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INTRODUCTION TO BIOPHARMACEUTICALS

Biopharmaceuticals, otherwise known as the application of biomolecules as therapeutic products, have benefited from advances in the study of biology and biological interactions of simple and complex organisms including prokaryotes, eukaryotes, and mammalian systems. Basic discoveries and a greater understanding of biochemistry and biophysics have shed light on the abnormalities of the highly coordinated biological systems in humans that are related to disease symptoms. These discoveries have allowed for innovations to be made in the design and development of biopharmaceuticals for treating a wide range of human diseases. While biotechnology today is synonymous with advanced technologies, the technology of using biological molecules as therapeutics has been in existence since the 1800s. Ever since elucidating that the human body is composed of specialized cells and proteins, exponential advances have provided enabling technologies that consistently produce high-quality proteins, antibodies, and peptides for pharmaceutical applications. Continued refinement and optimization of the production of recombinant macromolecules—enzymes, growth hormones, vaccines, and monoclonal antibodies—have fueled, and will continue to fuel, the growth and influence in overall drug development. When this text was first published in 2003, only a handful of biopharmaceuticals reached US $1 billion in annual sales. At the time of writing this second edition, the top-selling biopharmaceuticals reached US $7.3 billion, and the top 25 biopharmaceutical products generated US $74.7 billion in 2010. With over 200 biopharmaceutical products on the market, these achievements were possible because of the outstanding contribution of scientists and clinicians and their collective efforts to collaborate and integrate innovations into novel therapeutic products. This chapter defines the differences between small-molecule or traditional drugs and biologics or biotherapeutics—proteins, peptides, and biological materials—that are much larger molecules. A small change at the atomic level for a small-molecule drug typically leads to a new drug with a unique set of therapeutic and side effects, whereas a modification of amino acids (with multiple atomic modifications) on protein-based biotherapeutics, such as insulin and hepatitis B vaccine, retains a very similar therapeutic profile and clinical application. This chapter introduces in an easy-to-read level the growth in new biopharmaceuticals reaching the market, their therapeutic importance, and their overall contribution to health care. It is intended for students, health professionals, legislators, decision makers, and pharmaceutical researchers who want to learn about the science and business of biotechnology and its role in transforming biological discoveries into therapeutic products.

Biotechnology and Biopharmaceuticals: Transforming Proteins and Genes into Drugs, Second Edition. Rodney J. Y. Ho.

1.1. BACKGROUND AND SIGNIFICANCE

For most people, *biotechnology* is synonymous with "*high-technology* or *advanced technology*". However, the idea to use technology or products derived from biological molecules and processes for disease treatment is not new. Even before the discovery that the human body is composed of cells and proteins, humans were constantly being challenged by invading pathogenic microbes and other deadly infections. These real and perceived battlefields of disease necessitated innovations for developing curative medicines—biologically active therapeutic products now recognized as biopharmaceuticals. While biotechnology today is seen as the cutting edge of life sciences, the use of biological molecules as therapeutic agents or biologics has existed since the 1800s. In fact, the word *biotechnology* can be traced back to the 1919 writing of Kark Erely in his 84-page publication entitled, "*Biotechnologie der Fleisch-, Fett- und Milcherzeugung im landwirtschafttichen Gross-betrieb*" (Bud 1989). The coining of the term *biotechnologie* or "biotechnology" by Erely was likely intended to describe the interaction of biology with technology, thus essentially implying inclusion of all biological and related technologies in product transformation. Today, the therapeutic products of biotechnologies, which are referred to as *biologics* or *biopharmaceuticals*, are central in providing hope and in making advances for treating human diseases ranging from infections, diabetes, and immune disorders to cancers. Biopharmaceuticals are derived from peptides and proteins, which are often referred to as *biologics*, *biomolecules*, *biotherapeutics*, *macromolecules*, and *protein therapeutics*. In this book, we will use these terms interchangeably when referring to biopharmaceuticals.

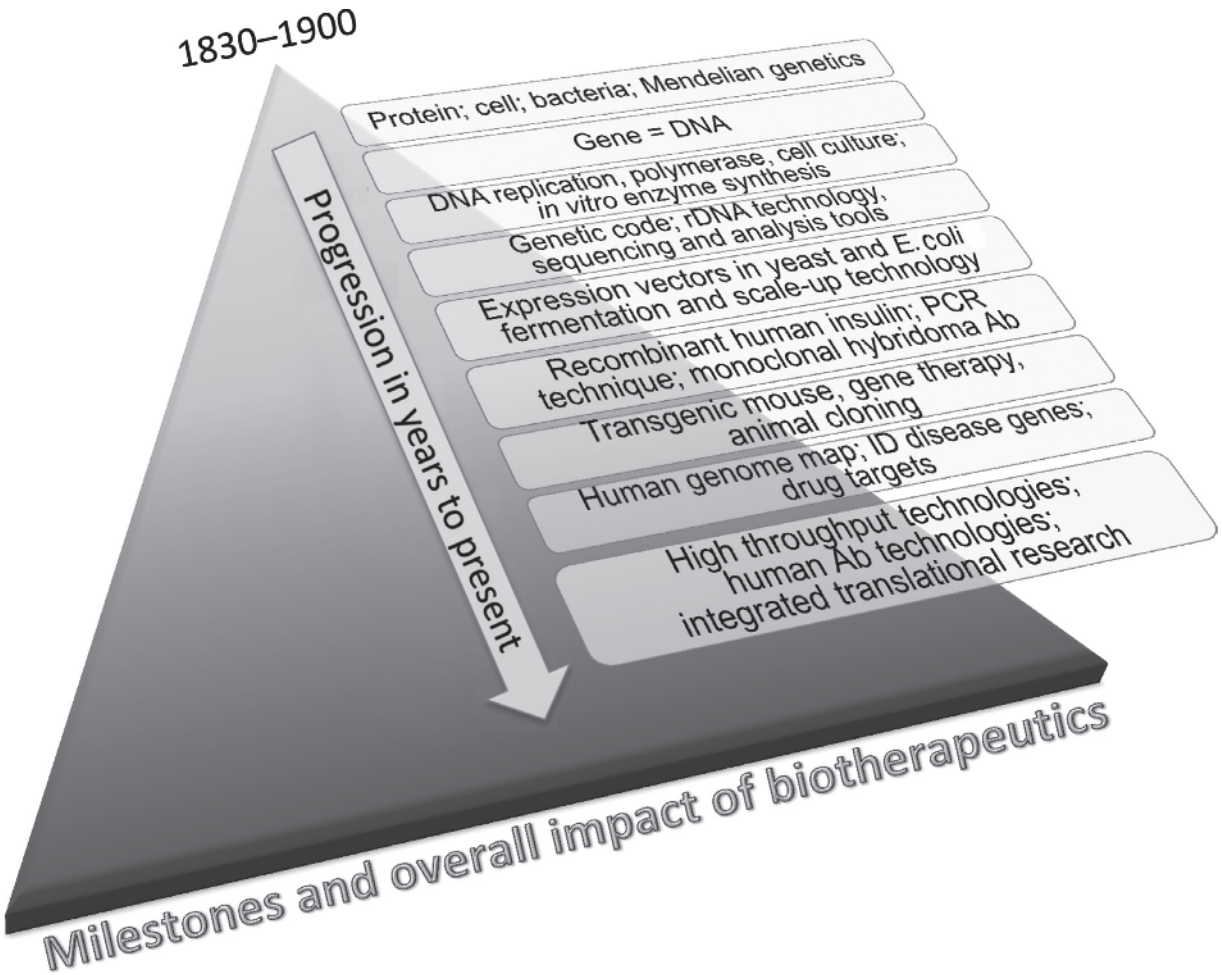

Figure 1.1. Time progression of milestones and overall impact on translation of biological molecules into therapeutic products. The discovery of protein, cell, bacteria, and Mendelian genetics in 1830–1900, and the innovative milestones in modern genetics and molecular engineering, provided the basis for exponential growth in the ability to identify, validate, and produce biological molecules for therapeutic applications. The accumulation and expansion of impact is represented on the x-axis. For color detail, please see color plate section.

The transformation of basic biological processes and endogenous proteins to biopharmaceuticals that treat disease and provide cures requires integration of scientific discovery and ingenuity into product development. The synthesis of biopharmaceuticals—proteins, peptides, and genetic materials— at a quality and quantity suitable for therapeutic use is a recent achievement. Some of the milestones and innovations pivotal to therapeutic achievements are highlighted in Figure 1.1. Clearly, basic knowledge about the DNA and the genetic code, different cells that make up tissues and organs, and protein synthesis and cellular mechanisms provided the foundation for exponential growth in biotechnology. Some of the significant biotechnology milestones and innovations are (1) recombinant DNA technology (procedures that join together, or recombine, DNA segments) to produce human protein in foreign host cells (Cohen, Chang et al. 1973); (2) cell and fermentation technologies for large-scale protein production (Goeddel 1990); and (3) monoclonal antibody technologies (Kohler and Milstein 1975) that provide antibody therapeutics for treating immune or other disorders and cancers. These technological milestones have enabled transformation of biomolecules into biotherapeutics, which now impact health every day. Without transformational biotechnologies, the health impacts of biotherapeutics such as proteins, antibodies, and enzymes (some of which are still available as tissue- or plasma-extracted products), would have been realized much later. Figure 1.1 also highlights the integration and potential impact due to the ever-expanding knowledge of biological processes and bioengineering. These scientific and engineering achievements have allowed development and use of protein- and antibody-based therapies that require large doses (typically in milligrams or higher amounts) to impact patient health.

Translating biotechnology innovations into therapeutic products requires investment by biopharmaceutical companies that focus on preclinical and clinical product development. While there are many entrepreneurial biotechnology start-up companies working on early-stage therapeutics, a majority of pioneering biotechnology companies, such as Genentech, Chiron, Cetus, and Immunex, that had success in developing therapeutic products, are eventually acquired by large pharmaceutical companies. This strategic acquisition of biotechnology companies has accelerated over the past 10 years. As a result, as shown in Table 1.1, Amgen is the only independent biotechnology company on the list.

TABLE 1.1. Comparison between a select list of established biotechnology and integrated biopharmaceutical companies with respect to revenue, market share, productivity, and research investments.[a]

		Revenue (2010)		R & D Expenditure	
Company	Employees	Total (in millions)	Per Employee (in thousands)	Total (in millions)	% Revenue
Biotechnology					
Amgen	17,400	14,660	843	2,888	20%
Genzyme	12,000	4,049	337	848	21%
Biogen Idec	4,850	3,470	715	1,249	36%
(Mean)		**7,393**	**632**	**1,662**	**26%**
Integrated Biopharmaceutical					
Pfizer	110,600	67,809	613	9,425	14%
Johnson & Johnson	114,000	61,587	540	6,836	11%
Novartis	99,834	50,624	507	9,062	18%
Bayer	108,400	46,530	429	6,142	13%
Merck & Co	93,000	45,987	494	10,991	24%
Roche	81,507	45,507	558	9,602	21%
GlaxoSmithKline	99,913	43,869	439	5,323	12%
Sanofi-Aventis	104,867	40,292	384	5,842	14%
Abbott	90,000	35,166	391	3,728	11%
AstraZeneca	62,700	33,269	531	5,323	16%
Eli Lilly & Co	38,350	23,076	602	4,892	21%
Bristol Meyer Squibb	27,000	19,484	722	3,566	18%
Novo Nordisk	30,483	11,297	371	1,762	16%
(Mean)		**40,346**	**506**	**6,346**	**16%**

[a] Data were collected from annual reports and sponsor's filing documents, including those reported in the Securities and Exchange Commision form F-20 or 10-K. The data reported in foreign currencies were converted from a 3-year average as follows: 1€ = US $1.33, ICHF = US $1.066, 5.38DKK = US $1.

TABLE 1.2. Top 25 biotechnology medicines based on reported worldwide sales.[a]

Product[b]	Common Name[c]	Sponsor(s)[d]	Indication(s)[e]	Annual sales (in millions)[f] 2010	2009	2008
Remicade	Infliximab	J & J; Centocor → Merck	Crohn's disease; colitis; arthritis	7,324	6,631	5,856
Enbrel	Etanercept	Amgen; Wyeth → Pfizer	RA and psoriasis	6,808	5,916	6,191
Humira	Adalimumab	Abbott	Rheumatoid and psoriatic arthritis	6,500	5,500	4,500
Avastin	Bevacizumab	Genentech → Roche	Colorectal, lung, breast, renal and brain cancer	6,061	5,837	2,908
Rituxan	Rituximab	Genentech → Roche	NHL; leukemia (CLL); RA	5,962	5,710	2,852
Herceptin	Trastuzumab	Genentech → Roche	Breast and gastric cancer	5,093	4,940	1,819
Lantus	Insulin-glargine	Sanofi-Aventis	Diabetes	4,668	4,096	3,259
Epogen; Procrit/ Eprex	Epoetin alfa	Amgen; J & J	Anemia	4,458	4,814	4,916
Novolog	Insulin-asp	Nova Nordisk	Diabetes	3,666	3,020	2,503
Neulasta	Pegfilgrastim	Amgen	Febrile neutropenia	3,558	3,355	3,318
Aranesp	Darbepoetin alfa	Amgen	Anemia	2,486	2,652	3,137
Novolin	rh-Insulin	Nova Nordisk	Diabetes	2,198	2,103	2,194
Humalog	Insulin-lispro	Eli Lilly & Co	Diabetes	2,054	1,959	1,736
Pegasys	Peginterferon alfa-2a	Roche	Hepatitis C	1,543	1,553	1,534
NovoSeven	rh-Factor VIIa	Nova Nordisk	Hemophilia A and B	1,493	1,314	1,189
Lucentis	Ranibizumab	Genentech → Roche	Macular edema and degeneration	1,368	1,124	887
Sandostatin	Octreotide acetate	Novartis	Acromegaly; carcinoid tumors; intestinal tumors	1,291	1,155	1,100
Neupogen	Filgrastim	Amgen	Febrile neutropenia	1,286	1,288	1,341
NeoRecormon	Epoetin alfa	Roche	Anemia	1,205	1,463	1,664
Humulin	rh-Insulin	Eli Lilly & Co	Diabetes	1,089	1,022	1,063
Synagis	Palivizumab	Medimmune → AstraZeneca	Prevention of respiratory syncytial virus infection	1,038	1,082	1,230
Gardasil	Quarivalent rHPV vaccine	Merck	Prevention of human papilloma virus infection	988	1,118	1,403
Norditropin	Somatropin	Nova Nordisk	Growth failure	893	818	718
Genotropin	Somatropin	Pfizer	Growth failure	885	887	989
Forteo	Teriparatide	Eli Lilly & Co	Osteoporosis	830	816	779
			Total annual sales	**74,746**	**70,174**	**59,086**

[a] Abbreviations: J & J, Johnson and Johnson; NHL, non-Hodgkin's lymphoma; rh, recombinant human product; CLL, chronic lymphocytic leukemia; RA, rheumatoid arthritis; HPV, human papilloma virus.

[b] Product of the same common name and original source were combined regardless of sponsor or marketing company for U.S. and international sales. Follow-on or bio-similar products, such as *NeoRecormon*, *Norditropin*, and *Genotropin*, are treated as separate products.

[c] Common names of the biological molecules are provided for each branded product as reference.

[d] The semicolon indicates there are more than one sponsor for the same product with an identical common name. The arrow → symbol indicates the merger/acquisition of two company sponsors.

[e] Indications or FDA-approved intended therapeutic uses were provided in an abbreviated form; please see Part II of this book for the additional details.

[f] Data were collected from annual reports and sponsor's filing documents, including those reported in the Securities and Exchange Commission form F-20 or 10-K. The data reported in foreign currencies were converted from a 3-year average as follows; 1€ = $1.33 US; 1CHF = $1.066 US; 5.38DKK = $1 US.

The other two companies, Genzyme and Biogen Idec, are part of or in the process of being integrated into large pharmaceutical companies. Table 1.1 also compares biotechnology and integrated biopharmaceutical companies and their 2010 revenue, market share, productivity as measured by revenue per employee, and investment in research and development (R&D). Although the total employee numbers are still relatively small, all of the listed biotechnology companies have grown to realize multi-billion dollar annual revenues, and their productivity is comparable to that of integrated biopharmaceutical companies ($632,000 vs. $506,000

per employee, respectively; Table 1.1). Biotechnology companies spend more than 20% (mean = 26%) of their revenue on R&D. This is well above the 11%–24% (mean = 16%) of revenue invested in R&D by integrated biopharmaceutical companies (Table 1.1). The difference is due, at least in part, to the high cost of biotechnology research and perhaps to the intellectual climate and culture at biotechnology-based companies compared to that at the more established companies.

A survey of the 25 top-selling biotechnology drugs identified 21 products that achieved nearly US $1 billion or more in revenue for two consecutive years (Table 1.2). In 1999 (Ho and Gibaldi 2003), only four products achieved this milestone, and none were above the US $2 billion mark. For 2010, the annual revenue for each of the top six products—*Remicade*, *Enbrel*, *Humira*, *Avastin*, *Rituxan*, and *Herceptin*—reached more than US $5 billion each. The top product, *Remicade*, had worldwide sales of over $7.3 billion per year (equivalent to over US $20 million per day or US $610 million in sales per month). The sponsor companies listed in Table 1.2 include most of the major pharmaceutical companies. It is also interesting to note that generic versions of biotherapeutics (follow-on biologics) such as *NeoRecormon*, *Genotropin*, and *Norditropin* also made it into the top 25 products, with annual sales reaching about US $1 billion. These follow-on biologics are marketed by integrated pharmaceutical companies. For the past 10 years, most large pharmaceutical companies with little or no biological drug development programs have become central players in the development of biotechnology products by merging and acquiring start-up and successful biotechnology companies. As a result, there are hundreds of start-up companies, but the number of independent biotechnology-based companies is diminishing. The major pharmaceutical companies, which are now referred to as integrated biopharmaceutical companies, showcase biotechnology products as their top revenue generators in their respective annual reports. In essence, biotechnology drugs not only have a significant impact on health care, but also have become pivotal to the commercial vitality and success of the pharmaceutical industry. In 2010, the top 25 biotechnology drugs generated $74.7 billion within the health-care economy.

The availability of vast amounts of biological and genomic data coupled with exponential growth in computing power means that potential drug target numbers have increased exponentially. Thus, we are no longer limited by the ability to identify targets and clone recombinant macromolecules. The focus has now shifted to linking these molecules with disease symptoms. Nevertheless, we now have more targets than we can develop into pharmaceuticals. Therefore, drug candidate selection must be refined with the experience gained in using macromolecules as therapeutic agents. We must focus on drug candidates that will be safe and effective and also have desirable clinical pharmacokinetic profiles. Compounds that exhibit high-affinity binding to receptor targets but fail to penetrate target tissue or persist long enough to produce desirable biological responses cannot be considered for development as biopharmaceuticals.

Because the rate at which new biotechnology-based pharmaceuticals reach the market is no longer inhibited by the availability of novel targets, therapeutic importance and overall health-care cost now play central roles. Therefore, it is essential for health professionals, legislators, decision makers, and pharmaceutical researchers to understand the application of biotechnology to transform biological molecules and processes into pharmaceuticals and other therapeutic modalities.

In what follows, we will define biotechnology from the perspective of pharmaceuticals and then provide a historical overview of pharmaceutical biotechnology and a discussion of how macromolecules are named and used as therapeutic agents.

1.2. TRANSLATION OF BIOTECHNOLOGY FOR DEVELOPING BIOPHARMACEUTICALS

Biotechnology, like beauty, is in the eye of the beholder: a last hope for a patient with Alzheimer's disease or cancer; an anathema to an environmentalist. Seeking a broad consensus, biotechnology is an integrated application of scientific and technical understanding of a biological molecule or process for developing a useful product. Biological processes of interest include cellular activities such as protein synthesis, DNA replication, transcription (DNA to RNA), protein processing, receptor–ligand interactions at cell surfaces, and fermentation of bacteria, yeast, and mammalian cells.

A broad definition of biotechnology includes beer and wine fermentation technology to produce distinctive beverages with commercial advantages, the identification of non-virulent variants to use as vaccines, genetic manipulation to coax bacteria to express metabolic enzymes that transform petroleum products into water-soluble forms for environmental clean-up, and the development of a recombinant, disease-resistant fruit or vegetable crop with prolonged freshness. Very often, biotechnology means commercialization of biological and life sciences by integrating discoveries from many disciplines, including microbiology, biochemistry, genetics, chemical biology, and bioengineering.

Currently, biotechnology is an integral component of many industries, in addition to pharmaceutical companies. This book will focus on the application of biotechnology to biological molecules and processes to develop pharmaceutical products or medicine and medical devices.

1.3. HISTORICAL PERSPECTIVE OF PHARMACEUTICAL BIOTECHNOLOGY

The application of biological processes to develop useful products is as old as Mendel's pea experiment, conducted in 1866 (Mendel 1950) (Figure 1.1). As a result of the experiment, Mendel developed the principles of heredity and thereby formed the basis of modern genetics. Although the addition of the word *biotechnology* to the dictionary did not occur until 1979, the fermentation technology we use today to produce recombinant proteins was first used in World War I to ferment corn starch (with the help of *Clostridium acetobutylicum*) (Weizmann and Rosenfeld 1937) and produce acetone for manufacturing explosives. Fermentation technology took on even greater importance after World War II with the development of antibiotics (Fleming 1929).

In the latter half of the 20th century, the revelation of protein structure, the elucidation of cell replication and protein synthesis, and the isolation of DNA replication enzymes, including restriction enzymes and polymerases, led to the rapid development of recombinant DNA technology. DNA replication technology in a test tube (*in vitro*) permitted cloning and expression of proteins and peptides in bacteria with much greater efficiency. This particular advance provided therapeutic candidate proteins that previously eluded efforts to isolate and harvest proteins just a few years earlier. At about the same time, in 1975, scientists developed monoclonal antibody (also known as hybridoma) technology (Kohler and Milstein 1975), which allowed for large-scale, reproducible preparation of purified, highly specific antibodies with monospecific binding sites (spanning 6–10 amino acids in length). This technology also allowed for the generation and use of monoclonal antibodies as a tool to characterize and purify proteins that would selectively bind to respective antibodies with high specificity. These tools for preparation and characterization of recombinant products have proved to be essential for developing macromolecules into therapeutic products.

The biotechnology milestones, presented in Figure 1.1, may not have by themselves permitted the rapid application of biotechnology to drug development, but in aggregate, they have led to the development of pharmaceutical products that could not have been realized without these technologies. Advances in technology make the process possible, accelerate it, or simply make products cost-effective and safer than the same material extracted from native tissues. A notable example is the development of an expression vector from a yeast plasmid (Valenzuela, Medina et al. 1982), which permitted mass production of the hepatitis B surface antigen for vaccine development and made economical manufacture of recombinant human insulin possible. Similar recombinant technology is still used today to produce recombinant papilloma virus particles (Zhou, Sun et al. 1991) as a vaccine (*Gardasil*) to prevent cervical cancer.

Almost all of the biopharmaceuticals available today are proteins or peptides. Of considerable importance among this array of products are monoclonal antibodies. These "magic bullets" became a reality with the marketing approval of *Orthoclone* (muromonab) in 1986. At present, monoclonal antibodies are the fastest growing category of biopharmaceuticals approved for therapeutic use. In fact, seven of the top-selling 2010 biotechnology drugs (with common names ending in "*mab*") are antibodies (Table 1.2). The ability to identify novel, potentially therapeutic proteins and peptides, like monoclonal antibodies, has advanced at such a rate that we are now limited by resources and the number of workers available to develop and demonstrate the clinical efficacy and safety of these candidates.

1.4. DISTINCTIONS BETWEEN CHEMICAL DRUGS VERSUS BIOPHARMACEUTICALS

Most small-molecule or chemical drugs typically exhibit a molecular weight of about 500 dalton (usually less than 1,000 dalton). Because of this small size, any chemical modification in a small-molecule drug can dramatically change its pharmacological activity and typically leads to new drugs for new uses or indications. For example, the addition of methyl groups at position 1, 3, and 7 of the natural substance xanthine produces the widely consumed compound caffeine; the addition of methyl groups at position 1 and 3 or 3 and 7 produces the bronchodilator, theophylline, or a related compound, theobromine(Figure 1.2). One would not substitute xanthine or caffeine for theophylline as a

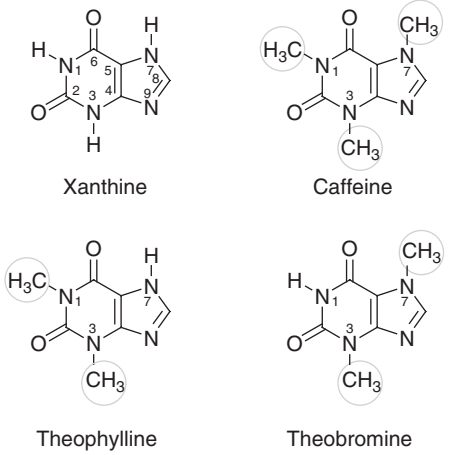

Figure 1.2. Molecular structures of xanthine, caffeine, theophylline, and theobromine. The addition of two or three methyl groups to specific locations on the natural substance xanthine can produce caffeine, theophylline, and theobromine.

bronchodilator. By the same token, the addition of a hydroxy-methyl group to the anti-herpes simplex drug acyclovir results in ganciclovir, which has anticytomegalovirus activity (Figure 1.3). Acyclovir is widely used and considered much safer for treating herpes infection and preventing herpes reactivation, whereas ganciclovir is used only to treat cytomegalovirus (which is one of the herpes viruses) reactivation and exhibits significant side effects.

One can find many more examples in which a subtle modification in a side chain leads to a new drug that produces a drastically different therapeutic or toxicological outcome. This is poignantly illustrated by the nonsedating antihistamine terfenadine (*Seldane*), which produces cardiotoxicity when given with certain drugs that inhibit its metabolism. For this reason, this product is no longer marketed, and it has been replaced by its safer but no less effective carboxylic oxidative metabolite fexofenadine (*Allegra*), which substitutes the methyl side chain with carboxylic acid (Figure 1.3). These examples clearly demonstrate that a small change—methylation, carboxylation, or hydroxylation—in a small-molecule chemical drug leads to a new chemical entity with a distinctly different therapeutic and toxicology profile.

On the other hand, biopharmaceuticals based on natural proteins and peptides are often called by the same name as the natural material despite differences in one or more amino acid residues. In other words, a small change does not lead to a new biotherapeutic product. For example, insulin, which is used to treat diabetes, has several variants that are approved for human use. Insulin contains two A and B polypeptide chains linked together by two disulfide bridges to assume a biologically active conformation (Figure 1.4). Compared with endogenous or recombinant human insulin, insulin extracted from beef tissue exhibits threonine→alanine and isoleucine→valine substitutions at positions 8 and 10 of the insulin A chain, respectively, whereas insulin extracted from pork tissue contains a threonine→alanine substitution at position 30 of the insulin B chain (Table 1.3). Yet, both pork and beef insulins have been used successfully to treat diabetes. Although trade names may differ, all the insulins, including those that are modified to produce more desirable pharmacokinetic and disposition profiles, such as insulin-lispro, insulin-glargine, insulin-glulisine, and insulin-aspart, are still known as insulins by physicians and researchers alike. All of these variants of insulin are used for the same treatment indication—to control blood glucose—and are efficacious as long as the dose and dosing frequency are determined on a product-by-product basis.

The same name is also used for some vaccines that differ in potency. As shown in Table 1.4, the two approved vaccines against hepatitis B, *Recombivax HB* and *Engerix-B*, are both known as (recombinant) hepatitis B vaccine. However, the dose and volume required to produce a satisfactory immune response are different for each product and age group. Despite these differences, physicians use the two vaccines interchangeably. The difference in dose between the two may be due to sequence and production variations of the recombinant proteins used to prepare the vaccines. When used as directed, the vaccines are therapeutically equivalent in terms of their ability to induce antibodies that protect vaccinated individuals from hepatitis B virus infection.

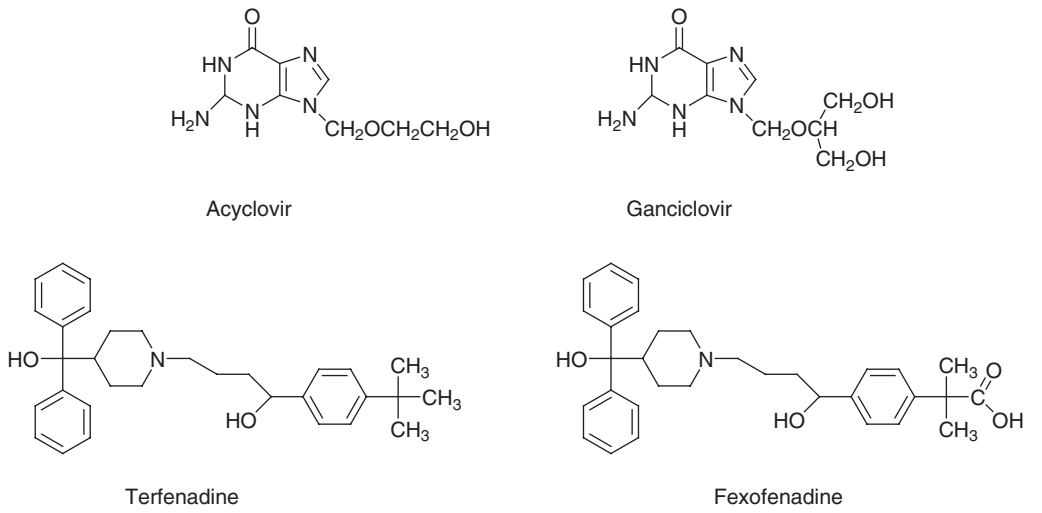

Figure 1.3. Molecular structures of acyclovir, ganciclovir, fexofenadine, and terfenadine. Modification of a side chain changes acyclovir to ganciclovir and terfenadine to fexofenadine.

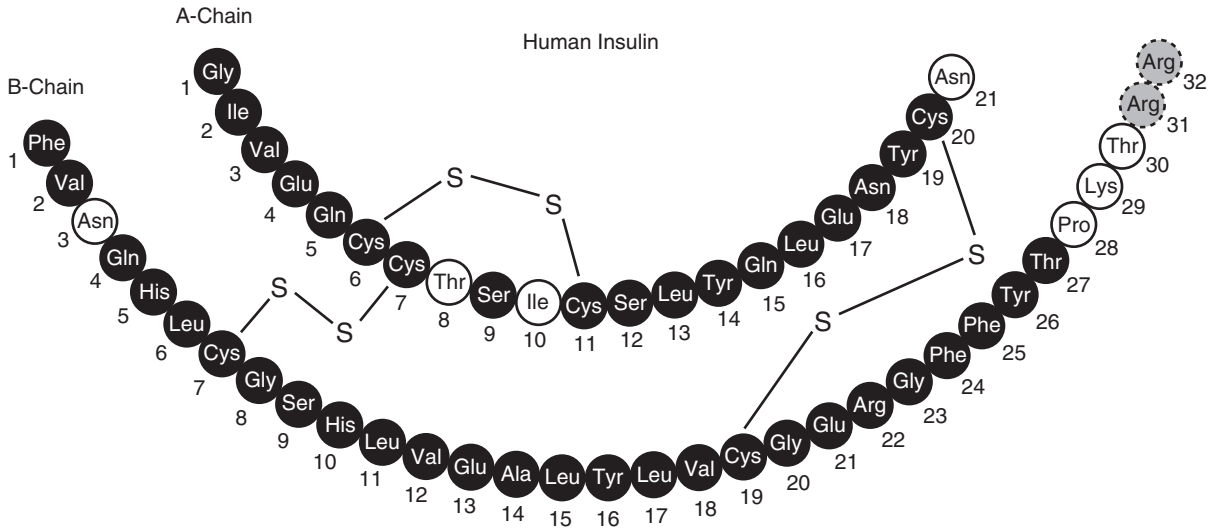

Figure 1.4. Schematic presentation of insulin A and B chains and the amino acid sequence of human insulin. The clear circles with black letters indicate where sequence modifications are made to provide insulin derivatives with varying rates of therapeutic response. The dotted circles represent where amino acid (Arg) additions are made to provide sustained release of insulin from the injection site.

TABLE 1.3. Sequence variation between some insulins available for human administration.

	Insulin Amino Acid (sequence position)[a]							
	A Chain			B Chain				
Name	8	10	21	3	28	29	30	31 & 32 insertion
Insulin-human	Thr	Ile	Asn	Asn	Pro	Lys	Thr	None
Insulin-beef	***Ala***	***Val***	Asn	Asn	Pro	Lys	***Ala***	None
Insulin-pork	Thr	Ile	Asn	Asn	Pro	Lys	***Ala***	None
Insulin-lispro	Thr	Ile	Asn	Asn	***Lys***	***Pro***	Thr	None
Insulin-aspart	Thr	Ile	Asn	Asn	***Asp***	Lys	Thr	None
Insulin-glargine	Thr	Ile	***Gly***	Asn	Pro	Lys	Thr	***Arg & Arg***
Insulin-glulisine	Thr	Ile	***Gly***	***Lys***	Pro	***Glu***	Thr	None

[a] The amino acid for a specific sequence position or respective insulin A or B chain are annotated in three-letter codes. Variations and modifications made to the human insulin sequence are highlighted in bold and italic codes. For amino acid abbreviations, please see Appendix IV.

TABLE 1.4. Comparison of recombinant hepatitis B vaccines dose recommendations.

	Recombivax HB		Engerix-B	
Group of Patient	Dose (μg)	Volume (mL)	Dose (μg)	Volume (mL)
Infants (HB^-), children < 11yr	2.5	0.25	10	0.5
Infants (HB^+)	5	0.5	10	0.5
Children, 11–19	5	0.5	20	1.0
Adult ≥20	10	1.0	20	1.0
Dialysis/immune-compromised patients	40	1.0[a]	40	2.0

[a] Special formulation

1.5. SUMMARY

Pharmaceutical biotechnology is a process of translation and integration of biological and life science discoveries to produce biologics and therapeutic products. It has had great impact on human health. Today, biopharmaceuticals are central to treatments of infections, diabetes, immune disorders, and cancers. In 2010, the top revenue-generating biotechnology product reached $7.3 billion, and collectively, the top 25 biopharmaceutical products

generated $74.7 billion. These achievements would not have been possible without the cumulative advancements in basic science discoveries and innovations that led to successful product developments. This chapter defines the differences between small-molecule traditional drugs and biologics, which are biotherapeutics consisting of proteins, peptides, and biological materials that are much larger molecules. A small change at the atomic level for a small-molecule drug typically leads to a new drug with a unique set of therapeutic and side effects, whereas a modification of amino acids (with multiple atomic modifications) on protein-based biotherapeutics, such as insulin and hepatitis B vaccine, retain a very similar therapeutic profile and clinical application. Given the growth in new biotechnology-based pharmaceuticals reaching the market, their therapeutic importance, and the overall growth in the health-care economy, it is essential for health professionals, legislators, decision makers, and pharmaceutical researchers to understand how the science and business of biotechnology is applied to transform biological molecules and processes into pharmaceuticals.

SUGGESTED READINGS

National Health Museum. A timeline of biotechnology. http://www.accessexcellence.org/RC/AB/BC/

Ernst & Young LLP, *The Biotechnology Industry Report*, 2011. http://www.ey.com/GL/en/Industries/Life-Sciences/Beyond-borders---global-biotechnology-report-2011

Also see annual reports from respective pharmaceutical and biopharmaceutical companies for financial information.

REFERENCES

Bud, R. (1989). "History of 'biotechnology'." *Nature* **337**(6202): 10.

Cohen, S. N., A. C. Chang, et al. (1973). "Construction of biologically functional bacterial plasmids in vitro." *Proc Natl Acad Sci U S A* **70**(11): 3240–44.

Fleming, A. (1929). "On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to their Use in the Isolation of *B. influenzae*." *Br J Exp Pathol* **10**(3): 226–36.

Goeddel, D. V. (1990). "Systems for heterologous gene expression." *Methods Enzymol* **185**: 3–7.

Ho, R. J. Y. and M. Gibaldi (2003). *Biotechnology and biopharmaceuticals: transforming proteins and genes into drugs*. Hoboken, N.J., Wiley-Liss.

Kohler, G. and C. Milstein (1975). "Continuous cultures of fused cells secreting antibody of predefined specificity." *Nature* **256**(5517): 495–97.

Mendel, G. (1950). "Gregor Mendel's letters to Carl Nageli, 1866–1873." *Genetics* **35**(5:2): 1–29.

Valenzuela, P., A. Medina, et al. (1982). "Synthesis and assembly of hepatitis B virus surface antigen particles in yeast." *Nature* **298**(5872): 347–50.

Weizmann, C. and B. Rosenfeld (1937). "The activation of the butanol-acetone fermentation of carbohydrates by *Clostridium acetobutylicum (Weizmann)*." *Biochem J* **31**(4): 619–39.

Zhou, J., X. Y. Sun, et al. (1991). "Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles." *Virology* **185**(1): 251–57.