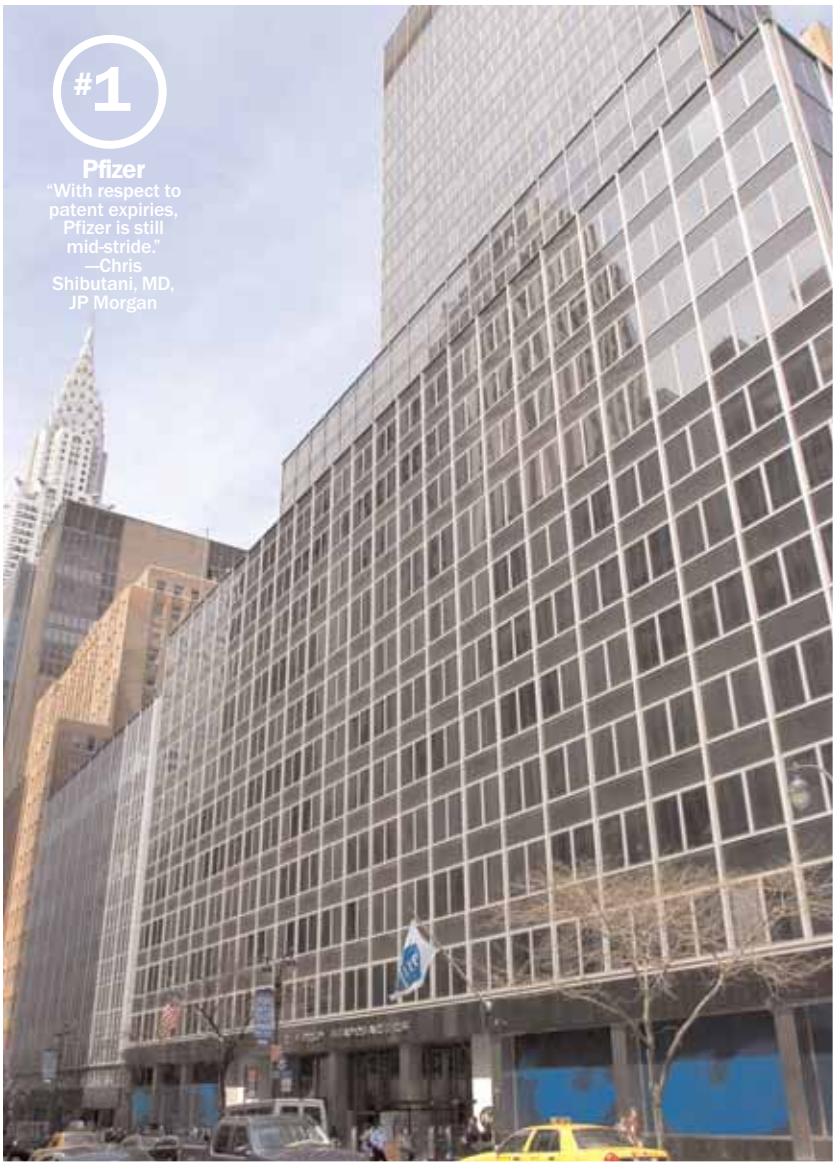
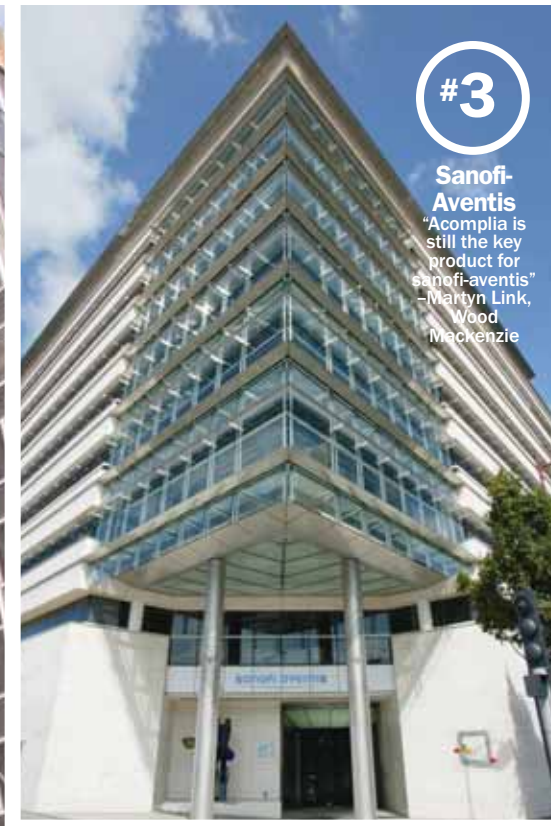


#1

Pfizer

"With respect to patent expiries, Pfizer is still mid-stride."
—Chris Shibutani, MD, JP Morgan



#3

Sanofi-Aventis

"Acomplia is still the key product for sanofi-aventis"
–Martyn Link, Wood Mackenzie

OUR 7TH ANNUAL REPORT ON

THE WORLD'S TOP 50

PHARMACEUTICAL COMPANIES

#30

Akzo Nobel

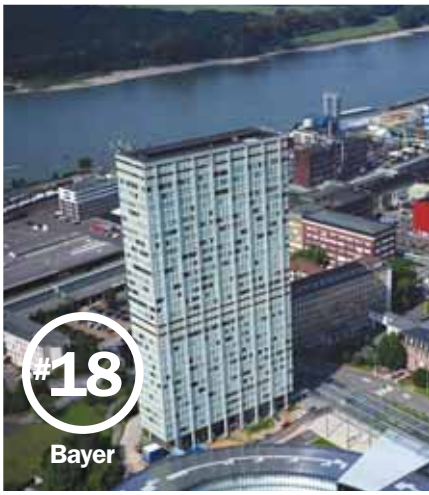
#5

AstraZeneca

"We expect further in-licensing."
–Alex Grosvenor, Wood Mackenzie

#12

Roche



CHANGING LANDSCAPES

A Special Report on the World's Top 50 Pharma Companies

BY NICOLE GRAY

THE PHARM EXEC 50

1 Pfizer	11 Abbott Labs	21 Novo Nordisk	31 Altana	41 Watson
2 GlaxoSmithKline	12 Roche	22 Eisai	32 Chugai	42 Biogen Idec
3 Sanofi-Aventis	13 Amgen	23 Teva	33 Solvay	43 Shire
4 Novartis	14 Boehringer-Ingelheim	24 Merck KGaA	34 UCB	44 Shionogi Seiyaku
5 AstraZeneca	15 Takeda	25 Sankyo	35 Genzyme	45 King
6 Johnson & Johnson	16 Astellas	26 Otsuka	36 Serono	46 Tanabe Seiyaku
7 Merck	17 Schering-Plough	27 Forest Labs	37 Allergan	47 Kyowa Hakko
8 Wyeth	18 Bayer	28 Daiichi	38 Mitsubishi	48 Mylan Labs
9 Bristol-Myers Squibb	19 Schering AG	29 Baxter	39 Gilead Sciences	49 MedImmune
10 Eli Lilly	20 Genentech	30 Akzo Nobel	40 Lundbeck	50 Ono

Generic prescription volume surpassed branded volume for the first time in US history, as generic drug manufacturers became more aggressive in their efforts to gain market share.

SOME NOTES ON THE LIST

Sales figures represent global sales of human prescription drugs for the fiscal year ending in 2005 as reported in annual reports or other filings. When necessary, figures have been converted to US dollars using Federal Reserve exchange rates. Despite our efforts, there are a number of companies, most of them privately held, for which we have not been able to obtain reliable figures. They include Servier, RatioPharm, Menarini, Apotex, Alpharma, and Procter & Gamble (which has products large enough to warrant inclusion on the list, but does not release sales figures on them.) Graphs are based on data kindly supplied by IMS. These data are collected with a different methodology than ours. As a result, tables and graphs may disagree in some respects.

TWO THOUSAND AND FIVE was a year of extremes. While IMS reports that the global market grew by 7 percent (at constant exchange rates) to $602 billion, the North American market grew by an anemic 5.2 percent. The key European markets—Germany, the United Kingdom, France, Italy, and Spain—were just behind the United States in their growth rates. Collectively, these five markets grew just 5 percent. In contrast, developing markets experienced robust double-digit growth across Latin America, Eastern Europe, and Asia. China, in particular, emerged as a growth superstar based on a 20.4 percent increase in pharmaceutical sales.

Once again, the biologics sector dramatically outperformed the overall market. In 2005, biologics as a group grew by 17.1 percent, amassing total sales in excess of $52 billion. Comparatively, the small molecule market grew only 5.2 percent.

Another area of rapid and well-publicized growth in 2005 was the generic market, which grew by 13 percent in the top eight countries to $55 billion. Along the way, generic prescription volume surpassed branded volume for the first time in US history. As generic drug manufacturers became more aggressive in their efforts to gain share in markets formerly dominated by branded products, companies with significant brand franchises tried to protect their revenues by going after line extensions, defending patents, and reallocating their product portfolios.

Companies that rose in the ranks in 2005 included Novartis (from 7 to 4) and Novo Nordisk (from 25 to 21). The Fujisawa-Yamanouchi merger was completed and Astellas was born into the top 50, coming in at number 16. Ongoing consolidation has made room for this year's newcomers, including Daiichi at 28, Lundbeck at 40, and MedImmune at 49. Gilead Sciences, best known for its HIV products, was a welcome addition to this year's top 50, coming in at 39.

Globally, 30 new products were introduced. Concerns about regulatory setbacks, patent expiration, and cost containment cast a pall on the industry's mood in 2005, but there were many reasons for optimism. The top 10 companies each had sales of $14 billion or more. Together, they grossed more than $230 billion in prescription drug revenues. A total of 13 products broke into the ranks of blockbusters, bringing the number of products selling more than $1 billion annually to 94.

And, for the most part, the top 10 companies held their own in the ranking—even Pfizer, despite decreased revenues.

Clearly, Pfizer had a challenging year, as it faced the combined impact of loss of exclusivity in certain key medications and the suspension of Bextra sales. But Pfizer, along with its neighbors on the top 50, is taking a future-forward stance, confident in a brighter tomorrow.

Rank ['04 Rank]	Company & Headquarters [Web site]	2005 Global Pharma Sales [change from 2004]	R&D Spend	2005 Top Selling Drugs [2005 sales]
1 [1]	**Pfizer** New York, NY [pfizer.com]	$44.28 B [-4%]	$7,440 M	Lipitor $12.19 B Norvasc $4.71 B Zoloft $3.27 B
2 [2]	**GlaxoSmithKline** London, England [gsk.com]	$33.96 B [8%]	$5,708 M	Advair/Seretide $5.65 B Lamictal $1.55 B Zorfran $1.52 B
3 [3]	**Sanofi-Aventis** Paris, France [sanofi-aventis.com]	$32.34 B [-5%]*	$4,789 M	Lovenox $2.54 B Plavix $2.40 B Taxotere $1.91 B
4 [7]	**Novartis** Basel, Switzerland [novartis.com]	$24.96 B [16%]	$4,484 M	Diovan $3.67 B Gleevec/Glivec $2.17 B Zometa $1.22 B
5 [6]	**AstraZeneca** London, England [astrazeneca.com]	$23.95 B [12%]	$5,356 M	Nexium $4.63 B Seroquel $2.76 B Seloken/Toporl-XL $1.74 B
6 [4]	**Johnson & Johnson** New Brunswick, NJ [jnj.com]	$22.32 B [1%]	$6,312 M	Risperdal $3.55 B Eprex/Procrit $3.32 B Topamax $1.68 B
7 [5]	**Merck** Whitehouse Station, NJ [merck.com]	$22.01 B [2%]	$3,848 M	Zocor $4.40 B Singulair $3.00 B Cozaar/Hyzaar $3.00 B
8 [9]	**Wyeth** Madison, NJ [wyeth.com]	$15.32 B [10%]	$1,262 M	Effexor $3.46 B Protonix $1.68 B Prevnar $1.51 B
9 [8]	**Bristol-Myers Squibb** New York, NY [bms.com]	$15.25 B [-1%]	$2,746 M	Plavix $3.82 B Pravachol $2.26 B Abilify $0.91 B
10 [11]	**Eli Lilly** Indianapolis, IN [lilly.com]	$14.65 B [12%]	$3,025 M	Zyprexa $4.20 B Gemzar $1.33 B Evista $1.04

Key Insights on the Top 10

AstraZeneca » Sales of Symbicort, an inhaled steroid for asthma and COPD, surpasses the $1 billion mark. » Crestor achieves $1.3 billion in sales » Files a lawsuit against Ranbaxy for willful patent infringement, after Ranbaxy submits an ANDA for esomeprazole magnesium, the active ingredient in Nexium.

Johnson & Johnson » Expands key therapeutic franchises through a series of acquisition deals, including plan to acquire Peninsula Pharmaceuticals, which focuses on developing antibiotics; completion of the TransForm Pharmaceuticals acquisition; and agreement to acquire Closure Medical Corporation.

*2004 figures from pro forma

Pfizer » In April, FDA and EMEA requested that Bextra be taken off the market. Bextra contributed $1.29 billion in revenues in 2004. » In October, shares fell to an 8-year low after Pfizer cut its 2005 profit outlook. » Patent protection efforts in US District Court to retain exclusivity for Lipitor are successful. Adjudicators determine that Ranbaxy Laboratories is guilty of patent infringement and extend Lipitor's exclusivity until June 2011. » One of 10 companies that helped launch the new prescription drug savings card.

Lilly » Cymbalta approved in Europe for use in depression. » Federal court upholds Lilly's patent on Zyprexa (to expire in 2011).

BMS » Baraclude approved for chronic hep. B infections with active viral replication. » Orencia approved for the treatment of rheum. arthritis.

GSK » FDA approves Fluarix, the first biological product to be reviewed under accelerated-approval regulations.

Merck » Grows funding for Vioxx-related legal costs to $685 million. » Establishes a generic company, GenPharm.

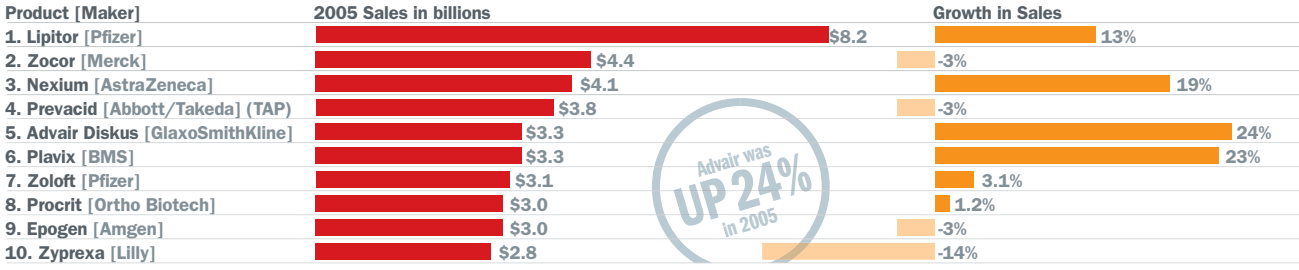
Sanofi-Aventis » In August, FDA approves Actonel with calcium, the first prescription osteoporosis therapy to include calcium in the United States. » Awarded a five-year, $97 million contract by US DHHS to support the development of cell culture-based influenza vaccines. » Receives approval for Ambien CR, an extended release formulation of Ambien, indicated for the induction and maintenance of sleep. » FDA approves a new Eloxatin formulation. » EMEA approves two new indications for Taxotere. » Landmark Taxotere study published in the *New England Journal of Medicine*.

Novartis » Bolsters its position in generics, announcing the acquisition of Hexal, a privately held German generic company, and acquisition of a 67.7 percent stake in Eon Labs. » Announces plans to fully acquire Chiron Corporation.

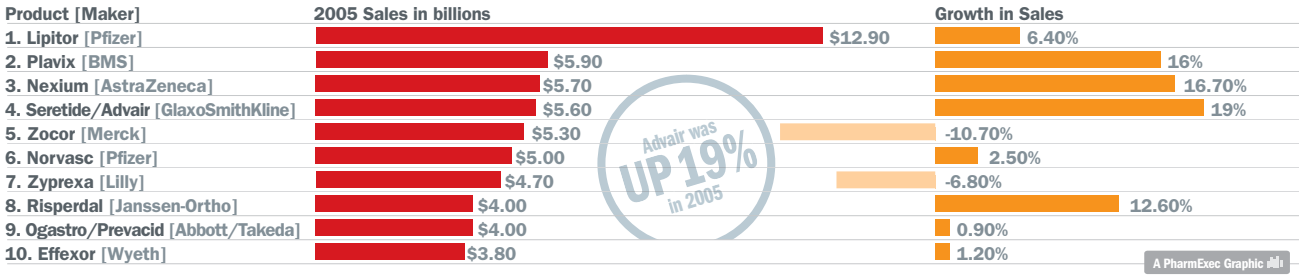
Wyeth » Announces 30 percent decrease in primary care sales force. » Receives a five-year, $32 million NIH contract for development of HIV vaccines.

Rank ['04 Rank]	Company & Headquarters [Web site]	2005 Global Pharma Sales [change from 2004]	R&D Spend	2005 Top Selling Drugs [2005 sales]
11 [10]	**Abbott Labs** Abbott Park, IL [abbott.com]	$13.99 B [16%]	$1,821 M	Humira $1.40 B
12 [12]	**Roche** Basel, Switzerland [roche.com]	$12.90 B [5%]	$3,792 M	MabThera/Rituxan $3.16 B
13 [13]	**Amgen** Thousand Oaks, CA [amgen.com]	$12.02 B [13%]	$2,302 M	Epogen $2.46 B
14 [14]	**Boehringer-Ingelheim** Ingelheim, Germany [boehringer-ingelheim.com]	$10.84 B [2%]	$1,148 M	Spiriva $0.80 B
15 [15]	**Takeda** Osaka, Japan [takeda.com]	$8.53 B [3%]	$1,320 M	Prevacid $3.48 B

TOP 10 US PRODUCTS OF 2005



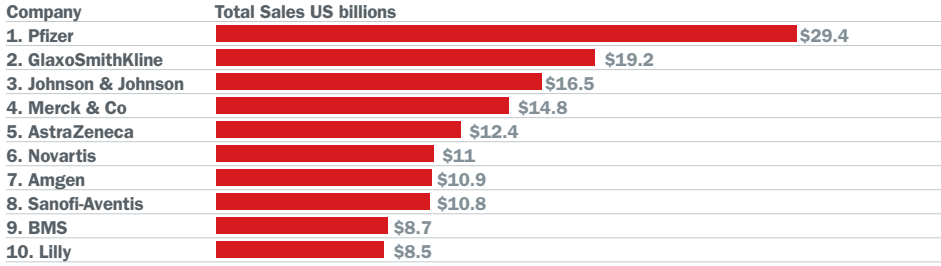
TOP 10 GLOBAL PRODUCTS OF 2005



16 [N/A]	**Astellas** Tokyo, Japan [astellas.com]	$8.04 B [N/A]	$1,259 M	Prograf $1.32 B
17 [16]	**Schering-Plough** Madison, NJ [sch-plough.com]	$7.56 B [18%]	$1,865 M	Remicade $0.94 B
18 [18]	**Bayer** Leverkusen, Germany [bayer.de]	$7.56 B [18%]	$1,130 M	Kogenate $0.79 B
19 [17]	**Schering AG** Berlin, Germany [schering.de]	$6.29 B [3%]	$1,163 M	Betaferon $1.03 B
20 [22]	**Genentech** South San Francisco, CA [gene.com]	$5.49 B [46%]	$1,261 M	Rituxan $1.83 B

Rank ['04 Rank]	Company & Headquarters [Web site]	2005 Global Pharma Sales [change from 2004]	R&D Spend	2005 Top Selling Drugs [2005 sales]
21 [25]	**Novo Nordisk** Bagsvaerd, Denmark [novonordisk.com]	$5.36 B [1%]	$807 M	Antidiabetic products $3.81 B
22 [19]	**Eisai** Tokyo, Japan [eisai.co.jp]	$4.77 B [-5%]	$730 M	Aricept $1.52 B
23 [20]	**Teva** Petach Tikva, Israel [tevapharm.com]	$4.70 B [10%]	$369 M	Copaxone $1.18 B
24 [21]	**Merck KGaA** Darmstadt, Germany [merck.de]	$4.61 B [21%]	$686 M	Beta-blocker products $0.41 B
25 [28]	**Sankyo*** Tokyo, Japan [sankyo.co.jp	$4.25 B [46%]	$807 M	Mevalotin $1.48 B

TOP 10 COMPANIES US SALES



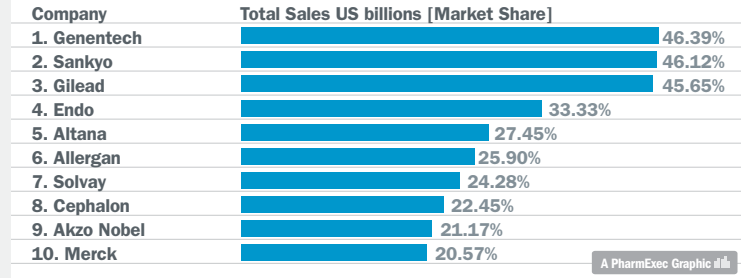
[5.4%] AMOUNT SALES GREW IN THE US FOR 2005. TOTAL US SALES WERE $251.8 BILLION, COMPARED WITH $239.9 BILLION IN 2004

SOURCE: IMS Health, MIDAS, December 2005

[30] THE NUMBER OF NEW PRODUCTS THAT WERE LAUNCHED IN 2005

With a growth rate of 17.4 percent in 2005, "biologics" is still the fastest growing segment in the pharmaceutical market. It generated $52.7 billion in sales in 2005.

TOP 10 MOVERS



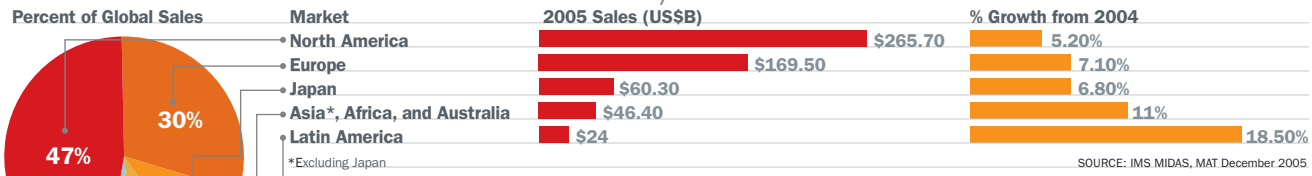
SOURCE: PHARM EXEC 50

26 [24]	**Otsuka** Tokyo, Japan [otsuka.co.jp]	$3.30 B [-11%]	$490 M	Abilify $1.30 B
27 [29]	**Forest Labs** New York, NY [frx.com]	$3.16 B [19%]	$293 M	Lexapro $1.61 B
28 [N/A]	**Daiichi*** Tokyo, Japan [daiichipharm.co.jp]	$3.06 B [-1%]	$536 M	Levoflaxacin $2.80 B
29 [26]	**Baxter** Deerfield, IL [baxter.com]	$3.02 B [11%]	$533 M	Recombinant Factor VIII products $1.53 B
30 [31]	**Akzo Nobel** Arnhem, Netherlands [akzonobel.com]	$2.87 B [21%]	$516 M	Puregon/Follistim $0.42 B

* merged with Daiichi, September 2005

Rank ['04 Rank]	Company & Headquarters [Web site]	2005 Global Pharma Sales [change from 2004]	R&D Spend	2005 Top Selling Drugs [2005 sales]
31 [32]	**Altana** Bad Homburg, Germany [altana.de]	$2.84 B [27%]	$496 M	Pantoprozole $1.66 B
32 [30]	**Chugai** Tokyo, Japan [chugai-pharm.co.jp]	$2.77 B [6%]	$425 M	Epogin $0.61 B
33 [34]	**Solvay** Brussels, Belgium [solvay.com]	$2.69 B [24%]	$391 M	Androgel $0.28 B
34 [35]	**UCB** Brussels, Belgium [ucb-group.com]	$2.42 B [16%]	$605 M	Zyrtec $0.67 B
35 [36]	**Genzyme** Cambridge, MA [genzyme.com]	$2.41 B [9%]	$503 M	Cerezyme $0.93 B

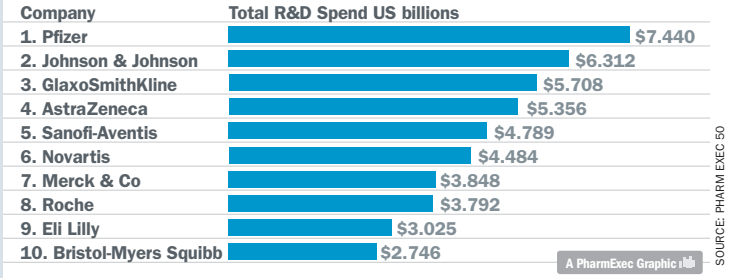
GLOBAL PHARMACEUTICAL SALES BY REGION, 2005



The global pharmaceutical market grew by **7 percent** to approximately **$602 billion,** at constant exchange rates.

[40] PERCENT OF GROWTH IN THE MARKETPLACE FUELED BY THE INTRODUCTION OF NEW PRODUCTS, ACCORDING TO IMS

TOP 10 R&D SPEND



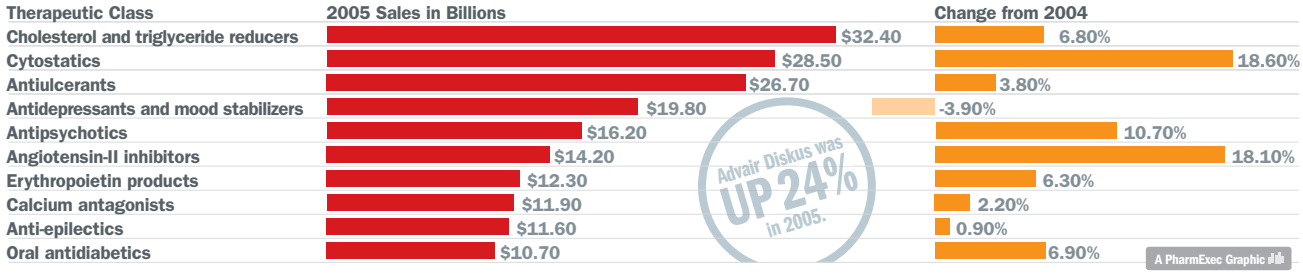
THE COMBINED R&D INVESTMENT OF PhRMA MEMBERS IN 2005 **[$39.4B]**

36 [33]	**Serono** Geneva, Switzerland [serono.com]	$2.34 B [7%]	$594 M	Rebif $1.27 B
37 [37]	**Allergan** Irvine, CA [allergan.com]	$2.32 B [26%]	$387 M	Botox $0.83 B
38 [38]	**Mitsubishi** Osaka, Japan [m-pharma.co.jp]	$1.89 B [4%]	$471 M	Omeprazon NA B
39 [N/A]	**Gilead Sciences** Foster City, CA [gilead.com]	$1.81 B [46%]	$278 M	Viread $0.78 B
40 [N/A]	**Lundbeck** Copenhagen, Denmark [lundbeck.com]	$1.65 B [7%]	$324 M	Cipralex $0.39 B

* merged with Sankyo, September 2005

Rank ['04 Rank]	Company & Headquarters [Web site]	2005 Global Pharma Sales [change from 2004]	R&D Spend	2005 Top Selling Drugs [2005 sales]
41 [40]	**Watson** Corona, CA [watsonpharm.com]	$1.65 B [0.3%]	$125 M	Generic oral contraceptives $0.32 B
42 [44]	**Biogen Idec** Cambridge, MA [biogen.com]	$1.62 B [9%]	$747 M	Avonex $1.54 B
43 [46]	**Shire** Hampshire, England [shire.com]	$1.60 B [17%]	$286 M	Adderall XR $0.73 B
44 [39]	**Shionogi Seiyaku** Osaka, Japan [shionogi.co.jp]	$1.57 B [-4%]	$274 M	Flomax $0.31 B
45 [49]	**King** Bristol, TN [kingpharm.com]	$1.54 B [18%]	$263 M	Altec $0.55 B

TOP THERAPEUTIC CLASSES



SOURCE: IMS Health, MIDAS, December 2005

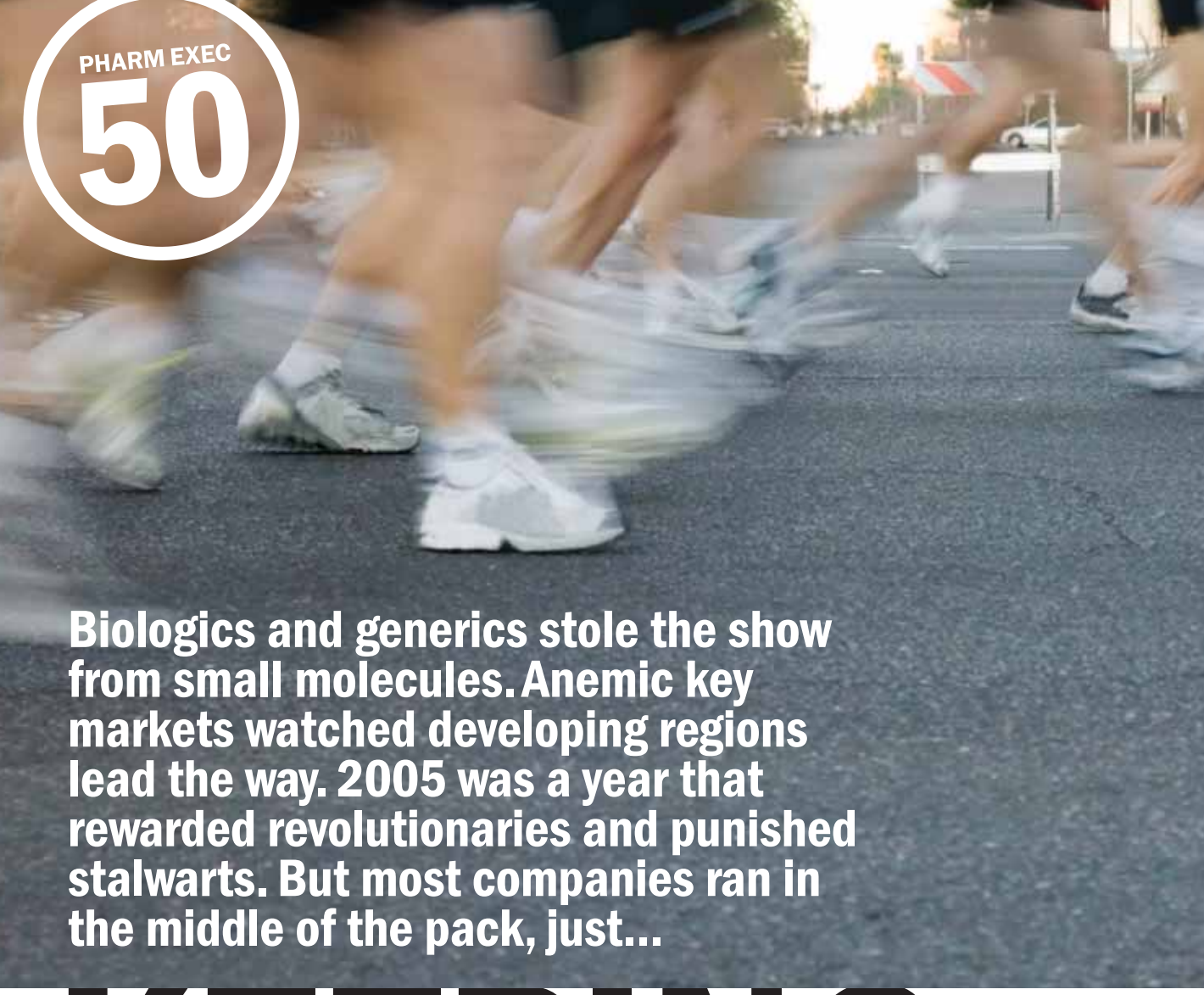
[12.6] PERCENT THAT SALES OF GENERICS GREW IN THE TOP 8 MARKETS

THE NUMBER OF PRODUCTS IN CLINICAL DEVELOPMENT GREW 9 PERCENT TO [2,300]

[4.7] PERCENT THAT VOLUME OF PRESCRIPTION SALES ROSE BY

THE JAPANESE MARKET FOR CANCER-RELATED THERAPIES GREW BY 14 TO 20 PERCENT IN 2005. HERCEPTIN, ARIMIDEX, CASODEX, AND GLIVEC EMERGED AS WINNERS.

46 [N/A]	**Tanabe Seiyaku** Osaka, Japan [tanabe.co.jp]	$1.48 B [14%]	$259 M	Herbesser $0.14 B
47 [N/A]	**Kyowa Hakko** Tokyo, Japan [kyowa.co.jp]	$1.36 B [7%]	$268 M	Itrizole $0.28 B
48 [45]	**Mylan Labs** Canonsburg, PA [mylan.com]	$1.25 B [-9%]	$88 M	Generics $1.01 B
49 [N/A]	**MedImmune** Gaithersburg, MD [medimmune.com]	$1.24 B [9%]	$385 M	Synagis $1.06 B
50 [50]	**Ono** Osaka, Japan [ono.co.jp]	$1.24 B [3%]	$286 M	Opalmon $0.26 B



PHARM EXEC 50

Biologics and generics stole the show from small molecules. Anemic key markets watched developing regions lead the way. 2005 was a year that rewarded revolutionaries and punished stalwarts. But most companies ran in the middle of the pack, just...

KEEPING PACE

with the Evolving Pharmaceutical Business Model.

By Nicole Gray

In times of intensive change, prognosticators with proven insight are valued for their ability to predict the future. Financial and sector analysts have helped industry adjust to the idea that the prevailing pharmaceutical business model is evolving. They remain hard at work, however, on guiding a sector uncomfortable with change toward complete digestion of the concept. Eventually, stakeholders will be obligated to metabolize change in order to survive.

At face value, many things in 2005 held steady: Seventeen products achieved blockbuster status, the same number as in 2004; Pfizer topped the list; and many trends continued—consolidation increased, double-digit growth occurred in developing markets, and biologics grew more than twice as fast as the overall market. But, there's no doubt about it—an evolution is underway. The combined effect of regulatory setbacks, safety-related issues, generic challenges, cost-containment efforts put forth by third-party payers, and the countdown to Part D implementation, all point to one central fact: 2005 was a threshold year.

GENERICS BECOME EQUALS

Barbara Ryan, senior pharma analyst for Deutsche Bank, attributes pharma's underperformance in the financial markets in the last five years to the "cannibalistic effect of generic substitution," and widespread loss of patent protection.

"In 2001, Prozac lost 90 percent of its value in several weeks when generic fluoxetine was introduced," Ryan says. She cites a constellation of factors that are driving the ascendancy of generics as a category, including pressure from managed care organizations (MCOs) to contain costs, automatic substitution at the pharmacy level, sampling of generics, and the fact that critical players in the channel, including pharmacists, pharmacy benefits managers (PBMs), and distributors are incentivized financially to favor generics over branded products. "The generics issue is here to stay and will absolutely change the operating structure of businesses in this industry," Ryan says.

In 2005, for the first time in US history, generic prescription volume was higher than branded volume. According to IMS, generic prescriptions grew by 13 percent, compared with 7 percent growth for the overall market. In all, generic prescription volume reached 60 percent—an all-time high.

Two thousand and five also was a banner year for widespread patent expirations, with $17 billion worth of products losing their patents, including such key blockbusters as Duragesic (fentanyl), Allegra (fexofenadine), Zithromax (azithromycin), and Rocephin (ceftriazone).

While the language used to describe the move away from branded products toward generics reeks of violence ("cannibalization" and "onslaught" are frequently used terms), some pharma companies are taking steps to make generic products a significant part of their offerings.

Novartis epitomizes this approach. In the July 2005 issue of Wood Mackenzie's *Horizons* publication, authors Cliff Kalb, vice president, life sciences, and Keith Redpath, head of life sciences research, acknowledge the potential advantages of this approach. According to the authors, Novartis' acquisition of Eon and Hexal for its generics division, Sandoz, represents the largest investment in the generics industry ever made by an innovative pharma company. Add to this Novartis' plan to fully acquire Chiron and further build out its vaccines business, and a definitive strategy emerges. As a result, Novartis has gained two major advantages: Having substantial interests in both sides of the generics and branded pharma business makes it possible to benefit from R&D investments after patent expiry, and it gives Novartis the opportunity to position itself to governments and MCOs as a one-stop shop for formulary needs.

INNOVATION MATTERS

Clearly, the prospect of contending with this type of change has led to a spate of creative strategizing, by which companies are acquiring, merging, diversifying, and restructuring at a rapid clip. But as much as these efforts help, there is no substitute for innovation in the lab. "The best way around uncertainty and concerns about pricing is to continue to be innovative," says Ryan. "If you're driving value and you're unique, you can set pricing."

Murray Aitken, senior vice president, corporate strategy for IMS, in *IMS Intelligence 360*, an annual publication that provides global coverage of pharma, says the industry is suffering its "slowest rate of growth since 1963." He notes, however, that there were pockets of innovation in 2005 that brought therapeutic value to the marketplace. Examples include Byetta (exanatide) for improved blood sugar control in patients with type 2 diabetes; Lunesta (eszoplicone) indicated to address insomnia, decrease sleep latency, and improve sleep maintenance; and Macugen (pegatanib) for neovascular age-related macular degeneration.

Ryan adds that Pfizer's Exubera (insulin), approved in January 2006, was an important addition in the diabetes category. "Exubera's delivery format can lower the barrier to adoption that often exists when patients need to step up to insulin therapy," she says.

Although only 30 new products were launched in 2005, there were clear winners. Categorically, biologics have continued to

what the experts think

EXPECTATIONS AROUND [GSK'S] FLUARIX WERE PRETTY LOW, BUT **BECASUSE OF CONCERNS ABOUT A FLU PANDEMIC** AND THE STOCKPILING THAT FOLLOWED, FLUARIX WAS A HIT. IT BECAME THE FIRST BIOLOGIC TO RECEIVE EXPEDITED APPROVAL. —JANE KIDD, WOOD MACKENZIE

THE BAR IS HIGHER THAN IT USED TO BE FOR PRODUCTS OF ANY TYPE. THERE **MUST BE A DEMONSTRATED THERAPEUTIC SUPERIORITY** AND COST-EFFECTIVENESS, ESPECIALLY CONSIDERING THE COMPETITION POSED BY GENERICS. —MURRAY AITKEN, IMS

Nicole Gray is a contributing writer. She can be reached at http://nicolegray.home0.com

what the experts think

THE GENERICS ISSUE IS HERE TO STAY
AND WILL ABSOLUTELY CHANGE THE OPERATING STRUCTURE OF BUSINESSES IN THIS INDUSTRY.
—BARBARA RYAN, DEUTSCHE BANK

NOVARTIS' ACQUISITION OF EON ANDHEXAL
REPRESENTS THE LARGEST INVESTMENT IN THE GENERICS INDUSTRY EVER MADE BY AN INOVATIVE PHARMA COMPANY.
—KEITH REDPATH, WOOD MACKENZIE

outperform the overall market, and the stage is set for continued growth. Biologics grew by more than 17 percent for the second year in a row, to amass more than $52 billion in sales in 2005. Strong showings in this sector included Aranesp (darbepoetin alfa) for anemia secondary to kidney disease or chemotherapy, with sales that grew by 46 percent to $2.7 billion; Enbrel (etanercept) for the treatment of moderate-to-severe rheumatoid arthritis, with sales that grew by 36 percent to $2.6 billion; and Neulasta (pegfilgrastim) used to decrease the incidence of febrile neutropenia during chemotherapy, with sales that grew by 30 percent to $2.2 billion.

This category seems to be in its golden era now, but competitive dynamics may change that. "Second-generation products are coming into the marketplace and products are getting approved for expanded indications," says Aitken.

SYSTEMATIC COST CONTAINMENT

As a therapeutic category, oncology is the perfect example of the convergence of some of the most dramatic trends in the industry. IMS reports that growth in this area has kept pace with the dynamic biologics market—both have grown at a rate of roughly 17 percent per year. Oncology alone reached $29 billion in 2005, making it the fastest growing therapeutic category of the year. Major players in this space—Genentech, Biogen Idec, Novartis, Sanofi-Aventis, and ImClone—have come to the market in the last several years with a bevy of useful therapeutics, including proteins and small-molecule drugs. This reflects the growing trend of using combinatorial approaches comprised of traditional cytotoxic chemotherapies with pharmacogenomics for select patients based on molecular-targeted treatments.

In 2005, treatments have become so effective that for the first time in 70 years, the death rate from cancer decreased. The 2005 launch of Genentech's Clolar (clofarabine), a purine nucleoside analog for the treatment of pediatric acute myeloid leukemia, the most common cancer in children, epitomizes the productivity occurring in oncology research, even as overall R&D productivity has faltered.

However, the advent of access barriers, formulary restrictions, higher copays, and price scrutiny is making it harder for patients to obtain reimbursement for high-priced cancer drugs, forcing them to take on more of the costs or forgo certain treatments.

Endpoints that were previously accepted as the basis to justify both treatment and reimbursement, including remission in late-stage patients and small increments of survival time or time-to-regression, may not be enough to satisfy payers. In light of this conservative trend, the burden of proof is on manufacturers to conduct studies at each stage of development, show stronger evidence of remission, and to focus on managing affordability despite long-held assumptions that drugs addressing unmet needs—especially oncology drugs—can command high prices across their life cycle.

The United States is still only poised on the threshold of change when it comes to the full-scale implementation of intensive cost-containment efforts. But in Europe, initiatives to control costs have been underway for some time. In 2005, Germany pulled back from some of the draconian measures that were in place in 2004. Compulsory discounts on non-referenced drugs were reduced from 16 percent in 2004 to six percent in 2005; co-payment exemptions were increased; and prescription volume increased by five percent, when much of hospital-based treatment was shifted to the ambulatory setting.

When examining Germany's $1.9 billion oncology market, a dichotomized utilization pattern emerged. The market was divided between high-cost new drugs, such as Lilly's Alimta (pemetrexed) and targeted therapies, such as Roche's Avastin (bevacizumab), Tarceva (erlotinibib), and Herceptin, as well as Erbitux (cetuximab), manufactured by Merck KGaA. These products were deemed reimburseable and enjoyed rapid uptake as a result. On the other side, generic cytotoxic drugs decreased in price as generic companies Stada and Ratiopharm competed for market share.

In November 2005, England's efforts to contain healthcare costs were successfully challenged by a 41-year-old woman, who demanded that she receive treatment with Herceptin despite her Primary Care Trust's (PCTs) original claim denial. (In England, PCTs manage government health services related to primary care.) "The holy grail of 'the payers must pay' is no longer true in the UK," says Alex Grosvenor, senior analyst, life sciences at Wood Mackenzie.

The National Institute for Health and Clinical Excellence (NICE), a British regulatory agency, uses economic modeling tools to rate cost-effectiveness and make therapeutic recommendations—and sometimes the results are not favorable for the medications in question. Despite this pushback, the NICE model is being adopted and modified in most European countries.

The consumer movement—patient activism—will become a force to reckon

with as the impact of payer conservation increases. As it turns out, when the British woman who was refused coverage for the breast cancer treatment Herceptin took action, she succeeded not only in getting coverage, but also prompting Prime Minister Tony Blair to push for fast-track review. In Canada, patient activists presented Canada's Health Minister, Ussal Dosanjh, with five coffins, representing AIDS patients who had been denied combination therapy treatment. The result: Health Canada, the government department of Canada with responsibility for national public health, brokered a clinical trial protocol for the patients.

PREVENTION ENTERS THE EQUATION

In 2005, both Merck and GlaxoSmithKline announced ongoing development of competing vaccines for the human papilloma virus (HPV), the most important risk factor for developing cervical cancer. (For more on HPV, see "Cervical Cancer: Endangered Species," page 154).

"Vaccines will go from understudy to star performer," predicts Aitken.

Indeed, from a health economics perspective, prevention is cheaper than treatment, especially when prevalence is high. The World Health Organization estimates that approximately 80 percent of all sexually active adults are infected with HPV worldwide. Merck's Gardisil is scheduled to launch in 2006, while GSK's Cervarix is scheduled to launch in 2007.

There are currently 598 vaccines in development—across a range of therapeutic areas, including breast cancer, genitourinary cancer, hepatitis, and HIV. IMS predicts a 20 percent growth rate, to $20 billion, for vaccines over the next five years. Large companies, such as Novartis and GSK, are heavily invested in vaccines, and others are expected to follow suit. (For more on vaccines, see "Vaccines: Market on the Rebound," page 110.)

DIGESTING CHANGE

According to IMS, by the end of 2006, the Centers for Medicare and Medicaid Services will be paying for 50 percent of all prescription drugs. Once the effects of Medicare Part D are understood and assimilated, the United States will join other countries in becoming more aggressive about containing costs. The first real signs have been the introduction of exorbitant copays, which went as high as $100 for the first time in 2005.

The advent of health technology assessments (HTAs) is another sign of change. HTAs are designed to systematically compare and contrast various therapeutic options to determine cost-effectiveness relative to outcomes. By definition, HTAs are complex. IMS' Aitken advises companies to "maintain a close dialogue with authorities, starting before a drug's marketing approval."

The primary care category may be where the most profound changes are occuring in prevailing industry paradigms. In Wood Mackenzie's *Horizons*, authors Kalb and Redpath suggest that the operative business model is shifting in favor of specialist products, away from the stan-

dard model of vertically integrated companies that are therapy-area-focused and enjoy double-digit growth year after year. They predict a $700 billion market by 2009, with very little contribution from growth in blockbuster revenues.

They say pharma may come to define blockbusters as $500 million products (versus the $1 billion definition employed today), which seems radical when viewed in perspective of the days when the $1 billion threshold seemed too *low*. But, the role of primary care products as blockbuster candidates is diminishing—as evidenced by the declining number of launches in this space and the fact that there were no launches in 2005 for cardiovascular disorders. "There must be demonstrated therapeutic superiority and cost-effectiveness," says Aitken, "especially considering the competition posed by generics."

Indeed, the generic challenge looms large, especially with statins, a category that still serves as an important source of revenue. As 2005 ended, Lipitor (atorvastatin), Plavix (clopidogrel), and Zocor (simvastatin) were firmly ensconced as numbers one, two, and five, in the roster of the top-earning products globally—but as a group, revenues from statins only grew five percent. Two notable breakthroughs in this space were Crestor (rosuvastatin) and Vytorin (ezetimbe/simvastatin), which both achieved blockbuster status in 2005.

Crestor's success, says Wood Mackenzie's Grosvenor, was helped by the fact that target cholesterol guidelines have featured progressively lower optimal levels for total and LDL cholesterol. AstraZeneca took this challenge one step further and conducted head-to-head trials versus Lipitor, Zocor, and Pravachol (pravastatin). Crestor emerged as the most effective at reducing LDL cholesterol levels.

Opportunities outside of mature markets in Asia, Latin America, and Eastern Europe are ripe for investment. "Companies are investing in becoming insiders and partners of the healthcare system with a stake in the development of pharmacotherapeutic and preventive areas of focus," says Aitken. Based on IMS figures for 2005, growth rates in China, Korea, Turkey, and the Russian Federation were 20.4 percent, 14.6 percent, 54.3 percent, and 19.9 percent, respectively.

Ultimately, the way to confront change is to be flexible. Already, the numbers reflect some of the steps pharma is taking to survive: While the number of blockbuster drugs increased between 2000 and 2005, from 36 to 94, the percentage of specialty drugs rose from 28 to 44 percent for the same period. In addition, sales forces are being downsized, detailing is being refined, and portfolios are being realigned. Safety issues continue to be a concern, and there is a universal understanding that all stakeholders must confront challenges associated with payment and reimbursement. Developing markets are challenging, yet compelling. Changes abound, but year after year, the ability to bring value to the therapeutic market while improving and extending life remains a constant.