1

Pharmaceuticals, biologics and biopharmaceuticals

1.1 Introduction to pharmaceutical products

Pharmaceutical substances form the backbone of modern medicinal therapy. Most traditional pharmaceuticals are low molecular weight organic chemicals (Table 1.1). Although some (e.g. aspirin) were originally isolated from biological sources, most are now manufactured by direct chemical synthesis. Two types of manufacturing company thus comprise the 'traditional' pharmaceutical sector: the chemical synthesis plants, which manufacture the raw chemical ingredients in bulk quantities, and the finished product pharmaceutical facilities, which purchase these raw bulk ingredients, formulate them into final pharmaceutical products, and supply these products to the end user.

In addition to chemical-based drugs, a range of pharmaceutical substances (e.g. hormones and blood products) are produced by/extracted from biological sources. Such products, some major examples of which are listed in Table 1.2, may thus be described as products of biotechnology. In some instances, categorizing pharmaceuticals as products of biotechnology or chemical synthesis becomes somewhat artificial. For example, certain semi-synthetic antibiotics are produced by chemical modification of natural antibiotics produced by fermentation technology.

1.2 Biopharmaceuticals and pharmaceutical biotechnology

Terms such as 'biologic', 'biopharmaceutical' and 'products of pharmaceutical biotechnology' or 'biotechnology medicines' have now become an accepted part of the pharmaceutical literature. However, these terms are sometimes used interchangeably and can mean different things to different people.

Although it might be assumed that 'biologic' refers to any pharmaceutical product produced by biotechnological endeavour, its definition is more limited. In pharmaceutical circles, 'biologic' generally refers to medicinal products derived from blood, as well as vaccines, toxins and allergen products. 'Biotechnology' has a much broader and long-established meaning. Essentially, it refers

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Table 1.1 Some traditional pharmaceutical substances that are generally produced by direct chemical synthesis

Drug	Molecular formula	Molecular mass	Therapeutic indication
Acetaminophen (paracetamol)	$C_8H_9NO_2$	151.16	Analgesic
Ketamine	$C_{13}H_{16}C/NO$	237.74	Anaesthetic
Levamisole	$C_{11}H_{12}N_2S$	204.31	Anthelmintic
Diazoxide	C_8H_7C/N_2O_2S	230.7	Antihypertensive
Acyclovir	$C_8H_{11}N_5O_3$	225.2	Antiviral agent
Zidovudine	$C_{10}H_{13}N_5O_4$	267.2	Antiviral agent
Dexamethasone	$C_{22}H_{29}FO_5$	392.5	Anti-inflammatory and immunosuppressive agent
Misoprostol	$C_{22}H_{38}O_5$	382.5	Anti-ulcer agent
Cimetidine	$C_{10}H_{16}N_6$	252.3	Anti-ulcer agent

to the use of biological systems (e.g. cells or tissues) or biological molecules (e.g. enzymes or antibodies) for/in the manufacture of commercial products.

The term 'biopharmaceutical' was first used in the 1980s and came to describe a class of therapeutic proteins produced by modern biotechnological techniques, specifically via genetic engineering (Chapter 3) or, in the case of monoclonal antibodies, by hybridoma technology (Chapter 13). Although the majority of biopharmaceuticals or biotechnology products now approved or in development are proteins produced via genetic engineering, these terms now also encompass nucleic-acid-based, i.e. deoxyribonucleic acid (DNA)- or ribonucleic acid (RNA)-based products, and whole-cell-based products.

1.3 History of the pharmaceutical industry

The pharmaceutical industry, as we now know it, is barely 60 years old. From very modest beginnings, it has grown rapidly, reaching an estimated value of US$100 billion by the mid 1980s. Its current value is likely double or more this figure. There are well in excess of 10 000 pharmaceutical companies in existence, although only about 100 of these can claim to be of true international significance. These companies manufacture in excess of 5000 individual pharmaceutical substances used routinely in medicine.

Table 1.2 Some pharmaceuticals that were traditionally obtained by direct extraction from biological source material. Many of the protein-based pharmaceuticals mentioned are now also produced by genetic engineering

Substance	Medical application
Blood products (e.g. coagulation factors)	Treatment of blood disorders such as haemophilia A or B
Vaccines	Vaccination against various diseases
Antibodies	Passive immunization against various diseases
Insulin	Treatment of diabetes mellitus
Enzymes	Thrombolytic agents, digestive aids, debriding agents (i.e. cleansing of wounds)
Antibiotics	Treatment against various infections agents
Plant extracts (e.g. alkaloids)	Various, including pain relief

The first stages of development of the modern pharmaceutical industry can be traced back to the turn of the twentieth century. At that time (apart from folk cures), the medical community had at their disposal only four drugs that were effective in treating specific diseases:

- Digitalis (extracted from foxglove) was known to stimulate heart muscle and, hence, was used to treat various heart conditions.
- Quinine, obtained from the barks/roots of a plant (*Cinchona* genus), was used to treat malaria.
- Pecacuanha (active ingredient is a mixture of alkaloids), used for treating dysentery, was obtained from the bark/roots of the plant genus *Cephaelis.*
- Mercury, for the treatment of syphilis.

This lack of appropriate, safe and effective medicines contributed in no small way to the low life expectancy characteristic of those times.

Developments in biology (particularly the growing realization of the microbiological basis of many diseases), as well as a developing appreciation of the principles of organic chemistry, helped underpin future innovation in the fledgling pharmaceutical industry. The successful synthesis of various artificial dyes, which proved to be therapeutically useful, led to the formation of pharmaceutical/chemical companies such as Bayer and Hoechst in the late 1800s. Scientists at Bayer, for example, succeeded in synthesizing aspirin in 1895.

Despite these early advances, it was not until the 1930s that the pharmaceutical industry began to develop in earnest. The initial landmark discovery of this era was probably the discovery, and chemical synthesis, of the sulfa drugs. These are a group of related molecules derived from the red dye *prontosil rubrum*. These drugs proved effective in the treatment of a wide variety of bacterial infections (Figure 1.1). Although it was first used therapeutically in the early 1920s, large-scale industrial production of insulin also commenced in the 1930s.

The medical success of these drugs gave new emphasis to the pharmaceutical industry, which was boosted further by the commencement of industrial-scale penicillin manufacture in the early 1940s. Around this time, many of the current leading pharmaceutical companies (or their forerunners) were founded. Examples include Ciba Geigy, Eli Lilly, Wellcome, Glaxo and Roche. Over the next two to three decades, these companies developed drugs such as tetracyclines, corticosteroids, oral contraceptives, antidepressants and many more. Most of these pharmaceutical substances are manufactured by direct chemical synthesis.

1.4 The age of biopharmaceuticals

Biomedical research continues to broaden our understanding of the molecular mechanisms underlining both health and disease. Research undertaken since the 1950s has pinpointed a host of proteins produced naturally in the body that have obvious therapeutic applications. Examples include the interferons and interleukins (which regulate the immune response), growth factors, such as erythropoietin (EPO; which stimulates red blood cell production), and neurotrophic factors (which regulate the development and maintenance of neural tissue).

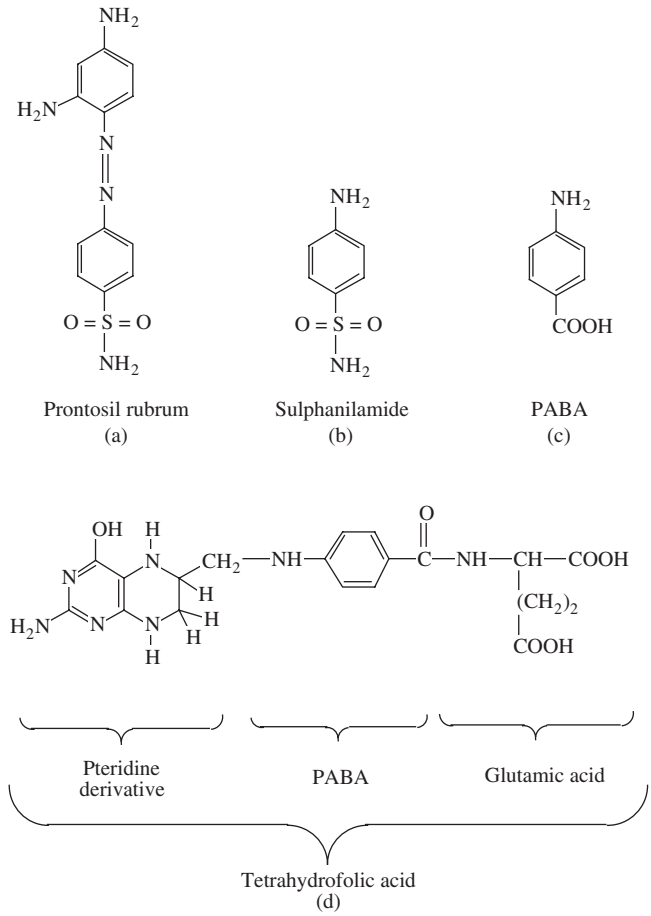

Figure 1.1 Sulfa drugs and their mode of action. The first sulfa drug to be used medically was the red dye prontosil rubrum (a). In the early 1930s, experiments illustrated that the administration of this dye to mice infected with haemolytic streptococci prevented the death of the mice. This drug, although effective *in vivo*, was devoid of *in vitro* antibacterial activity. It was first used clinically in 1935 under the name Streptozon. It was subsequently shown that prontosil rubrum was enzymatically reduced by the liver, forming sulfanilamide, the actual active antimicrobial agent (b). Sulfanilamide induces its effect by acting as an anti-metabolite with respect to *para*-aminobenzoic acid (PABA) (c). PABA is an essential component of tetrahydrofolic acid (THF) (d). THF serves as an essential cofactor for several cellular enzymes. Sulfanilamide (at sufficiently high concentrations) inhibits manufacture of THF by competing with PABA. This effectively inhibits essential THF-dependent enzyme reactions within the cell. Unlike humans, who can derive folates from their diets, most bacteria must synthesize it *de novo,* as they cannot absorb it intact from their surroundings

Although the pharmaceutical potential of these regulatory molecules was generally appreciated, their widespread medical application was in most cases rendered impractical due to the tiny quantities in which they were naturally produced. The advent of recombinant DNA technology (genetic engineering) and monoclonal antibody technology (hybridoma technology) overcame many such difficulties, and marked the beginning of a new era of the pharmaceutical sciences.

Recombinant DNA technology has had a fourfold positive impact upon the production of pharmaceutically important proteins:

- *It overcomes the problem of source availability.* Many proteins of therapeutic potential are produced naturally in the body in minute quantities. Examples include interferons (Chapter 8), interleukins (Chapter 9) and colony-stimulating factors (CSFs; Chapter 10). This rendered impractical their direct extraction from native source material in quantities sufficient to meet likely clinical demand. Recombinant production (Chapters 3 and 5) allows the manufacture of any protein in whatever quantity it is required.

- *It overcomes problems of product safety.* Direct extraction of product from some native biological sources has, in the past, led to the unwitting transmission of disease. Examples include the transmission of blood-borne pathogens such as hepatitis B and C and human immunodeficiency virus (HIV) via infected blood products and the transmission of Creutzfeldt–Jakob disease to persons receiving human growth hormone (GH) preparations derived from human pituitaries.

- *It provides an alternative to direct extraction from inappropriate/dangerous source material.* A number of therapeutic proteins have traditionally been extracted from human urine. Follicle-stimulating hormone (FSH), the fertility hormone, for example, is obtained from the urine of post-menopausal women, and a related hormone, human chorionic gonadotrophin (hCG), is extracted from the urine of pregnant women (Chapter 11). Urine is not considered a particularly desirable source of pharmaceutical products. Although several products obtained from this source remain on the market, recombinant forms have now also been approved. Other potential biopharmaceuticals are produced naturally in downright dangerous sources. Ancrod, for example, is a protein displaying anti-coagulant activity (Chapter 12) and, hence, is of potential clinical use. It is, however, produced naturally by the Malaysian pit viper. Although retrieval by milking snake venom is possible, and indeed may be quite an exciting procedure, recombinant production in less dangerous organisms, such as *Escherichia coli* or *Saccharomycese cerevisiae*, would be considered preferable by most.

- *It facilitates the generation of engineered therapeutic proteins displaying some clinical advantage over the native protein product.* Techniques such as site-directed mutagenesis facilitate the logical introduction of predefined changes in a protein's amino acid sequence. Such changes can be as minimal as the insertion, deletion or alteration of a single amino acid residue, or can be more substantial (e.g. the alteration/deletion of an entire domain, or the generation of a novel hybrid protein). Such changes can be made for a number of reasons, and several engineered products have now gained marketing approval. An overview summary of some engineered product types now on the market is provided in Table 1.3. These and other examples will be discussed in subsequent chapters.

Despite the undoubted advantages of recombinant production, it remains the case that many protein-based products extracted directly from native source material remain on the market. In certain circumstances, direct extraction of native source material can prove equally/more attractive than recombinant production. This may be for an economic reason if, for example, the protein is produced in very large quantities by the native source and is easy to extract/purify, e.g. human serum albumin (HSA; Chapter 12). Also, some blood factor preparations purified from donor blood actually contain several different blood factors and, hence, can be used to treat several haemophilia patient types. Recombinant blood factor preparations, on the other hand, contain but a single blood factor and, hence, can be used to treat only one haemophilia type (Chapter 12).

The advent of genetic engineering and monoclonal antibody technology underpinned the establishment of literally hundreds of start-up biopharmaceutical (biotechnology) companies in

Table 1.3 Selected engineered biopharmaceutical types/products that have now gained marketing approval. These and additional such products will be discussed in detail in subsequent chapters

Product description/type	Alteration introduced	Rationale
Faster acting insulins (Chapter 11)	Modified amino acid sequence	Generation of faster acting insulin
Slow acting insulins (Chapter 11)	Modified amino acid sequence	Generation of slow acting insulin
Modified tissue plasminogen activator (tPA; Chapter 12)	Removal of three of the five native domains of tPA	Generation of a faster acting thrombolytic (clot degrading) agent
Modified blood factor VIII (Chapter 12)	Deletion of 1 domain of native factor VIII	Production of a lower molecular mass product
Chimaeric/humanized antibodies (Chapter 13)	Replacement of most/virtually all of the murine amino acid sequences with sequences found in human antibodies	Greatly reduced/eliminated immunogenicity. Ability to activate human effector functions
'Ontak', a fusion protein (Chapter 9)	Fusion protein consisting of the diphtheria toxin linked to interleukin-2 (IL-2)	Targets toxin selectively to cells expressing an IL-2 receptor

the late 1970s and early 1980s. The bulk of these companies were founded in the USA, with smaller numbers of start-ups emanating from Europe and other world regions.

Many of these fledgling companies were founded by academics/technical experts who sought to take commercial advantage of developments in the biotechnological arena. These companies were largely financed by speculative monies attracted by the hype associated with the establishment of the modern biotech era. Although most of these early companies displayed significant technical expertise, the vast majority lacked experience in the practicalities of the drug development process (Chapter 4). Most of the well-established large pharmaceutical companies, on the other hand, were slow to invest heavily in biotech research and development. However, as the actual and potential therapeutic significance of biopharmaceuticals became evident, many of these companies did diversify into this area. Most either purchased small, established biopharmaceutical concerns or formed strategic alliances with them. An example was the long-term alliance formed by Genentech (see later) and the well-

Table 1.4 Pharmaceutical companies who manufacture and/or market biopharmaceutical products approved for general medical use in the USA and EU

Sanofi-Aventis	Hoechst AG
Bayer	Wyeth
Novo Nordisk	Genzyme
Isis Pharmaceuticals	Abbott
Genentech	Roche
Centocor	Novartis
Boehringer Manheim	Serono
Galenus Manheim	Organon
Eli Lilly	Amgen
Ortho Biotech	GlaxoSmithKline
Schering Plough	Cytogen
Hoffman-la-Roche	Immunomedics
Chiron	Biogen

established pharmaceutical company Eli Lilly. Genentech developed recombinant human insulin, which was then marketed by Eli Lilly under the trade name Humulin. The merger of biotech capability with pharmaceutical experience helped accelerate development of the biopharmaceutical sector.

Many of the earlier biopharmaceutical companies no longer exist. The overall level of speculative finance available was not sufficient to sustain them all long term (it can take 6–10 years and US$800 million to develop a single drug; Chapter 4). Furthermore, the promise and hype of biotechnology sometimes exceeded its ability actually to deliver a final product. Some biopharmaceutical substances showed little efficacy in treating their target condition, and/or exhibited unacceptable side effects. Mergers and acquisitions also led to the disappearance of several biopharmaceutical concerns. Table 1.4 lists many of the major pharmaceutical concerns which now manufacture/market biopharmaceuticals approved for general medical use. Box 1.1 provides a profile of three well-established dedicated biopharmaceutical companies.

Box 1.1

Amgen, Biogen and Genentech

Amgen, Biogen and Genentech represent three pioneering biopharmaceutical companies that still remain in business.

Founded in the 1980s as AMGen (Applied Molecular Genetics), Amgen now employs over 9000 people worldwide, making it one of the largest dedicated biotechnology companies in existence. Its headquarters are situated in Thousand Oaks, California, although it has research, manufacturing, distribution and sales facilities worldwide. Company activities focus upon developing novel (mainly protein) therapeutics for application in oncology, inflammation, bone disease, neurology, metabolism and nephrology. By mid 2006, seven of its recombinant products had been approved for general medical use (the EPO-based products 'Aranesp' and 'Epogen' (Chapter 10), the CSF-based products 'Neupogen' and 'Neulasta' (Chapter 10), as well as the interleukin-1 (IL-1) receptor antagonist 'Kineret', the anti-rheumatoid arthritis fusion protein Enbrel (Chapter 9) and the keratinocyte growth factor 'Kepivance', indicated for the treatment of severe oral mucositis. Total product sales for 2004 reached US$9.9 billion. In July 2002, Amgen acquired Immunex Corporation, another dedicated biopharmaceutical company founded in Seattle in the early 1980s.

Biogen was founded in Geneva, Switzerland, in 1978 by a group of leading molecular biologists. Currently, its global headquarters are located in Cambridge, MA, and it employs in excess of 2000 people worldwide. The company developed and directly markets the interferon-based product 'Avonex' (Chapter 8), but also generates revenues from sales of other Biogen-discovered products that are licensed to various other pharmaceutical companies. These include Schering Plough's 'Intron A' (Chapter 8) and a number of hepatitis B-based vaccines sold by SmithKline Beecham (SKB) and Merck (Chapter 13).

Genentech was founded in 1976 by scientist Herbert Boyer and the venture capitalist Robert Swanson. Headquartered in San Francisco, it employs almost 5000 staff worldwide and has 10 protein-based products on the market. These include hGHs (Nutropin, Chapter 11), the antibody-based products 'Herceptin' and 'Rituxan' (Chapter 13) and the thrombolytic agents 'Activase' and 'TNKase' (Chapter 12). The company also has 20 or so products in clinical trials. In 2004, it generated some US$4.6 billion in revenues.

1.5 Biopharmaceuticals: current status and future prospects

Approximately one in every four new drugs now coming on the market is a biopharmaceutical. By mid 2006, some 160 biopharmaceutical products had gained marketing approval in the USA and/or EU. Collectively, these represent a global biopharmaceutical market in the region of US$35 billion (Table 1.5), and the market value is estimated to surpass US$50 billion by 2010. The products include a range of hormones, blood factors and thrombolytic agents, as well as vaccines and monoclonal antibodies (Table 1.6). All but two are protein-based therapeutic agents. The exceptions are two nucleic-acid-based products: 'Vitravene', an antisense oligonucleotide, and 'Macugen', an aptamer (Chapter 14). Many additional nucleic-acid-based products for use in gene therapy or antisense technology are in clinical trials, although the range of technical difficulties that still beset this class of therapeutics will ensure that protein-based products will overwhelmingly predominate for the foreseeable future (Chapter 14).

Many of the initial biopharmaceuticals approved were simple replacement proteins (e.g. blood factors and human insulin). The ability to alter the amino acid sequence of a protein logically coupled to an increased understanding of the relationship between protein structure and function (Chapters 2 and 3) has facilitated the more recent introduction of several engineered therapeutic proteins (Table 1.3). Thus far, the vast majority of approved recombinant proteins have been produced in the bacterium *E. coli*, the yeast *S. cerevisiae* or in animal cell lines (most notably Chinese hamster ovary (CHO) cells or baby hamster kidney (BHK) cells. These production systems are discussed in Chapter 5.

Although most biopharmaceuticals approved to date are intended for human use, a number of products destined for veterinary application have also come on the market. One early such example is that of recombinant bovine GH (Somatotrophin), which was approved in the USA in the early 1990s and used to increase milk yields from dairy cattle. Additional examples of approved veterinary biopharmaceuticals include a range of recombinant vaccines and an interferon-based product (Table 1.7).

Table 1.5 Approximate annual market values of some leading approved biopharmaceutical products. Data gathered from various sources, including company home pages, annual reports and industry reports

Product (Company)	Product description (use)	Annual sales value (US$, billions)
Procrit (Amgen/Johnson & Johnson)	EPO (treatment of anaemia)	4.0
Epogen & Aranesp combined (Amgen)	EPO (treatment of anaemia)	4.0
Intron A (Schering Plough)	IFN-α (treatment of leukaemia)	0.3
Remicade (Johnson & Johnson)	Monoclonal antibody based (treatment of Crohn's disease)	1.7
Avonex (Biogen)	Interferon-β (IFN-β; treatment of multiple sclerosis)	1.2
Embrel (Wyeth)	Monoclonal antibody based (treatment of rheumatoid arthritis)	1.3
Rituxan (Genentech)	Monoclonal antibody based (non-Hodgkin's lymphoma)	1.5
Humulin (Eli Lilly)	Insulin (diabetes)	1.0

Table 1.6 Summary categorization of biopharmaceuticals approved for general medical use in the EU and/or USA by 2006

Product type	Examples	No. approved	Refer to
Blood factors	Factors VIII and IX	8	Chapter 12
Thrombolytic agents	tPA	6	Chapter 12
Hormones	Insulin, GH, gonadotrophins	33	Chapter 11
Haematopoietic growth factors	EPO, CSFs	8	Chapter 10
Interferons	IFN-α, -β, -γ	16	Chapter 8
Interleukin-based products	IL-2	3	Chapter 9
Vaccines	Hepatitis B-surface antigen	20	Chapter 13
Monoclonal antibodies	Various	30	Chapter 13
Nucleic acid based	Antisense and aptamer	2	Chapter 14
Additional products	Tumour necrosis factor (TNF), therapeutic enzymes	18	Various chapters

At least 1000 potential biopharmaceuticals are currently being evaluated in clinical trials, although the majority of these are in early stage trials. Vaccines and monoclonal antibody-based products represent the two biggest product categories. Regulatory factors (e.g. hormones and

Table 1.7 Some recombinant (r) biopharmaceuticals recently approved for veterinary application in the EU

Product	Company	Indication
Vibragen Omega (r-feline interferon omega; IFN-ω)	Virbac	Reduction of mortality/clinical symptoms associated with canine parvovirus
Fevaxyl Pentafel (combination vaccine containing r-feline leukaemia viral antigen as one component)	Fort Dodge Laboratories	Immunization of cats against various feline pathogens
Porcilis porcoli (combination vaccine containing r-*E. coli* adhesins)	Intervet	Active immunization of sows
Porcilis AR-T DF (combination vaccine containing a recombinant modified toxin from *Pasteurella multocida*)	Intervet	Reduction in clinical signs of progressive atrophic rhinitis in piglets
Porcilis pesti (combination vaccine containing r-classical swine fever virus E_2 subunit antigen)	Intervet	Immunization of pigs against classical swine fever
Bayovac CSF E2 (combination vaccine containing r-classical swine fever virus E_2 subunit antigen)	Intervet	Immunization of pigs against classical swine fever

cytokines) and gene therapy and antisense-based products also represent significant groupings. Although most protein-based products likely to gain marketing approval over the next 2–3 years will be produced in engineered *E. coli*, *S. cerevisiae* or animal cell lines, some products now in clinical trials are being produced in the milk of transgenic animals (Chapter 5). Additionally, plant-based transgenic expression systems may potentially come to the fore, particularly for the production of oral vaccines (Chapter 5).

Interestingly, the first generic biopharmaceuticals are already entering the market. Patent protection for many first-generation biopharmaceuticals (including recombinant human GH (rhGH), insulin, EPO, interferon-α (IFN-α) and granulocyte-CSF (G-CSF)) has now/is now coming to an end. Most of these drugs command an overall annual market value in excess of US$1 billion, rendering them attractive potential products for many biotechnology/pharmaceutical companies. Companies already/soon producing generic biopharmaceuticals include Biopartners (Switzerland), Genemedix (UK), Sicor and Ivax (USA), Congene and Microbix (Canada) and BioGenerix (Germany). Genemedix, for example, secured approval for sale of a recombinant CSF in China in 2001 and is also commencing the manufacture of recombinant EPO. Sicor currently markets hGH and IFN-α in eastern Europe and various developing nations. A generic hGH also gained approval in both Europe and the USA in 2006.

To date (mid 2006), no gene-therapy-based product has thus far been approved for general medical use in the EU or USA, although one such product ('Gendicine'; Chapter 14) has been approved in China. Although gene therapy trials were initiated as far back as 1989, the results have been disappointing. Many technical difficulties remain in relation to, for example, gene delivery and regulation of expression. Product effectiveness was not apparent in the majority of trials undertaken and safety concerns have been raised in several trials.

Only one antisense-based product has been approved to date (in 1998) and, although several such antisense agents continue to be clinically evaluated, it is unlikely that a large number of such products will be approved over the next 3–4 years. Aptamers represent an additional emerging class of nucleic-acid-based therapeutic. These are short DNA- or RNA-based sequences that adopt a specific three-dimensional structure, enabling them to bind (and thereby inhibit) specific target molecules. One such product (Macugen) has been approved to date. RNA interference (RNAi) represents a yet additional mechanism of achieving downregulation of gene expression (Chapter 14). It shares many characteristics with antisense technology and, like antisense, provides a potential means of treating medical conditions triggered or exacerbated by the inappropriate overexpression of specific gene products. Despite the disappointing results thus far generated by nucleic-acid-based products, future technical advances will almost certainly ensure the approval of gene therapy and antisense-based products in the intermediate to longer term future.

Technological developments in areas such as genomics, proteomics and high-throughput screening are also beginning to impact significantly upon the early stages of drug development (Chapter 4). By linking changes in gene/protein expression to various disease states, for example, these technologies will identify new drug targets for such diseases. Many/most such targets will themselves be proteins, and drugs will be designed/developed specifically to interact with. They may be protein based or (more often) low molecular mass ligands.

Additional future innovations likely to impact upon pharmaceutical biotechnology include the development of alternative product production systems, alternative methods of delivery and the development of engineered cell-based therapies, particularly stem cell therapy. As mentioned previously, protein-based biotechnology products produced to date are produced in either microbial

or in animal cell lines. Work continues on the production of such products in transgenic-based production systems, specifically either transgenic plants or animals (Chapter 5).

Virtually all therapeutic proteins must enter the blood in order to promote a therapeutic effect. Such products must usually be administered parenterally. However, research continues on the development of non-parenteral routes which may prove more convenient, less costly and obtain improved patient compliance. Alternative potential delivery routes include transdermal, nasal, oral and bucal approaches, although most progress to date has been recorded with pulmonary-based delivery systems (Chapter 4). An inhaled insulin product ('Exubera', Chapters 4 and 11) was approved in 2006 for the treatment of type I and II diabetes.

A small number of whole-cell-based therapeutic products have also been approved to date (Chapter 14). All contain mature, fully differentiated cells extracted from a native biological source. Improved techniques now allow the harvest of embryonic and, indeed, adult stem cells, bringing the development of stem-cell-based drugs one step closer. However, the use of stem cells to replace human cells or even entire tissues/organs remains a long term goal (Chapter 14). Overall, therefore, products of pharmaceutical biotechnology play an important role in the clinic and are likely to assume an even greater relative importance in the future.

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