CASE 1

# The Pharmaceutical Industry: An Industry Note

The pharmaceutical industry consisted of all enterprises that were involved in the invention of drugs, production of the active substances in drugs, formulation of the drugs, and promotion of them to the public, as well as the specialists who prescribed them.

## The Products

A drug was considered to be any article (other than food) that was intended to be used in diagnosis, treatment, prevention, mitigation, or cure for humans or other animals. Drugs were classified as prescription, generic, or over-the-counter (OTC). Prescription drugs were sold only in pharmacies and required an authorization to sell the drug to a patient written by a physician (a prescription). Generic (or generic equivalent) drugs contained the same active ingredient as a specific brand name prescription drug and required a prescription, but were only allowed to be produced after the brand name drug's patent had expired. OTC drugs were freely available to the public.

---

This case was written by Leonidas Kyriazis, MBA, and Linda E. Swayne, PhD, both from The University of North Carolina at Charlotte. It is intended as a basis for classroom discussion rather than to illustrate either effective or ineffective handing of an administrative situation. 

## *Prescription versus OTC*

The Food and Drug Administration (FDA) through its *OTC Drug Monographs* defined 80 therapeutic categories and 800 significant active ingredients that could be used by consumers in self-diagnosis and self-treatment without prescriptions. More than 100,000 products were manufactured (mainly by pharmaceutical companies) for the OTC market. The pharmaceutical companies had some, but not complete, freedom to decide whether a product would be sold as an OTC drug – when the preparation contained, as an active ingredient, one or more of those included in the list of 800. If a product contained an active ingredient that was not on the OTC list, it had to be registered with the FDA and usually became a prescription drug. Pharmaceutical companies were able to request that any prescription product be transferred to the OTC list, but FDA approval for the change depended on the nature of the product and its safety for public use.

In the US market, prescription drug sales (in dollars) predominated; however, OTC sales numbers were rather inaccurate as the data collection method was continuously changed (Exhibit 1/1).

## *Generic Drugs*

New products that were the result of research and development (R&D) by pharmaceutical companies were usually covered by patents. Patented products enjoyed exclusivity in the market to sell the active ingredient for a specific indication, as long as the patent was valid (20 years, starting from the day of patent application). For the period that the drug was protected by a patent, monopoly pricing was in effect and the price was usually well above the price of the same product after the patent expired. Exhibit 1/2 compares the average price of patented, brand name, and generic drugs.

A drug could become generic after the expiration of the patent. Competitive firms could produce the drug and sell it at lower prices, effectively competing with

Exhibit 1/1: Sales of Prescription and Over-The-Counter Drugs

| **Year** | **1999** | **2000** | **2001** | **2002** |
|---|---|---|---|---|
| Prescription sales (in billions) | $125.8 | $145.6 | $164.1 | $182.7 |
| *Prescription as % of all drug sales* | *87%* | *90%* | *91%* | *91%* |
| Increase in prescription sales | | 15.7% | 12.7% | 11.3% |
| OTC sales (in billions) | $18.9 | $16.7[a] | $17.1[a] | $17.2[a] |
| *OTC as % of all drug sales* | *13%* | *10%* | *9%* | *9%* |
| Increase of OTC sales | | −11.6% | 2.4% | 0.6% |
| **Total** (in billions) | **$144.7** | **$162.3** | **$181.2** | **$199.9** |

[a]Does not include WalMart

***Sources:*** National Association of Chain Drug Stores (www.nacds.org); Consumer HealthCare Products Association (www.chpa-info.org)

Exhibit 1/2: Average Retail Prescription Prices of Drugs

| Year | Brand Name | Generic | Average |
|---|---|---|---|
| 2002 | $75.82 | $27.16 | $54.73 |
| 2003 | $84.21 | $30.56 | $59.30 |

***Source:*** National Association of Chain Drug Stores (www.nacds.org/wmspage.cfm?parm1=507)

the innovator. When a drug came "off patent" and became generic, it was usually referred to by the name designating the active chemical ingredient. Thus, when the patent for PRILOSEC (manufactured by AstraZeneca) expired, the generic appeared in the market as *omeprazole*. A patent could expire but a brand name, once registered and protected, belonged to the company that registered it.

## Market Size and Major Players

Although the world pharmaceutical market represented about $0.5 trillion in sales, more than 80 percent of these sales were in 10 nations (Exhibit 1/3). The United States alone was responsible for approximately 45 percent of world spending. In the United States the spending was $793 per capita, representing 2.1 percent of GDP. The United States was the only leading market without general government price controls on drugs.

Similar to other industries in the 1990s and the early 2000s, the pharmaceutical industry responded to the challenges of globalization. Many smaller companies

Exhibit 1/3: Pharmaceuticals Sales, Top 10 Markets, June 2003 to June 2004

| | | Sales (in billions) | Population | Per capita spending | GDP (in billions) | % of GDP |
|---|---|---|---|---|---|---|
| 1 | US | $228.7 | 288,368,698 | $793 | 10,857.2 | 2.1% |
| 2 | Japan | $55.4 | 127,619,000 | $434 | 4,317.1 | 1.3% |
| 3 | Germany | $27.8 | 82,537,000 | $337 | 2,403.1 | 1.2% |
| 4 | France | $26.4 | 58,518,748 | $451 | 1,757.6 | 1.5% |
| 5 | UK | $18.4 | 58,789,194 | $313 | 1,798.5 | 1.0% |
| 6 | Italy | $17.9 | 56,305,568 | $318 | 1,465.8 | 1.2% |
| 7 | Spain | $12.8 | 42,717,064 | $300 | 838.6 | 1.5% |
| 8 | Canada | $10.5 | 31,413,990 | $334 | 853.8 | 1.2% |
| 9 | China | $6.6 | 1,284,530,000 | $5 | 1,409.8 | 0.5% |
| 10 | Mexico | $6.3 | 97,483,412 | $65 | 615.1 | 1.0% |

***Source:*** "Health Care in Focus," *Chemical and Engineering News* 82, no. 49 (2004), p.18

merged to form large conglomerates to create worldwide strength. The merger history for the major players over the past five years is summarized in Exhibit 1/4.

As the largest market in the world, the US pharmaceutical companies were actively involved in mergers. As a result, the largest players world wide were also generally the largest in the United States (see Exhibit 1/5).

## Exhibit 1/4: Five-year Merger History of the World Top 10 Pharmaceutical Companies

| | Corporation | Market Share based on sales 2003 | 1998 | Agglomerate of |
|---|---|---|---|---|
| 1 | Pfizer | 10.1% | 9.0% | Pfizer, Pharmacia, Upjohn, Warner-Lambert, Searle |
| 2 | GlaxoSmithKline | 6.6% | 7.2% | Glaxo, Wellcome, SmithKline French, Beecham |
| 3 | Sanofi-Aventis | 5.4% | 5.8% | Sanofi, Syntelabo, Hoechst, Rohne-Poulenc, Fisons |
| 4 | Merck & Co | 4.8% | 4.2% | |
| 5 | Johnson & Johnson | 4.8% | 3.6% | |
| 6 | Novartis | 4.3% | 4.2% | Ciba-Geigy, Sandoz |
| 7 | AstraZeneca | 4.1% | 4.3% | Astra, Zeneca |
| 8 | Bristol-Myers Squibb | 3.4% | 4.2% | Bristol-Myers Squibb, DuPont Pharma |
| 9 | Hoffmann-La Roche | 3.3% | 3.1% | |
| 10 | Abbott | 2.8% | 3.3% | Abbott, BASF Pharma (Knoll) |
| | Total 10 Corporations | 49.6% | 48.9% | |

***Source:*** "Health Care in Focus," *Chemical and Engineering News* 82, no. 49 (2004), p.18

## Exhibit 1/5: Leading 20 Corporations by US Sales, 2004

| | Corporation | Total Sales[a] (in billions) | Growth | Market Share | | Corporation | Total Sales[a] (in billions) | Growth | Market Share |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Pfizer | $30.7 | 5% | 13.1% | 11 | Lilly | $8.0 | 6% | 3.4% |
| 2 | GlaxoSmithKline | $18.8 | 1% | 8.0% | 12 | Abbott | $6.5 | 16% | 2.8% |
| 3 | Johnson & Johnson | $16.2 | 7% | 6.9% | 13 | Hoffmann-La Roche | $6.1 | 16% | 2.6% |
| 4 | Merck & Co | $15.0 | 8% | 6.4% | 14 | TAP Pharmaceutical | $4.7 | −5% | 2.0% |
| 5 | AstraZeneca | $11.3 | 12% | 4.8% | 15 | Boehringer Ingelhein | $3.7 | 21% | 1.6% |
| 6 | Novartis | $10.2 | 7% | 4.3% | 16 | Forest Lab | $3.4 | 16% | 1.4% |
| 7 | Sanofi-Aventis | $10.0 | 12.6% | 4.3% | 17 | Teva | $3.4 | 17% | 1.4% |
| 8 | Amgen | $9.5 | 23% | 4.1% | 18 | Schering Plough | $2.9 | −27% | 1.2% |
| 9 | Bristol-Myers Squibb | $9.2 | −4% | 3.9% | 19 | Eisai | $2.5 | 11% | 1.1% |
| 10 | Wyeth | $8.2 | 11% | 3.5% | 20 | Watson | $2.4 | 18% | 1.0% |

[a]Represents prescription pharmaceutical purchases including insulin at wholesale prices by retail, food stores and chains, mass merchandisers, independent pharmacies, mail services, non-federal and federal hospitals, clinics, closed-wall HMOs, long-term care pharmacies, home health care, and prisons/universities. Excludes co-marketing agreements. Joint-ventures were assigned to the product owner. Data were run by custom redesign to include completed mergers and acquisitions.

***Source:*** IMS Health, IMS National Sales Perspectives™, 2/2005 (see http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695983_69891374,00.html)

To be successful, pharmaceutical companies attempted to discover medications that improved the medical condition of human beings but at the same time had to be able to recover the huge R&D expenses. Thus, most major pharmaceutical companies targeted the largest therapeutic classes (Exhibit 1/6) with brand name (patented) products (Exhibit 1/7).

## Exhibit 1/6: Leading 20 Therapeutic Classes by US Sales, 2004

| | Indication or Class Description | Class | Sales[a] (in billions) | Growth | Market Share |
|---|---|---|---|---|---|
| 1 | Hypercholesterolemia (cholesterol-lowering drugs) | HMG – COA Reductase Inhibitors (Statins) | $15.50 | 12% | 6.6% |
| 2 | Antiulcerants (Gastric Ulcers, GERD[b]) | Proton Pump Inhibitors | $12.50 | −3% | 5.3% |
| 3 | Antidepressants (depression fighting drugs) | Selective Serotonin Reuptake Inhibitor, Selective Norepinephrine Reuptake Inhibitor (SSRI/SNRI) | $11.00 | 1% | 4.7% |
| 4 | Antipsychotics (Schizophrenia, mental illness) | Antipsychotics, Other | $9.10 | 12% | 3.8% |
| 5 | Antiepileptics (Epilepsy) | Seizure Disorders | $8.20 | 19% | 3.5% |
| 6 | Anemia (blood disorder) | Erythropoietins | $8.00 | 8% | 3.4% |
| 7 | Antiarthretics (relieve pain of arthritis) | COX-2 Inhibitors | $5.30 | 0% | 2.3% |
| 8 | Hypertension (reduce high blood pressure) | Calcium Blockers | $4.40 | 1% | 1.9% |
| 9 | Hypertension (reduce high blood pressure) | Angiotensin II Antag | $4.40 | 24% | 1.9% |
| 10 | Hypertension (reduce high blood pressure) | Ace Inhibitors | $3.90 | −5% | 1.7% |
| 11 | Osteoporosis (bone disease) | Bisphosphonates | $3.60 | 15% | 1.5% |
| 12 | Diabetes | Insulin Sensitizer | $3.40 | 12% | 1.4% |
| 13 | Pain Relief | Codeine and combinations | $3.30 | 5% | 1.4% |
| 14 | Blood-Thinner, Antistroke | Antiplatelets, Oral | $3.30 | 31% | 1.4% |
| 15 | Antiallergic | Antihistamines, Caps/Tabs | $3.20 | −9% | 1.4% |
| 16 | HIV | HIV-Reverse Trans Inhibitors | $3.10 | 8% | 1.3% |
| 17 | Asthma | Steroid, Inhaled | $2.90 | 26% | 1.2% |
| 18 | Contraceptive | Oral Contraception | $2.80 | −2% | 1.2% |
| 19 | AIDS, Multiple Sclerosis | Immunologic Interferons | $2.80 | 5% | 1.2% |
| 20 | Ulcerative Colitis, Crohn's Disease | Gastrointestinal Antiinflammatory | $2.70 | 15% | 1.2% |

[a]Represents prescription pharmaceutical purchases at wholesale prices by retail, food stores and chains, mass merchandisers, independent pharmacies, mail services, non-federal and federal hospitals, clinics, closed-wall HMOs, long-term care pharmacies, home health care, and prisons/universities.

[b]GastroEsophageal Reflux Disease

***Source:*** IMS Health, IMS National Sales Perspectives™, 2/2005 (see http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695983_69891394,00.html)

## Exhibit 1/7: Leading 20 Products by US Sales, 2004

| | Brand | Marketer | Action | Indication | Sales[a] (in billions) | Growth | Market Share |
|---|---|---|---|---|---|---|---|
| 1 | LIPITOR | Pfizer | Circulatory and blood | Hypercholesterolemia | $7.70 | 14% | 3.3% |
| 2 | ZOCOR | Merck | Circulatory and blood | Hypercholesterolemia | $4.6 | 4% | 1.9% |
| 3 | PREVACID | Takeda, Abbott | Stomach | Gastric ulcers, GERD[b] | $3.8 | −5% | 1.6% |
| 4 | NEXIUM | AstraZeneca | Stomach | Gastric ulcers, GERD[b] | $3.8 | 23% | 1.6% |
| 5 | PROCRIT | Johnson & Johnson | Circulatory and blood | Anemia | $3.2 | −3% | 1.4% |
| 6 | ZOLOFT | Pfizer | Antipsychotic | Depression | $3.1 | 8% | 1.3% |
| 7 | EPOGEN | Amgen | | Anemia | $3.0 | −4% | 1.3% |
| 8 | PLAVIX | Sanofi-Aventis, Bristol-Myers Squibb | Circulatory and blood | Acute coronary syndrome, stroke, thrombosis, blood thinner | $3.0 | 33% | 1.3% |
| 9 | ADVAIR DISKUS | GlaxoSmithKline | Breathing | Asthma | $2.9 | 26% | 1.2% |
| 10 | ZYPREXA | Lilly | Antipsychotic | Schizophrenia | $2.8 | −10% | 1.2% |
| 11 | CELEBREX | Pfizer | Pain relief and anti-inflammatories | Arthritis | $2.7 | 7% | 1.2% |
| 12 | EFFEXOR XR | Wyeth | Antidepressant | Anti-aging, anti-depressant | $2.6 | 22% | 1.1% |
| 13 | NEURONTIN | Pfizer | Pain relief and anti-inflammatory | Postherpetic neuralgia (PHN). | $2.6 | 5% | 1.1% |
| 14 | NORVASC | Pfizer | Blood pressure | Hypertension, angina | $2.4 | 10% | 1.0% |
| 15 | PROTONIX | Wyeth | Stomach | Gastric ulcers, GERD[b] | $2.2 | 28% | 1.0% |
| 16 | SINGULAIR | Merck | Breathing | Asthma | $2.1 | 25% | 0.9% |
| 17 | RISPERDAL | Janssen | Antipsychotic | Schizophrenia | $2.0 | 2% | 0.9% |
| 18 | PRAVACHOL | Sanofi-Aventis, Bristol-Myers Squibb | Circulatory and blood | Hypercholesterolemia | $2.0 | −2% | 0.8% |
| 19 | FOSAMAX | Merck | Osteoporosis | Osteoporosis | $2.0 | 9% | 0.8% |
| 20 | SEROQUEL | AstraZeneca | Antipsychotic | Schizophrenia | $2.0 | 31% | 0.8% |

[a]Represents prescription pharmaceutical purchases at wholesale prices by retail, food stores and chains, mass merchandisers, independent pharmacies, mail services, non-federal and federal hospitals, clinics, closed-wall HMOs, long-term care pharmacies, home health care, and prisons/universities.

[b]GastroEsophageal Reflux Disease

***Source:*** IMS Health, IMS National Sales Perspectives™, 2/2005 (see http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_49695983_69890133,00.html)

# R&D

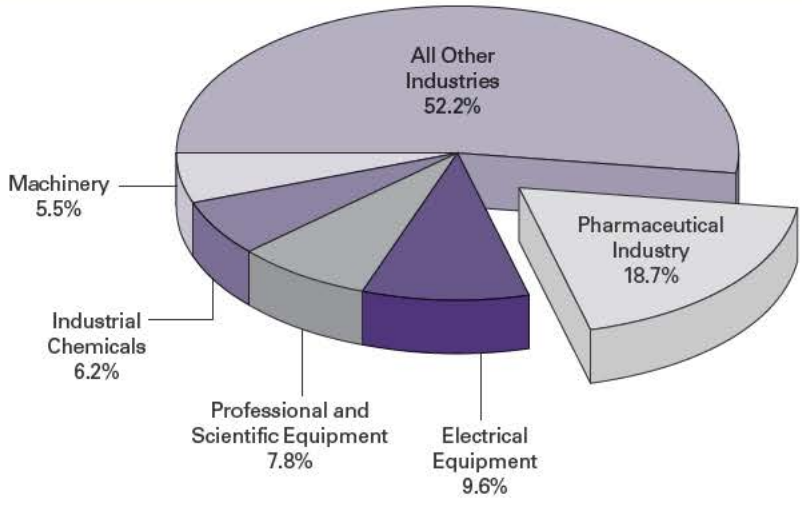
The pharmaceutical industry relied on new product development. In 2004, the pharmaceutical industry spent 18.7 percent of all self-performed R&D in the United States, more than any other single industry (Exhibit 1/8). R&D spending reached the record amount of $38.8 billion in 2004, an increase of 12.6 percent over 2003 (not including the $10.5 billion R&D spending by Biotech companies).[1]

Worldwide pharmaceutical industry R&D spending increased eight times between 1980 when it was $2 billion and 2004 when it was $38.8 billion (Exhibit 1/9).

R&D spending for the top 10 US leading corporations as a percentage of revenue was between about 11 and 25 percent (Exhibit 1/10).

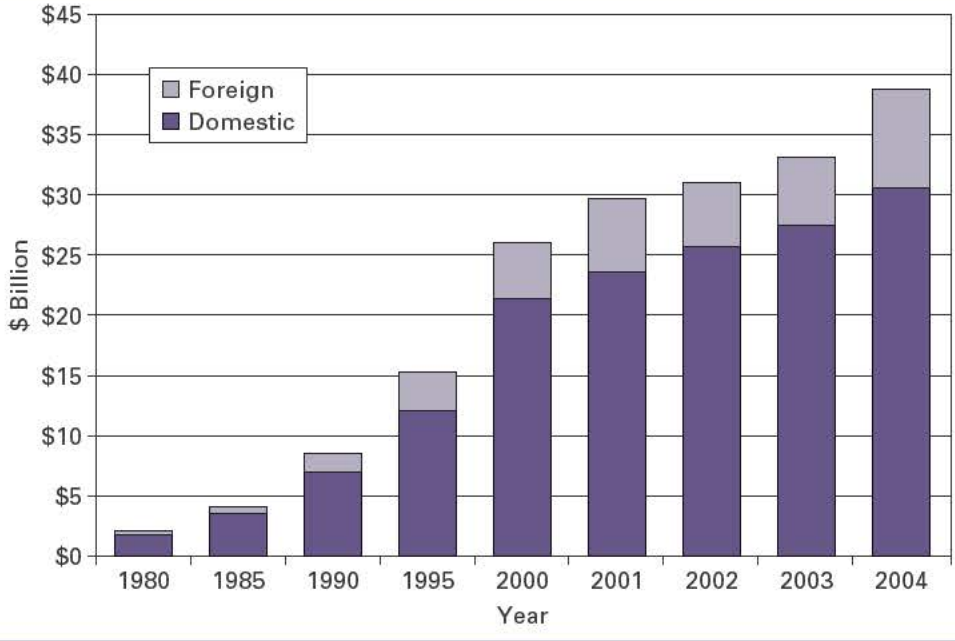
Although the money spent increased rapidly over time, the number of products in the late development stage in 2004 were fewer in number than there were in the mid-1990s, indicating that the R&D productivity had not increased.[2] R&D money was spent searching for new molecules, preparing for pre-clinical trials, and undergoing

## Exhibit 1/8: 2004 Self-Performed Basic R&D Spending



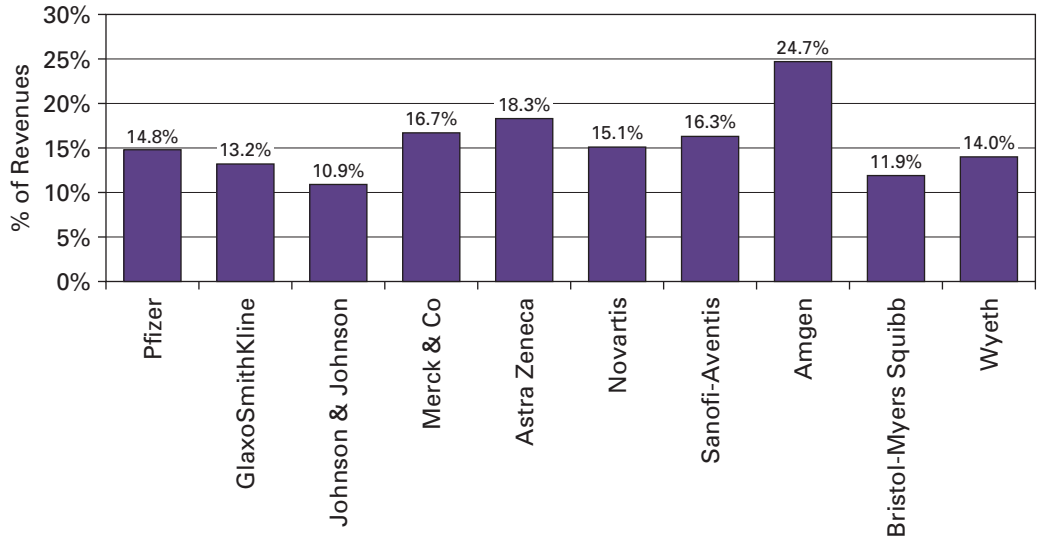

***Source:*** Profile Pharmaceutical Industry 2004 (www.phrma.org)

## Exhibit 1/9: R&D Spending by US Pharmaceutical Industry in US and Other Countries




***Source:*** Profile Pharmaceutical Industry 2004 (www.phrma.org)

Exhibit 1/10: R&D Spending of the 10 Leading Pharmaceutical Corporations




***Source:*** SEC filings (www.Morningstar.com)

clinical trials. Drug development was a highly speculative process and R&D expenses were spread between the successful and unsuccessful trials. Only one molecule out of 1,000 entering the R&D pipeline emerged as an approved drug.[3] Despite a drug passing the pre-clinical trials and reaching Phase I, it only had a probability of 10 percent to make it to the market. Even if it reached the market, it had only a 30 percent probability of becoming profitable.[4] Of the new drug applications approved by the FDA in 2002, only 22 percent were for new chemical entities; the majority were new formulations or line extensions of existing products.

The pharmaceutical industry operated under constant pressure to produce new products – especially those that could be patent protected and become profitable. And at the same time that productivity of R&D spending was not improving early in the 21st century, important and profitable products were coming "off patent" further pressuring pharmaceutical companies (see Exhibit 1/11).

As their blockbuster drugs came off patent, the pharmaceutical companies counted on R&D for new products that would take their place – or they tried to extend the successful patents they had. For example, AstraZeneca's PRILOSEC (*omeprazole*), with sales over $5 billion, came off patent in 2002 but AstraZeneca managed to replace it with a slightly modified product – NEXIUM (*esomeprazole*).

As the costs for R&D soared, research productivity did not improve and pressures for profitability did not change, many of the large companies turned to in-licensing.[5] In the past, small R&D companies had difficulty engaging large partners to in-license drugs, and even if they managed to reach an agreement, their products were not actively promoted because the large companies' in-house products had priority. With fewer breakthrough discoveries, licensing became

Exhibit 1/11: Drugs Lost (or Losing) US Patent Protection

| | Product | Marketer | Action | Indication | When | Global Sales (in billions) |
|---|---|---|---|---|---|---|
| 1 | PRILOSEC (*omeprazole*) | AstraZeneca | Stomach | Gastric ulcers, GERD | Dec 2002 | $5.70 |
| 2 | PAXIL (*paroxetine*) | GlaxoSmithKline | Antipsychotic | Depression | Sep 2003 | $3.3 |
| 3 | CLARITIN (*loraladine*) | Schering-Plough | Allergy | Allergic rhinitis | Dec 2002 | $3.2 |
| 4 | NEURONTIN (*gapapentin*) | Pfizer | Pain relief, anti-inflammatory | Epilepsy, neuropathic pain | Oct 2004 | $2.7 |
| 5 | AUGMENTIN (*amoxilin, clavulanate*) | GlaxoSmithKline | Antibiotic | Bacterial infections | Jul 2002 | $2.1 |
| 6 | OXYCONTIN (*oxycodone*) | Purdue Pharma | Narcotic | Pain | Mar 2004 | $2.1 |
| 7 | CIPRO (*ciprofloxasin*) | Bayer | Antibiotic | Bacterial infections | Jun 2004 | $1.6 |
| 8 | DIFLUCAN (*fluconazole*) | Pfizer | Antifungal | Fungal infections | Jul 2004 | $1.2 |
| 9 | CELEXA (*citalopram*) | Forest | SSRI | Depression | Oct 2004 | $1.1 |
| 10 | ZOCOR (*simvastatin*) | Merck | Circulatory and blood | Hypercholesterolemia | 2006 | $5.0 |
| 11 | NORVASC (*amlodipine*) | Pfizer | Blood pressure | Hypertension, angina | 2006 | $4.3 |
| 12 | ZOLOFT (*sertraline*) | Pfizer | Antipsychotic | Depression | 2006 | $3.1 |
| 13 | PRAVACHOL (*pravastatin*) | Sanofi-Aventis, Bristol-Myers Squibb | Circulatory and blood | Hypercholesterolemia | 2006 | $2.8 |
| 14 | ZITHROMAX (*azithromycin*) | Pfizer | Antibiotic | Bacterial infections | 2005 | $2.0 |
| 15 | AMBIEN (*zolpidem*) | Sanofi-Aventis, Bristol-Myers Squibb | Sleep aid | Insomnia | 2006 | $1.5 |
| 16 | ZYRTEC (*cetirizine*) | Pfizer | Allergy | Allergic rhinitis | 2007 | $1.3 |
| 17 | ZOFRAN (*ondansetron*) | GlaxoSmithKline | Antinausea | Chemotherapy induced nausea | 2005 | $1.2 |

***Source:*** IMS Health, IMS National Sales Perspectives™, 2/2005 (see: http: //www. imshealth.com) and "Health Care in Focus," *Chemical and Engineering News* 82, no. 49 (2004), p. 18.

more important and the large companies became more willing to acquire or promote licensed products. In 2001, in-licensed products generated 16 to 20 percent of the revenue of the 20 largest pharmaceutical corporations; revenue generated by in-licensed product was expected to reach 40 percent by 2007. Many of the

agreements made during 2004 were with biotech companies that co-promoted the in-licensed products. In 2003, the large corporations were paying an average of $110 million as up-front payment rights for a product that had reached Phase III clinical trials.[6]

Some analysts believed that the pharmaceutical industry was effectively dividing into two sectors: companies that were becoming very specialized R&D organizations and others that were focusing on sales and marketing. However, the largest organizations attempted to continue doing both.

# Regulation

## *FDA Approval Process*

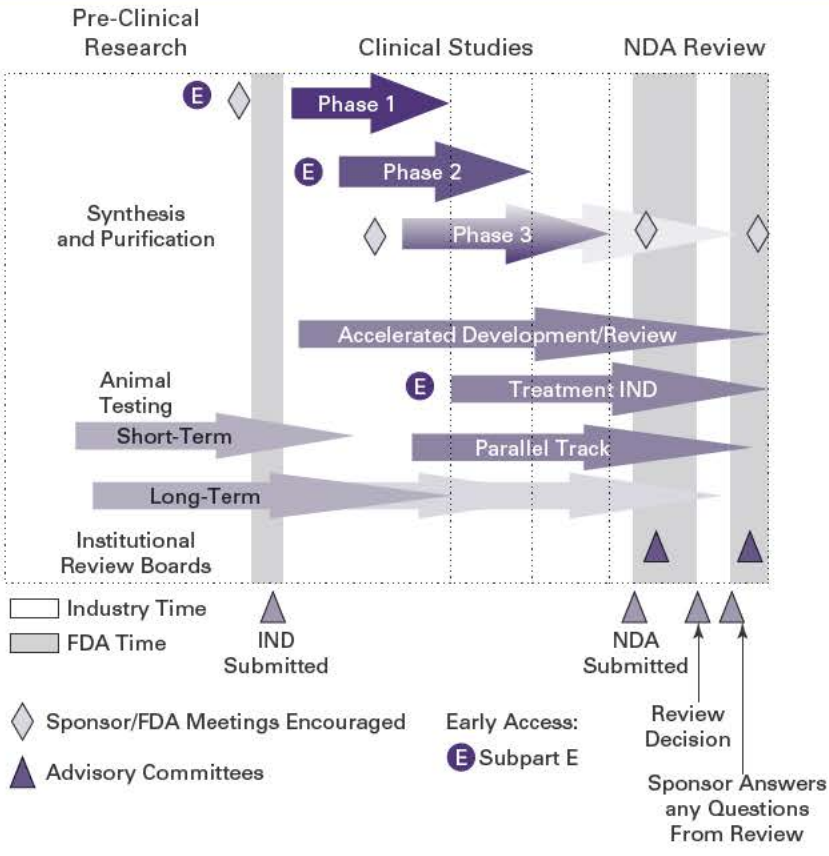
To introduce a new drug to the US market, FDA approval was required – a complicated, time-consuming, and expensive process (see Exhibit 1/12). The organization seeking approval (the "sponsor") went through two different evaluation stages:

1. The Investigational New Drug (IND) Review Process to determine whether the product was suitable for use in clinical trials, and
2. The New Drug Application (NDA) Review Process to determine the benefit/risk profile of a drug prior to its approval for marketing.

One of the most important parts of the drug approval process was the clinical studies that were designed to distinguish the drug's effect from other influences on humans – for example, a spontaneous change in disease progression or the effect of a placebo (an inactive ingredient that looked like the test drug). These studies were typically conducted in the United States under an approved investigational new drug application, in accord with FDA rules on human studies and informed consent of participants. There were three different phases of trials in the pre-approval stage and one in the post-marketing stage:

- **Phase I**: The first trials in humans to test a compound for safety tolerance and pharmacokinetics.[7] These trials usually employed normal, healthy volunteers.
- **Phase II**: Pilot studies to define efficacy and safety in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented. Dose and dosing regimens were assigned for magnitude and duration of effect.
- **Phase III**: Expanded clinical trials intended to gather additional evidence of effectiveness for specific indications and to better understand safety and drug-related adverse effects.
- **Phase IV**: Post-marketing studies were conducted to determine the incidence of adverse reactions. These studies could result in serious consequences for the company if they proved that serious adverse effects existed that were not identified in Phases I–III.

Exhibit 1/12: New Drug FDA Approval Process




*Source:* Food and Drug Administration (www.fda.gov)

New drugs were usually protected by patents. Once a patented drug exceeded its protected time period, market exclusivity could be sought (the patent would expire, however competitors would still not be allowed to offer the product as long as the exclusivity period lasted). When the patent protection and market exclusivity were exhausted, other manufacturers could begin offering a generic version – provided that the generic product was evaluated (tested) to be certain that it was equally safe and offered the same efficacy[8] as the branded product. Typically, the manufacturers of generic drugs did not need to repeat all the studies originally done for a drug's approval. This kept the cost for the introduction of a generic drug down, encouraged competition, and kept drug costs lower for patients.

Exhibit 1/13 lists the control stages that both brand name and generic drugs were required to go through to be approved. A generic drug supplier was required to go through the abbreviated new drug application (ANDA) review process for the

Exhibit 1/13: NDA vs. ANDA Review Process

| **Brand Name Drug** NDA Requirements | **Generic Drug** ANDA Requirements |
|---|---|
| Chemistry | Chemistry |
| Manufacturing | Manufacturing |
| Controls | Controls |
| Labeling | Labeling |
| Testing | Testing |
| Animal Studies<br>Clinical Studies<br>Bio-availability | Bio-equivalence |

***Source:*** Food and Drug Administration (www.fda.gov)

active ingredient(s). The possible generic was rigorously reviewed – its labeling, chemistry, manufacturing, and controls had to be identical (excluding the parts indicating the patent protection) and the testing procedure must be repeated similarly to the new drug application process. The difference for generics was that the animal studies, the clinical studies, and the bio-availability were replaced by bio-equivalence studies. Two products are considered bio-equivalent if, when they were given to the same individual patient, the patient absorbed the same amount of drug into the bloodstream and at the same rate.

The procedure used to verify the bio-equivalence was to measure the concentration of the drug in the blood of the patient at different times after administering it. If the measures were the same, the brand name and the generic drug were considered therapeutically equivalent. Only when the drug was not absorbed into the bloodstream – a rather rare case – would clinical studies have to be redone.

## *Market Exclusivity*

Because the FDA approval process was lengthy (and totally out of the control of the organization submitting a drug for review and approval), US lawmakers decided to incorporate a provision into the Hatch–Waxman Act that allowed the innovator to apply for an extension of the patent coverage based on the length of the FDA approval process.[9] According to the statute, no ANDA filings (request to begin the generic drug approval process) could be submitted during a granted exclusivity period. A 5-year period of exclusivity (past the patent expiration) could be granted to new drug applications for products containing chemical entities either alone or in combination that had never previously been approved by the FDA.

A 3-year period of exclusivity could be granted for a drug that contained an active moiety[10] that had been previously approved, when the application contained reports of new clinical investigations conducted by the sponsor that were essential to approval of the application. For example, the changes in an approved

drug product that affected its active ingredient(s), strength, dosage form, route of administration or conditions of use might be granted exclusivity if clinical investigations were essential to the approval of the application containing those changes.

For drugs whose NDA was submitted before January 1, 2002, six additional months of exclusivity could be obtained under the Food and Drug Administration Modernization Act of 1997, if the sponsor submitted requested information relating to the use of the active moiety in the pediatric population.

Finally, a reason for a sponsor to be granted exclusivity beyond the patent protection period was if the drug was developed to cure diseases affecting less than 200,000 people. Such a drug could be designated an "orphan drug" by the FDA.[11] Sponsors of orphan drugs were granted 7 years of market exclusivity as well as tax incentives for clinical research.

## *Liability and Unforeseen Effects*

On September 30, 2004, Merck voluntarily withdrew its second best-selling drug, VIOXX, as the pain medication for arthritis seemed to be responsible for increased risk of cardiovascular disease.[12] Pfizer admitted that one of its best-selling medicines, CELEBREX, could impose increased risk of heart problems. AstraZeneca reported that a trial of IRESSA, a lung cancer drug approved in 2003, showed that the drug did not prolong life. Eli Lilly warned doctors that STRATTERA, its drug to treat attention deficit disorder (ADD), had caused severe liver injury in at least two patients.[13]

These examples illustrated the uncertainty facing the pharmaceutical industry. Long-term use of some drugs proved to be harmful to some patients and the drug had to be removed from the market after huge investments in R&D and marketing. New drugs not only had to be tested thoroughly before their approval but also as they were being used after introduction. Enormous liabilities occurred if a product failed to be as safe as was predicted through the pre-approval studies (Phase I, II, and III trials).

## *Off-Label Promoting of Pharmaceuticals*[14]

The FDA approved a medicine for a specific indication and the marketer was obligated to inform physicians and the public not only about the specific indication but also about the recommended dosage and duration. Promotion (advertising or personal selling) for a different indication was not permitted and could result in substantial penalties from the FDA if its rules were violated.

Although the marketer of a drug was restricted to a specific indication, physicians had the discretion to prescribe a drug for any indication and in combination with any other medication that they believed might help their patients. The term "off-label" was used to describe the prescribing of a medication for an indication that had not been FDA approved. Physicians might prescribe off-label products

on the basis of their own clinical experience or on published clinical studies by other physicians. Not all physicians were eager to do so, however, because their recommendations exposed them to malpractice lawsuits.

The pharmaceutical companies were often reluctant to seek approval for additional indications of a drug because the market might not be of sufficient size to justify the added expense. The Food and Drug Administration Modernization Act of 1997 provided a way for pharmaceutical companies to legally disseminate information on off-label use of their products. According to this Act, when asked by a physician, a firm could distribute peer-reviewed journal articles about off-label indications, provided that the company made commitments to the FDA to submit a supplemental new drug application (SNDA).

If the off-label usage for a drug was sufficiently different from its previously approved use, a patent might be granted that would provide exclusivity for that specific use. Such was the case with WELLBUTRIN and ZYBAN produced by GlaxoWellcome.[15] WELLBUTRIN was prescribed for depression, but it also was used off-label for smoking cessation. In this case, the $350 million spent for its SNDA approval provided Glaxo with a new patent that protected the company's interests and enabled it to sell ZYBAN to a wide customer base of smokers who wanted to quit.

## The Drug Crisis or Who Pays the R&D Cost?

US prescription drug sales grew 8.3 percent to $235.4 billion in 2004. "*This is the first year since 1995 that the pharmaceutical industry has scored less than double-digit growth,*" explained Bruce Boggs, president of IMS Americas (a pharmaceutical market research firm). "*However, the industry delivered solid performance overall despite significant business pressures in areas such as drug safety, pricing, and generic competition.*"[16] See Exhibit 1/14 for sales between 1995 and 2004.

From 2000 to 2005, prescription drugs sales increased more than 47 percent using constant 2004 dollars, a figure that was more than five times the increase in the consumer price index during that same time period. The fact that the cost of the average prescription increased no more than 30 percent over these years suggested that the usage of drugs was increasing.

During the years 1999 to 2005, the top pharmaceutical companies started spending a higher percentage of their cost for operating expenses (R&D, sales, administration), thus the manufacturing cost of the drugs (cost of goods sold) became a smaller percentage of costs (see Exhibit 1/15). This increase in spending for operating expenses was attributed to direct to customer advertising, increased cost for research and development, and expenses related to mergers.

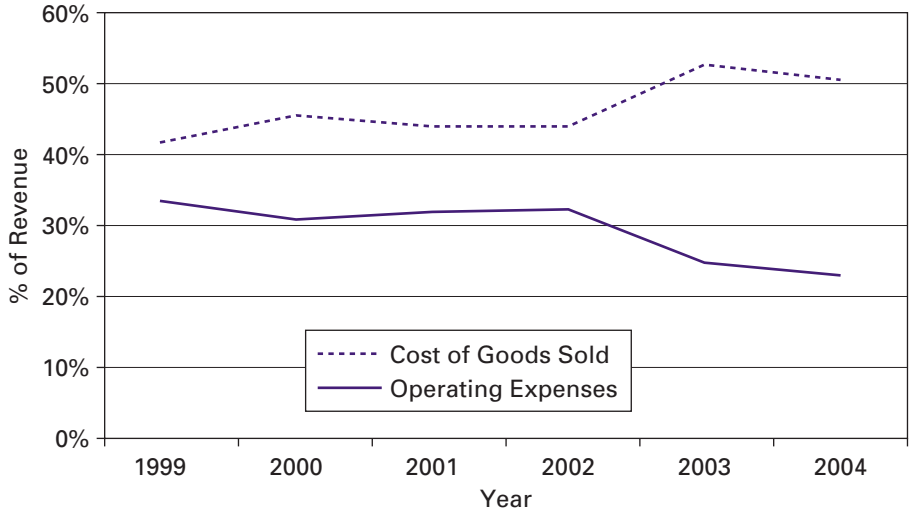
Brand name drugs operated in a protected environment and enjoyed premium prices, often two to three times more expensive than generics. After 2000, generic drug sales increased by an average of 26 percent per year. However, by 2004, this increase had slowed to only 10 percent.[17]

Exhibit 1/14: US Prescription Drug Sales 1995–2004

| Year | 1995 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 |
|---|---|---|---|---|---|---|---|
| Consumer price index | 152.4 | 166.6 | 172.2 | 177.1 | 179.9 | 184.0 | 188.9 |
| Prescription drug sales (in millions) | $72,200 | $125,800 | $145,600 | $164,100 | $182,700 | $203,100 | $235,400 |
| Adjusted sales (constant 2004 dollars) (in millions) | $89,492 | $142,639 | $159,720 | $175,034 | $191,840 | $208,509 | $235,400 |
| Prescriptions (in millions) | 2,125 | 2,707 | 2,865 | 3,009 | 3,138 | 3,215 | 3,318 |
| Cost per prescription (constant 2004 dollars) | $42.1 | $52.7 | $55.7 | $58.2 | $61.1 | $64.9 | $70.9 |
| Change | | 25.1% | 5.8% | 4.3% | 5.1% | 6.1% | 9.4% |
| Inflation | | 9.3% | 3.4% | 2.8% | 1.6% | 2.3% | 2.7% |

***Source:*** IMS Health, IMS National Sales Perspectives.™ 2/2005 (see: http://www.imshealth.com)

Exhibit 1/15: Ten Largest US Pharmaceutical Companies Expense Allocation




***Source:*** SEC filings (www.Morningstar.com)

## *Medicare Part D*

US spending on health care was expected to soar in 2006 when Medicare[18] was scheduled to start covering the cost of prescription drugs. Medicare Part D provided for the elderly who could not afford the prescriptions their doctors ordered. Estimates were that the expansion of Medicare's drug coverage would inflate

health care spending by more than $50 million per year for the next decade.[19] The forecast was that, for the decade 2006 to 2015, the cost of prescription drugs to the US government would be $724 billion (almost double the figure of $400 billion that Congress had in mind in December 2003 when it approved the Medicare Modernization Act).[20]

## *Formularies and Pharmacy Benefit Managers*

To reduce the costs associated with pharmaceuticals, insurance companies and hospitals developed clinical formularies.[21] The lower cost was achieved by selecting lower cost drugs or those that generated "rebates" directly from the manufacturers of the drugs. Rebates occurred by having only one or two brands for the treatment of various conditions, thereby limiting competition – in some cases, severely. The physicians were required to choose drugs from the formulary or their patients were required to pay the full cost of the drug. Formularies were used primarily by hospitals and managed care insurance programs.

Because the prescribing physicians and the patients were not particularly happy with the restrictions forced by the formularies, companies such as MedCo emerged. These companies, called pharmacy benefit managers (PBMs), claimed that they could offer prescription drugs at lower costs by negotiating significant volume discounts with drugmakers. Many insurance carriers used PBMs.

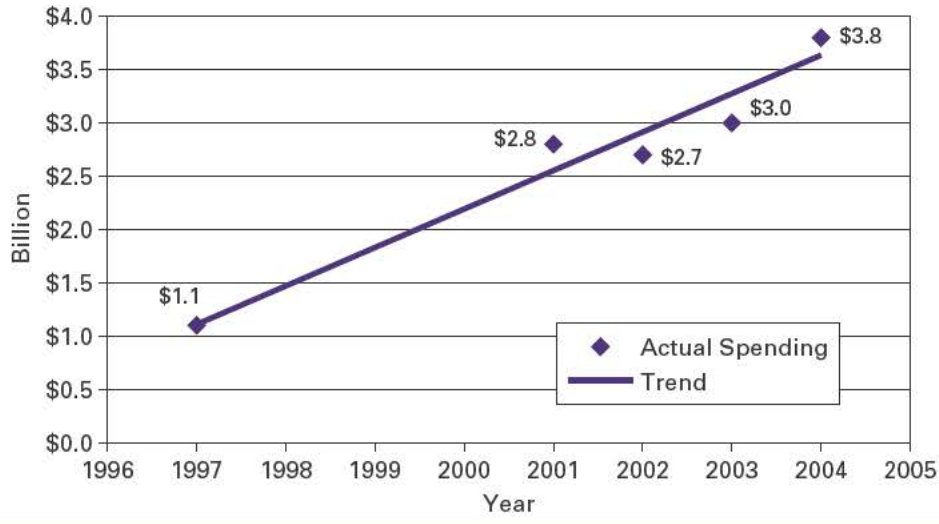
## *Industry Criticisms*

Many critics claimed that the cost of brand name drugs was not justified by the benefits offered to the public and accused the pharmaceutical companies of having no interest in supplying the public with safe medicines at affordable prices. In addition, critics claimed that the new drugs did not necessarily have improved properties against existing drugs but only showed positive results against placebos.[22] Further, critics felt that pharmaceutical companies inflated their expenses by performing unnecessary R&D and promoted expensive drugs of dubious value.[23]

Other critics claimed that the pharmaceutical companies overcharged the public for their products because they charged by the pill and not by the active substance.[24] They claimed that the pharmaceutical companies were "bribing" physicians by subsidizing their lifestyles in the name of professional education.[25] Still other critics complained that pharmaceutical companies actively lobbied the US Congress to maintain high drug prices; however, those very same pharmaceutical companies sold the same products at much cheaper prices in other countries.

Many critics went beyond accusations and proposed a reorganization in the way drugs were priced. One recommendation was that the government would buy patent rights from the innovators and provide them for public usage at generic prices rather than the monopoly prices associated with patents.[26] Another recommendation was that drug companies should be regulated as "public utilities."[27]

Exhibit 1/16: Evolution of DTCA Spending in US (1997–2004)




***Source:*** See references 28 and 29

Finally, there was a strong debate about direct to consumer advertising (DTCA) of drugs. DTCA reached $3.8 billion in 2004[28] from $1.1 billion in 1997[29] when the FDA lessened regulations for advertising prescription drugs in the media (see Exhibit 1/16).

On a global scale only the United States and New Zealand permitted DTCA, whereas the European Parliament overwhelmingly voted against it. The total sum spent in 2004 on DTCA was more than Coca-Cola, Pepsi Cola and Cadbury Schweppes together spent each year to promote their soft drink beverages.[30]

Among the leading 10 drugs in the US market, the promoters spent from 1.6 percent to 5.8 percent of the sales for DTCA in 2004 (see Exhibit 1/17).[31]

The critics claimed that DTCA, accounting for 14 percent of promotional activities (see Exhibit 1/18), was not only increasing the cost of drugs but also drug utilization, and was usually deceptive, misleading, and irresponsible.[32]

The pharmaceutical industry rejected these accusations claiming that innovative brand name medicines did not contribute more than 7 percent to US health care costs. The industry presented cases where the cost of the medication at $1,000 saved the patient $14,000 that otherwise would have been spent on surgery and hospital expenses.[33]

## The Future

The pharmaceutical industry remained very profitable. The high investment in R&D and the resulting new products made the industry one of the most innovative in the United States as well as world wide. Cost/benefit analysis of the facts

Exhibit 1/17: Leading 10 Products by US Sales, 2004, and $ Spent on DTCA

| | Product | Marketer | Sales (in Billions) | Media Expenditures (in millions) | % |
|---|---|---|---|---|---|
| 1 | Lipitor | Pfizer | $7.7 | $119.4 | 1.6% |
| 2 | Zocor | Merck | $4.6 | $95.4 | 2.1% |
| 3 | Prevacid | Takeda, Abbott | $3.8 | $125.0 | 3.3% |
| 4 | Nexium | AstraZeneca | $3.8 | $219.3 | 5.8% |
| 5 | Procrit | Johnson & Johnson | $3.2 | $62.3 | 1.9% |
| 6 | Zoloft | Pfizer | $3.1 | $80.9 | 2.6% |
| 7 | Epogen | Amgen | $3.0 | N/A | N/A |
| 8 | Plavix | Sanofi-Aventis, Bristol-Myers Squibb | $3.0 | $118.1 | 3.9% |
| 9 | Advair Diskus | GlaxoSmithKline | $2.9 | $98.9 | 3.4% |
| 10 | Zyrpexa | Eli Lilly | $2.8 | N/A | N/A |

***Source:*** Jim Edwards, "Sleep, Diet Awaken as Pharma Regroups," *Brandweek* 46, no. 21 (2005), p. 60.

Exhibit 1/18: Promotional Spending by Pharmaceutical Companies for Prescription Drugs, 2001

| Promotional Activity | Spending |
|---|---|
| Free samples | 55% |
| Detailing (rep activities directed towards physicians) | 29% |
| Direct-to-consumer advertising | 14% |
| Medical journal advertising | 2% |
| **Total** | **100%** |

***Source:*** The H.J. Kaiser Family, News Release, June 11, 2003 (see http://www.kff.org/rxdrugs/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=14379)

indicated that many drugs were good value for the money compared to other health services; however, criticisms increased along with the price of the drugs.

The industry looked to the future with cautious optimism but was skeptical as to its ability to maintain high growth rates and whether the investment in R&D would provide lucrative pay back. In addition, industry leaders were concerned that the high (and rising) costs for drugs resulting in increased total spending in the United States compared to the rest of the world, would result in government intervention to reduce margins.

Further, recent advances in science represented both threats and opportunities for the industry. Advances in biotechnology could make many traditional drugs obsolete, as could genome mapping whereby patient-specific drugs might completely transform the entire industry.

## NOTES

1. Pharmaceutical Industry Profile 2005, PhRMA (March 2005).
2. Stephen McGuire, "Priming the Pipeline," *Medical Marketing and Media* 39, no. 12 (December 2004), p. 42.
3. "The Drug Crisis," *CA Magazine* 137 (2004), p. 10.
4. "Health Care in Focus", *Chemical & Engineering News* 82, no. 49 (2004), p.18.
5. Intellectual property rights acquired for a fee to use or commercialize drugs. (See www.cticseattle.com/abou_frame-glos.htm)
6. "Health Care in Focus," p. 18.
7. Pharmacokinetics: how the drugs moved through the body after they were swallowed or injected.
8. Efficacy: ability to control or cure an illness.
9. Frequently Asked Questions for New Drug Product Exclusivity. (See FDA: http://www.fda.gov/cder/about/smallbiz/exclusivity.htm)
10. Moiety: ingredient or part. According to the FDA, "an *active moiety* means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance."
11. Orphan Drugs. (See FDA: http://www.fda.gov/cder/handbook/orphan.htm)
12. Information for Patient. (See http://www.vioxx.com/vioxx/documents/english/information_for_patients.pdf)
13. Alex Berenson, "Bad Time for Pillmakers," *New York Times* (December 18, 2004), p. A1.
14. Scott, Harris, *Regulatory Strategy: Off-Label Promotion of Pharmaceuticals: Overview and Regulatory Strategy* RAPS 2004 Annual Conference & Exhibition, October 10–13, 2004. (See http://www.raps.org/s_raps/sec.asp?TRACKID=&CID=1892&DID=24200)
15. "FAQ on Off-Label Prescribing," *Obesity Meds and Research News*. (See http://www.obesity-news.com/offlabel.htm)
16. *IMS Reports 8.3 Percent Dollar Growth in 2004 U.S. Prescription Sales* (IMS Press Room February 14, 2005). (See http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_70069264,00.html)
17. Ibid.
18. Medicare: United States federal government plan for paying certain hospital and medical expenses for persons qualifying under the plan, usually those over 65.
19. Eduardo Porter, "Do New Drugs Always Have To Cost So Much?" *New York Times* (November 14, 2004), pp. 3-5.
20. Jill Wechsler , "The Main Event Begins," *Pharmaceutical Executive* 25, no. 3 (March 2005), p. 42.
21. Formulary: lists of drugs or collections of recipes, formulas, and prescriptions for the compounding of medicinal preparations.
22. Rita Rubin, "Vioxx, Celebrex Oversubscribed?" *USA Today* (January 23, 2005).
23. Joseph Cohen, "The Ethics of Pharma," *Pharmaceutical Executive* 24, no. 12 (December 2004), p. 88.
24. "To Make a Pill More Affordable, Cut It in Half," *New York Times*, (April 13, 2004), p. G10.
25. Marcia Angell, *The Truth about the Drug Companies: How Do they Deceive us and What to Do About It* (New York: Random House, 2004).
26. Porter, p. 3–5.
27. Angell, *The Truth about Drug companies.*
28. Lee Richardson and Vince Luchsinger, "Direct-To-Customer Advertising of Pharmaceutical Products: Issue Analysis and Direct-To-Customer Promotion," *Journal of American Academy of Business* 7, no. 2 (2005), pp. 100–104.
29. J. M. Jeffords, "Direct To Consumer Drug Advertising: You Get What You Pay For," *Health Affairs* (April 28, 2004), pp. 253–255.
30. Richardson and Luchsinger, p. 100.
31. Jim Edwards, "Sleep, Diet Awaken as Pharma Regroups," *Brandweek* 46, no. 21 (2005), p. 60.
32. Mathews Meril Jr., "Direct To Consumer Ads," *USA Next* (April 21, 2005).
33. "Profile: Pharmaceutical Industry 2004. Focus on Innovation" (see www.phrma.org).