

A golden era of medicines research

The past years have seen a revolution in our understanding of disease and its prevention and treatment. It has been a time in which:

- The structure of DNA was elucidated, opening the way for the detailed understanding of inherited diseases and their treatment through genetic engineering;
- Transplantation became a practical alternative for treating end-stage organ failure;
- Interferon, the first of a family of naturally occurring molecules called cytokines, was isolated, named and introduced to therapeutic use;
- Advanced scanning techniques were developed that have transformed the diagnosis and understanding of many human diseases;
- Monoclonal antibodies were discovered, enabling highly specific targeting of medicines;
- Techniques for *in vitro* fertilisation were developed, bringing hope to many childless couples;
- Smallpox, a centuries-old scourge of mankind, was eradicated from the planet;
- A family of human viral pathogens called retroviruses, of which HIV is one, emerged, leading to entirely new medicines to contain them;
- Hitherto unknown infectious pathogens were isolated, such as the causes for peptic ulcers, Legionnaires' disease, Lyme disease, haemorrhagic fevers, Toxic Shock Syndrome, Hepatitis C, D, and E, which led to the discovery and clinical use of new medicines;
- The human genome was sequenced, laying the foundations for the development of many treatments for major diseases in the coming decades.



Built on these and other developments, there has been a revolution in the number, specificity and safety of human medicines.

Industry (EFPIA total)*	1990	2000	2001	2002
Production	63,142	130,060	149,792	160,000 (e)
Exports	23,180	89,065	114,182	130,000 (e)
Imports	16,113	63,863	80,353	90,000 (e)
Trade balance	7,067	25,202	33,829	40,000 (e)
R&D expenditure	7,941	17,202	18,869	19,800 (e)
Employment (units)	500,762	559,410	582,341	582,500 (e)
R&D employment (units)	76,287	88,258	91,433	91,500 (e)
Pharmaceutical market at ex-factory prices	42,997	89,603	98,662	105,000 (e)

*Value in € millions unless otherwise stated - * Including Turkey as of 1997 - Source: EFPIA member associations (official figures) - (e: EFPIA estimate)*

FIGURE 1: The pharmaceutical industry in Europe - Key data

The industry can also be proud of the contribution it makes to the European economy. Besides driving medical progress and improving public health, the research-based industry is a key asset to the European economy. It is one of Europe's best performing high-technology growth sectors. It performs well on most standard measures, such as trade surplus and employment. EU earnings from the export of medicines exceeded imports by €33,800 million in 2001 and the industry has been a net earner for Europe throughout all of the past 25 years. On top of that, the industry invested €18,800 million in EU research and development in 2001 and employs the skills of about 582,500 people, including 91,500 highly-trained researchers, generating another 1,000,000 jobs in related industries.

These figures show that the European pharmaceutical industry is strong in terms of creativity and diversity. Its strength is retained against a background of major changes arising from a range of political, social, economic and scientific pressures. It is responding to the challenge with a keen eye on the future and will build further on its reputation for innovation and progress over the next years.

The stages in the medicines research and development process

Throughout the brochure, terms such as 'discovery research', 'development' and 'phase 1, 2, or 3 clinical trials' are used. It is important to understand these terms. The time it takes to develop a new medicine is surprisingly long – on average around 12 years. The main stages involved in developing a conventional medicine (FIGURE 2) are described below. Procedures for biological products (cytokines, growth factors, gene therapy, etc.) differ in a number of respects and are covered by their own requirements and regulations.

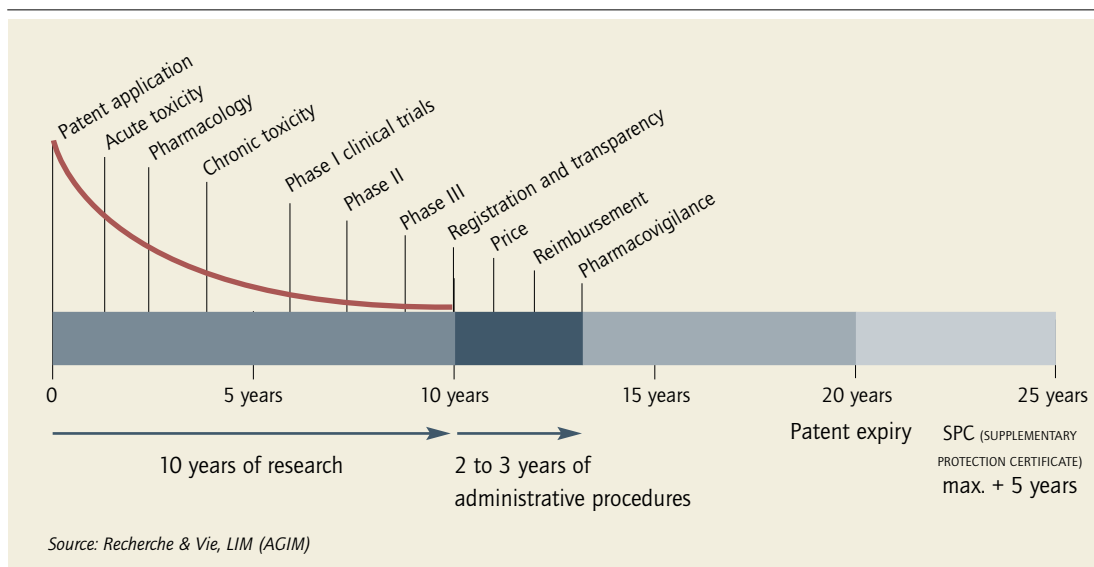


FIGURE 2: Route of a new substance from discovery to patient access

- **Discovery research.** This relates to the 'pre-clinical' activities of chemists, biologists and pharmacologists, who originate and test new active substances. In the past, many new medicines have been sought among compounds occurring naturally, for example, in plants, fungi or marine organisms. On discovering a new biological activity, the molecule causing it would be extracted from its natural source, identified and synthesised (usually chemically). Chemists would then seek to optimise its structure by making many close variations (called *analogues*), to try and maximise the desired effects.

- Nowadays, these slow and laborious 'traditional' methods have been supplemented by two new techniques, *combinatorial chemistry* and *high-throughput screening*, which have greatly speeded up the identification of potential new medicines, allowing companies to examine hundreds of thousands of new molecules in a relatively brief time. (The need to do this arises from the fact that for every new medicine that reaches the patient, many thousands of candidate molecules fall by the wayside). Once a suitable 'lead compound' has been identified, the optimised molecule enters the development stage.
- **Development research.** In preparation for giving a potential new medicine to humans, much work has to be done to determine whether it is acceptably safe and sufficiently stable, and to find out how it is likely to be absorbed and excreted by the body. It is also necessary to prepare a dosage form that suits specific medical needs, such as an injection, a capsule, a tablet, an aerosol, or a suppository. In tandem with this, a large-scale manufacturing process must be worked out, enabling the medicinal product to be made in sufficient quantity for large-scale clinical testing and eventual use in the general public.
- Turning a scientific theory into a new medicine now takes around 12 years. During this time, computer models of new molecules will be studied, thousands of variations will be investigated in the test tube and a small number will eventually go on to be studied in animals. Then, if doctors and scientists are confident that they can do so without undue risks, the potential new medicine will be studied in people. Animal research is essential to help scientists evaluate the safety and effectiveness of new medicines, providing guidance to enable researchers to bridge the gap between the test tube and the patient. The use of animals in research is carried out under strict legislative controls.



Before a new medicine may be given to humans, an application has to be made to the national authorities of European Member States for a certificate to conduct clinical trials. The application is reviewed by independent medical and scientific experts, who make their recommendation on whether trials can start or whether more information is required. If a certificate is granted, a new medicine will pass through a long and complex process of clinical studies before the company can seek authorisation for its widespread use. These trials are conventionally divided into three phases, although companies may sometimes combine two of the three phases (1 + 2 or 2 + 3).

Phase 1 trials are the first time the new substance is administered to humans, usually in studies of healthy, informed volunteers conducted under the close supervision of a qualified doctor. The purpose is to determine if the new compound is tolerated and behaves in the way predicted by all the previous experimental investigations. Initial doses will be the lowest possible consistent with obtaining the required information, but may gradually be raised to the expected therapeutic dose level. If the compound under investigation is particularly powerful, as in cancer treatments, for example, it may be that people who actually have the condition will take part in these trials.

Phase 2 trials are the first time the medicine is given with the objective of treating an illness. Different doses are given to establish whether the compound is tolerated as well as in healthy volunteers, to see if it affects the disease or its symptoms, and to identify a suitable dose for large-scale (Phase 3) studies. Patient numbers in Phase 2 trials are usually limited.

Phase 3 trials only follow if there are encouraging results in the Phase 2 study. The new medicine is compared with a 'dummy' medication, called a placebo, or with another medicine already used for the disease under investigation, to provide a reference standard. Patients are allocated randomly to one of the groups and during the trial, neither the doctor nor the patient knows which preparation is being given. (Such a trial is termed a *double-blind, randomised, controlled trial* and is regarded as the

type of trial that is most likely to give a clear, unbiased result.) When the code is broken, a positive result would be indicated by an improvement in those patients who received the real medication as compared with those on placebo. Phase 3 trials usually involve much larger numbers of patients (hundreds, or even thousands), so that the results can be analysed statistically. If the medicine proves to be successful and well-tolerated at this stage, the way is open for an application for a marketing authorisation to be made (FIGURE 3). This includes all aspects of the data generated on the new medicine and runs to many volumes.

Out of 10 to 15 compounds entering Phase 1 studies, only one is likely to survive through to authorisation. Also, the time scales for the above studies are very variable. Thus, if a new compound is an antibiotic for urinary tract infections, a positive result will be apparent in each patient within a few days as the infection is eradicated. However, in chronic diseases, such as Alzheimer's, multiple sclerosis, AIDS, arthritis, or some forms of cancer, the trial may last a year or more in each patient and involve long-term follow-up to verify that clinical benefits persist over time.

Despite these complexities, the number of new medicines reaching the European public has remained fairly steady for the last ten years at around 35 per year, with the time from discovery to launch averaging 10 to 12 years over this period.

The changing face of medicines research

Despite its high level of investment and the successful flow of compounds, the European industry has been undergoing radical change over the last decade. There have been:

- Escalating costs pressure leading to mergers and takeovers;
- A major growth in inter-company collaborations in development and marketing;
- A growing reliance on biotechnological methods and compounds;
- A huge impact of computerisation in all aspects of the industry's activities;
- A quantum leap in technology for originating and screening novel compounds; and
- A dramatic focus on genomic sciences precipitated by the Human Genome Project.

While pharmaceutical companies have traditionally had long time-horizons arising from the extended process involved in getting a new medicine to market, they have had to adjust over the last two decades to a rapid and accelerating pace of environmental and technological change that has brought profound alterations in the way that they address the discovery process.

Mergers and Takeovers: For many decades, the pharmaceutical industry has been a highly fragmented one, with no individual company having more than 2-3% of the global market and a large number of small to medium-sized firms of mainly national or regional importance. This situation has changed dramatically over the last decade, in particular, with a rising number of company mergers and takeovers.

This merger and acquisition activity has been undertaken for a variety of reasons, but has typically led to a rationalisation and realignment of research, with the development of a portfolio of core areas in which the combined company aims to be a major player, both in terms of research and subsequent commercialisation. As well as having a clearer R&D focus, the combined company may be able to bring larger resources to the development of new medicines in diseases lacking satisfactory therapies than would have been possible before the merger.

Collaborations: Even large, post-merger companies cannot be equally strong in all fields, and a striking feature of industry evolution has been the considerable growth in collaborations, either between 'big pharma' companies or between such companies and specialist biotechnology and genomics companies.

These collaborations have become the norm for large pharmaceutical companies seeking to ensure a constant flow of high-potential new medicines, and may either centre around a particular active substance, or provide access to new discovery and development technologies. For example, it has been estimated that up to 30% of the compounds now in clinical development were originated by biotech firms.

Portfolio management: Increasing competitive and financial pressures on pharmaceutical companies have forced them to try to improve the efficiency of their research and development. This includes a tightening of 'portfolio management', to eliminate unpromising or 'non-core' candidate medicines before large amounts of money have been spent on developing them, and 'out-sourcing' activities that can be performed more efficiently or quickly by outside companies. In-licensing and collaborative agreements, as described above, are other ways in which companies have sought to optimise their product development pipeline.

Outsourcing has been little used in discovery research, partly to safeguard intellectual property rights, but is more commonly applied in the fields of pre-clinical research, especially toxicology research, and clinical trials. Smaller specialised service companies called Contract (sometimes Clinical) Research Organisations (CROs) have grown considerably in size and scope and now comprise an industry in their own right.

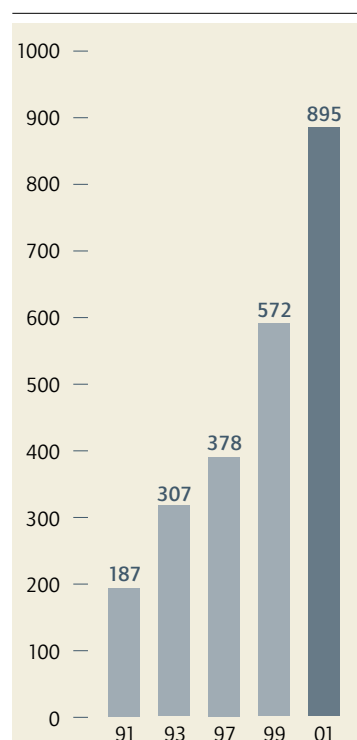
Biotechnology: Originally used to describe the manufacture of biological, as distinct from chemical, medicines, 'biotechnology' now encompasses a huge range of technologies that are used not only in medicines, but also in research and manufacturing. Although monoclonal antibodies were discovered in the early 1970s, they have only entered clinical use relatively recently, along with 'recombinant' medicines, such as hormones, cytokines, growth factors, etc.

Genetic engineering is the other aspect of biotechnology that is having an enormous impact on new medicines discovery and development. Cloning of specific cells is now common practice in pharmaceutical research aimed at selecting potential targets for new therapies, and the direct introduction of human genes for therapeutic purposes is under development in a number of diseases.

Computerisation: It would be difficult to overstate the impact that the advent of widespread computerisation has had on the medicines discovery and development process. Medicines R&D is a data-intensive process and mastering IT skills of data handling, analysis, networking and integration has never been more important. At the discovery stage, high-speed techniques, such as high-throughput screening, create huge volumes of data that require sophisticated 'data-mining' and visualisation methods to identify promising compounds. Combining these with computer-based modelling tools and other computational approaches also helps to improve the efficiency of the screening process.

During clinical development, computerisation can greatly aid the running of clinical trials, particularly where large numbers of patients are enrolled and many clinical and laboratory measurements are made, both for data-gathering and for statistical analysis of the results. Lastly, fully electronic methods have now been sanctioned for submitting applications for regulatory approval, reducing the labour of earlier paper-based systems and improving the ability of regulatory examiners to access individual patient and other data, improving regulatory scrutiny.

Combinatorial chemistry and high-throughput screening: One area of pharmaceutical R&D which would be impossible without computerisation is the large-scale generation of new 'lead' molecules through combinatorial chemistry and high-throughput screening. All of the major pharmaceutical companies have invested large amounts of time and money in developing these two techniques over the last decade, in the hope of boosting the number of compounds going into their development pipelines, and a



Note: Data have been expressed in € million at current exchange rates. Original data in \$ million: 231 (1991), 359 (1993), 429 (1997), 610 (1999), 802 (2001)

Sources: Di Masi J. et al., Tufts University, 1991; Office of Technology Assessment (OTA), 1993; Myers and Howe, 1997; Office of Health Economics & Lehman Brothers, U.K., 1999; Di Masi J., Tufts University - Center for the Study of Drug Development, 2001.

FIGURE 3: Estimated full cost of bringing a new chemical or biological entity to market (€ million)

pilot survey of 17 leading companies by the Centre for Medicines Research International in 1999 found that they accounted for over 50% of all spending on new discovery technologies (FIGURE 3).

Combinatorial chemistry is a method of synthesising groups of compounds (called 'libraries') in parallel, using specially designed machines, rather than one-by-one as in traditional medicinal chemistry approaches. Synthesis is often carried out using solid phase techniques, originally developed for the production of polypeptides, and quickly generates huge numbers of new compounds (FIGURE 4). Typical library sizes vary from 10,000 to 500,000 compounds and these libraries are tested by high-throughput screening methods to identify compounds with activities that would make them useful as candidate medicines.

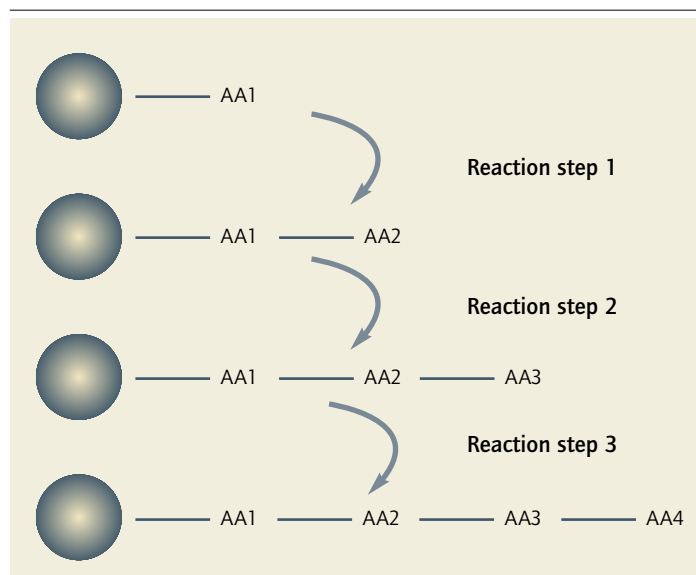


FIGURE 4: The principle of solid phase synthesis, illustrated for combinations of the 23 naturally occurring amino acids (AAs). Starting with all 23 "AA1" monomers and reacting these in parallel at each of three stages with all 23 AAs, gives a 'library' containing $23 \times 23 \times 23 \times 23$ (=279,841) possible combinations. Combinatorial techniques allow chemistries other than sequential coupling of AAs and can generate large numbers of variant compounds for screening.

High-throughput screening (HTS) methods now have the capacity to test as many as 100,000 compounds in a day, thanks to automation and miniaturisation, and are thus fully capable of analysing in a short time the enormous libraries produced by combinatorial chemistry. HTS methods generate enormous quantities of data that can only be managed by using sophisticated data storage and computerised analysis techniques.

While combinatorial chemistry and high-throughput screening are still relatively recent innovations, the first candidate medicines to emerge from these programmes are beginning to make their way into clinical trials, and it will become clear over the next few years whether this high-volume approach to medicines discovery does, indeed, increase the number of viable new medicines at an affordable cost, as compared with more traditional techniques.

Genomics, post-Genomics and Proteomics: Perhaps the most important scientific achievement of the last half-century is the completion of a draft sequence of the entire human genome. The impact that the availability of this sequence is going to have on medicines research is only beginning to be realised, but there is little doubt that it is going to be profound. For example, all the medicines currently available target a total of about 500 gene products, but the sequencing of the genome is yielding information about some 60,000 to 80,000 potential targets, greatly expanding the scope for medicines research.

The genome, or genetic library, of individual genes, spread over 23 pairs of chromosomes in the nucleus of each human cell, is the instruction manual from which an individual is built. It governs not just the nature of the cells produced, but also how they are organised into body structures such as limbs and organs. In a growing cell, each individual blueprint (gene) in the library in the cell nucleus is, when needed, read out into a working copy called messenger RNA that is used as a template for making a required protein. It is these proteins that carry out the functions of the cell, by acting as cell surface receptors (that enable the cell to respond to the outside environment), enzymes (that synthesise other cell components such as carbohydrates and lipids) and other structural and functional elements.

It has been known for some time that certain diseases (e.g., Cystic Fibrosis, alpha1-antitrypsin deficiency, Huntington's chorea and Duchenne muscular dystrophy) are caused by one or more mutations in a single gene. In the most extreme case, a mutation that alters a single nucleotide base letter in the DNA of the gene may be enough to cause disease (as in sickle cell anaemia), but more often, several changes are

involved (for example, three letters are missing in the case of cystic fibrosis). Gene therapies hold out the promise of treating, or even curing, some single-gene diseases. Single-gene diseases are, however, relatively rare. Much more common are diseases in which multiple genes are involved. Here, a gene mutation may 'predispose' an individual to a particular illness rather than cause it directly. Examples are some forms of cancer, osteoporosis, rheumatoid arthritis and schizophrenia.

It is common for single-letter variations in genes (called *single nucleotide polymorphisms* or SNPs) to occur between different people. While these do not necessarily directly cause any specific disease, they may contribute to disease susceptibility, particularly in combination with environmental factors, and they may affect an individual's response (both positive and negative) to a medication. In April 1999, 11 major companies joined forces with academic institutions and foundations in an initiative to map these (an estimated 300,000) SNPs on the human genome, placing the results in the public domain for use by medical researchers and others. This was called the SNP Consortium. Until today, more than 1.8 million SNPs have been found, much more than anticipated.

One of the major surprises of the Human Genome Project was the realisation that the entire human genome contains only about 35,000 individual genes – a considerably smaller number than originally thought. By contrast, the human proteome – the total collection of proteins that can be made by the genetic information in the genome – is thought to number 160,000 or more. As proteins can act on other proteins and bring about changes known as 'post-translational modifications', the actual number of different proteins expressed is thought to be in the region of a million. Proteins, rather than genes themselves, are the targets of all the medicines in current use and to find new targets, it is necessary to identify a protein that is involved in a disease process and develop candidate medicines that will interact with it.

The sequence of a particular gene, however, merely establishes the sequence of the protein it codes for, without any information about the function of that protein. This is where yet another new skill set (proteomics) is needed, to generate information about how a protein with a given sequence will interact with other proteins and with small-molecule drug candidates. One part of this (bioinformatics) involves the use of computers to calculate the three-dimensional structure of the protein from its sequence, while other aspects examine protein interactions. For example, a research group has recently published a protein interaction map for the bacterium *Helicobacter pylori*, which causes gastric ulcers in humans, that shows over 1,200 such interactions. When it is remembered that all current antibacterial medicines target only about 15 different microbial genes, it is clear that the new information from human genomics and proteomics offers the prospect of generating many more candidates for medicines development.

A future full of opportunities...

With the new developments outlined above, it is clear that the pharmaceutical industry faces a future full of new opportunities. Medicines research has developed powerful new tools over the last decades. This brochure attempts to give a snapshot of where we stand now and what may lie in store over the next few years, but it is clear that the gene revolution and other factors are changing the picture at an ever-faster pace. For anyone contemplating joining the industry today, it is clear that the future will be full of excitement and promises to bring major advances in treating disease. A specific aim for the industry is to encourage a partnership approach, embracing politicians, medical professionals, medical charities, patients and patient support groups and the wider biomedical community. By adopting such a joint approach, society will be better equipped to make the difficult choices which we will all face as we move further into the 21st century.

