 (100)	36 (9.4)	348 (90.6)	384 (100)	49 (14.3)	293 (85.7)	342 (100)
Total	2230 (55.6)	1781 (44.4)	4011 (100)	391 (19.5)	1616 (80.5)	2007 (100)	477 (32.5)	991 (67.5)	1468 (100)
US firms									
In-House	849 (54.8)	700 (45.2)	1549 (100)	108 (17.0)	528 (83.0)	636 (100)	126 (33.2)	254 (66.8)	380 (100)
Licensed	129 (39.4)	198 (60.6)	327 (100)	21 (9.7)	195 (90.3)	216 (100)	22 (13.9)	136 (86.1)	158 (100)
Total	978 (52.1)	898 (47.9)	1876 (100)	129 (15.1)	723 (84.9)	852 (100)	148 (27.5)	390 (72.5)	538 (100)
European firms									
In-House	764 (61.6)	477 (28.4)	1241 (100)	176 (28.9)	433 (71.1)	609 (100)	189 (40.4)	279 (59.6)	468 (100)
Licensed	35 (36.8)	60 (63.2)	95 (100)	10 (11.9)	74 (88.1)	84 (100)	19 (20.1)	73 (79.9)	92 (100)
Total	799 (59.8)	537 (40.2)	1336 (100)	186 (26.8)	507 (73.2)	693 (100)	208 (37.1)	352 (62.9)	560 (100)
Japanese firms									
In-House	327 (61.8)	202 (28.2)	529 (100)	55 (19.0)	235 (81.0)	290 (100)	89 (39.9)	134 (60.1)	223 (100)
Licensed	8 (19.5)	33 (80.5)	41 (100)	3 (4.6)	62 (95.4)	65 (100)	8 (11.6)	61 (88.4)	69 (100)
Total	335 (58.8)	235 (41.2)	570 (100)	58 (16.3)	297 (83.7)	355 (100)	97 (33.2)	195 (66.8)	292 (100)

Source: Our calculations from PHID, University of Siena (*) Drug compounds developed in-house vs acquired through licenses in Phase I, II, or III of clinical research by the top 100 pharmaceutical corporations, worldwide. Percentages in parenthesis are conditional probabilities of success and failure.

Source: (Gambardella 2000)

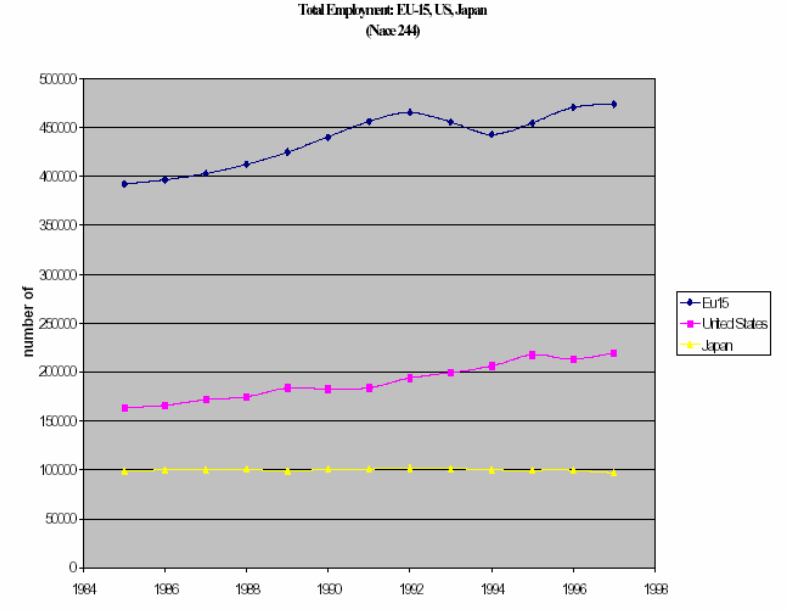
Figure 15

Location of R&D spending by European companies



Source: (EFPIA Report 1)

Figure 16



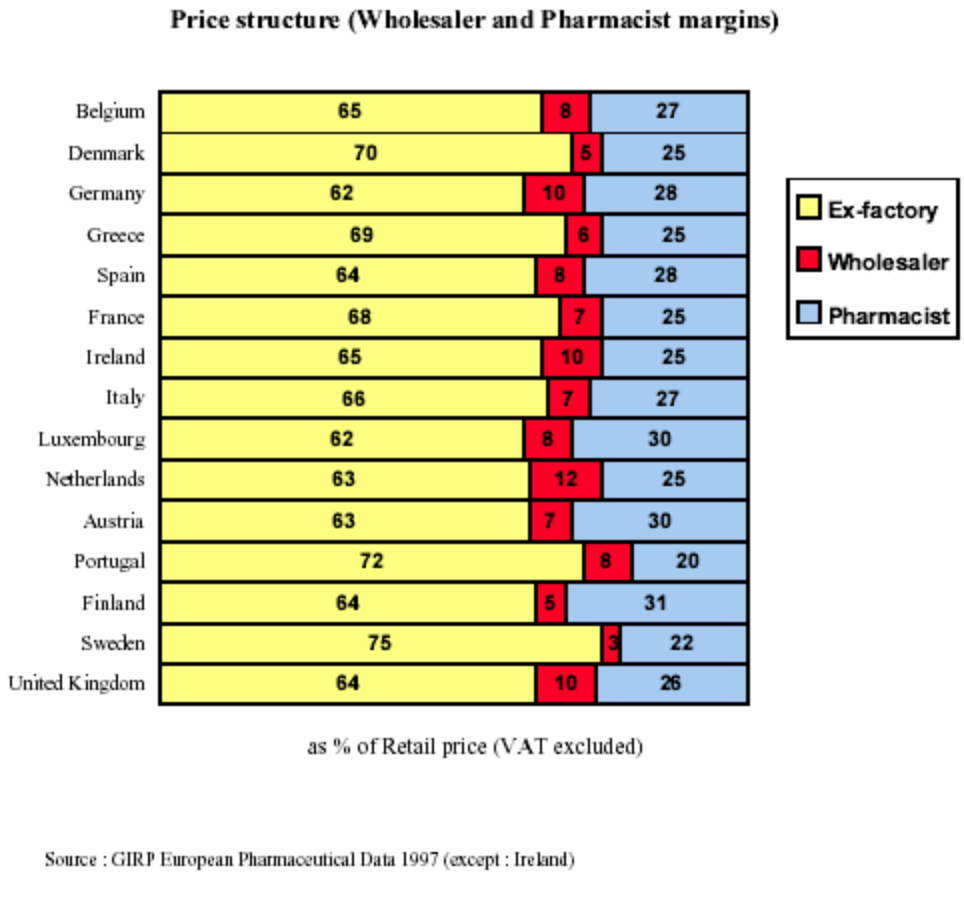
Labour share and share of other non-labour inputs on production value (avg for 1992-1997 and 1986-1991)

	1992-1997			1986-1991		
	Share of personnel costs	Share of non-labour inputs (*)	Share of value added	Share of personnel costs	Share of non-labour inputs (*)	Share of value added
EU-15	23.21%	16.58%	39.78%	24.92%	15.64%	40.56%
United States	13.50%	57.55%	71.05%	15.58%	55.32%	70.89%
Japan	12.57%	53.60%	66.17%	12.90%	53.31%	66.21%
Denmark	26.50%	26.99%	53.49%	26.99%	21.78%	48.77%
Germany	33.11%	9.36%	42.47%	31.81%	12.00%	43.81%
Spain	23.00%	14.33%	37.33%	27.73%	10.56%	38.29%
France	18.87%	14.00%	32.87%	20.18%	13.22%	33.39%
Ireland	10.69%	42.18%	52.87%	14.11%	33.06%	47.17%
Italy	22.74%	13.99%	36.73%	23.46%	13.50%	36.96%
Netherlands	18.43%	14.91%	33.33%	22.86%	11.18%	34.05%
Austria	23.17%	17.80%	40.97%	Na	Na	Na
Finland	26.44%	21.68%	48.12%	24.12%	25.14%	49.26%
Sweden	18.42%	30.59%	49.01%	Na	Na	Na
United Kingdom	21.69%	28.40%	50.09%	23.60%	30.23%	53.83%

Na = not available
Source: Our calculations from Eurostat data
(*) Value of non labour inputs computed as total value added minus personnel costs.

Source: (Gambardella 2000)

Figure 17



Source: (CC final report 1998)

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