CHEMICAL ENGINEERING IN THE PHARMACEUTICAL INDUSTRY

R&D to Manufacturing

Edited by

DAVID J. AM ENDE

WILEY
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PREFACE

Chemical Engineering in the Pharmaceutical Industry is unique in many ways to what is traditionally taught in schools of chemical engineering. This book is therefore intended to cover many important concepts and applications of chemical engineering science that are particularly important to the Pharmaceutical Industry. There have been several excellent books written recently on the subjects of process chemistry in the pharmaceutical industry and separately on formulation development, but relatively little has been published specifically with a focus on chemical engineering.

The intention of the book is to highlight the importance and value of chemical engineering to the development and commercialization of pharmaceuticals covering active pharmaceutical ingredient (API) and drug product (DP) as well as analytical methods. It should serve as a resource for practicing chemical engineers as well as for chemists, analysts, technologists, and operations and management team members—all those who partner to bring pharmaceuticals successfully to market. The latter will benefit through an exposure to the mathematical and predictive approach and the broader capabilities of chemical engineers and also by the illustration of chemical engineering science as applied specifically to pharmaceutical problems. This book emphasizes both the need for scientific integration of chemical engineers with synthetic organic chemists within process R&D and the importance of the interface between R&D engineers and manufacturing engineers. The importance of analytical chemists and other scientific disciplines necessary to deliver pharmaceuticals to the market place is also emphasized with chapters dedicated to selected topics.

Although specific workflows for engineers in R&D depend on each company's specific organization, in general it is clear that, as part of a multidisciplinary team in R&D, chemical engineering practitioners offer value in many ways including API and DP process design, scale-up assessment from laboratory to plant, process modeling, process understanding, and general process development that ultimately reduces cost and ensures safe, robust, and environmentally friendly processes are transferred to manufacturing. How effective the teams leverage each of the various skill sets (i.e., via resource allocation) to arrive at an optimal process depends in part on the roles and responsibilities as determined within each organization and company. In general, it is clear that with increased cost pressures facing the pharmaceutical industry, including R&D and manufacturing, opportunities to leverage the field of chemical engineering science continue to increase. Indeed I have observed a significant increase in chemical engineering emphasis in API process development within Pfizer over the 15 years since I joined the company and especially in the past 5 years.

This book is divided into four main parts:

(1) Introduction
(2) Active Pharmaceutical Ingredient (API)
(3) Analytical Methods and Applied Statistics
(4) Drug Product (DP)

The introductory chapters span roles and opportunities for chemical engineering in small-molecule API, biologicals, drug products, as well as environmental sustainability and quality by design (QbD) concepts. The Active Pharmaceutical Ingredient part consists of 23 chapters covering chemical engineering principles applied to pharmaceutical specific unit operations (reaction engineering, crystallization, chromatography, filtration, drying, etc.) as well as pilot plant and scale-up manufacturing assessment chapters, including process safety. Process modeling promises

to have significant payback as more *in silico* screening enables process design to be performed with fewer resources (for selection process conditions/optimization, solubility, distillation, and extraction design, etc.). Several chapters are devoted to process modeling with emphasis on several of the software tools currently available. The section on drug product includes formulation chapters as well as chapters highlighting unit operations specific to drug product (wet granulation, dry granulation, extrusion, controlled release, and lyophilization). In addition, process modeling within drug product chapter describes the various modeling approaches used to understand and predict performance of powder blending, mixing, tablet presses, tablet coating, and so on. The Analytical Methods and Applied Statistics part describes important topics on chemometrics, statistics, and analytical methods applied toward chemical engineering problems (e.g., material balance, kinetics, design of experiments, or quality by design for analytical methods).

The contributors were encouraged to provide worked out examples—so in most chapters a quantitative example is offered to illustrate key concepts and problem-solving approaches. In this way, the chapters will serve to help others solve similar problems.

There are many people to thank who made this work possible. First, I would like to thank all the contributors of this book. I also would like to thank my colleagues at Pfizer for writing many of the chapters and for my management (past and present) who encouraged and made this effort possible and who continue to encourage the role of chemical engineering in chemical R&D and pharmaceutical sciences.

Special thanks to my family (Mary, Nathan, Noah, and Brianna) for their support during the preparation of this book. Special thanks to Mary, not only for contributing two chapters to this book but also for her assistance in all phases of the project including the cover art. Finally, a special thanks to my parents for their encouragement to pursue chemical engineering in 1983 and their support through my attendance at the University of Iowa and Purdue University.

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CONVERSION TABLE

Quantity	Equivalent Values
Length	$1\,m = 100\,cm = 1000\,mm = 10^6\,\mu m = 10^{10}$ Å $= 39.37\,in = 3.2808\,ft = 1.0936$ yards $= 0.0006214$ mile $1\,ft = 12\,in = 0.3048\,m = 1/3$ yard $= 30.48\,cm$
Area	$1\,m^2 = 10.76\,ft^2 = 1550\,in^2 = 10{,}000\,cm^2$ $1\,in^2 = 6.4516\,cm^2 = 645.16\,mm^2 = 0.00694\,ft^2$ $1\,ft^2 = 929.03\,cm^2 = 0.092903\,m^2$
Volume	$1\,m^3 = 1000\,L = 10^6\,cm^3$ (mL) $= 1000\,dm^3$ $= 35.3145\ ft^3 = 220.83$ imperial gallons $= 264.17$ gal (U.S.) $1\,ft^3 = 1728\,in^3 = 7.4805$ U.S. gallons $= 0.028317\,m^3 = 28.317\,L$ 1 gal (U.S.) $= 3.785\,L = 0.1337\,ft^3 = 231\,in^3$
Mass	$1\,kg = 1000\,g = 0.001$ metric ton (MT) $= 2.20462\,lb_m = 35.27392\,oz$ $1\,lb_m = 16\,oz = 453.593\,g = 0.453593\,kg$ 1 MT $= 1000\,kg = 2204.6\,lb_m$
Pressure	1 atm $= 1.01325$ bar $= 1.01325 \times 10^5\,N/m^2$ (Pa) $= 0.101325$ MPa $= 101.325\,kPa = 1.01325 \times 10^6$ dynes/cm^2 $= 760$ mmHg @ 0 °C (Torr) $= 10.333$ m H_2O @ 4 °C $= 14.696\,lb_f/in^2$ (psi) $= 33.9$ ft H_2O @ 4 °C $= 2116\,lb_f/ft^2$ $= 29.921$ in Hg @ 0 °C
Temperature	$°C = \frac{5}{9}(°F - 32)$ $°F = (9/5°C) + 32$ $K = °C + 273.15 = \frac{5}{9}°R$ $°R = °F + 459.67$
Density	$1\,g/cm^3 = kg/L = 62.4\,lb_m/ft^3$ $1\,lb_m/ft^3 = 16.0185\,kg/m^3 = 0.01602\,g/cm^3$

Quantity	Equivalent Values
Force	$1\,N = 1$ kg-m/s$^2 = 10^5$ dynes $= 10^5$ g-cm/s^2 $= 0.22481\,lb_f$ $1\,lb_f = 32.174\,lb_m\,ft/s^2 = 4.4482\,N$ $= 4.4482 \times 10^5$ dynes
Energy	Based on conventional thermochemical definitions of calorie and Btu, $1\,J = 1\,N\,m = 0.23901$ cal $= 10^7$ ergs $= 10^7$ dyne cm $1\,J = 2.778 \times 10^{-7}$ kW-h $= 0.7376$ ft-lb$_f$ $= 0.00094845$ Btu 1 cal $= 4.184$ J (exact) 1 Btu $= 1054.35\,J = 1.054\,kJ = 251.9958$ cal $= 0.2930$ W-h $= 10.406$ L-atm 1 kW-h $= 3.6$ MJ *Note*: The international steam table (IT) convention defines (calorie)$_{IT} = 4.1868$ J and (Btu)$_{IT} = 1055.056$ J.
Heat generation	$1\,Btu/lb_m$-h $= 0.64612\,W/kg$
Heat transfer coefficient	$1\,W/(m^2\,K) = 0.1761\,Btu/(h\text{-}ft^2\,°F)$ $1\,Btu/(h\text{-}ft^2\,°F) = 5.678\,W/(m^2\,K)$ $= 4.886\,kcal/(h\text{-}m^2\,°C)$
Latent heat	$1\,Btu/lb_m = 2.326\,kJ/kg$ $1\,J/g = 0.23901$ cal/g
Power	$1\,W = 1\,J/s = 1$ kg-m^2/s$^3 = 1$ Nm/s $= 0.23901$ cal/s $= 0.7376$ ft-lb$_f$/s $= 0.0009486$ Btu/s $= 3.414\,Btu/h = 0.001341$ hp
Power/volume	$1\,W/L = kW/m^3 = 0.03798\,hp/ft^3$ $= 96.67\,Btu/h\text{-}ft^3$ $= 12.9235\,Btu/h\text{-}gal$
Specific heat	$1\,kJ/(kg\text{-}K) = J/(g\text{-}K) = 0.2389\,kcal/(kg\,°C)$ $= 0.2389\,Btu/(lb_m\,°F)$ $1\,Btu/(lb_m\,°F) = 1\,cal/(g\,°C)$

(*Continued*)

Quantity	Equivalent Values
Thermal conductivity	1 Btu/(h-ft °F) = 1.7307 W/(m-K) = 0.00413 cal/(s cm-K) 1 W/(m-K) = 0.5779 Btu/(h-ft °F) = 0.85984 kcal/(h-m °C)
Throughput (continuous @ 365 days/year)	1 year = 365 days = 8760 h = 5.256×10^5 min 1 kg/h = 16.67 g/min = 24 kg/day = 8760 kg/year = 8.76 MT/year 10 MT/year = 10,000 kg/year = 27.4 kg/day = 1.14 kg/h = 19.03 g/min 1 Billion tablets/year = 2.74×10^6 tablets/day = 114,155 tablets/h = 31.7 tablets/s 10 MT API/year = 10,000 kg API/year formulated as a 10 mg dose API/tablet = 1.0 Billion tablets/year

Quantity	Equivalent Values
Diffusivity	1 m^2/s = 10.76 ft^2/s = 38749 ft^2/h 1 ft^2/s = 929.03 cm^2/s = 0.092903 m^2/s
Viscosity	1 centipose (cp) = 0.01 poise = 0.01g/(cm-s) = 0.001 N-s/m^2 (Pa-s) = 3.6 kg/(m-h) = 0.001 kg/(m-s) = 2.419 lb_m/(ft-h) 1 centistoke (cs) = 1×10^{-6} m^2/s = 0.01 stoke = 0.0036 m^2/h = 0.0388 ft^2/h
Gas constant R	8.31451 J/(mol-K) = 1.987 cal/(mol-K) = 1.987 Btu/(lb-mol °R) 0.0820578 L-atm/(mol-K) = 82.057 atm-cm^3/(mol-K) = 10.73 psi-ft^3/(lb-mol °R)
Gravitational force	g = 9.8066 m/s^2 = 32.174 ft/s^2

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

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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

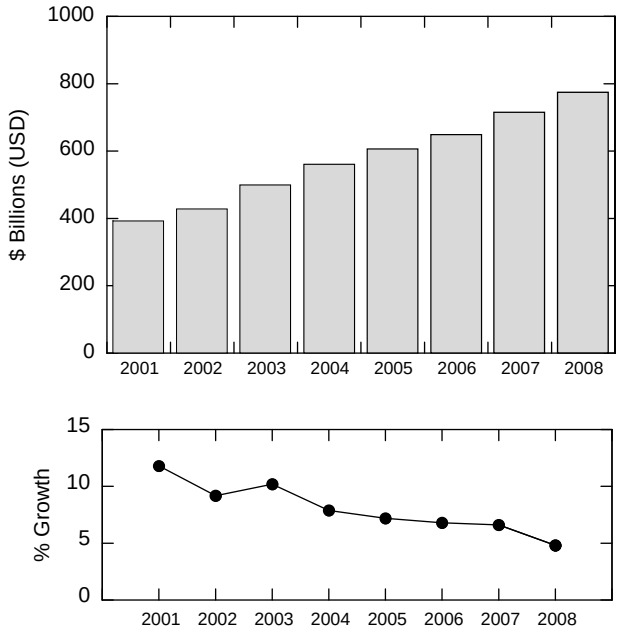


FIGURE 1.1 *Top*: Global pharmaceutical sales with worldwide pharmaceuticals sales approaching $725 billion for year ending 2008. *Bottom*: Declining growth rate based on global sales is defined as percentage change in global sales over the previous year. *Source*: Ref. 15.

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.

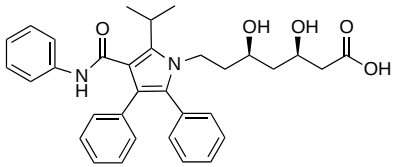
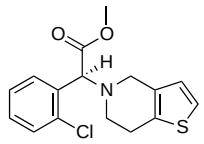
generic competition from 2009 to 2013 according to IMS Health [15], which represents approximately 17% of current global pharmaceutical sales. In addition, the United States is in the midst of U.S. health care reform (2010). It remains unclear whether the higher volume of prescription drugs that the 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.

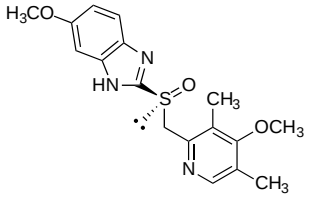
Companies in general are broadly looking for ways to reduce costs to offset the exposure of patent expirations, rising generic competition, and current market pressures. The cost of advancing candidates and entire pharmaceutical portfolios in R&D is significant. In 2001, the average cost for an approved 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.



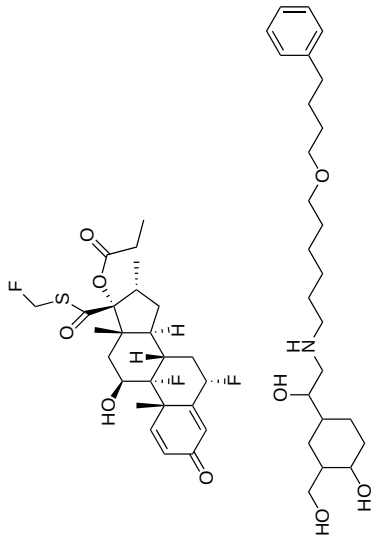
Nexium / Esomeprazole
AstraZeneca
$5.2 Billion in sales

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

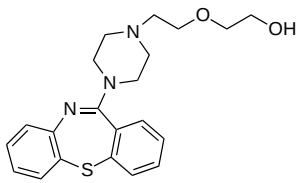
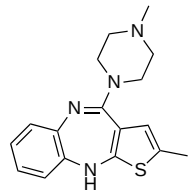
Salmeterol xinafoate is white to off-white crystalline powder with a melting point ~123°C.
Solubility:
In water ~0.07 mg/mL (pH = 8)
In methanol ~40 mg/mL
In ethanol ~7 mg/mL
In chloroform ~3 mg/mL
In isopropanol ~2 mg/mL
Fluticasone propionate is white to off-white powder. It is freely soluble in DMSO 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.

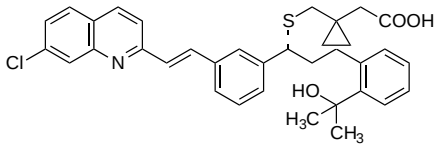
Dry powder inhaler
50 μg salmeterol with 100, 250, or 500 μg fluticasone propionate/blister
Aerosol
25 μg salmeterol with
50, 125, or 250 μg fluticasone propionate/ metered dose

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

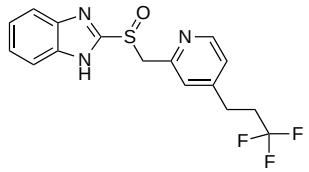
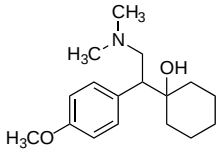
Oral disintegrating tablets also contain the following inactives: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

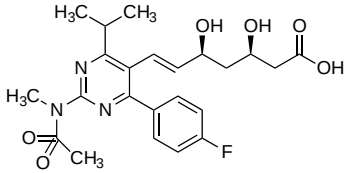
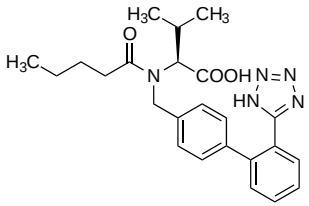
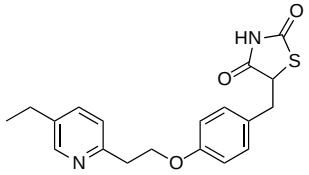
Each 10 mg film-coated Singulair tablet contains montelukast sodium and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of hydroxypropyl methylcellulose, hydroxypropyl 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*)

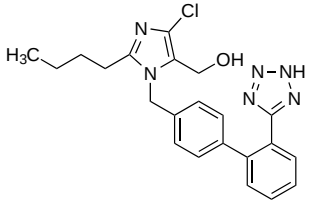
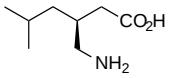
TABLE 1.3 (*Continued*)

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.