PART I

INTRODUCTION

1

CHEMICAL ENGINEERING IN THE PHARMACEUTICAL INDUSTRY: AN INTRODUCTION

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Although recently several excellent books have been published geared toward process chemistry [1–3] or formulation development in the pharmaceutical industry [4], relatively little has been published specifically with a chemical engineering (ChE) focus. This book, therefore, is about chemical engineering applied to the process research, development, and manufacture of pharmaceuticals. Across the pharmaceutical industry, chemical engineers are employed in R&D through to full-scale manufacturing in technical and management capacities. The following chapters provide an emphasis on the application of chemical engineering science to process development and scale-up for active pharmaceutical ingredients (APIs), drug products (DPs), and biologicals including sections on analytical methods and computational methods. This chapter briefly highlights a few industry facts and figures, in addition to some of the challenges facing the industry, and touches on how ChE can contribute to addressing those challenges. Chapter 2 by Kukura and Thien provides further perspective on the challenges and opportunities in the pharmaceutical industry and the role of chemical engineering.

In general, pharmaceuticals are drug delivery systems in which drug-containing products are designed and manufactured to deliver precise therapeutic responses [5]. The drug is considered the "active," that is, active pharmaceutical ingredient, whereas the formulated final drug is simply referred to as the drug product.

In the United States, federal and state laws exist to control the manufacture and distribution of pharmaceuticals. Specifically, the Food and Drug Administration (FDA) exists by the mandate of the U.S. Congress with the Food, Drug & Cosmetics Act as the principal law to enforce and constitutes the basis of the drug approval process [6]. Specifically in the United States, "The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health [7]."

A review of the structure within the FDA and the drug review process can be found in the cited references [8]. In Europe, the European Agency for the Evaluation of Medicinal Products (EMEA) is a decentralized body of the European Union with headquarters in London whose main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use [9].

According to PhRMA statistics, more than 300 new medicines have been approved in the past 10 years that have contributed to increases in life expectancy. For example, since 1980, life expectancy for cancer patients has increased by about 3 years, and 83% of those gains are attributable to new treatments, including medicines. Death rates for cardiovascular disease fell a dramatic 26.4% between 1999 and 2005 [10]. The value of the biopharmaceutical industry to the American economy is substantial. In 2006, the industry employed over 680,000 people with each job indirectly supporting an additional 3.7 jobs. Thus, as an aggregate, the

Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing Edited by David J. am Ende

industry supported 3.2 million jobs in 2006 contributing $88.5 billion in 2006 to the nation's gross domestic product [11]. In terms of the total value that the pharmaceutical sector outputs (sum of the direct value of goods produced, indirect value of goods and services that support the sector, and economic activity induced by the direct/indirect employees), it is estimated to be over $635 billion for 2006 [12].

As an industry, global pharmaceutical sales have steadily increased over the past decade and are now approaching an $800 billion industry based on 2009 revenues. Despite the slowing growth rate over the past decade (Figure 1.1), sales are still expected to grow at 4–7% per year to approach $975 billion by 2013 [13]. This is due, in part, from emerging market countries (China, Brazil, Russia, Mexico, India, Turkey, South Korea) where sales are expected to grow by 13–16% annually over the next 5 years (IMS Health). Amid the uncertainty in long-term growth, as an industry sector, the pharmaceutical industry still ranks near the top of most profitable industries with approximately 19% return on revenues according to Fortune 500 rankings [14]. The top 15 pharmaceutical companies are listed in Table 1.1 according to IMS Health.

The top 15 global selling drugs are shown in Table 1.2, with Lipitor/atorvastatin topping the list with 2008 global sales of $13.7 billion. The top 15 drugs total nearly $90 billion and comprise approximately 12% of the global market of $724 billion in 2008. Table 1.3 includes some of the top selling small-molecule APIs, including their formulation type and formulation ingredients.

With patent expirations and fewer blockbusters on the horizon, the pharmaceutical industry is undergoing a transformation in part through consolidation of drug portfolios via mergers and acquisitions. At the time of this writing, further consolidation of the list in Table 1.1 includes Pfizer's acquiring Wyeth and Merck's acquisition of Schering-Plough in 2009. Patent expirations for branded pharmaceuticals create significant financial exposure to the industry. Specifically, products that generated $137 billion in sales face

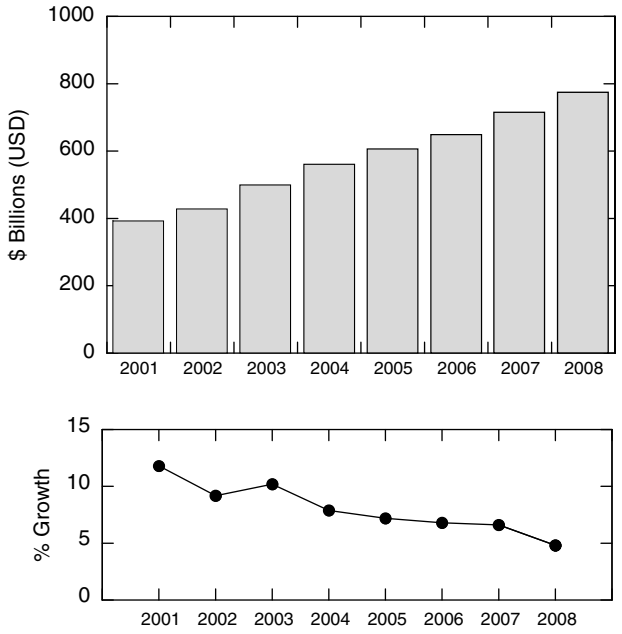


FIGURE 1.1 *Top*: Global pharmaceutical sales with worldwide pharmaceuticals sales approaching $725 billion for year ending 2008. *Bottom*: Declining growth rate based on global sales is defined as percentage change in global sales over the previous year. *Source*: Ref. 15.

TABLE 1.1 Top 15 Pharmaceutical Corporations in 2008 as Listed by IMS Health[15]

	2008 Rank (US$)	2008 Sales (US$ million)	2007 Sales (US$ million)	2006 Sales (US$ million)	2005 Sales (US$ million)	2004 Sales (US$ million)
Global market	0	724,465	673,043	612,013	572,659	530,909
Pfizer	1	43,363	44,651	45,622	45,869	49,401
GlaxoSmithKline	2	36,506	37,951	37,516	32,256	33,231
Novartis	3	36,172	34,409	31,560	29,616	26,404
Sanofi-Aventis	4	35,642	33,819	31,460	30,953	28,446
AstraZeneca	5	32,516	30,107	27,540	24,741	22,526
Roche	6	30,336	27,578	23,354	20,105	16,787
Johnson & Johnson	7	29,425	29,092	27,730	27,190	26,919
Merck & Co.	8	29,191	27,294	25,174	23,872	24,334
Abbott	9	19,466	17,587	16,065	14,849	13,310
Lilly	10	19,140	17,386	15,388	14,232	13,042
Amgen	11	15,794	16,536	16,270	13,435	10,944
Wyeth	12	15,682	15,965	14,695	14,469	14,019
Teva	13	15,274	13,547	12,001	10,053	8,675
Bayer	14	15,660	14,178	12,553	11,828	11,019
Takeda	15	13,819	12,778	11,880	11,370	10,707

S*ource*: Ref. 15.

TABLE 1.2 Top 15 Global Pharmaceutical Products (in 2008)

Rank	Brand Name	Compound	Marketer	Indication	2008 Sales ($ Billion)
1	Lipitor	Atorvastatin	Pfizer	Hypercholesterolemia	13.655
2	Plavix	Clopidogrel	Bristol-Myers Squibb	Atherosclerotic events	8.634
3	Nexium	Esomeprazole	AstraZeneca	Acid reflux disease	7.842
4	Seretide/ Advair	Fluticasone and salmeterol	GlaxoSmithKline	Asthma	7.703
5	Enbrel	Etanercept	Amgen and Wyeth	Rheumatoid arthritis	5.703
6	Seroquel	Quetiapine	AstraZeneca	Bipolar, schizophrenia	5.404
7	Zyprexa	Olanzapine	Eli Lilly & Co.	Schizophrenia	5.023
8	Remicade	Infliximab	Centocor	Crohn's disease, rheumatoid arthritis	4.935
9	Singulair	Montelukast	Merck & Co.	Asthma, allergies	4.673
10	Lovenox	Enoxaparin	Sanofi-Aventis	Anticoagulant	4.435
11	MabThera	Rituximab	Roche	Lymphoma	4.321
12	Takepron/ Prevacid	Lansoprazole	Takeda	Antiulcer/gastric proton pump inhibitor	4.321
13	Effexor	Venlafaxine	Wyeth	Depression	4.263
14	Humira	Adalimumab	Abbott	Rheumatoid arthritis, Crohn's disease	4.075
15	Avastin	Bevacizumab	Genentech/Roche	Metastatic cancers	4.016

S*ource*: Refs 13 and 15. Global sales figures are listed in US$ for 2008.

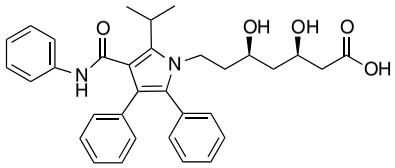
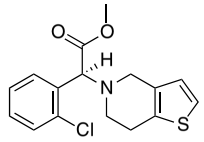
generic competition from 2009 to 2013 according to IMS Health [15], which represents approximately 17% of current global pharmaceutical sales. In addition, the United States is in the midst of U.S. health care reform (2010). It remains unclear whether the higher volume of prescription drugs that the program intends to ultimately provide coverage for, to the newly insured, will offset the lower price demands and how this will impact the industry as a whole.

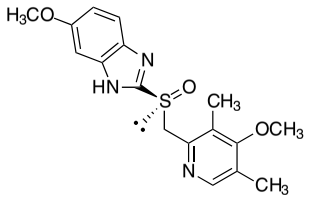
Companies in general are broadly looking for ways to reduce costs to offset the exposure of patent expirations, rising generic competition, and current market pressures. The cost of advancing candidates and entire pharmaceutical portfolios in R&D is significant. In 2001, the average cost for an approved medicine was estimated to be $802 million as reported by Tufts Center for the Study of Drug Development. In 2008, the cost of advancing a drug through clinical trials and through FDA approval was estimated to range from $1 billion to $3.5 billion in 2008 dollars [16]. Although these figures clearly depend on the drug type, therapeutic area, and speed of development, the bottom line is that the upfront investments required to reach the market are massive especially when considering the uncertainty whether the upfront investment will pay back.

Given there might be 10 or more years of R&D costs without any revenue generated on a new drug, the gross margins of a successful drug need to cover prior R&D investments as well as cover the continuing marketing and production costs. Figure 1.2 shows the classic cash flow profile for a new drug developed and marketed. First, there is a period of negative cash flow during development. When the drug is approved and launched, only then are revenues generated, and the drug has to be priced high enough to recoup the investment and provide a return on the investment. The net present value (NPV) calculation is one way to assess return on investment; it considers the discounted revenue minus the discounted costs and is computed over the product development and marketing life cycle. These calculations are used to rationalize investment decisions. For example, a minimum threshold product price can be computed for which the NPV calculation hits a desired return on investment target. If this price is sustained by the market, then the investment can be considered viable. A discount rate of 10–12% is generally chosen in the pharmaceutical industry as the rate to which to value products or programs for investment decisions [17]. Patents typically have a validity of 20 years from the earliest application grant date based on applications filed after 1995, so it is in the company's best interest to ensure that the best patent protection strategy is in place to maximize the length of market exclusivity. Related to this is that patents and intellectual property in general need enforcement on a global basis to ensure fair competition and realize benefit in growth into emerging markets.

In some cases, time of market exclusivity can be extended through new indications, new formulations, devices, and so on, which are themselves patent protected. Once market exclusivity ends, generic competition is introduced, which will erode sales. It should be noted that independent of patent position or patent exclusivity, the FDA grants new drug product exclusivity (also known as Hatchman–Wax exclusivity) with specific periods of exclusivity. For example, the

TABLE 1.3 Top Selling Marketed Small-Molecule APIs and Dosage Formulations

Structure/Name/Company (2008 Sales)	Molecular Weight	Properties	Dosage Form	Formulation
 Lipitor / Atorvastatin Pfizer $12.4 Billion in sales in 2008	*Atorvastatin* Free acid: MW 558.64 Sodium salt: MW 580.62 Calcium salt trihydrate: $(C_{33}H_{34}FN_2O_5)_2Ca{\cdot}3H_2O$, MW 1209.39 *For the treatment of cardiovascular disease*	Calcium salt trihydrate: white to off-white crystalline powder. Freely soluble in methanol, slightly soluble in ethanol, very slightly soluble in acetonitrile, distilled water, and phosphate buffer (pH 7.4), and insoluble in aqueous solutions of pH 4 and below.	*Tablets* 10, 20, 40, or 80 mg	Lipitor tablets for oral administration contain atorvastatin calcium and the following inactives: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.
 Plavix / Clopidogrel Bristol-Myers Squibb/Sanofi-Aventis $4.9 Billion BMS + €2.6 Billion S-A	*Clopidogrel* Free base: $C_{16}H_{16}ClNO_2S$, MW 321.82 Hydrogen sulfate: $C_{16}H_{16}ClNO_2S{\cdot}H_2SO_4$, MW 419.9 *Proton pump inhibitor; for the treatment of acid reflux disease*	Clopidogrel bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether.	*Tablets* 75 and 300 mg	Each tablet contains clopidogrel bisulfate and the following inactives: hydrogenated castor oil, hydroxypropylcellulose, mannitol, microcrystalline cellulose, and polyethylene glycol 6000. The pink film coating contains ferric oxide, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin. The tablets are polished with carnauba wax.



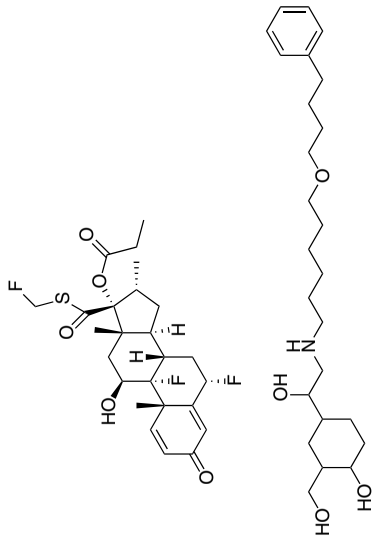
Nexium / Esomeprazole
AstraZeneca
$5.2 Billion in sales

Esomeprazole
Free base: $C_{17}H_{19}N_3O_3S$, MW 345.42
Magnesium salt: $C_{34}H_{36}MgN_6O_6S_2$, MW 713.12
Magnesium salt trihydrate: $(C_{17}H_{18}N_3O_3S)_2Mg{\cdot}3H_2O$, MW 767.2
For the treatment of acid reflux disease

Esomeprazole magnesium trihydrate is a white to slightly colored crystalline powder. The solubility in water is 0.3 mg/mL, and the solubility in methanol is initially high, but followed by precipitation. The pK_a of the benzimidazole (omeprazole base) is 8.8, and that of the pyridinium ion is 4.0.

Capsules (delayed release)
20 and 40 mg
Sachet
10 mg

Each delayed release capsule contains esomeprazole magnesium trihydrate in the form of enteric-coated granules with the following inactive ingredients: glyceryl monostearate 40–55, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, *n*-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C Yellow #10.



Advair (US)/Seretide(EU)
fluticasone + salmeterol
GlaxoSmithKline
£4.137 Billion in sales

Fluticasone propionate
$C_{25}H_{31}F_3O_5S$, MW 500.6
Salmeterol xinafoate
$C_{25}H_{37}NO_4{\cdot}C_{11}H_8O_3$, MW 603.8
For the treatment of asthma and chronic obstructive pulmonary disease

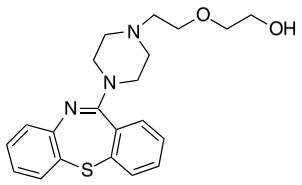
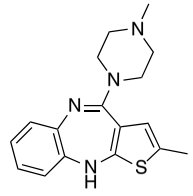
Salmeterol xinafoate is white to off-white crystalline powder with a melting point ~123°C.
Solubility:
In water ~0.07 mg/mL (pH = 8)
In methanol ~40 mg/mL
In ethanol ~7 mg/mL
In chloroform ~3 mg/mL
In isopropanol ~2 mg/mL
Fluticasone propionate is white to off-white powder. It is freely soluble in DMSO and DMF, sparingly soluble in acetone, dichloromethane, ethyl acetate, and chloroform, slightly soluble in methanol and 95% ethanol, and practically insoluble in water. Fluticasone propionate decomposes without melting.

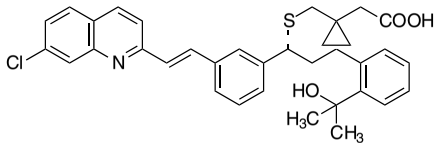
Dry powder inhaler
50 μg salmeterol with 100, 250, or 500 μg fluticasone propionate/blister
Aerosol
25 μg salmeterol with
50, 125, or 250 μg fluticasone propionate/ metered dose

Dry powder inhaler device containing a foil strip with 28 or 60 regularly placed blisters, each containing salmeterol (as the xinafoate salt) and fluticasone propionate. The inactives include lactose (milk sugar) and milk protein, which acts as the "carrier."
Aerosol comprises a suspension of salmeterol and fluticasone propionate in the propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no excipients.

(*continued*)

TABLE 1.3 (*Continued*)

Structure/Name/Company (2008 Sales)	Molecular Weight	Properties	Dosage Form	Formulation
 Seroquel/Quetiapine AstraZeneca $4.452 Billion in sales	*Quetiapine* $C_{21}H_{25}N_3O_2S$, MW 383.51 *Quetiapine fumarate* $(C_{21}H_{25}N_3O_2S)_2{\cdot}C_4H_4O_4$, MW 883.1 *For the treatment of schizophrenia and bipolar disorder*	Quetiapine fumarate is a white to off-white powder. It is only very slightly soluble in ether, slightly soluble in water, and soluble in 0.1 N HCl. Ionization constant: $pK_{a1} = 6.83$ in phosphate buffer at 22°C; $pK_{a2} = 3.32$ in formic buffer at 22°C. Partition coefficient: log $P = 0.45$ (octanol/water). Melting point: 172.0–174°C.	*Immediate release tablet* 25, 100, 200, and 300 mg	Seroquel is available in four strengths containing 25, 100, 200, or 300 mg quetiapine per tablet (as quetiapine fumarate). The core of the tablet contains the following excipients: calcium hydrogen phosphate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate type A. The coating of the tablet contains hydroxypropyl methylcellulose 2910, polyethylene glycol 400, red ferric oxide (25 mg tablets), titanium dioxide, and yellow ferric oxide (25 and 100 mg tablets).
 Zyprexa/olanzapine Eli Lilly & Co. $ 4.7 Billion in Sales	*Olanzapine* $C_{17}H_{20}N_4S$, MW 312.43 *For the treatment of schizophrenia and bipolar disorder*	Crystals from acetonitrile, mp 195°C. Practically insoluble in water.	*Tablets* 2.5, 5, 7.5, 10, 15, and 20 mg *Orally disintegrating tablets* zyprexa zydis 5, 10, 15, and 20 mg *Intramuscular injection* 10 mg vial	*Tablets*: inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains titanium dioxide (all strengths), FD&C Blue No. 2 aluminum lake (15 mg), or synthetic red iron oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink that contains FD&C Blue No. 2 aluminum lake.



Singulair/montelukast
Merck & Co.
$4.337 Billion in Sales

Montelukast
Free acid: $C_{35}H_{36}ClNO_3S$, MW 586.18
Montelukast sodium: $C_{35}H_{35}ClNNaO_3S$, MW 608.18
For the treatment of asthma

Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Tablet
10 mg
Chewable tablets
4 and 5 mg
Granules
4 mg

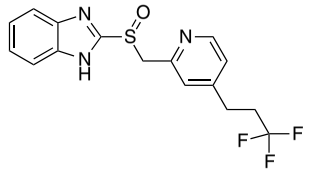
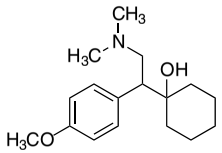
Oral disintegrating tablets also contain the following inactives: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

Each 10 mg film-coated Singulair tablet contains montelukast sodium and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

Each 4 and 5 mg chewable Singulair tablet contains montelukast sodium, with the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

(*continued*)

TABLE 1.3 (*Continued*)

Structure/Name/Company (2008 Sales)	Molecular Weight	Properties	Dosage Form	Formulation
 Prevacid/Lansoprazole Takeda / Abbott $4.321 Billion in Sales (IMS Health)	*Lansoprazole* $C_{16}H_{14}F_3N_3O_2S$, MW 369.36 *For the treatment for peptic ulcer*	Lansoprazole is a white to brownish-white odorless, crystalline powder that melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in DMF, slightly soluble in methanol, sparingly soluble in ethanol, slightly soluble in ethyl acetate, dichloromethane, and acetonitrile, very slightly soluble in ether, and practically insoluble in water and hexane. Octanol/water partition coefficient = 240 at pH 7.	*Capsules* Delayed release capsules contain enteric-coated granules and are available in two dosage strengths: 15 and 30 mg of lansoprazole per capsule. *Oral suspension sachets*	In addition to lansoprazole, each delayed release capsule contains the following inactive ingredients: cellulosic polymers, colloidal silicon dioxide, D&C Red No. 28, FD&C Blue No. 1, FD&C Green No. 3 (15 mg capsules only), FD&C Red No. 40, gelatin, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar spheres, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Oral suspension sachets include lansoprazole granules and inactive granules composed of the following ingredients: confectioner's sugar, mannitol, docusate sodium, ferric oxide, colloidal silicon dioxide, xanthan gum, crospovidone, citric acid, sodium citrate, magnesium stearate, and artificial strawberry flavor.
 Effexor/venlafaxine Wyeth $3.928 Billion in sales	*Venlafaxine* $C_{17}H_{27}NO_2$, MW 277.40 Venlafaxine hydrochloride: $C_{17}H_{27}NO_2 \cdot HCl$, MW 313.86 *Antidepressant*	Venlafaxine HCl: white to off-white crystalline solid. *Solubility*: Water: 540, 542, 501, and 21.6 mg/mL at pH 1.0, 5.38, 7.09 and 7.97 Ethanol: 91.7 mg/mL Propylene glycol: 200 mg/mL Glycerin: 115 mg/mL pK_a value: 9.4	*Capsules* Effexor XR Hard gelatin capsule 37.5, 75, and 150 mg	*Composition*: venlafaxine hydrochloride, ethylcellulose, NF; gelatin, NF; hydroxypropyl methylcellulose, USP; iron oxide, NF; microcrystalline cellulose, NF 60; titanium dioxide, USP; White Tek SB-0007 and/or Opacode Red S-1-15034 ink; talc, USP.

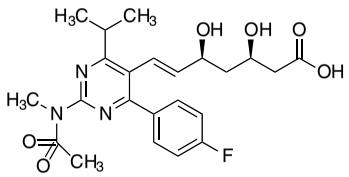
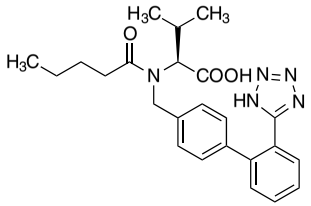
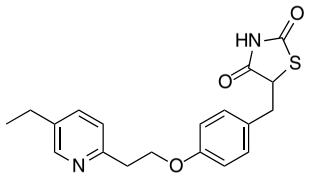
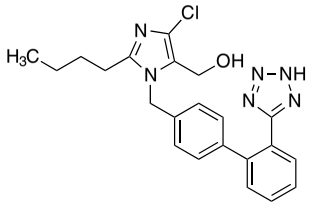
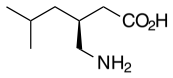
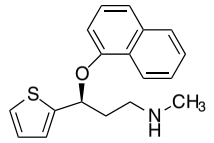
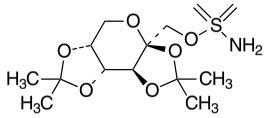
 Crestor/Rosuvastatin AstraZeneca $3.597 Billion in sales	*Rosuvastatin* $C_{22}H_{28}FN_3O_6S$, MW 481.54 Rosuvastatin calcium salt: $(C_{22}H_{27}FN_3O_6S)_2Ca$, MW 1001.14 *For the treatment of high cholesterol*	Rosuvastatin calcium salt: white powder from water as the monohydrate; begins to melt at 155°C with no definitive melting point. Sparingly soluble in water, methanol and slightly soluble in ethanol.	*Tablets* 5, 10, 20, and 40 mg	*Composition*: each tablet contains 5, 10, 20, or 40 mg of rosuvastatin as rosuvastatin calcium. Each tablet also contains the following nonmedicinal ingredients: calcium phosphate, crospovidone, glycerol triacetate, hydroxypropyl methylcellulose, lactose monohydrate, microcrystalline cellulose, magnesium stearate, ferric oxide red, ferric oxide yellow, and titanium dioxide.
 Diovan / valsartan Novartis $5.74 Billion in Sales	*Valsartan* $C_{24}H_{29}N_5O_3$, MW 435.52 *For the treatment of hypertension*	Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water Crystals from diisopropyl ether, mp 116–117°C. Partition coefficient (*n*-octanol/aqueous phosphate buffer): 0.033. Soluble in water at 25°C.	*Tablets* 40, 80, 160, or 320 mg	The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black, and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.
 Actos / Pioglitazone Takeda Pharmaceuticals $3.87 Billion in sales	*Pioglitazone* $C_{19}H_{20}N_2O_3S$, MW 356.44 Pioglitazone hydrochloride: $C_{19}H_{20}N_2O_3S{\cdot}HCl$, MW 392.90 *For the treatment of diabetes mellitus type 2*	Pioglitazone hydrochloride: colorless prisms from ethanol, mp 193–194°C. Soluble in DMF, slightly soluble in ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.	*Tablets* 15, 30, and 45 mg	Actos is available as a tablet for oral administration containing 15, 30, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate, NF; hydroxypropylcellulose, NF; carboxymethylcellulose calcium, NF; magnesium stearate, NF. (*continued*)

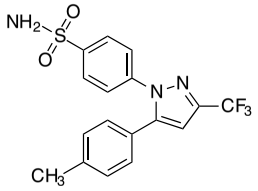
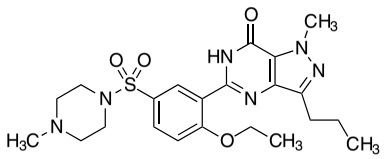
TABLE 1.3 (*Continued*)

Structure/Name/Company (2008 Sales)	Molecular Weight	Properties	Dosage Form	Formulation
 Cozaar (losartan potassium) Merck & Co. $3.558 Billion in sales	*Losartan* $C_{22}H_{23}ClN_6O$, MW 422.91 Losartan potassium: $C_{22}H_{22}ClKN_6O$, MW 461.00 *For the treatment of hypertension*	Losartan potassium is a white to off-white free-flowing crystalline powder. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.	*Tablets* 25, 50, or 100 mg	Cozaar contains losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hypromellose, titanium dioxide, D&C Yellow No. 10 aluminum lake, and FD&C Blue No. 2 aluminum lake.
 Lyrica / pregabalin Pfizer $2.6 Billion in sales	*Pregabalin* $C_8H_{17}NO_2$, MW 159.23 *For the treatment of neurologic pain*	Pregabalin is a white crystalline solid. It is soluble in water and in both basic and acidic aqueous solutions.	*Capsules* 25, 50, 75, 100, 150, 200, 225, and 300 mg	Each capsule of Lyrica contains pregabalin, lactose monohydrate, maize starch, and talc. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide.

 Cymbalta/duloxetine HCl Eli Lilly & Co. $2.697 Billion in Sales	*Duloxetine* Free base: $C_{18}H_{19}NOS$, MW 297.41 Hydrochloride: $C_{18}H_{19}NOS{\cdot}HCl$, MW 333.88 *Antidepressant and analgesic*	Duloxetine hydrochloride is white to slightly brownish white solid. pK_a in DMF–water (66 : 34): 9.6. Slightly soluble in water. Freely soluble in methanol.	*Capsules* 30 and 60 mg	Each capsule contains enteric-coated pellets of duloxetine hydrochloride equivalent to 30 or 60 mg of duloxetine that are designed to prevent degradation of the drug in the acidic environment of the stomach. Nonmedicinal ingredients include FD&C Blue No.2, gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 60 mg capsules also contain yellow iron oxide.
 Topamax /Topiramate Johnson & Johnson $2.731 Billion in Sales	*Topiramate* $C_{12}H_{21}NO_8S$, MW 339.36 *Anticonvulsant; antimigraine*	Topiramate is a white crystalline powder; bitter taste. Crystals from ethyl acetate + hexane, mp 125–126°C. Most soluble in alkaline solutions containing NaOH or sodium phosphate, pH 9–10. Freely soluble in acetone, chloroform, DMSO, and ethanol. Solubility in water: 9.8 mg/mL.	*Tablets* 25, 50, 100, and 200 mg *Capsules* 15 and 25 mg	Topiramate tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, titanium dioxide, polyethylene glycol, synthetic iron oxide (25, 50, 100, and 200 mg tablets) and polysorbate 80. (Topiramate capsules) Sprinkle capsules contain topiramate-coated beads in a hard gelatin capsule. The inactive ingredients are sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, sorbitan monolaurate, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

(*continued*)

TABLE 1.3 (*Continued*)

Structure/Name/Company (2008 Sales)	Molecular Weight	Properties	Dosage Form	Formulation
 Celebrex/Celecoxib Pfizer, Inc $2.489 Billion in Sales	*Celecoxib* $C_{17}H_{14}F_3N_3O_2S$, MW 381.38 *Nonsteroidal anti-inflammatory drug (NSAID)*	Celecoxib is a white powder. mp 160–164°C. Celecoxib is a neutral molecule at physiologic pH. Celecoxib is "practically insoluble" in water (with an *n*-octanol/water partition coefficient of 10,000 at pH 7.0). Celecoxib is weakly acidic with a pK_a of 11.1.	*Capsules* 100 and 200 mg	The inactive ingredients in Celebrex 100 and 200 mg capsules include croscarmellose sodium, lactose monohydrate, magnesium stearate, povidone, and sodium lauryl sulfate. The capsules are made of gelatin and contain titanium dioxide (E171) and edible inks (ferric oxide (E172) for 200 mg capsules and indigotine (E132) for 100 mg capsules).
 Viagra/Sildenafil Pfizer, Inc $1.934 Billion in Sales	*Sildenafil* Free base: $C_{22}H_{30}N_6O_4S$, MW 474.58 Citrate salt: $C_{22}H_{30}N_6O_4S{\cdot}C_6H_8O_7$, MW 666.70 *For the treatment of erectile dysfunction*	Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water at 23°C, mp 187–189°C. pK_a (protonation of tertiary amine): 6.53. pK_a (deprotonation of pyrimidinone moiety): 9.17. Solubility at 23°C in 1 M HCl is 5.8 mg/mL and in 1 M NaOH is 42.3 mg/mL.	*Tablets* 25, 50, and 100 mg	Sildenafil citrate is formulated as blue, film-coated rounded-diamond-shaped tablets equivalent to 25, 50, and 100 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose, triacetin, and FD&C Blue #2 aluminum lake.

Source: Merck Index (14th edition), Physicians Desk Reference, individual product monographs, and 2008 Annual Reports.

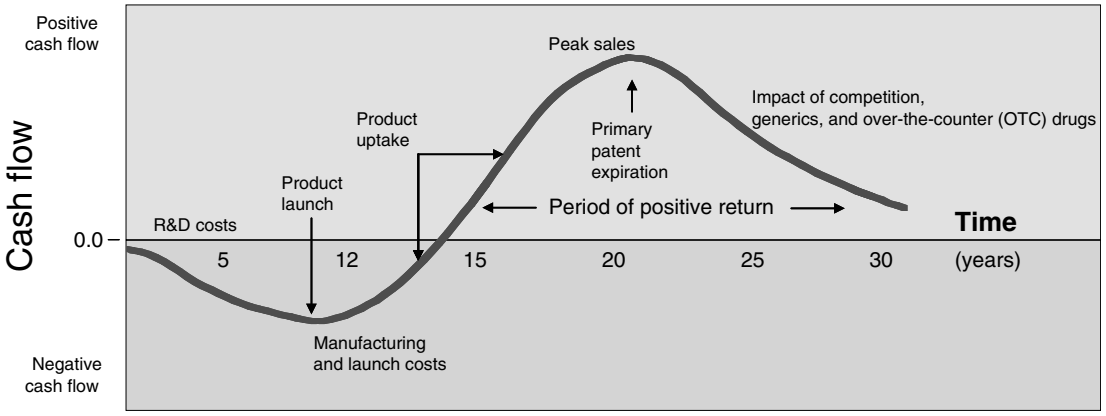


FIGURE 1.2 A hypothetical cash flow curve for a pharmaceutical product includes 10–15 years of negative cash flows of typically $1–3 billion. Reasonably high margins are needed, once the drug is on the market, if it is to recoup and provide a positive return on investment (ROI) over its life cycle.

following key points are quoted from the FDA on the subject of new drug product exclusivity.

> "Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product." "A 5-year period of exclusivity is granted to new drug applications for products containing chemical entities never previously approved by FDA either alone or in combination." "A 3-year period of exclusivity is granted for a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the sponsor that were essential to approval of the application. For example, the changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use may be granted exclusivity if clinical investigations were essential to approval of the application containing those changes." "The Center for Drug Research and Evaluation (CDER) makes exclusivity determinations on all relevant applications. There is a procedure in CDER that provides review of all relevant applications, with or without a request from the applicant, for an exclusivity determination [18]."

The pharmaceutical industry invested approximately $60 billion into R&D in 2007. It now takes 10–15 years for a new medicine to go from the laboratory to the pharmacy. Figure 1.3 shows the typical development activity timeline from discovery to launch. From thousands of compounds evaluated for potential therapeutic effect, very few will clear all the safety, efficacy, and clinical hurdles to make it to approval. Figure 1.3 also shows how a general range of volunteers, and therefore clinical supplies, increases for clinical development through phases I to II with clinical development lasting 6–7 years. The cost of product development that includes the cost to manufacture clinical supplies is estimated to be in the range of 30–35% of the total

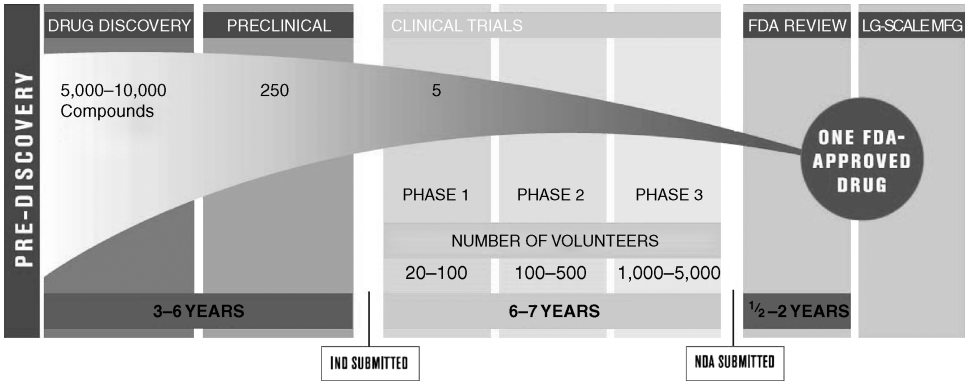


FIGURE 1.3 Drug research and development can take 10–15 years with one approval from 5 to 10,000 compounds in discovery. IND: investigational new drug; NDA: new drug application. *Source*: *Pharmaceutical Industry Profile 2009*, Pharmaceutical Research and Manufacturers of America (PhRMA) (www.phrma.org).

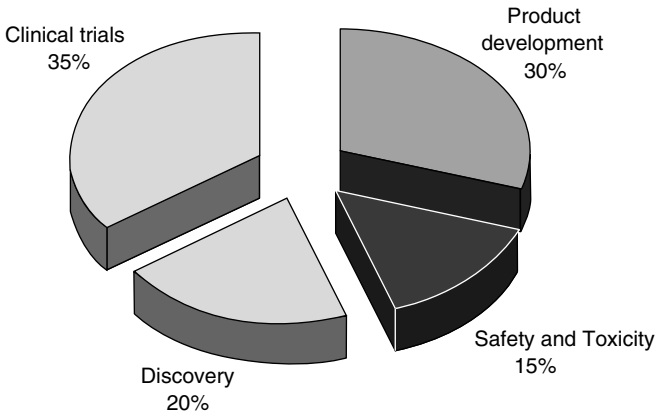


FIGURE 1.4 Estimated distribution of product development costs within R&D with the total cost to bring a new chemical entity to market in the range of $1–3.5 billion. *Source*: Ref. 16.

cost of bringing a new chemical entity to market with the following breakdown of development costs: discovery 20–25%, safety and toxicity 15–20%, product development 30–35%, and clinical trials 35–40%. The distribution is graphically displayed in Figure 1.4. Clearly, the distribution will depend on the specific drug, its therapeutic area, dose, and specific company [16].

1.1 PHARMACEUTICAL DEVELOPMENT

In general, pharmaceutical product development is different from most other research-intensive industries. Specifically in the pharmaceutical industry, there is a consistent need to ensure that clinical supplies are manufactured and delivered in a timely manner regardless of the current state of development or efficiency of the process. In other words, delivering clinical supplies when they are needed requires using technology that is good enough at the time even if it is not a fully optimized process. Further, process development, optimization, and scale-up historically tend to be an iterative approach [19]—clinical supply demands are met by scale-ups to kilo lab or pilot plant through phase I, phase II, and phase III and it is through this period R&D development teams (including chemist/engineers/analysts, referred to as the ACE model) refine, optimize, and understand the API and DP processes to enable them to be eventually transferred to manufacturing. Manufacturing of clinical supplies in kilo lab, pilot plant, solid dosage plants, and so on occurs under the constraints of current good manufacturing practices (cGMP) conditions, which is discussed further in Chapter 22 by Hamm et al. The pilot plant and kilo lab are also sometimes used to "test" the scalability of a process. In this way, they serve a dual purpose, which make them unique compared to nonpharmaceutical pilot plants. In terms of cost, however, large-scale experimentation in kilo lab or pilot plant can be significant, so there has been a shift toward greater predictability at lab scale to offset the need for pilot plant-scale "technology demonstration" experiments. Engineers through their training are well versed with scale-up or scale-down processes and can effectively model the chemical and physical behaviors in the lab to ensure success on scale. This helps to reduce the number of larger scale "experiments," thereby lowering costs during R&D. In this way, with the recent trend toward increasing efficiency and continuous improvement, the pilot plant and kilo labs are preferentially utilized to manufacture toxicological and clinical supplies rather than being used to "test" or verify that the chemistry or process will work on scale. This concept of "lean manufacturing" will be touched on in more detail later in this chapter.

The aim of process development is to drive down the cost contribution of the API to the final formulated pharmaceutical product cost, while at the same time optimizing process robustness. The impact of API costs on overall manufacturing costs is approximated in Figure 1.5. The cost contribution of API is expected to increase with increasing complexity of molecular structures of APIs. It is interesting to note that API molecular complexity can often impact API cost more than formulation or packaging costs. Federsel points out that, "Given the importance of 'time to market' which remains one of the highest priorities of pharmaceutical companies, the need to meet increasingly stretched targets for speed to best route has come to the forefront in process R&D" [20]. Recently, it was considered satisfactory to have a good enough synthetic route that was fit for purpose (i.e., could support the quantities of material needed) but not one having best or lowest cost ($/kg of API). The prevailing view was that the market would bear higher product pricing as compensation for higher cost of goods. Further cost reduction through new routes could be and was pursued post-launch with savings realized later in the life cycle. According to Federsel, and evidenced frequently in contemporary R&D organizations, this approach is no longer viable, at least not as a default position. Instead, the best synthetic route to API (i.e., route with ultimate lowest cost materials) coupled with best process design and engineering (process with lowest processing costs) must be worked out as early as possible in

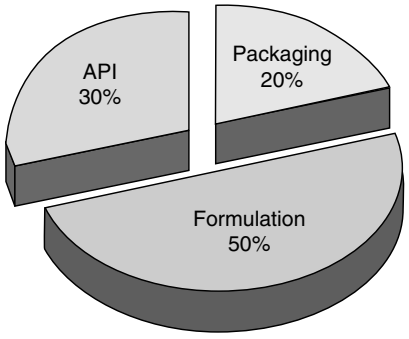


FIGURE 1.5 Average COG components in final dosage form across a large product portfolio, but for individual drugs this could vary widely (e.g., for API from 5% to 40%). *Source*: Ref. 19.

API process development [21]. The best API process developed by the time of launch is necessary to extract additional revenues and respond to reduced cost of goods margins. Achieving this requires continuous improvement in scientific and technical tools as well as multidisciplinary skill sets in the R&D labs, including chemical engineering science. Specific areas of opportunity for engineering are described in more detail in Chapter 2. The implementation of process design principles, drawing on the right skill sets, from both chemistry and engineering perspectives during clinical phase II is considered such an important step toward leaner more cost-effective processes readied for launch that several portions of this book will expand on this concept.

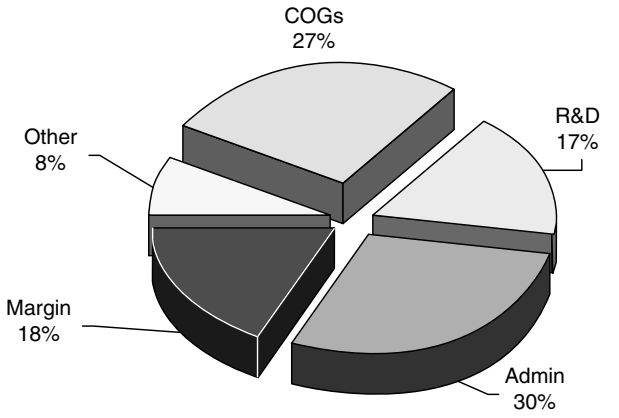


FIGURE 1.6 Distribution of revenue and expenses as a percentage of sales was averaged over 17 major pharmaceutical companies (listed in Table) based on 2008 annual reports.

1.2 MANUFACTURING

Pharmaceutical production plants of APIs and drug products can be generally characterized as primarily batch-operated multipurpose manufacturing plants. At these facilities, commercial supplies of API intermediates, APIs, and drug products are manufactured before being packaged, labeled, and distributed to various customers. Pharmaceutical production plants were typically designed to be flexible to allow a number of different products to be run in separate equipment trains, depending on the demand. Further, these facilities have various degrees of automation, relatively high levels of documentation, and change control to manage reconfigurations, with relatively long down times for cleanup and turnover of the plant between product changes [22]. Manufacturing often accounts for more than one-third of a company's human resources and a third of the total costs with expenses exceeding that of R&D [23]. Figure 1.6 shows the major components of revenues based on 2008 annual reports averaged over the 17 pharmaceutical companies shown in Table 1.4. Figure 1.6 shows that the manufacturing costs or costs of goods (COGs) are on average 27% of revenues where R&D represents 17% of revenues. The margin, shown in Figure 1.6, refers to the profit margin at 18%. As an industry with annual sales of over $700 billion, COGs of 27% represent close to $200 billion for the industry. For this reason, COGs have received considerable attention as an area of opportunity for potential savings [24].

It has been claimed that through adopting quality by design principles and principles of lean manufacturing, pharmaceutical companies, on average, could save in the range of $20–50 billion/year by eliminating inefficiencies in current manufacturing [25]. This translates to an improvement of 10–25% in reducing current COGs. Another critical factor in API cost determinations is the tax savings provided to companies who manufacture in selected countries. At present, for United States based pharmaceutical companies, significant tax savings are realized by locating production in tax-advantaged locations such as Ireland, Singapore, Puerto Rico, and Switzerland. Manufacturing in tax-advantaged locations can realize tax savings with tax rates of 2–12% versus the U.S. rate of 38% [26], so the cost advantages of any process or operational change need to be carefully determined and location-specific factors taken into consideration.

The principles of lean manufacturing are often cited as an approach to reduce COGs in pharmaceutical development and manufacturing. Lean manufacturing describes a management philosophy concerned with improving profitability through the systematic elimination of activities that contribute to waste; thus, the central theme to lean manufacturing is the elimination of waste where waste is considered the opposite of value. Based on the work of Taiichi Ohno, creator of the Toyota Production System, the following are considered wastes [27]:

- Overproduction
- Waiting
- Transportation
- Unnecessary processing
- Unnecessary inventory
- Unnecessary motion
- Defects

All of these wastes have the effect of increasing the proportion of nonvalue-added activities. Lean thinking is obviously applicable to many industries including pharmaceutical manufacturing as well as pharmaceutical development. Continuous processing, for pharmaceutical APIs and DPs, is one application of lean thinking applied to pharmaceutical manufacturing. The challenge that batch processing inherently leads to overproduction (e.g., inventory buildup of intermediates), leading to longer cycle times and excess inventory, is addressed through the concepts of continuous manufacturing.

According to Ohno, "The greatest waste of all is excess inventory" where in simplest terms excess inventory incurs

TABLE 1.4 Financial Data from 17 Pharmaceutical Companies Obtained from 2008 Year-End Reports

Stock ticker Revenues (in millions of USD)		Abbott ABT 29,526	Amgen AMGN 14,687	Astra AZN 31,601	BMS BMY 20,579	Boeh-ringer BOE[d] 16,139	GSK[a] GSK 35,592	J&J JNJ 63,747	Lilly LLY 20,378	Merck MRK 23,850	Novar-tis NVS 41,459	Pfizer PFE 48,296	Roche[b] RHHB-Y 33,692	Sanofi[c] SNY 38,372	Scher-Plough SGP 18,502	Takeda TKPHF 13,748	Teva TEVA 11,085	Wyeth WYE 22,833	Average AVG 28,476
Cost of sales		12,612	2,296	6,598	6,396	N/A	9,376	18,511	4,383	5,582	11,439	8,112	8397	10,212	7,307	2,786	5,117	6,248	7,836
Percent of revenues		42.71	15.63	20.88	31.08	N/A	26.34	29.04	21.51	23.40	27.59	16.80	24.92	26.61	39.49	20.26	46.16	27.36	27
R&D		2,687	3,030	5,179	3,585	2,936	5,380	7,577	3,841	4,805.30	7,217	7,945	7,405	6.368	3,529	2,757	786	3,373	4,612
Percent of revenues		9.10	20.63	16.39	17.42	18.19	15.12	11.89	18.85	20.15	17.41	16.45	21.98	16.60	19.07	20.05	7.09	14.77	17
Selling, informational, and administrative, expenses		8,436	3,789	10,913	4,792	N/A	11,190	12,490	6,626	7,377	11,852	14,537	7,746	9,977	6,823	6,730	1,842	6,838	8,247
Percent of revenues		28.57	25.80	34.53	23.29	N/A	31.44	19.59	32.52	30.93	28.59	30.10	22.99	26.00	36.88	48.95	16.62	29.95	29
Net income (margin)		4,881	4,196	6,130	5,247	1,983	6,887	12,949	−2,072	7,808.40	8,163	8,104	9,691	5,974	1,903	4,231	635	4,417	5,360
Percent of revenues		16.53	28.57	19.40	25.50	12.29	19.35	20.31	−10.17	32.74	19.69	16.78	28.76	15.57	10.29	30.78	5.73	19.34	18
Employees		68,000	17,500	67,000	41,000	39,800	99,003	119,200	40,600	59,800	96,717	81,800	78,604	100,000	55,000	15,717	38,000	50,527	62,839
Inventories	Finished goods	1,546	444	596	707	802	2.388	2,841	771	433	4,813	2,024	4,184	2,017	1,212	457	1,904	996	1,655
	Work-in-process	698	1,519	631	738	869	1,893	1,372	1,657	Incl. below	N/A	1,527	940	2,823	1,428	337	559	1,540	1,235
	Raw materials + consumables	532	112	409	320	487	1,647	839	236	2245.6	979	830	758	856	679	367	903	460	745
Total inventories		2,776	2,075	1,636	1,765	2,158	5,928	5,052	2,493	2,678	5,792	4,381	5,882	5,696	3,319	1,161	3,366	2,996	3,480

Source: Respective companies' 2008 annual reports. [Revenues, cost of sales, R&D net income, and inventory data are listed in the table. The averages listed in the last column were used for the distribution shown in Figure 1.6.] Cost of sales = cost of goods: Costs of sales include manufacturing costs such as raw materials, salaries of production labor, depreciation of equipment, production lines, infrastructure, utilities, maintenance costs, subcontractors, and other manufacturing costs. R&D: Research and development expenditures include raw materials, salaries of R&D, depreciation and infrastructure, and cost of utilities for R&D and professional services used in R&D. Selling, informational, and administrative expenses: They include sales, promotions, customer support and training, marketing, advertising campaigns, public relations, distribution, sponsorships, general corporate activities, and compensation of senior executives. The negative net income of Lilly is due to acquisitions including ImClone for $6.5 billion (See notes to consolidated statement—note 3,2008 Lilly financial report).

[a]British pounds converted to USD (1 GBP = 1.4619 USD) based on exchange rate as of December 31, 2008.

[b]Swiss francs converted to USD (1 CHF = 0.936944 USD) based on exchange rate as of December 31, 2008.

[c]Euros converted to USD (1 EUR = 1.3919 USD) based on exchange rate as of December 31, 2008.

[d]Abbreviated BOE—privately held company.

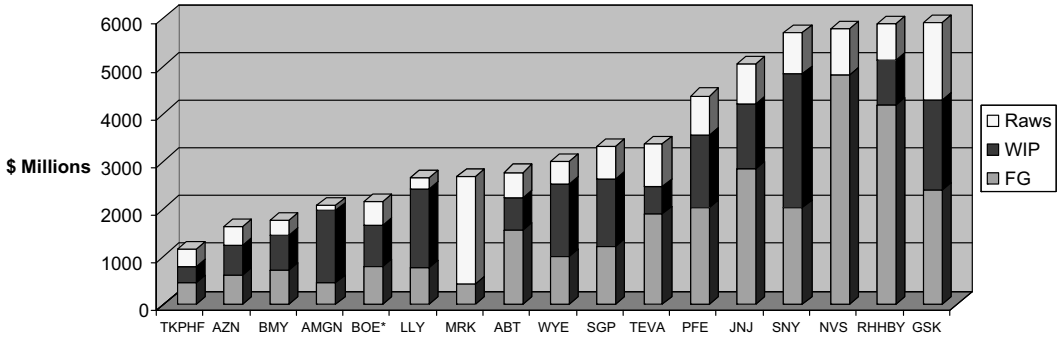


FIGURE 1.7 Inventory holdings for 17 pharmaceutical companies (numerical details shown in Table 1.4) based on inventories listed in each individual company's 2008 annual report. FG, Raws, and WIP refer to finished goods, starting materials, and work in process, respectively.

cost associated with managing, transporting, and storing inventories adding to the waste. Large inventories also tie up large amounts of capital. Implementation of lean manufacturing principles can be used to develop workflows and infrastructures to reduce inventories. One way to reduce inventories is through continuous processing. Chapter 23 by LaPorte et al. discusses the technical benefits of continuous manufacturing. A reliable steady delivery of product API and DP through small product-specific continuous plants could potentially reduce the level of inventory required in a dramatic way if the workflows were designed to ensure consistent delivery of product to packaging and distribution. The facilities of continuous production trains would likely be significantly smaller. Excess inventory represents an opportunity cost where capital is held up in the form of work in process (WIP), API finished goods, and formulated finished goods versus what could be invested elsewhere or back into R&D.

The costs of inventory holdings are significant, including both the carrying cost and the cash value of the inventory. Reductions in inventory equate to a one-time savings of the value of the inventory saved, which represents real savings and positive cash flow. The carrying costs of inventory include two main contributions: (1) weighted average cost of capital (WACC) and (2) overhead [28].

The weighted average cost of capital for the pharmaceutical industry is estimated to be 12% based on 2007 data and overhead costs are approximately 8% [29]. Estimates for the combined carrying cost of WACC and overhead range from 14% to 25%, which translates to approximately 20% return for every dollar of inventory reduction [28, 30]. In addition, every dollar of inventory reduced yields a one-time cash cost savings that can be invested to bolster the company's bottom line, for example, in R&D. Technology platforms and new workflows designed to minimize the need for stockpiling API and DP inventories across the industry therefore would seem to offer very rapid payback.

Figure 1.7 shows the range of inventories for the 17 pharmaceutical companies profiled in Table 1.4. For a large pharmaceutical company carrying $5 billion in inventories, the holding cost based on the combined WACC and overhead of 20% is approximately $1 billion/year. Considered another way, technologies that ensure a reliable and steady distribution of product with the result of eliminating the need to build and store massive inventories can return the company cost savings equivalent to a blockbuster drug (generating billions of dollars per year). Indeed, one of the three factors having the biggest impact on the profitability of a manufacturing organization is inventory with the other two being throughput and operating expense according to Goldratt and Cox [31]. Continuous processing if designed for reliable operations essentially year-round could potentially eliminate the need to accumulate significant inventories above and beyond 2–4 weeks of critical safety stocks of finished goods. Continuous manufacturing across API and DP integrated under one roof as a platform technology is one long-term approach to transforming the way the industry manages their commercial supply chain.

One textbook puts it, "Even for very small processes, continuous processes will prove to be less expensive in terms of equipment and operating costs. Dedicated continuous processes often put batch processes out of business" [32]. The real point here is that continuous manufacturing is one approach to lean manufacturing and to reducing inventories and costs but certainly not the only approach. Other lean systems can be devised that utilize the existing batch facilities as well.

1.3 SUMMARY

With current cost pressures on the pharmaceutical industry, there is an ever-increasing need for chemical engineering skill sets in process development and manufacturing. Chemical engineers are uniquely positioned to help address these needs in part derived from their ability to predict using mathematical models and their understanding of equipment and manufacturability. As Wu et al. highlighted, chemical engineers can help transform pharma from an industry focusing on inventing and testing to a process and product

design industry [33]. Significant pressure exists on what historically used to be a high-margin nature of the pharmaceutical industry to deliver safe, environment-friendly, and economic processes in increasingly shorter timelines. This means fewer scale-ups at kilo and pilot plant scales, with expectation that a synthesis or formulation can be designed in the lab to perform as expected (and right the first time) at the desired manufacturing scale.

From R&D through manufacturing within the pharmaceutical industry, chemical engineering can be leveraged to bring competitive advantage to their respective organizations through process and predictive modeling that lead to process understanding, improving speed of development, and developing new technology platforms and leaner manufacturing methods. The chapters in this book are intended to provide examples of chemical engineering principles specifically applied toward relevant problems faced in the pharmaceutical sciences and manufacturing areas. Further, the broader goal of this work is to promote the role of chemical engineering within our industry, promote the breadth of skill sets therein, and showcase the critical synergy between this discipline and many other scientific disciplines that combine to bring pharmaceutical drugs and therapies to patients in need around the world.

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