

CHAPTER 1

INTRODUCTION

1.1 AIM OF THIS BOOK

The pharmaceutical industry is one of the most regulated industries in the world. From discovering a new drug to registering it for marketing and commercialization, pharmaceutical organizations have to negotiate through very complex and lengthy processes. These processes are necessary to ensure drug products are safe and efficacious, and that their benefits far outweigh their risks.

The intention of this book is to provide an overview of how a drug is discovered, the number and types of laboratory tests that are performed, and the conduct of clinical trials before a drug is ready to be registered for human use. Regulatory authorities play an important role in these processes, overseeing the safety and efficacy of drugs through legislation. This book aims to integrate, in a simplified manner, the relationships between all these complex processes and procedures.

To establish a frame of reference, it is necessary to commence with a definition for the term “drug”. Generally, a drug can be defined as a substance that induces a response within the human body, whether that response is beneficial or harmful. In this context, toxins and poisons can be classified as drugs. However, the term “drug” used in this book is strictly reserved for medicinal substances or pharmaceutical products, which provide favorable therapeutic or prophylactic pharmaceutical benefits to the human body. Readers are referred to Exhibit 1.1 for a definition of drug according to the Food and Drug Administration (FDA) of the United States.

Exhibit 1.1 FDA Definition of a Drug

A drug is defined as:

- A substance recognized by an official pharmacopeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process vs biological process).

Source: Data from 1. Food and Drug Administration 2012, *Drugs@FDA Glossary of Terms*, viewed January 6, 2014, <http://www.fda.gov/drugs/informationondrugs/ucm079436.htm>; 2. World Health Organization 2014, *International Nonproprietary Names*, viewed Jun 19, 2014, <http://www.who.int/medicines/services/inn/en/>

It should be noted that there are normally three names associated with a drug: the trade or proprietary name (e.g., Lipitor), generic name, or nonproprietary name (e.g., atorvastatin), and a specific chemical name for the active ingredient (e.g., $[R-(R^*,R^*)]$ -2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate).

The International Nonproprietary Names (INN) of the World Health Organization (WHO) are the unique standard names, also known as generic names, for the active pharmaceutical ingredients in drug products.

The descriptions in this book on discovery and regulatory processes are primarily concerned with ethical drugs, as opposed to over-the-counter (OTC) drugs. Ethical drugs are prescription drugs that require prescriptions by physicians, whereas OTC drugs can be purchased from pharmacies without prescriptions. OTC drugs are mainly established drugs with long histories of use and are deemed to be safe to be taken without supervision by physicians.

There is a further differentiation of ethical drugs into new drugs (those covered by patents) and generics (copies of drugs that have expired patents – refer to Case Study #10.2). Most of the descriptions in this book apply to new drugs.

1.2 AN OVERVIEW OF THE DRUG DISCOVERY TO APPROVAL PROCESS

Although human civilization has been experimenting and consuming drugs for many centuries, it is only in the past hundred years that a foundation has been laid for the systematic research and development (R&D) of drugs. Readers are referred to

Appendix 1 for a brief description of the history of drug development since ancient times.

Today, personnel from many fields are involved in the process of drug discovery and development, namely, scientists, clinicians, medical practitioners, and statisticians. Even persons from seemingly disparate occupations, such as economists, lawyers, and regulatory staff, play vital roles. Previously, the main scientific personnel involved in the discovery process have been synthetic chemists. However, drug discovery and development has made a quantum leap forward in recent times with progress in genomics/proteomics and biotechnology. This has led to an increased importance in the role of molecular biologists, biochemists, microbiologists, engineers, and even computer scientists in the discovery and development of drugs. In addition, advances in laboratory equipment automation and high-speed computing have assisted in analyzing and processing of large data sets. Personnel with different disciplines and expertise are needed to contribute to discover and develop drugs targeting diseases at the cellular and molecular levels.

It is estimated that, on average, a drug takes 10–12 years to progress from initial research to the commercialization stage. The cost of this process was estimated to be more than US\$1 billion in the early 2000s, compared to US\$140 million in the 1970s. It should be noted that this expenditure is not because of the cost of developing successful drugs alone; it is exacerbated by the amortized cost of failed drugs that do not demonstrate sufficient benefits over risks during clinical trials. From discovery to marketing approval of a drug, the following stages are involved (Figure 1.1):

Drug Discovery: The process begins with discovering the target that causes or leads to the disease. Next, chemical or biological compounds are screened using specific assays and tested against these targets to find leading candidates for further development. Many new scientific approaches are now used to determine targets (most targets are

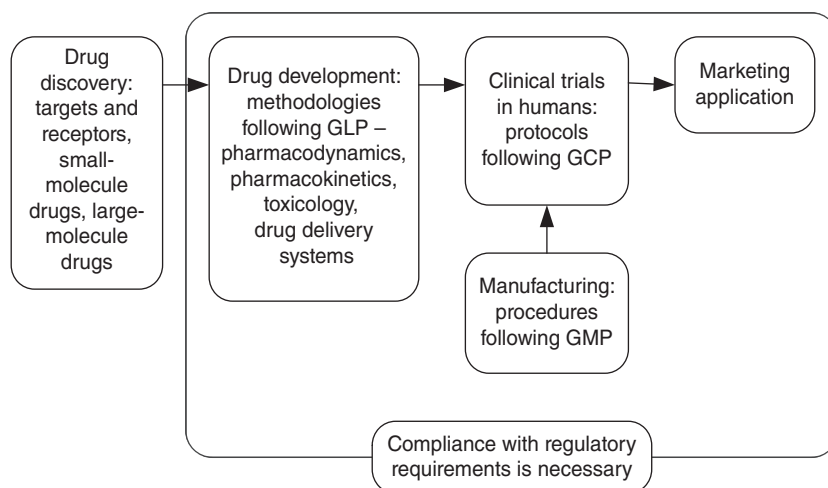


Figure 1.1 The stages from drug discovery to marketing approval.

receptors or enzymes) and obtain the lead compounds, including the use of genomic and proteomic technologies, synthetic chemistry, recombinant DNA (rDNA) technology, laboratory automation, and bioinformatics.

Preclinical Drug Development: Tests are performed with the lead compounds in test tubes (laboratory, *in vitro*) and on animals (*in vivo*) to check how they affect the biological systems. The tests, often called preclinical (sometimes also called nonclinical, these terms are used interchangeably) research activities, include toxicology, pharmacodynamics, and pharmacokinetics, as well as optimization of drug delivery systems. Many iterations are carried out, and the leading compounds are modified and synthesized to improve their interactions with the targets, to reduce toxicity or to improve pharmacokinetic performance. At the end of this process, an optimized compound is found and it becomes a potential drug ready for clinical trial in humans. The development work has to follow Good Laboratory Practice (GLP) to ensure that proper quality system and ethical considerations are established. Only compounds that satisfy certain performance and safety criteria will proceed to the next stage of clinical trial.

Clinical Development: Clinical trials using the drug dosage form intended for marketing are conducted on human subjects. The pertinent parameters for clinical trials are protocols (methods about how trials are to be conducted), safety and respect for human subjects, responsibilities of investigators, institutional review board, informed consent, trial monitoring, and adverse event reporting. These parameters form the basis of Good Clinical Practice (GCP). Clinical trials must follow regulations and guidelines from the US FDA, the European Medicines Agency (EMA) of the European Union (EU) or European Member States, Japan's Pharmaceuticals and Medical Devices Agency (PMDA), or regulatory authorities in other prospective countries where the drug is intended to be registered and commercialized.

Manufacturing: The drug designated for clinical trials has to be manufactured in compliance with current Good Manufacturing Practice (cGMP; the word "current" denotes that regulations change from time to time and the current regulations have to be applied) following US FDA requirements, EU Regulations or Directives, or International Conference on Harmonization (ICH) guidelines (refer to Chapter 7). Regulatory authorities have the right to conduct inspections on pharmaceutical manufacturing plants to ensure they follow cGMP guidelines so that the drug manufactured is safe and effective. A quality system has to be set up such that the drug is manufactured in accordance with approved procedures. There must also be an audit trail, that is, traceability of materials, processes, and personnel involved, as well as appropriate tests being conducted on the raw materials, intermediates, and finished products. The emphasis is that drugs should be safe, pure, effective, and of consistent quality to ensure they are fit for their intended functions.

Marketing Application, Approval, and Postapproval: A drug is not permitted for sale until the marketing application for the new drug has been reviewed and approved by regulatory authorities such as the US FDA, the EU EMA, or Japan's

PMDA. Extensive dossiers and samples, if required, are provided to the authorities to demonstrate the safety, potency, efficacy, and purity of the drug. These are provided in the form of laboratory (pharmacology, toxicology), clinical (on humans), and manufacturing data, which comply with GLP, GCP, and GMP requirements, respectively. After the drug has been approved and marketed, the safety and performance of the drug is continually monitored to ensure that it is prescribed correctly, and adverse events (side effects) are reported and investigated. The advertising of drugs is also scrutinized by regulatory authorities to ensure there are no false representations of or claims about the drugs. Furthermore, the commercial-scale manufacture of drugs must comply with GMP, and manufacturing facilities are inspected by regulatory authorities at periodic intervals. Variations to manufacturing processes, materials or specifications, and changes to labeling are to be reported to the regulatory authorities, and in some cases variations require prior regulatory approvals before implementations.

The subsequent chapters elaborate on each of these processes. An example of the complexity, time, and cost of developing a new drug is shown in Exhibit 1.2.

Exhibit 1.2 Did You Know?

Total drug development time grew from an average of 8.1 years in the 1960s to 11.6 years in the 1970s, to 14.2 in the 1980s, to 15.3 years for drugs approved from 1990 through 1995. A time span of 10–12 years is now generally ascribed to the discovery and development process, despite many new methods and technologies being utilized in an attempt to shorten the period. Pharmaceutical companies and regulatory authorities are working together to reduce this time span to control costs and expedite the time frame for drug marketing approval to cater to unmet medical needs.

The average cost of developing a new drug is estimated to be about US\$1–1.2 billion, including expenditures on failed projects. This amount is about three times the price of an Airbus A380-800 at US\$400 million, or five times that of a Boeing B-787 Dreamliner at US\$250 million.

Typically, tens of thousands of compounds are screened and tested, and only a handful makes it into the market as drug products. The statistics are such that, of the 5,000–10,000 compounds that show initial promise, five will go into human clinical trials, and only one will become an approved drug.

Source: Data from 1. Pharmaceutical Research and Manufacturers of America 2013, *Statement on Prescription Medicine Cost Growth* – Press Releases Apr 30, 2013, viewed December 16, 2013, http://www.phrma.org/phrmapedia/search?search_api_views_fulltext=R%26D+cost, 2. Airbus 2013, *New Airbus Aircraft: List Prices for 2013*, viewed December 16, 2013, <http://www.airbus.com/presscentre/pressreleases/press-release-detail/detail/new-airbus-aircraft-list-prices-for-2013/>, 3. Boeing 2013, *Commercial Airplanes: Jet Prices*, viewed December 16, 2013, <http://www.boeing.com/boeing/commercial/prices/>, 4. Tufts Center for the Study of Drug Development 2006, *No shortage of controversy in biotech drug creation costs*, viewed December 16, 2013, <http://www.bizjournals.com/sanfrancisco/stories/2006/12/04/newscolumn3.html>

1.3 THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry as we know it today began in the late 1800s. It started with the synthetic versions of natural compounds in Europe (refer to Appendix 1).

Drug discovery and development are primarily carried out by pharmaceutical companies, universities, and government research agencies, although there are increasing activities in smaller companies and start-ups that specialize in particular fields of research. A substantial number of the research findings and potential drugs from start-ups, smaller companies, universities, and research organizations are, however, licensed to multinational pharmaceutical companies that have the resources for clinical trials, manufacturing, marketing, and distribution. Alternatively, alliances are formed with the multinational pharmaceutical companies to develop or market the drugs. A primary reason for these business relationships is the huge cost involved in drug discovery, development, and commercialization.

In 2012, the combined worldwide pharmaceutical market was around US\$962 billion. The distribution of the market (in US\$ billion) is shown in Table 1.1. From this data, it is evident that the United States, Europe, and Japan accounted for more than 70% of the worldwide pharmaceutical market. Therefore, the regulatory authorities in these countries are very important to the pharmaceutical companies to ensure their products are approved for commercialization.

Table 1.2 shows the top 10 best-selling drugs in 2012; five of them are small molecule synthetic drugs (refer to Chapter 3) and five are biopharmaceuticals (biologics) or large molecule drugs (refer to Chapter 4). Six years ago only one biopharmaceutical, Enbrel, was in the top 10 list. All of the top 10 drugs are “blockbuster” drugs, meaning each has sales exceeding US\$1 billion. While the majority of drugs have been based on small molecules for many years, biopharmaceuticals have become increasingly important in the past three decades since the first one was introduced. The biopharmaceutical market has grown substantially compared to that of the small molecule drugs. For comparison,

TABLE 1.1 Global Pharmaceutical Sales by Region, 2012

World	2012 sales (US\$ billion)	% Global sales	% Growth from previous year
North America	348.7	36.2	−1.0
Europe (EU + non-EU)	221.8	23.1	−0.8
Asia (including Indian subcontinent/ Africa/Australia)	168.3	17.5	+12.8
Japan	112.1	11.7	0.0
Latin America	72.5	7.5	+10.9
Others	38.7	4.0	+4.5
Total	962.1	100.0	+2.4

Source: Adapted from IMS Health Reports: Global Pharmaceutical Market by Region. Available at: http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20Room/Total_World_Pharma_Market_Topline_metrics_2012-17_regions.pdf. Accessed December 14, 2013.

TABLE 1.2 The Top 10 Best-selling Products, 2012

Product	Therapy	Company
Seretide/Advair	Asthma, chronic obstructive pulmonary diseases	GlaxoSmithKline
Humira	Rheumatoid arthritis, autoimmune diseases	Abbott
Crestor	Cholesterol lowering	AstraZeneca
Nexium	Peptic ulcer and gastroesophageal diseases	AstraZeneca
Enbrel	Rheumatoid and psoriatic arthritis	Amgen
Remicade	Crohn's disease, rheumatoid arthritis, and ulcerative colitis	J&J, Merck
Abilify	Schizophrenia, bipolar disorder, depressive disorder	Otsuka/Bristol-Myers-Squibb
Lantus	Insulin analog for diabetes	Sanofi-Aventis
Rituxan/Mabthera	Lymphomas, leukemias, transplant rejection, autoimmune diseases	Biogen Idec/Roche
Cymbalta	Depressive and anxiety disorders	Eli Lilly

Source: Data from IMS. *Top 20 Global Products 2012*. Available at: http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-Line%20Market%20Data%20&%20Trends/Top_20_Global_Products_2012_2.pdf. Accessed December 14, 2013.

TABLE 1.3 The Top 10 Best-selling Biopharmaceuticals, 2013

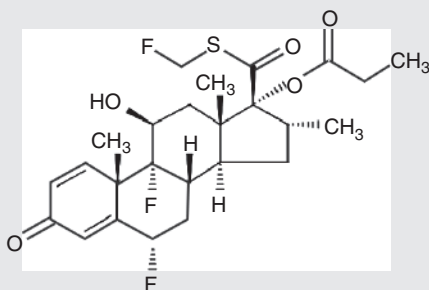
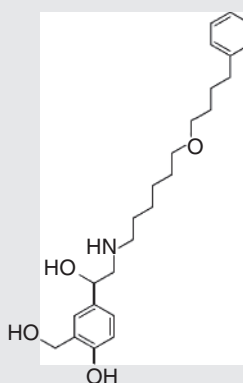
Product	Therapy	Company
Humira	Rheumatoid arthritis, autoimmune diseases	Abbott
Enbrel	Rheumatoid and psoriatic arthritis	Amgen
Remicade	Crohn's disease, rheumatoid arthritis, and ulcerative colitis	J&J, Merck
Neulasta	Neutropenia	Amgen
Rituxan	Lymphomas, leukemias, transplant rejection, autoimmune diseases	Biogen Idec/Roche
Lantus	Insulin analog for diabetes	Sanofi-Aventis
Avastin	Cancers: colorectal, lung, breast, glioblastoma, kidney, and ovarian	Roche
Epogen	Anemia	Amgen
Herceptin	Breast cancer	Roche
Lucentis	Macular degeneration	Roche

Source: Data from Drug.com 2014, *US Pharmaceutical Sales – Q3 2013*, viewed December 16, 2013, <http://www.drugs.com/stats/top100/sales>

Table 1.3 presents the top 10 best-selling biopharmaceuticals in 2013. Of the top 100 drugs in United States in Q3 2013, 32 are biopharmaceuticals, up from 18 in 2006. Exhibits 1.3 and 1.4 describe the top two drugs, Seretide/Advair and Humira, and their mechanisms of action in the treatment of asthma and inflammation, respectively.

Exhibit 1.3 Seretide/Advair – Treatment of Asthma and COPD

Seretide and Advair are different trade names of the same drug marketed by GlaxoSmithKline in different parts of the world. It is a combination of oral and inhalation product consisting of fluticasone and salmeterol. The active ingredients are fluticasone propionate and salmeterol xinafoate. Seretide/Advair is used in the management of asthma and chronic obstructive pulmonary disease (COPD).

Fluticasone*Salmeterol*

Fluticasone propionate is a corticosteroid with anti-inflammatory actions. It targets the human glucocorticoid receptor as an agonist. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediate the production of histamine, eicosanoids, leukotrienes, and cytokines that are involved in the asthmatic response.

Salmeterol xinafoate is a long-acting β_2 -adrenergic agonist. Its mechanism of action is to stimulate the enzyme adenyl cyclase that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). An increase in cyclic AMP relaxes the bronchial smooth muscle and inhibits production of hypersensitive mediators such as mast cells.

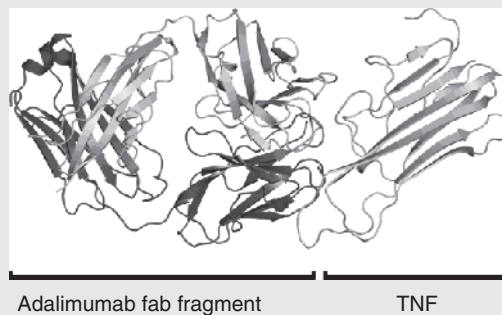
Seretide/Advair is supplied in 100, 250, or 500 mcg fluticasone propionate and 50 mcg salmeterol xinafoate formulated as inhalation powder. The powder is contained within blister packs in a metered dosed disposable inhalation device.

Source: Data from Food and Drug Administration 2003, *Advair*, viewed December 17, 2013, http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21077slr019_advair_lbl.pdf

Exhibit 1.4 Humira – Treatment of Rheumatoid Arthritis and Autoimmune Diseases

Humira is a tumor necrosis factor (TNF) blocker indicated for treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and plaque psoriasis. The active ingredient, adalimumab, is a recombinant human IgG1 monoclonal antibody that targets the human TNF. Adalimumab is produced by recombinant DNA technology using a mammalian cell system. It has 1,330 amino acids and a molecular weight of approximately 148 kDa.

Crystal structure of Humira (adalimumab) interacting with TNF



Source: Protein Data Bank in Europe <http://www.ebi.ac.uk/pdbe-srv/view/entry/3wd5/summary.html>, viewed Nov 8, 2014. Reproduced with permission of European Bioinformatics Institute.

Humira is supplied in prefilled pen or prefilled syringe. Each prefilled syringe delivers 0.8 mL (40 mg) of the drug product. Other ingredients are sodium chloride, monobasic sodium phosphate dihydrate, dibasic sodium phosphate dihydrate, sodium citrate, citric acid monohydrate, mannitol, polysorbate 80, and water for injection, USP. Sodium hydroxide is added as necessary to adjust the pH to 5.2.

Source: Data from 1. Hu, S et al. 2013, 'Comparison of the inhibition mechanisms of Adalimumab and Infliximab in treating TNFalpha-associated diseases from a molecular view', *J. Biol. Chem.*, 288, 27059-27067; 2. Food and Drug Administration 2013, *Humira*, viewed Nov 11, 2014, http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125057s310lbl.pdf

The top 10 pharmaceutical companies (according to market capitalization) in December 2013 are shown in Table 1.4. These 10 companies account for more than half of the global drug sales. In the same period, the top three companies collectively spent in excess of US\$25 billion in R&D; this amount comprises more than 15% of their sales revenues, demonstrating the importance of R&D for these companies.

TABLE 1.4 The Top 10 Pharmaceutical Companies: Dec 18, 2013

Rank	Company	Market Capitalization* (US\$ billion)
1	Roche	230.86
2	Pfizer	199.42
3	Novartis	188.80
4	Merck & Co	143.11
5	Sanofi-Aventis	135.50
6	GlaxoSmithKline	126.01
7	Bayer	112.13
8	Bristol-Myers-Squibb	86.59
9	AbbVie	86.25
10	Amgen	85.01

Source: Data from Google Finance 2013, *Market Summary 2013*, viewed December 18, 2013, <http://www.google.com/finance?ei=2YOyUqjXJMidkgWc1QE>

*Market capitalization is based on Dec 18, 2013 data, Roche acquired Genentech in 2009.

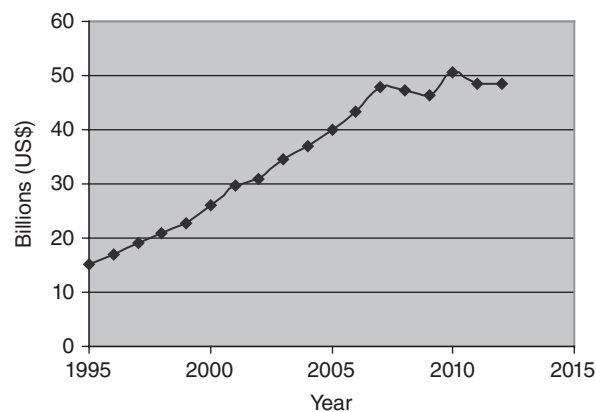


Figure 1.2 R&D investments by research-based US pharmaceutical companies. (Source: Pharmaceutical Research and Manufacturers of America. 2013 *BIOPharmaceutical Research Industry Profile*. Washington, DC: PhARMA. Available at: <http://phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf>. Accessed December 18, 2013. Reproduced with permission of the Pharmaceutical Research and Manufacturers of America.)

Further examples of R&D investments into drug research by research-based US pharmaceutical companies from 1995 to 2012 are shown in Figure 1.2. According to reports by the Pharmaceutical Research and Manufacturers of America (PhRMA), US pharmaceutical companies have almost doubled their R&D spending every 5 years since 1980. Out of every five dollars earned in sales, one dollar is put back into R&D. In 2012, the US pharmaceutical industry spent US\$48.5 billion in developing new drugs.

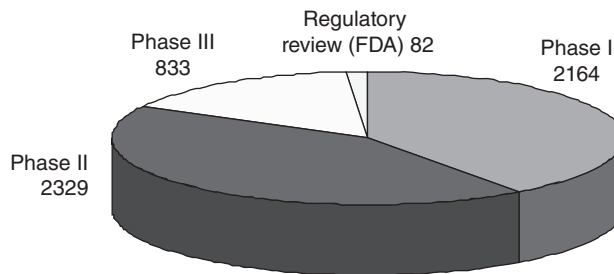


Figure 1.3 New drugs in development by regulatory phases, 2011. (Source: Pharmaceutical Research and Manufacturers of America. 2013 *BIOPharmaceutical Research Industry Profile*. Washington, DC: PhARMA. Available at: <http://phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf>. Accessed December 18, 2013. Reproduced with permission of the Pharmaceutical Research and Manufacturers of America.)

Pharmaceutical firms have to ensure there is a pipeline of new and better drugs to return the substantial investments made. It is estimated that large pharmaceutical firms need four–five new drugs approved every year to maintain their premium positions. However, most firms fall far short of this target, with only about one–two new drugs approved per year. From 2000 to 2012, it is estimated that around 400 new drugs were approved by FDA. Figure 1.3 presents a snapshot of the pipeline of new drugs at various phases of development in 2011. The areas of development are neurology, cardiovascular, cancer, psychiatry, diabetes, human immunodeficiency virus (HIV/AIDS), and infectious diseases.

The growth rate for biopharmaceuticals is high, and it is expected that half the total pharmaceutical market will be biopharmaceuticals within the next 10–20 years. The top 10 biopharmaceutical companies in 2012 are listed in Table 1.5. The rise of Roche, the largest pharmaceutical company with an extensive portfolio of biopharmaceutical products, shows the importance of biopharmaceuticals.

1.4 ECONOMICS OF DRUG DISCOVERY AND DEVELOPMENT

The pharmaceutical market is very competitive. It is imperative that pharmaceutical companies (including biopharmaceutical companies), large or small, discover and develop drugs efficiently and within the shortest possible time span to remain competitive.

Figure 1.4 shows the expenses versus revenues regarding a company's investment in developing a new drug. Up until the clinical stage, the investment is substantial in the discovery and development processes. The largest cash demand is in the clinical trial stages where hundreds to thousands of human subjects are recruited to test the drug.

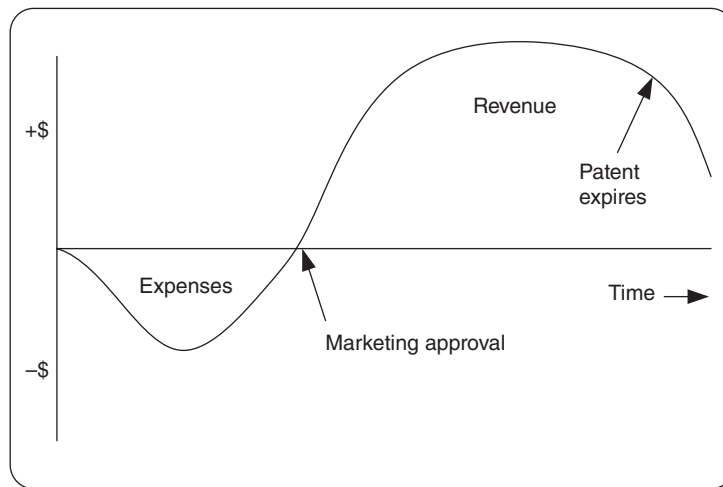
A positive return of revenue occurs only after the drug has been approved by regulatory authorities for marketing. The overall profitability of a drug is the difference between the positive returns and the negative expenses within the patent period of 20 years. After that period, if the patent is not extended, there is no further protection on the intellectual rights for the drug.

TABLE 1.5 The Top 10 Biopharmaceutical Companies: 2012

Rank	Company	Market Capitalization* (US\$ billion)
1	Roche	230.86
2	NovoNordisk	76.9
3	Amgen	60.1
4	Gilead Sciences	40.2
5	BiogenIdec	34.3
6	Teva	34.2
7	Baxter	32.3
8	Celgene	28.4
9	Merck	21.2
10	CSL	21.1

Source: Data from Genetic Engineering and Biotechnology News 2012. Top 25 Biotech Companies. Available at: <http://www.genengnews.com/insight-and-intelligenceand153/top-25-biotech-companies/77899671/?page=2>. Accessed December 19, 2013.

*Market capitalization is based on Dec 18, 2013 data, Roche acquired Genentech in 2009.

**Figure 1.4** Expenses and revenues curve for a new drug.

After patent expiry, generic drugs from other companies are unencumbered by patent rights infringement and can encroach into the profitability of the company that developed the original patented drug. It is thus crucial that drugs are marketed as quickly as possible to maximize the length of patent coverage period and to be “first to market,” to establish a premium position. When atorvastatin (Lipitor, Pfizer) lost its patent exclusivity in November 2011, the sales of this best-ever-selling drug plunged from US\$13.7 billion in 2006 to \$US3.45 billion in 2013. Clopidogrel (Plavix,

Exhibit 1.5 Patents

A patent is a right granted by a government for any device, substance, method, or process that is new, inventive, and useful. The patent discloses all information pertaining to the invention. In return for this disclosure, the owner of a patent is granted a 20-year period of monopoly rights to the commercial returns from the exploitation of the invention.

There are two ways to register patents: either through applying in individual countries (which means multiple applications for different countries) or through designating the desired countries in a single application using the Patent Cooperation Treaty (PCT) mechanism. There are more than 140 member countries belonging to the PCT, including major developed countries.

PCT does not grant patents. Application with PCT goes through two phases: an international phase and a national phase. The international phase is where the application is searched, published, and subjected to preliminary examination. Then, the application enters into the national phase in each country. The application is subjected to examination and granting procedures in each country.

Another important aspect of a patent is the priority date. The priority date is established when a patent application is filed for the first time. If the invention is known before this date, then the patent is not granted. Most countries are first-to-file countries, meaning that the patent is awarded to the person with the earliest filing date. In the United States, patents are awarded to the first person to invent. The inventor can claim priority by proving the invention was made before another person's filing date.

Source: Data from World Intellectual Property Organization, *The Patent Cooperation Treaty*, viewed January 6, 2014, <http://www.wipo.int/patentscope/en/patents/>

Bristol-Myers Squibb) experienced a similar nosedive in sales, dropping from \$US7.09 billion in 2011 to \$US0.3 billion in 2013, a 95% loss within two years of the patent expiry in May 2012 (refer to Case Study #1.2).

Exhibit 1.5 provides a brief explanation of patents. Patents are the pillars that support the drug industry. In contrast, traditional medicines, which are mainly derived from natural products of plant or animal origins, are not patentable. This is because traditional medicines consist of a multitude of compounds and it is difficult to establish patent claims on the basis of varying quantities of materials. Refer to Section 11.15 for further discussions on patents and marketing exclusivities.

1.5 TRENDS IN DRUG DISCOVERY AND DEVELOPMENT

The approach to drug discovery and development can generally be classified into the following areas:

- Irrational approach

- Rational approach
- Antisense approach
- RNA interference approach
- Biopharmaceuticals/biologics
- Gene therapy
- Stem cell therapy – both somatic cell and germ cell.

Irrational Approach: This approach is the historical method of discovering and developing drugs. It involves empirical observations of the pharmacological effects from screening of many chemical compounds, mainly those from natural products. The active component that gives rise to the observed effects is isolated. The chemical formula is determined, and modifications are made to improve its properties. This approach has yielded many drugs that are available today.

Rational Approach: This approach requires three-dimensional knowledge of the target structure involved in the disease. Drugs are designed to interact with this target structure to create a beneficial response. Having been established during the past three decades, the rational approach has become an important field in drug discovery.

Antisense Approach: This is a relatively new approach and it requires the modifications to oligonucleotides that can bind to RNA and DNA (refer to Appendix 2 for a description of cell structure, genes, DNA, RNA, and proteins). Antisense drugs are used to stop transcriptional (from DNA) or translational (from RNA) pathways from proceeding and so interfere with the process of disease.

RNAi Approach: This uses short interfering RNA (siRNA, sometimes called small interfering or silencing RNA) to interfere with the expression of a particular gene. The siRNAs are double-stranded RNAs of 20–25 nucleotides. It is envisaged that if the biological pathway of a disease is identified, siRNA could interfere to turn off the activity of the gene involved in the pathway and provide therapeutic effect.

Biopharmaceuticals/Biologics: These are mainly protein-based drugs in the form of antibodies, vaccines, and cytokines. Their discovery generally starts from an understanding of the biological mechanistic pathways that cause specific diseases. Manufacture of these drugs is based mainly on rDNA technologies using living organisms such as bacteria, yeast, and mammalian and insect cells.

Gene Therapy: This therapy is based on remedying a diseased gene by inserting a missing gene or modified gene in the cells. This is an emerging field that raises many unresolved ethical considerations. The cells with the diseased gene are taken out of a patient, modified outside the body (*ex vivo*), and then reinserted back into the body. In the case of a missing gene, a copy of the new gene is inserted into the patient's cells. The aim is for the inserted gene to influence the disease pathway or to initiate synthesis of missing proteins or enzymes.

Stem Cell Therapy: The aim of stem cell therapy is to grow body parts to replace defective human organs and nerves. Stem cells are harvested from very early embryos or umbilical cord blood. Because of the very young age of these cells, they can be directed to grow into organ tissue to replace diseased tissue. Recent research has enabled adult stem cells to behave similarly to embryonic stem cells and differentiate into different cell types and tissues. The stem cell technology can provide an alternative to organ transplants with perhaps lower rates of rejection than the current practice of obtaining organs from a donor. Stem cell therapy using germ cells involves cloning, and there are strict regulatory guidelines on how research is to be conducted.

Through the Human Genome Project many novel disease targets have been discovered, which can be utilized to develop better and more effective drugs. Regardless of the approach used for discovering new drugs, pharmaceutical and biotechnology companies are now using a full suite of technologies to discover new drugs. These enabling technologies are as follows:

- Microarray for disease target identification
- High-throughput screening
- Combinatorial chemistry
- Structure–activity relationships: X-ray crystallography, nuclear magnetic resonance, computational chemistry
- Genomics and proteomics
- Metabolomics
- Systems biology
- Nanotechnology
- Bioinformatics: data mining
- rDNA technologies.

Detailed discussions of these technologies are presented in Chapters 2–5.

1.6 CASE STUDY #1.1

1.6.1 Roche, Pfizer, and Novartis

This case study introduces the top three pharmaceutical companies in the world and their products.

Roche, 2012: Roche is the largest pharmaceutical company in the world. The corporate headquarters is located in Basel, Switzerland.

In 2012, Roche sales amounted to 45.5 billion CHF (Swiss franc, 1CHF = US\$1.11, January 2014). Roche's R&D expenditure was 8.48 billion CHF. Table 1.6 clearly demonstrates that pharmaceutical companies are heavily research-based; Roche and Pfizer's R&D expenditure is comparatively more than other technology companies with much higher market capitalization. Roche employed 82,089 people in 2012. The company specializes in oncology and its top five products in 2012 were the following:

TABLE 1.6 R&D Expenditures in R&D-Based Companies

Company	Market Capitalization, US\$ Billion (December 18, 2013)	Revenue, US\$ Billion (2012)	R&D Expenditure, US\$ Billion (2012)
Roche	230.86	45.50	8.48
Pfizer	199.42	58.99	7.87
Apple	495.55	170.91*	4.48
Google	362.40	50.18	6.59
Microsoft	305.37	77.85*	10.41
Intel	125.27	53.34	10.15
Boeing	101.81	81.70	3.30

Source: Data from Google Finance 2013, *Market Summary* 2013, viewed December 18, 2013, <http://www.google.com/finance?ei=IH-yUpCVE8KRRkQXR6wE>

*Denotes July 2012 to June 2013.

- Rituxan/MabThera – an antibody for the treatment of hematological cancers such as non-Hodgkin's lymphoma, chronic lymphocytic leukemia, transplant rejection, and autoimmune disorders (sales 6.71 billion CHF)
- Herceptin – an antibody for the treatment of breast and gastric cancers (sales 5.89 billion CHF)
- Avastin – an antibody for the treatment of colon, lung, renal, ovarian, and breast cancers (sales 5.76 billion CHF)
- Pegasys – an antiviral drug for the treatment of hepatitis B and C (sales 1.65 billion CHF)
- Xeloda – a small molecule drug for the treatment of metastatic breast and colorectal cancers (sales 1.52 billion CHF).

Source: Roche, *2012 Annual Report*, viewed December 18, 2013, http://www.roche.com/investors/annual_reports/annual_reports_2012.htm

Pfizer, 2012: Pfizer is the second largest pharmaceutical company in the world. The corporate headquarters is located in New York, United States.

In 2012, Pfizer spent US\$7.87 billion on R&D, and its income for that year was US\$58.99 billion. Pfizer employed more than 91,500 people in 2012. The company focuses on five high-priority areas including small and large molecules in immunology and inflammation, oncology, cardiovascular and metabolic diseases, neuroscience and pain, and vaccines. The top five drugs marketed in 2012 by Pfizer were the following:

- Lyrica – a small molecule drug for the management of postherpetic neuralgia, neuropathic pain associated with diabetic peripheral neuropathy, the management of fibromyalgia, neuropathic pain because of spinal cord injury (sales US\$4.15 billion)
- Lipitor – a small molecule drug for the treatment of elevated LDL-cholesterol levels in the blood (sales US\$3.95 billion)

- Enbrel – an antibody for the treatment of moderate-to-severe rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, psoriatic arthritis, and plaque psoriasis and ankylosing spondylitis (sales US\$3.74 billion)
- Prevenar 13-valent pneumococcal conjugate vaccine – a vaccine for the prevention of various syndromes of pneumococcal disease in infants and young children and in adults (sales US\$3.72 billion)
- Celebrex – a small molecule drug for the treatment of osteoarthritis and rheumatoid arthritis and the management of acute pain (sales US\$2.72 billion).

Source: Pfizer, *2012 Financial Report*, viewed December 18, 2013, <http://www.pfizer.com/files/annualreport/2012/financial/financial2012.pdf>

Novartis, 2012: Novartis is the third largest pharmaceutical company in the world. The corporate headquarters is located in Basel, Switzerland.

In 2012, Novartis' sales income was US\$56.67 billion and R&D expenses \$9.3 billion. The company employed a total of 128,000 people. The top five products marketed by the company were the following:

- Gleevec/Glivec – a small molecule tyrosine kinase inhibitor in cancer treatment, in particular, Philadelphia chromosome-positive (Ph⁺) chronic myelogenous leukemia (sales US\$4.68 billion)
- Diovan – a small molecule angiotensin II receptor antagonist for the treatment of hypertension, congestive heart failure, and postmyocardial infarction (sales US\$4.42 billion)
- Lucentis – a monoclonal antibody for the treatment of macular degeneration (sales US\$2.40 billion world market except United States, which is under Genentech/Roche)
- Sandostatin – a small molecule drug for use in oncology to treat pituitary tumors and growth hormone-producing tumors (sales US\$1.51 billion)
- Exforge – a small molecule drug for the treatment of hypertension (sales US\$1.35 billion).

Novartis owns Sandoz, the second largest generics company in the world after Teva.

Table 1.7 lists the new drugs approved by FDA and EMA for Roche, Pfizer, and Novartis in 2012.

Source: Novartis, *Financial Report*, viewed December 16, 2013, http://www.novartis.com/downloads/investors/financial-results/quarterly-results/q4-2012-media-release_en.pdf

1.7 CASE STUDY #1.2

1.7.1 Lipitor and Plavix

This case study describes Lipitor and Plavix and their mechanisms of action. Lipitor and Plavix were the top two best-selling drugs in 2010 before their patents expired.

TABLE 1.7 New Drugs Approved by FDA and EMA for Roche, Pfizer, and Novartis, 2012

Company	Product	Indication
Roche	Erivedge	Advanced basal cell carcinoma
	Perjeta	Metastatic HER2+ breast cancer
	Zelboraf	BRAF V600 mutation-positive metastatic melanoma
	Avastin	Recurrent, platinum-sensitive ovarian cancer
Pfizer	Eliquis	Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
	Xeljanz	Treatment of moderate-to-severe active rheumatoid arthritis
	Bosulif	Treatment of previously treated chronic myelogenous leukemia
	Lyrica	Treatment of neuropathic pain because of spinal cord injury
	Elelyso	Treatment of adults with a confirmed diagnosis of type 1 Gaucher's disease
	Inlyta	Treatment of advanced renal cell carcinoma after failure of one prior systemic therapy
Novartis	Signifor	Cushing's disease
	Bexsero	Meningococcal serogroup B (MenB) vaccine
	Votubia	Noncancerous kidney tumors associated with tuberous sclerosis complex
	Exjade	Chronic iron overload

Source: Data from 1. Roche 2012, *Annual Report*, viewed December 19, 2013, http://www.roche.com/investors/annual_reports/annual_reports_2012.htm 2. Pfizer 2012, *Financial Report*, viewed December 19, 2013, <http://www.pfizer.com/files/annualreport/2012/financial/financial2012.pdf> 3. Novartis 2012, *Financial Report*, viewed December 19, 2013, http://www.novartis.com/downloads/investors/financial-results/quarterly-results/q4-2012-media-release_en.pdf

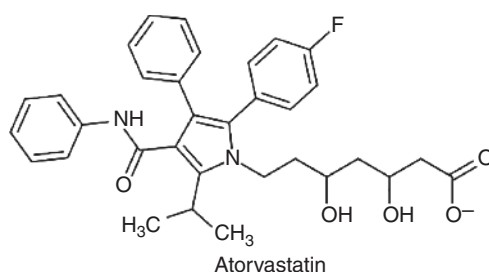
Lipitor: Statins such as Lipitor (atorvastatin) and Zocor (simvastatin) are competitive inhibitors of the enzyme HMG-CoA reductase, which is involved in the biosynthesis of cholesterol. Cholesterol is a fatlike substance (a sterol) that is present in our blood and all the cells of our body. It is synthesized within the body or derived from consumed foods. Cholesterol is an important constituent of cell membranes and hormones.

Cholesterol is carried in the bloodstream by lipoproteins such as low-density lipoprotein (LDL, or “bad cholesterol”) and high-density lipoprotein (HDL, “good cholesterol”). LDL carries cholesterol from the liver to other parts of the body. LDL attaches to receptors (refer to Chapter 2) on the cell surface and is taken into the cell interior. It is then degraded and the cholesterol is used as a component for the cell membrane. When there is excessive cholesterol inside the cell, it leads to a reduction in the synthesis of LDL receptors.

The number of active LDL receptors is also affected by a condition called familial hypercholesterolemia, in which there is a defective gene coding for the receptor. In either case, the reduction of active receptors means that the LDL carrying cholesterol is unable to enter the cell interior. Instead, it is deposited in the arteries leading to the

heart or brain. These deposits build up over time and may block blood supply to the heart muscle or brain, resulting in a heart attack or stroke. In contrast, HDL transports cholesterol from other parts of the body to the liver, where it is degraded to bile acids.

Lipitor inhibits cholesterol synthesis by increasing the number of LDL receptors to take up the LDL. The active ingredient is atorvastatin calcium. In addition to atorvastatin, Lipitor is formulated with other excipients: calcium carbonate, candellilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide), polysorbate 80, and simethicone emulsion.



Source: Food and Drug Administration 2009, *Lipitor*, viewed Jan 6, 2014, http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s0571bl.pdf

Plavix: Plavix (clopidogrel bisulfate) is used for inhibiting blood clots in coronary artery, cerebrovascular, and peripheral vascular diseases.

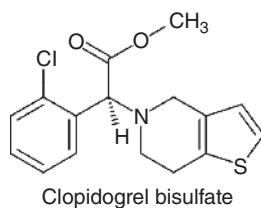
In the blood clot formation process, a protein called von Willebrand factor acts as a bridge for the platelets to attach to the collagen via its Ia/Ib glycoprotein surface receptors. This attachment activates the platelets, leading to the secretion of thromboxane A_2 (TXA_2), adenosine diphosphate (ADP), and serotonin (also known as 5-hydroxytryptamine, 5-HT). The secreted TXA_2 , ADP, and 5-HT also bind to the surface receptors of platelets and activate the platelets further. This leads to a change in the shape of the glycoprotein IIb/IIIa receptors on the surface of platelets, enabling them to bind to fibrinogen, a plasma protein. The process of aggregation then ensues with fibrinogen linking the receptors of different platelets, culminating in the formation of a platelet mass.

Concomitant with the formation of a platelet mass is the coagulation process whereby soluble fibrinogen is changed into insoluble fibrin to strengthen the platelet mass. A number of clotting factors are transformed from inactivated states into activated states in a series of reactions. The end result is the conversion of prothrombin to thrombin, which then changes fibrinogen to fibrin. Fibrin is a threadlike protein that traps platelets, blood cells, and fluid, leading to the formation of blood clots.

Plavix, through its metabolite, binds to the platelet receptors. It prevents the aggregation of platelets and thus stops the cross-linking process for forming blood clots.

20 INTRODUCTION

The active ingredient of Plavix is clopidogrel bisulfate, and the tablet is formulated with hydrogenated castor oil, hydroxypropylcellulose, mannitol, microcrystalline cellulose, and polyethylene glycol 6000. The tablet coating consists of ferric oxide, hypromellose 2910, lactose monohydrate, titanium dioxide, triacetin, and Carnuba wax.



Source: Food and Drug Administration 2010, *Plavix*, viewed January 6, 2014, http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s0481bl.pdf

1.8 SUMMARY OF IMPORTANT POINTS

1. The process from drug discovery to approval is

Discovery → Preclinical → Clinical → Marketing Application → Approval

2. The overall process takes 10–12 years and costs above US\$ 1 billion.
3. Regulatory supervision is an integral part of the pharmaceutical industry to ensure safety, efficacy, purity, and consistency of drugs for human use.
4. The global pharmaceutical market in 2012 was US\$962 billion. Biopharmaceuticals account for more than 10% of the market, with higher growth rate compared to conventional pharmaceuticals.
5. The top selling drug in 2012 was Seretide/Advair from GlaxoSmithKline, and the top biopharmaceutical was Humira from Abbott.
6. The pharmaceutical R&D expenditure, at more than 15% of revenue, is higher than many other technology-based industries.
7. Pharmaceutical companies draw on traditional as well as advances in new technologies to identify and develop new drugs.
8. Pharmaceutical companies rely on patents to protect their intellectual properties.

1.9 REVIEW QUESTIONS

1. Provide a definition for the term “drug” as adopted in this book.
2. Describe the process from drug discovery to approval.
3. Describe the role of regulatory bodies such as FDA and EMA. What are their main concerns regarding drugs?

4. Explain the terms GLP, GCP, and GMP. Why are these necessary?
5. Discuss how Humira and Lipitor work in the body.
6. Explain the reason for the high R&D cost for drugs and discuss how the cost can be reduced.
7. Explain why intellectual properties are important to the pharmaceutical companies and how they can be protected. Give examples to illustrate.
8. List some of the approaches for drug discovery.

1.10 BRIEF ANSWERS AND EXPLANATIONS

1. Refer to Section 1.1 and Exhibit 1.1 but note that drugs should be used according to the indications and contraindications provided by the manufacturer.
2. This is explained in Section 1.2. The importance of regulatory control is an integral part of the process.
3. FDA is the regulatory agency for drugs in United States whereas EMA is the centralized agency for the EU countries. Refer to Section 7.1 for further explanation. Regulatory agencies are concerned with the safety, efficacy, purity, and consistency of drugs. Their roles are to ensure that drugs are safe and fit for their purpose.
4. GLP stands for Good Laboratory Practice, GCP for Good Clinical Practice, and GMP for Good Manufacturing Practice. Together, these practices ensure there is planning, control, and monitoring of the drug development all the way from preclinical to clinical and manufacturing stages such that procedures are followed, records are kept, and processes are verified and tested.
5. Refer to Exhibit 1.4 and Case Study #1.2.
6. The high R&D cost stems from increasingly stringent regulatory compliance requirements and failures of drugs at later clinical phases mainly because of lack of efficacy and unacceptable adverse events. The introduction of risk-based approach, process analytical technology (refer to Section 9.8), and consolidation of regulatory documents (ICH, refer to Section 7.11) will reduce the regulatory burden. In addition, the development of more specific drugs, better understanding of biochemical pathways, followed by focused evaluation using more representative assays and biomarkers will reduce instances of failure at later stage clinical trials (refer to Section 6.4).
7. Patent rights protect intellectual properties and compensate the high R&D expenditure that pharmaceutical organizations spend on developing drugs. Without the protection of patents it would be difficult for pharmaceutical companies to justify R&D expenditure and continue with innovations. The way forward for the pharmaceutical industry may include the need to review patent law. This is particularly relevant with respect to the exclusivity period and the rules for revoking patent rights under compulsory licensing, whereby a government can force a patent holder to grant rights of the patent to the state or other parties without compensation in royalties.
8. Refer to Section 1.5.

1.11 FURTHER READING

- Bristol-Myers Squibb 2014, *Products Sales Summary*, viewed February 6, 2014, <http://phx.corporate-ir.net/phoenix.zhtml?c=106664&p=irol-sales>
- Campbell, JJ 2005, *Understanding Pharma: A Primer on How Pharmaceutical Companies Really Works*, Pharmaceutical Institute, Inc., Raleigh, NC.
- The Congress of the United States, Congressional Budget Office 2009, *Pharmaceutical R&D and the Evolving market for Prescription Drugs*, viewed January 8, 2014, <http://www.cbo.gov/publication/24983>
- Ellery, T and Hansen, N 2012, *Pharmaceutical Lifecycle Management*, Wiley & Sons, Inc., Hoboken, NJ.
- Food and Drug Administration 2006, *From Test Tube To Patient: Protecting America's Health Through Human Drugs*, 4th edn., Publication number FDA 06-1524G.
- Food and Drug Administration 2014, *Development and Approval Process (Drugs)*, viewed January 8, 2014, <http://www.fda.gov/drugs/developmentapprovalprocess/default.htm>
- Food and Drug Administration 2013, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, viewed January 9, 2014, <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>
- Jacobsen, TM and Wertheimer, AJ 2009, *Modern Pharmaceutical Industry: A Primer*, Jones and Barlett Publishers, Sudbury, MA.
- Lawrence, S 2007, 'Billion dollar babies – biotech drugs as blockbusters', *Nature Biotechnology*, vol. 25, no. 4, pp. 380–382.
- Paul, SM et al. 2010, 'How to improve R&D productivity: the pharmaceutical industry's grand challenge', *Nature Reviews Drug Discovery*, vol. 9, pp. 203–214.
- Pharmaceutical Research and Manufacturers of America 2000, *Why Do Prescription Drug Cost So Much?* PhRMA, Washington, DC.
- Smith, CG and O'Donnell, JT (eds.) 2006, *The Process of New Drug Discovery and Development*, 2nd edn., Informa Healthcare.
- Stroud, RM and Finer-Moore J (eds.) 2008, *Computational and Structural Approaches to Drug Discovery: Ligand-Protein Interactions*, Royal Society of Chemistry, Cambridge.
- Tufts Center for the Study of Drug Development 2013, *Biotech Products in Big Pharma Clinical Pipelines Have Grown Dramatically*, viewed December 16, 2013, http://csdd.tufts.edu/news/complete_story/pr_ir_nov_dec_2013
- Voet, MA 2011, *The Generic Challenge: Understanding Patents, FDA and Pharmaceutical Life-Cycle Management*, 3rd edn., Brown Walker Press, Boca Raton, Florida.