

TOP 50 PHARMACEUTICAL COMPANIES

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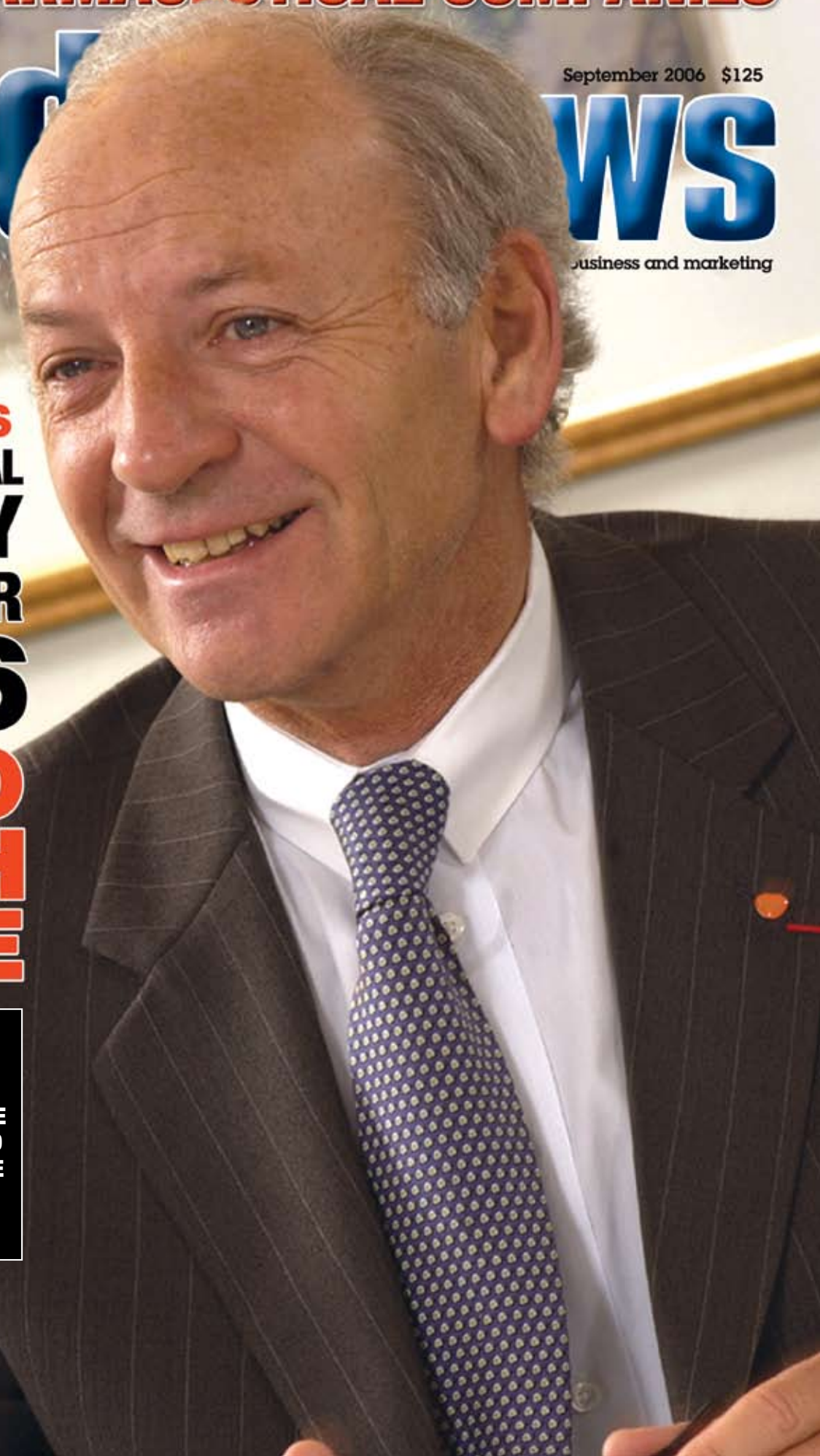
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MED AD NEWS PHARMACEUTICAL COMPANY OF THE YEAR 2006 GLAXO SMITH KLINE

CEO J.P. GARNIER LEADS A COMPANY WITH A PROMISING LATE-STAGE PRODUCT PIPELINE, A STRONG PRESENCE IN THE VACCINES MARKET, AND SOLID SALES GROWTH DESPITE PATENT EXPIRATIONS OF BLOCKBUSTER BRANDS.



A step ahead of the rest

GlaxoSmithKline has become a leader in the vaccines arena without losing sight of the R&D and marketing initiatives for its traditional pharmaceutical products. **By Rebecca Mayer**



GlaxoSmithKline Plc. in 2005 achieved record-breaking finances, several product launches, significant acquisitions, growth in the global vaccines arena, and substantial pipeline progress. The company is No. 1 globally in terms of its oncology and supportive-care pipeline projects, and the late-stage pipeline shows great promise with the advancement of the cervical-cancer drug Cervarix, Tykerb for breast and other cancers, eltrombopag for the treatment of thrombocytopenia, and a therapeutic cancer vaccine. All of these compounds, if successful, have the potential to achieve not only blockbuster status, but mega-blockbuster status, according to Sanford C. Bernstein & Co. analysts.

Maintaining its focus on vaccines, GlaxoSmithKline expects to launch five major vaccines throughout the next five years, including plans to complete filing of a pandemic flu vaccine in Europe and **Cervarix** in the United States by the end of the year. Cervarix will be in direct competition with **Merck & Co.**'s **Gardasil**. GlaxoSmithKline, however, has positioned Cervarix as more immunogenic than Gardasil,

according to analysts.

GlaxoSmithKline continues to be the global leader in respiratory pharmaceuticals. For 2005, the company's respiratory sales totaled £5.05 billion (\$9.2 billion), led by the mega blockbuster **Advair/Seretide**. At constant exchange rates, GlaxoSmithKline's respiratory sales last year represented an increase of 14% compared with 2004.

Driven by the growth of key products, GlaxoSmithKline delivered an excellent financial performance in 2005. The company recorded £21.66 billion (\$39.43 billion) in revenue, an increase of 7% compared with 2004 at constant exchange rates. Diluted earnings per share were 82 pence (\$1.49) in 2005, compared with 68 pence (\$1.24) in 2004. A number of the company's newer products, including **Avodart** for enlarging prostate, **Boniva/Bonviva** for osteoporosis, and **Requip** for restless legs syndrome, contributed to the company's banner year.

"These figures confirm the excellent growth of our key products and the efficiency of our global operations," says Jean-Pierre Garnier, Ph.D., CEO and director, GlaxoSmithKline (gsk.com).

GLAXOSMITHKLINE'S BEST-SELLING PRODUCTS

Product	2005 sales (\$ in millions)	2004 sales (\$ in millions)
Advair/Seretide	5,465	4,503
Avandia and Avandamet	2,419	2,042
Lamictal	1,545	1,241
Zofran	1,523	1,396
Imitrex/Imigran	1,269	1,248
Valtrex	1,265	1,045
Augmentin	1,212	1,296
Flonase/Flixonase	1,194	1,058
Wellbutrin XL	1,178	855
Flovent/Flixotide	1,161	1,131
Paxil/Seroxat	1,119	1,945
Combivir	1,061	1,045
Coreg	1,043	791
Hepatitis vaccines	808	743
Infanrix, Pediarix	784	653
Serevent	601	639
Trizivir	551	589
Epivir	475	538
Zantac	444	500
Fraxiparine	384	NA
Ceftin/Zinnat	359	399
Requip	284	212
Zeffix	264	238
Ziagen	248	284
Zovirax	238	269
Avodart	235	117
Epzicom/Kivexa	215	NA
Agenerase, Lexiva	204	115
Hycamtin	180	181
Wellbutrin IR, SR	167	519
Retrovir	75	79
Levitra	73	90
Arixtra	44	NA
Boniva/Bonviva	33	0
Vesicare	24	NA



Sales of **Seretide/Advair**, the world's best-selling product for asthma, grew 22% to \$5.47 billion in 2005.

PRODUCTS EXPECTED TO BE APPROVED/LAUNCHED IN 2006

Product	Indication
Rotarix	Rotavirus
Entereg	Post-operative bowel disorders
Trexima	Migraine
Avandaryl*	Diabetes
Coreg CR	Heart failure
Arranon	Cancer
Altanax	Infections

*Launched in February 2006

Source: GlaxoSmithKline 2005 Annual Report

Operating profit of £6.87 billion (\$12.5 billion) for 2005 grew 16%, which was above the company's revenue growth of 7%, reflecting flat selling, general, and administrative expenses — including lower costs for legal matters — and higher gains from asset disposals. These were partly offset by an increase in restructuring charges relating to cost saving programs. R&D expenditure grew 8% to £3.14 billion (\$5.71 billion), broadly in line with sales growth.

For the first half of 2006, GlaxoSmithKline reported sales of £11.62 billion (\$21.16 billion), 9% more at constant exchange rates than in first-half 2005. Operating profit was £4.09 billion (\$7.44 billion). Earnings per share were 49.8 pence (91 cents), 16% more at constant ex-

change rates than in the same period last year. For the first six months of 2006, the company generated £1.61 billion (\$2.84 billion) in total pharmaceutical sales, up 15% at constant exchange rates from the same period in 2005.

Looking at 2006 and beyond, the strong growth exhibited by the company's key products and its vaccines business is expected to continue. Company managers anticipate earnings-per-share growth of about 10% at constant exchange rates.

YEAR OF THE VACCINE

GlaxoSmithKline is a world-leading supplier of vaccines, and 2005 was a landmark year for the business. Sales in this segment increased 15%, compared with 2004, and will likely remain high due to several strategic acquisitions made last year.

The vaccines business performed well with sales totaling £1.4 billion (\$2.55 billion) in 2005, led by **Infanrix**. Vaccine sales were particularly strong in the United States, where revenue rose 26% to £338 million (\$615.3 million), helped by the launch of two new products — **Fluarix** and **Boostrix**.

Bernstein (bernstein.com) analysts expect the vaccines business to grow ahead of the general pharmaceutical market, and GlaxoSmithKline's strong presence in this market is likely to provide an ongoing positive contribution to earnings growth.

Last year, GlaxoSmithKline secured its position as a major force in vaccines against influenza, the subject of heightened global concern during the year.

The company invested more than £1 billion to expand its flu-vaccine manufacturing capabilities. This includes more than doubling production capacity at its Dresden, Germany, flu-vaccine manufacturing facility to 80 million doses per year by 2008. GlaxoSmithKline plans to invest about £94.3 million (\$171.7 million) to double the site's production capacity. The company also plans to build a second plant at the site to meet the increasing demand for flu vaccines worldwide.

GlaxoSmithKline completed its \$1.4 billion acquisition of the Canadian vaccine mak-

PHARMACEUTICAL SALES BY THERAPEUTIC AREA

Area	2005 sales (\$ in millions)	2004 sales (\$ in millions)
Respiratory	9,200	7,999
Central nervous system	5,860	6,302
Anti-virals	4,729	4,294
Anti-bacterials/anti-malarials	2,765	2,816
Metabolic	2,721	2,277
Vaccines	2,529	2,174
Cardiovascular and urogenital	2,423	1,697
Oncology and emesis	1,850	1,700
Other	1,893	1,870
Total	33,970	31,129

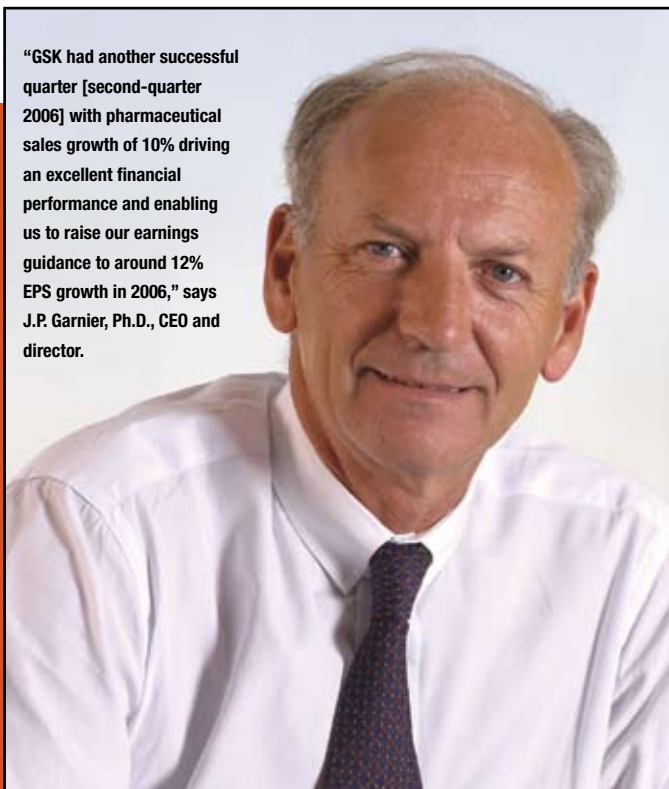
er **ID Biomedical Corp.** in December after regulatory clearance for the deal. The transaction is part of the company's strategic initiative to expand its vaccine research and production network in North America. ID Biomedical provides GlaxoSmithKline with a significant increase in flu-vaccine manufacturing capacity. This will improve GlaxoSmithKline's ability to address both seasonal and pandemic influenza threats. The combined seasonal flu-vaccine production capacity of the newly acquired Canadian facilities and of GlaxoSmithKline's Dresden plant is expected to reach about 150 million doses per year before the end of this decade.

"This is a major step toward fulfilling our mission of becoming a leading global influenza vaccine manufacturer," Dr. Garnier says. "We are actively working with governments and health authorities around the globe to support their plans for pandemic flu readiness, and we are committed to bring the capabilities of our flu-vaccine production facilities to the global preparation effort."

GlaxoSmithKline also acquired a plant in Marietta, Pa., which gives the company access to tissue-culture technology in vaccine manufacturing. The 90-acre manufacturing site, previously owned by **Wyeth** (wyeth.com), will be used to help develop the next generation of vaccines for GlaxoSmithKline. The Marietta site will focus on the development and production of tissue-culture technology that will be used for seasonal and pandemic flu vaccines.

GlaxoSmithKline expects to use the Marietta site for the secondary production of several new vaccines for distribution in the U.S. market, following their approval by FDA. The site has freeze-drying capabilities that will be used to enhance the shelf-life and stability of a number of the company's vaccines.

"GSK had another successful quarter [second-quarter 2006] with pharmaceutical sales growth of 10% driving an excellent financial performance and enabling us to raise our earnings guidance to around 12% EPS growth in 2006," says J.P. Garnier, Ph.D., CEO and director.





Overall sales of Avandia totaled \$2.1 billion last year, an increase of 18% compared with 2004.

In July 2005, GlaxoSmithKline finalized its acquisition of **Corixa Corp.** Corixa develops innovative adjuvants, which boost human immune responses to vaccines. The Corixa acquisition gives GlaxoSmithKline access to Corixa's novel adjuvant monophosphoryl lipid A, an important component in many of GlaxoSmithKline's most promising vaccines under development, such as Cervarix.

GlaxoSmithKline announced July 20, 2006, an agreement with the U.S. government to provide states with the antiviral **Relenza** as they prepare for a potential influenza pandemic. The Department of Health and Human Services is guaranteeing the initial purchase of \$16.8 million of Relenza. This purchase will help states, territories, and the District of Columbia to begin adding Relenza to their pandemic stockpiles at a federally subsidized price. During the two-year contract, these jurisdictions can make additional purchases of Relenza up to a potential total of 15.5 million treatment courses.

Relenza, comprising zanamivir, is approved for the prophylaxis and treatment of influenza A and B in children and adults. Relenza is an inhaled medicine delivered through a device called a Diskhaler to the surface of the upper respiratory tract.

During the next five years, the company hopes to launch at least five major new vaccines in some countries, including Cervarix; **Rotarix**, a vaccine against rotavirus already approved in 13 countries, including Mexico; a vaccine to prevent pneumococcal disease; an improved flu vaccine for the elderly; and a meningitis combination vaccine for infants in the United States.

PRODUCT REVENUE AND GROWTH

GlaxoSmithKline's total pharmaceutical revenue in 2005 amounted to £18.66 billion (\$33.97 billion), an increase of 8% at constant exchange rates compared with

2004. This increase was propelled by the company's key pharmaceutical growth drivers and vaccines. Growth was balanced across all regions with an increase of 8% to £9.1 billion (\$16.57 billion) in the United States, an increase of 8% in Europe with sales of £5.6 billion (\$10.19 billion), and sales of £4 billion (\$7.28 billion) in international markets, marking an increase of 9% compared with 2004 figures. New products also started to deliver significant sales. Avodart for enlarged prostate, for example, performed well and accounted for more than 40% of new prescription sales in its class in the United States.

GlaxoSmithKline's largest-selling product in 2003 and 2004, Advair/Seretide had another strong year in 2005 and continued to gain market share across all regions, driven by its efficacy in treating debilitating conditions. Sales grew 22% to £3 billion (\$5.47 billion) last year. For the six months ended June 30, 2006, Advair/Seretide sales came in at £1.64 billion (\$3 billion), a 12% increase when compared with the same period in 2005.

Advair/Seretide, a combination of **Serevent** and **Flovent**, offers a long-acting bronchodilator and an anti-inflammatory in a single inhaler. The drug is approved for the treatment of asthma and chronic obstructive pulmonary disease. Advair is the brand name in the United States, and Seretide is the trade name in international markets.

For 2005, the drug achieved market share by value in the anti-asthma and chronic obstructive pulmonary disease classes of 27% in Europe and 33% in the United States, an increase of two percentage points in both cases compared with 2004. In the United States, Advair sales rose 26% in 2005 to £1.7 billion (\$3.09 billion), with continued gains in market share throughout the year. Sales were strong in European and international markets. In Europe, sales of Seretide increased 16% to £1 billion (\$1.82 billion) and in international markets to £300 million (\$546 million).

Competition for Advair is expected to pick up when **AstraZeneca's** (astrazeneca.com) inhaled asthma drug **Symbicort** finally receives FDA approval. According to analysts with Kepler Equities (kepler-equities.com), Symbicort will likely receive approval in 2007.

Beyond that, industry experts expect few drugs that could significantly change the competitive environment during the medium term. Some experts believe that an old drug in a new and better inhaler is probably more useful than a new drug in an old and flawed inhaler. Partnerships with the right device companies could therefore help GlaxoSmithKline retain, and perhaps even improve, its competitive position in the asthma therapeutic area.

Serevent Diskus achieved £330 million (\$601 million) in sales in 2005, a decrease of 7% compared with full-year 2004. The prod-

uct's first-half 2006 sales totaled £148 million (\$269.4 million), a decrease of 11% compared with first-half 2005.

Serevent is indicated for long-term twice-daily administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years old and older with reversible obstructive airway disease. This includes patients with symptoms of nocturnal asthma who require regular treatment with inhaled, short-acting beta2-agonist.

In March 2006, GlaxoSmithKline agreed to FDA's recommendation regarding product labeling for Serevent Diskus and Advair Diskus. The agreement concludes ongoing discussions between GlaxoSmithKline and FDA following an earlier advisory committee meeting about the safety of long-acting beta2-agonists, including salmeterol, the active ingredient in Serevent and one of the active ingredients in Advair.

In 2005, Flovent, which is marketed overseas as **Flixotide**, generated £638 million (\$1.16 billion) in global sales, an increase of 2% from 2004. During the first six months of 2006, sales of the product grew 6% to £342 million (\$622.6 million), compared with the same period in 2005. Flovent/Flixotide is an inhaled steroid for the treatment of inflammation associated with asthma and chronic obstructive pulmonary disease.

Flonase/Flixonase sales were £656 million (\$1.19 billion) in full-year 2005, up 13% from 2004. In first-half 2006, the drug's sales decreased 39% to £199 million (\$362.3 million). Flonase/Flixonase is a steroid intranasal preparation for the treatment of perennial and seasonal rhinitis. Flonase received FDA approval Oct. 19, 1994.

Sales of central nervous system products declined 8% to £3.2 billion (\$5.86 billion) in 2005. Global **Paxil** sales fell 42% to £615 million (\$1.12 billion), due to generic competition and the interruption in supply of **Paxil CR** dur-



Lamictal sales grew 24% to \$1.55 billion in 2005.

Valtrex generated revenue of \$1.27 billion in 2005, a 21% increase compared with the previous year.



ing the year. Partially mitigating this decline was the strong performance of the product in Japan, up 17% in 2005 to £197 million (\$358.6 million).

Paxil is marketed primarily in the United States and Europe, where the drug is known as **Seroxat**, and is an immediate-release formulation prescribed for central nervous system disorders. Paxil is a selective serotonin re-uptake inhibitor. Paxil CR was approved by FDA in February 1999 for the treatment of depression. Paxil CR has been approved by FDA for four additional indications: panic disorder, the continuous treatment of premenstrual dysphoric disorder, social anxiety disorder, and the intermittent treatment of premenstrual dysphoric disorder.

Despite continued legal issues with the Paxil franchise, managers maintain the belief that the drug's benefits outweigh its risks. Trouble with the drug's safety profile came just on the heels of losing the product's market exclusivity.

Wellbutrin product sales decreased 2% to £739 million (\$1.35 billion) in 2005. Combined sales of **Wellbutrin IR** and **Wellbutrin SR** fell 68% to £92 million (\$167 million) due to generic competition, however, this was largely offset by 38% growth from **Wellbutrin XL** with 2005 sales of £647 million (\$1.18 billion).

FDA approved Wellbutrin XL in June 2006 for the prevention of seasonal major depressive episodes in patients with a diagnosis of seasonal affective disorder, a condition affecting about 6% of American adults. Wellbutrin XL is the first and only medication approved to prevent seasonal major depressive episodes.

Toronto-based **Biovail Corp.** (biovail.com) markets Wellbutrin XL through a partnership with GlaxoSmithKline. Biovail licensed the Wellbutrin XL formulation from a California-based company called PharmaPass, which Biovail acquired in 2002.

In August, a federal court judge ruled **Anchen Pharmaceuticals Inc.** (anchen.com) did not infringe on Biovail's patent for Wellbutrin XL. The ruling becomes final only after the court formally issues and enters a final order. Stalling Anchen's plans is a citizen petition filed by GlaxoSmithKline and Biovail. In December 2005, Biovail submitted a citizen petition to FDA to require rigorous bioequivalence testing for generic products that reference Wellbutrin XL before they can be approved. Biovail took this step to protect patients against potentially serious risks, particularly seizure, which are disclosed in the approved Wellbutrin XL labeling, and to ensure that generic versions of Wellbutrin XL are as safe and effective as the innovator product.

FDA may respond shortly to this citizen petition now that a court ruling is in hand, but the timing remains speculative. Prudential Equity Group (prudential.com) analysts are not making any changes to their GlaxoSmithKline model until they have a better idea of Anchen's launch timing. The current model has Wellbutrin XL facing generic competition in mid-2007.

Strong growth of GlaxoSmithKline's epilepsy and bipolar disorder medication **Lamictal** continued in 2005. Sales increased 24% to £849 million (\$1.55 billion), driven by the indication for the maintenance treatment of bipolar disorder. During the year, new guidelines were published that reinforced the use of Lamictal as first-line maintenance treatment for bipolar disorder where the license allows.

New data released in August demonstrate the effectiveness of Lamictal, comprising lamotrigine, as adjunctive therapy for children and adolescents with primary generalized tonic-clonic seizures. This is the first published analysis of data from a randomized, double-blind, controlled clinical trial of PGTC seizures focusing on patients 2 years old to 20 years old. Lamictal is not indicated for treating PGTC seizures.

Requip sales for last year rose 34% to £156 million (\$285 million) following its launch in the United States in second-quarter 2005. Requip is a specific dopamine D2/D3 receptor agonist indicated for the treatment of Parkinson's disease and is the first approved product for restless leg syndrome. Since the drug's launch, the volume of new prescriptions for Requip quadrupled in the United States. First-half 2006 sales of Requip rose 84% to £122 million (\$222.1 million), when compared with the same six months in 2005.

Requip, comprising ropinirole, is marketed as **Adartrel** for the treatment of restless legs syndrome in France and Switzerland. The drug is also marketed for the treatment of restless legs syndrome under the name **Repreve** in Australia. Final approval for the rest of the European Union, Norway, and Iceland was expected of Requip/Adartrel for restless legs syndrome in the first half of 2006.

Within the company's antiviral category, HIV product sales grew 5% in 2005 to £1.6 billion (\$2.91 billion). The growth can be attributed to sales from new products **Epzicom/Kivexa** and **Lexiva** offsetting the performance of **Trizivir** and **Epivir**.

Combivir, the category's top seller, is a combination of **Retrovir** and **Epivir** and has consolidated the position of these two reverse transcriptase inhibitors as the cornerstone of many multiple anti-HIV product regimens. Physician acceptance has clearly demonstrated the value placed on minimizing the pill burden faced by patients. Sales of Combivir totaled £583 million (\$1.06 billion) in full-year 2005 and £284 million (\$517 million) in first-half 2006.

Ziagen, for HIV treatment, is a reverse transcriptase inhibitor. In 2005, sales of the product were £136 million (\$248 million), down 14% from 2004.

Epzicom/Kivexa, approved for use in the United States and Europe, is a combination of Epivir and Ziagen that is taken as one tablet with once-daily dosing for HIV/AIDS in combination with at least one other anti-HIV drug. Epzicom/Kivexa generated £118 million (\$215 million) in 2005 sales during its first full year on the market.

Combined sales of Lexiva and **Agenerase** grew 77% to £112 million (\$204 million) in 2005. Combined sales of these products increased 31% to £65 million (\$118.3 million) in first-half 2006. Lexiva is indicated for the treatment of HIV infection in adults in combination with other antiretroviral medications. Lexiva, marketed in Europe as **Telzir**, is a protease inhibitor for the treatment of HIV that is well tolerated and more convenient than Agenerase, which the product supersedes. Lexiva may be taken twice daily or once daily when boosted with ritonavir.

Sales of Trizivir, for the treatment of HIV, decreased 6% to £303 million (\$551 million). Epivir's sales dropped 12% to £261 million (\$475 million) in 2005. Trizivir is a combina-

Coreg achieved sales of \$1.04 billion in 2005.





Wellbutrin XL had sales of \$1.18 billion last year, a 37.8% increase from 2004.

tion of Combivir and Ziagen, thereby combining three anti-HIV medications in one tablet for twice-daily administration.

The drop in Epivir's use is attributed to increased competition. According to two published studies, **Baraclude**, a chronic hepatitis B vaccine from **Bristol-Myers Squibb Co.** (bms.com), showed more benefit in treating patients than lamivudine, which GlaxoSmithKline markets as Epivir. Epivir was the most commonly used antiviral drug for treatment of chronic hepatitis B worldwide, but the Phase III trial found that treatment with Baraclude resulted in greater improvements in liver histology and reductions of hepatitis B virus DNA to undetectable levels.

Sales in 2005 of the herpes drug **Valtrex** grew 21% to £695 million (\$1.27 billion). Performance is being driven by the United States, where the product is the clear market leader among treatments for genital herpes. In the U.S. market, sales grew 26% from 2004 to £470 million (\$855.6 million). Valtrex is indicated to treat episodic genital herpes as well as the long-term suppression and reduction of transmission of genital herpes, zoster, cold sores, and chicken pox. Valtrex supersedes **Zovirax**, which is also used to treat herpes infections.

Anti-bacterial/anti-malarial sales in 2005 for GlaxoSmithKline declined 3% worldwide and 27% in the United States, reflecting generic competition. GlaxoSmithKline's best-selling anti-bacterial franchise, **Augmentin**, generated 2005 sales of £666 million (\$1.21 billion), down 7% from 2004. Generic drug-maker **Par Pharmaceutical Co.** (parpharm.com) was assigned **Ivax Corp.**'s (ivax.com) U.S. distribution rights to generic versions of Augmentin, **Augmentin ES-600**, and **Amoxil**. The assignment of these product rights became effective Dec. 19, 2005. As a result, sales of Augmentin fell 14% to £304 million (\$553.4 million) in first-half 2006.

Augmentin is a broad-spectrum antibiotic suitable for the treatment of a wide range of common bacterial infections and is particularly effective against respiratory-tract infections. Augmentin ES-600 is an extra-strength

suspension specifically designed to treat children with recurrent or persistent middle ear infections. **Augmentin XR** is an extra-strength tablet form for adults to combat difficult-to-treat infections.

Developed by GlaxoSmithKline and **Roche** (roche.com), **Boniva** was launched in the United States in April 2005 and **Boniva** was introduced in several European countries in September 2005 as the first oral treatment administered as a single once-a-month tablet for postmenopausal osteoporosis. Sales of **Boniva/Boniva** totaled £18 million (\$32.8 million) in 2005. Sales almost doubled to £34 million (\$62 million) in the first six months of 2006.

Since its launch, **Boniva** has achieved a 10% share of new prescriptions in the oral bisphosphonate market in the United States. The injectable form of **Boniva/Boniva** was approved for use in the United States and recommended for approval in Europe in January 2006. **Boniva/Boniva** is the first intravenous bisphosphonate to be approved for treating postmenopausal osteoporosis.

In the categories of oncology and emesis, sales of **Zofran** grew 9% to £837 million (\$1.52 billion), driven by the U.S. sales performance, which was up 12% to £639 million (\$1.16 billion).

In the cardiovascular and urogenital category, sales of the heart-disease drug **Coreg** grew 32% to £573 million (\$1.04 billion). GlaxoSmithKline filed once-daily **Coreg CR** with FDA at the end of 2005.

Avodart for benign prostatic hyperplasia had a very strong year with sales more than doubling to £129 million (\$235 million). By January 2006, the product accounted for 42% of new prescriptions in the U.S. 5-Alpha reductase inhibitor market.

In the metabolic category, the diabetes drugs **Avandia** and **Avandamet** continue to perform very strongly, with combined overall sales of £1.33 billion (\$2.42 billion), an increase of 18% when compared with 2004. In 2005, **Avandia** sales totaled £1.15 billion (\$2.1 billion) and **Avandamet** sales amounted to £175 million (\$319 million).

In the United States, combined sales of **Avandia** and **Avandamet** grew 14% to £977 million (\$1.78 billion). **Avandia** and **Avandamet** are establishing a strong position in Europe, with combined sales rising 52% to £157 million (\$285.8 million) helped by the launch of **Avandamet** throughout the region. Combined sales in international markets rose 13% to £195 million (\$355 million).

GlaxoSmithKline launched **Avandia** for type 2 diabetes in 1999 and the combination product **Avandamet**, which contains metformin, for blood-sugar control in 2002. FDA approved **Avandamet** in July for use as initial treatment. **Avandamet** was previously approved as a second-line therapy. In January, the company was

experiencing a shortage of **Avandamet** due to processing difficulties at a plant in Puerto Rico. GlaxoSmithKline's supply of **Avandamet** has been re-established.

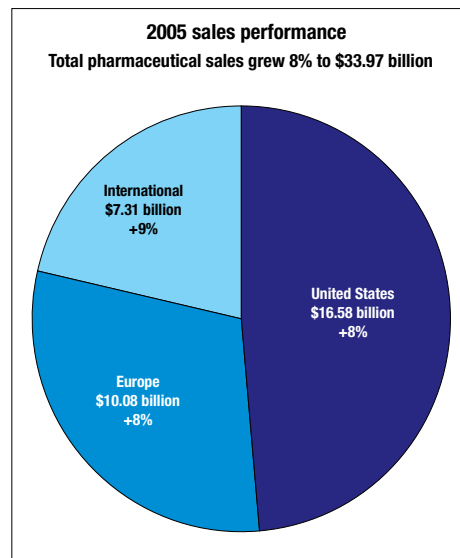
The product group was expanded in February 2006 with the U.S. launch of a fixed-dose combination product, **Avandaryl**, which combines **Avandia** with a sulfonyleurea. The product is known as **Avaglim** in Europe, where the drug was approved for use in June.

According to Bernstein analysts, the recent **Avandaryl** approval, the upcoming **Avandamet** relaunch in second-half 2006, increased **Avandia** capacity, outcomes data, and pancreas-sparing data on **Avandia** will reaccelerate **Avandia** sales.

GlaxoSmithKline vaccines revenue rose 15% to £1.39 billion (\$2.53 billion) in 2005, helped by the launch of two new products — **Fluarix** and **Boostrix**. The vaccines division also benefited from the continued strong performance of **Infanrix** and **Pediarix**, approved for the prevention of diphtheria, tetanus, and acellular pertussis. In 2005, **Infanrix** and **Pediarix** generated £431 million (\$784 million) in combined sales, an increase of 19% compared with 2004.

Infanrix is the U.S. and worldwide leader in diphtheria, tetanus, and acellular pertussis vaccine sales and is licensed in 80 countries. GlaxoSmithKline has distributed more than 29 million doses of its diphtheria, tetanus, and acellular pertussis vaccine in the United States since its launch in 1997 and more than 43 million doses worldwide.

In May 2005, GlaxoSmithKline submitted a biologics license application to FDA, seeking government approval to make **Fluarix** available in the United States in time for the 2005-2006 flu season. GlaxoSmithKline received FDA approval Aug. 31, 2005, for **Fluarix** in immunizing adults against influenza caused by virus types A and B. **Fluarix** is made using egg-based technology and is manufactured for the U.S. market





Zofran ODT helped boost sales of the Zofran product line to \$1.52 billion in 2005.

at the company's Dresden facility.

Approved in May 2005, Boostrix is indicated as a booster vaccination for the prevention of tetanus, diphtheria, and acellular pertussis as a single dose in individuals 10 years old to 18 years old. Sales in first-half 2006 totaled £24 million (\$43.7 million).

U.S. vaccine sales were particularly strong in second-quarter 2006, up 35% to £90 million (\$163.8 million). Sales benefited from a new broader pediatric indication for **Havrix**, the company's vaccine to prevent hepatitis A. Additionally, the Advisory Committee on Immunization Practices recently recommended the hepatitis A vaccination for all U.S. children between 1 year old and 2 years old. U.S. Havrix sales grew 50% to £16 million (\$29.1 million) in second-quarter 2006.

GLOBAL EXPANSION

GlaxoSmithKline experienced substantial growth in international and European markets in 2005. In the European and international markets, Advair, Seretide, Avandia, and the company's vaccine portfolio remain the significant growth drivers. Asia was the clear star in 2005. In Japan, the company's sales were up 13%, edging GlaxoSmithKline into the No. 9 position of pharmaceutical companies in the country.

Korea, China, and Taiwan also generated double-digit growth figures for the company. Canada and Australia continue to deal with either patent issues or tight governmental pressures, but fourth-quarter 2005 earnings reflected growth for the first time in a few years.

The company's European performance was solid with the exception of **Fraxiparine**, which the company acquired in late 2004 from **Sano-fi-Aventis** (sanofi-aventis.com). Fraxiparine is indicated for the treatment and prevention of deep-vein thrombosis. Revenue increased 5% in the European sector in 2005, and the company grew faster than the composite big pharma companies for the first time in a number of years.

This market is a challenge to GlaxoSmithKline because the company does not have the ability to launch many of the line expansions in Europe, as the company does in the United States. Furthermore, Lamictal went off patent halfway through the year in Europe. The company faces the 2006 patent expirations and potential generic introductions for Zofran and **Imigran**, the international brand name for the migraine drug **Imitrex**. Imitrex/Imigran sales in 2005 totaled £697 million (\$1.27 billion), up 1% at constant exchange rates compared with 2004 sales.

CONSUMER HEALTHCARE

To conduct business more effectively in the ever-changing market of over-the-counter products, GlaxoSmithKline's Consumer Healthcare segment has redefined its business strategy and operating model to deliver faster sales growth. **Aquafresh** and **Sensodyne** toothpaste, **Nicorette** and **NicoDerm** smoking-cessation products, and **Ribena** and **Lucozade** drinks are among the products that make GlaxoSmithKline Consumer Healthcare a leading manufacturer and marketer of consumer brands. The company's Consumer Healthcare sales in 2005 were £3 billion (\$5.46 billion), an increase of 2% compared with 2004 sales.

Like others in the consumer health-care industry, GlaxoSmithKline operates in a competitive and changing environment. "Consumers are demanding better quality, better value, and improved performance, while retailers have consolidated and strengthened their negotiating power," says John Clarke, president, Consumer Healthcare. Mr. Clarke succeeded Jack Ziegler in February 2006.

"We expect to achieve this growth through a vigorous focus on delivering new product developments that are tightly aligned with con-

sumer needs," Mr. Clarke says. "The new structure brings together our R&D, marketing, and commercial operating units and gives us greater focus, alignment, and simplicity."

Consumer Healthcare has a particularly exciting new growth opportunity for the business with **Alli**, comprising orlistat, as an over-the-counter weight loss medicine. Orlistat is the active chemical in the prescription weight-reducing medicine **Xenical**, which is marketed by Roche. In April 2005, GlaxoSmithKline Consumer Healthcare and Roche announced a deal in which GlaxoSmithKline Consumer Healthcare would detail and promote prescription orlistat to physicians. In January 2006, an FDA advisory committee recommended that Alli be approved for OTC use in the United States. If approved, Alli will be the only FDA-approved weight-loss medicine available over the counter and is expected to be launched in 2006, accompanied by a consumer-education program.

ONGOING PAXIL ISSUES

The U.S. Supreme Court in June 2006 turned away an appeal in a dispute involving **Apotex Inc.**'s development of a generic alternative to GlaxoSmithKline's anti-depressant drug Paxil. The high court rejected the appeal — filed by GlaxoSmithKline in opposition to a federal appeals court ruling — after the U.S. Solicitor General's office said the lower court had properly ruled against patent protection for the company.

GlaxoSmithKline's appeal asked the Supreme Court to rule on whether the company's patent on the main ingredient in Paxil was rightly ruled invalid because the compound was previously discovered on accident by separate inventors. The Washington-based Federal U.S. Circuit Court of Appeals, which handles pat-

GlaxoSmithKline's Consumer Healthcare business generated sales in 2005 of \$5.46 billion, an increase of 2% compared with 2004 sales.



Imitrex sales were \$1.27 billion in 2005, about the same as in 2004.



ent appeals, ruled against SmithKline Beecham Corp., now part of GlaxoSmithKline. The company's appeal to the Supreme Court argued the decision against the patent would harm innovation in pharmaceuticals and other industries.

GlaxoSmithKline and Apotex (apotex.com) have been embroiled in a patent dispute over Paxil since 1998, when SmithKline Beecham sued Apotex for infringing on the patent covering Paxil's main ingredient. The case went to trial in 2003, and at the time a U.S. District Judge said SmithKline Beecham's patent was valid. On appeal, the Federal Circuit overturned that ruling under two different theories with two separate rulings. The case is *SmithKline Beecham v. Apotex*, 05-489.

Paxil and other antidepressants have been linked to suicide risk in children, and doctors have been warned that these drugs generally should not be used by patients 18 years old and younger. In 2004, FDA ordered strong warnings about the pediatric risk of suicidal tendencies put on antidepressant labels and began analyzing whether adults face a similar risk. All antidepressants now carry warnings on their labels cautioning patients and doctors of the risk of suicidal behavior.

The company and FDA sent a letter warning physicians that Paxil may raise the risk of suicidal behavior in young adults. The warning letter was accompanied by changes to the labeling of Paxil and Paxil CR.

A recent analysis of clinical-trial data on almost 15,000 patients treated with Paxil and placebo revealed a higher frequency of suicidal behavior in young adults treated with the drug, according to the letter. FDA reported that there were 11 suicide attempts — none resulting in death — among the patients given Paxil in the trials. Just one of the placebo patients attempted suicide. Given that small number, the results should be interpreted with caution, according to FDA officials. Eight of the 11 attempts were

made by patients between 18 years old and 30 years old. All trial patients suffered from psychiatric disorders, including major depression.

Paxil was taken off the market for several months beginning in March 2005 due to quality-control problems. The drug was reintroduced in 2005 after GlaxoSmithKline corrected the problems.

In April 2005, **SkyePharma** Plc. entered into an amendment deal with GlaxoSmithKline whereby the royalty rate payable on GlaxoSmithKline's sales of Paxil CR was increased from 3% to 4%. GlaxoSmithKline also agreed to maintain royalty payments while the product was off the market.

In March 1996, SkyePharma entered into a license agreement with SmithKline Beecham for the development, manufacture, and marketing of a modified-release version of Paxil/Seroxat using a combination of SkyePharma's (skypepharma.com) geomatrix positioned release and zero order systems.

PRODUCT APPROVALS AND R&D

GlaxoSmithKline continues to increase its research and development productivity to discover new medicines faster and more economically. The company's pipeline is one of the largest and most promising in the industry, with more than 150 projects in clinical development, including about 95 new chemical entities, 29 product line extensions, and 25 vaccines. The company has advanced its pipeline with a more than 90% increase in the number of new chemical entities between 2000 and 2005.

GlaxoSmithKline has experienced an increase in not only the number of projects in its pipeline, but also in the diversity, quality, and novelty of the products. With 60 years of experience, the company continues to build a very productive R&D pipeline and, in the next

five years, expects five major new vaccines to be launched.

"In 2006, we anticipate further good news on GlaxoSmithKline's late-stage pipeline, which is developing at a fast pace," Dr. Garnier says. "Eight major new assets are scheduled to enter Phase III in 2006, doubling our late-stage pipeline."

GlaxoSmithKline received FDA approval June 8 for **Advair HFA** metered-dose inhaler and expects to launch the product in third-quarter 2006. This device offers a new, convenient alternative for patients, particularly for use in treating children with asthma. In October, the company expects to file with regulators, for inclusion in product labeling, the positive results of a landmark long-term chronic obstructive pulmonary disease mortality study.

Applications for marketing approval of **Allermist** were filed in the United States June 28 and in Europe July 21. Allermist is the company's enhanced-affinity intranasal corticosteroid for allergic rhinitis. The product is called **Avamys** in the European Union. Positive Phase II data on Allermist, presented at the European Academy of Allergology and Clinical Immunology meeting June 12, demonstrated a statistically significant improvement in nasal and ocular symptoms compared with placebo.

A response to FDA's approvable letter for **Entereg** for the treatment of post-operative ileus was submitted May 31, and the agency's action date for this indication is in November. Separately, Phase III trials for Entereg in the



Flonase generated sales of \$1.19 billion in 2005, an increase of almost 13%.

treatment of opioid-induced gastrointestinal side effects are under way, and filing in this indication is expected in mid-2007.

An approvable letter for **Trexima** for migraine was received June 9. FDA determined that Trexima is effective as an acute treatment for migraine headaches, but requested additional safety information. Discussions with the agency are under way. Bernstein analysts say data suggest Trexima could achieve a level of success in the migraines market similar to the level of success Advair has achieved in the treatment of asthma. Trexima was developed in collaboration with the specialty pharmaceutical company **Pozen Inc.** (pozen.com).

In July 2006, GlaxoSmithKline announced promising clinical-trial results for its avian flu vaccine, **H5N1**, that show great hope for addressing the threat of flu pandemic. New data show that GlaxoSmithKline's novel proprietary adjuvant technology provides protection at a very low dose. This means GlaxoSmithKline could make very large quantities of the vaccine if needed for a flu pandemic and potentially greatly increase the number of individuals that could be vaccinated.

The vaccine, which uses a proprietary adjuvant, enabled more than 80% of subjects who received 3.8 micrograms of antigen — the lowest dose tested in the study — to demonstrate a strong seroprotective immune response. This level of seroprotection exceeds target criteria set out by regulatory agencies for registration of influenza vaccines. Efficacy results at these levels have not been reported for any other H5N1 vaccine in development, including those using other adjuvants such as alum.

Further data from this trial and others are expected to be available in third-quarter 2006, including assessment of the vaccine's ability to offer cross protection against variants of the H5N1 strain.

Cervarix is indicated for the prevention of human papillomavirus, which causes cervical cancer, a disease second only to breast cancer in the list of most common cancers affecting women. Global clinical trials have shown that Cervarix provides excellent efficacy against HPV16 and HPV18, which are responsible for more than 70% of cervical cancers.

New data were published in July showing that Cervarix induced a consistently stronger and more sustained immune response during a three-and-a-half year period than the same vaccine formulated with a conventional aluminium adjuvant. Data presented at the American Society of Clinical Oncologists Convention on Cervarix also demonstrated significant immunogenicity in women 25 years old and older, the first data to be presented on an HPV vaccine in older women. Cervarix has been filed in Europe and in 28 international markets and remains on track for filing in the United States by the end of the year.

According to analysts with Wood Mackenzie (woodmac.com), Merck has only completed studies of its cervical cancer product Gardasil in younger women, although studies in older women are under way. GlaxoSmithKline, on the other hand, has tested Cervarix in women 55 years old and younger and demonstrated that its vaccine has the same immunogenic response in the older age group as in younger women — 100% protection. Even though Cervarix is a bivalent antigen against HPV strains 16 and 18, GlaxoSmithKline has managed to demonstrate that the vaccine provides cross-protection against other strains. According to analysts with Wood Mackenzie, GlaxoSmithKline has attempted to undermine the differences surrounding Gardasil, which is a quadravalent vaccine against four strains of HPV.

Another major new product expected in the next five years is Rotarix, which is indicated to treat rotavirus gastroenteritis. Rotarix is already launched in a number of countries in Latin America, Africa, and Asia, and launch in Europe was expected in the first half of 2006.

Streptorix, in clinical development for pneumococcal disease, is an improved influenza vaccine for older patients. Additionally, the company is developing vaccine combinations against meningitis.

At the American Society of Clinical Oncologists Convention, GlaxoSmithKline's **Tykerb** was deemed the "most interesting" product in clinical development. Tykerb was also mentioned by almost half of respondents as "the most important topic" discussed at ASCO. Additionally, 40% of oncologists indicated that their standard of care in renal cell carcinoma and breast cancer would change due to the new information disseminated at the convention.

Positive data on Tykerb were presented at ASCO showing that Tykerb significantly improved the time to disease progression for patients with advanced breast cancer whose disease progressed on **Herceptin**. Herceptin is marketed by **Genentech Inc.** (gene.com). Encouraging data demonstrating activity against brain metastases associated with breast cancer were also presented, as well as positive results in inflammatory breast cancer — a severely aggressive form of the disease. GlaxoSmithKline plans to file Tykerb for regulatory approval in the United States in third-quarter 2006 and in Europe later in the year.

GlaxoSmithKline is working on four antigen-specific cancer immunotherapeutics. The lead product, **MAGE-A3**, for refractory non-small cell lung cancer in the adjuvant setting, generated a good immune response and better disease-free survival.

GlaxoSmithKline presented results on its MAGE-A3 immunotherapeutic vaccine for non-small cell lung cancer at ASCO. The Phase II study showed a one-third reduction in relative risk of cancer recurrence following sur-

gery in those patients treated with MAGE-A3 compared with placebo. Although this reduction did not reach statistical significance at this interim stage, the trend was very encouraging. GlaxoSmithKline is planning to go into Phase III for that indication in 2007. This will be the first big pharmaceutical cancer immunotherapeutic vaccine to progress that far, according to Wood Mackenzie analysts.

According to these analysts, with the thrombocytopenia product **Promacta**, which contains the active ingredient eltrombopag, the company's initial strategy is to go for a very small niche indication: patients with idiopathic thrombocytopenia purpura. GlaxoSmithKline is additionally conducting another Phase II trial in chemotherapy-induced thrombocytopenia, which is a much larger market.

Positive Phase II data for Promacta, a novel oral platelet growth factor, were received in patients with hepatitis C associated thrombocytopenia. These results will be submitted for presentation at the American Association for the Study of Liver Disease meeting in October.

Enrollment was completed for a Phase III trial examining Promacta as a short-term treatment for idiopathic thrombocytopenic purpura and a Phase II trial for treating chemotherapy-induced thrombocytopenia.

According to analysts, GlaxoSmithKline's strategy is to test the product in a smaller population first. If the product looks to be successful in this indication, then the company will expand the drug into the larger market and run both programs in parallel. If the larger chemotherapy trial does better, or reaches the end result quicker, the company will likely move forward with the larger market and discontinue development of the smaller indication.

FDA granted **Myogen Inc.**'s pulmonary arterial hypertension drug **ambrisentan** fast-track status in March 2006. Ambrisentan is in Phase III trials. Myogen (myogen.com) and GlaxoSmithKline agreed on a two-part pulmonary arterial hypertension partnership. Myogen licensed the commercialization rights for ambrisentan to GlaxoSmithKline outside the United States. Ambrisentan reached its primary endpoint in a study involving pulmonary arterial hypertension patients.

Phase III trials for **Redona** began during the second-quarter 2006. Redona, comprising denagliptin, is a DPP-IV inhibitor for treating type 2 diabetes.

Phase III clinical trials involving more than 2,500 patients have begun to assess the use of **rosiglitazone XR** in treating Alzheimer's disease. This is a novel approach to treat Alzheimer's disease based on the growing body of scientific evidence that patients with the disease have reduced glucose metabolism in the brain.

Development of **radafaxine**, for depression, has been discontinued due to an unfavorable risk/benefit assessment.

DOWN THE ROAD FOR GSK

For 2006, GlaxoSmithKline managers expect to achieve a similar level of operating income to 2005. R&D as a percentage of sales is predicted to remain broadly in line with the percentage achieved in 2005. Newer products such as Avodart, Requip, and Boniva are expected to successfully grow.

"GSK had another successful quarter [second-quarter 2006] with pharmaceutical sales

growth of 10% driving an excellent financial performance and enabling us to raise our earnings guidance to around 12% EPS growth in 2006," Dr. Garnier says. "The pipeline is progressing well and we have received outstanding efficacy data for our H5N1 pandemic vaccine — these results are highly significant and mark real progress in our aspiration to develop a vaccine for use in preparing for an influenza pandemic."

Company officials expect seven products to be approved/launched during 2006. Additional-

ly, there are seven product filings planned and the company's late-stage pipeline continues to expand with eight major assets expected to enter Phase III development during 2006.

Analysts with The Goldman Sachs Group (goldman.com) predicted the following products will be filed with FDA in 2006: eltrombopag, **mepolizumab** for eosinophilic esophagitis, **Arixtra** for acute coronary syndrome, Lamictal XR, Allermist, Tykerb, H5N1, Cervarix, and Requip product line extensions. Wellbutrin XL is predicted to be filed in Europe.



CEO and Director J.P. Garnier, in an exclusive interview with *Med Ad News*, shares how GlaxoSmithKline has made a name for itself in the vaccines arena, developed an unparalleled product pipeline, and offset generic competition and legal issues.

Q: GlaxoSmithKline suffered setbacks with generic competition to Paxil IR and Wellbutrin SR in 2004, and Flonase in early 2006. How has the company successfully offset the sales losses from these former blockbusters as well as other products?

A: In 2006, it's Flonase, but if you look back, we had a much worse time a few years ago when we lost our top three products, which were at the time, Aug-

mentin, Paxil, and Wellbutrin XR, and we were able to grow at a significant pace despite those staggering losses in the United States. So in a way, the period we are facing now is much more favorable. If you are a very large company, you would expect to lose products as a cycle of patent protection goes over the various years and eventually comes to an end, so it should surprise no one that we have some challenges. But in the grand scheme of things, they are relatively minor compared to what we have just gone through three or four years ago.

How we managed to maintain above average growth despite those losses has to do with new products. If you have new products that are significant, then you develop new engines to propel the mother ship. Those new products more than make up for the losses to the generics of older brands. That's exactly what has happened. There is no other way to do it, except to be successful in innovation and introduce significant new products in various fields. If you look at some of our new products like, Advair in asthma and Avandia in diabetes, those products were fairly minor a few years ago and now they are multibillion-dollar brands, so they have allowed us to be successful financially despite the losses of significant products like Paxil.

Q: Generic drug manufacturers are seeking to market generic versions of many of GlaxoSmithKline's most important products, including Avandia, Zofran, Wellbutrin XL, Imitrex, Lamictal, Valtrex, and Paxil CR, before the expiration of GlaxoSmithKline's patents and have exhibited a readiness to do so for other products in the future. How is GlaxoSmithKline responding to these challenges?

A: Generics attack every single new chemical entity regardless of what is going on on the patent front. They take a shot. That's not specific to GlaxoSmithKline. The generic industry does its research in the legal library and we do our research in the laboratory. We discover drugs, the generics game is to try to gain access to those drugs, sometimes earlier than we would think is fair by trying to undermine some of the patents that protect our products. When the patent is a new chemical entity, such as Avandia, Imitrex, etc., it is very unlikely that a generic would be able to undermine what is essentially a rock-solid patent.

On the other hand, when you deal with Wellbutrin XL and products of that nature, where the patent is more on the delivery system, then there is a chance that the generic copycat can go around the technical patents to try to come up with something that looks like the target product. In some cases, there is no surprise at all, such as the case with Zofran. We know exactly when the product is going to go generic — later this year — because we have had no challenges of substance to the patent and the key patent on the product does expire toward the end of the year. If you look at the forecast for a company, the new products will help a lot and help to overcome those different vulnerabilities.

Q: About nine product filings are planned for GlaxoSmithKline in the United States in 2006. Are these compounds still on track? Is GlaxoSmithKline in a position to continue to deliver at this level in the years to come?

A: We have had two or three years with a record number of filings. Some of those products are coming to the market and some

will come as soon as the FDA clears them. I would say 2006 is a good crop because of the nature of three molecules that are substantial opportunities for GlaxoSmithKline. The first is Cervarix, which is a vaccine for cervical cancer; the second one is Tykerb for breast cancer; and the third one is Allermist for allergic rhinitis and has already been filed in the United States and Europe. We have a number of others, but those are the main assets. They will generate substantial revenue in the future.

Q: How does GlaxoSmithKline use life-cycle management and in-licensing to support growth as the company's pipeline matures?

A: Like everyone else, we try to improve on our molecules as we get to know them. Initially they are launched as they were discovered and then can sometimes, not always, find a way to make them more convenient or safer. It's not all about just changing a drug from a once-a-day to a twice-a-day dosage, but sometimes you are able to change the delivery system so that you reduce the level of peaks that are sometimes responsible for side effects. In the case of Paxil, Paxil CR does seem to be a better product in terms of safety to the original Paxil IR, although it has the same frequency, the once-a-day dosage. We work on those molecules and sometimes we find a superior formulation, such as Wellbutrin XL.

We are in favor of in-licensing significant assets, although the way we construct our pipeline is much broader in terms of the collaborations we have. We start collaborating with external companies and academia at a very early stage, and we have literally hundreds of such collaborations. Eventually they produce molecules and vaccines for us. Occasionally we

do late-stage in-licensing, but there are fewer and fewer of those available, so we do not rely on it. We have to aim at producing a pipeline that is sufficient for the long-term survival of the company, and if on top of that we can in-license a couple of assets, then that is great. But it is not always possible.

Q: How has GlaxoSmithKline developed such a strong late-stage pipeline? Will the changes made over the years in the company's R&D strategy sustain that level of development?

A: It is all about R&D strategy. A few years ago it became obvious to us that R&D productivity was eroding in the industry. Everybody was looking at fewer and fewer new chemical entities being discovered and approved. At the same time, the investments in R&D were increasing dramatically. The whole industry in 1980 spent about \$2 billion in R&D, all companies included. That year, the FDA approved close to 30 new chemical entities. Then move 20 years forward, and in 2000 the industry spent \$26 billion on R&D, 13 times more than in 1980. And yet that year, FDA only approved 30 molecules as well. So we can see the problem. There are multiple reasons why the industry seems to be discovering fewer molecules of major significance.

We decided to go back to the R&D process, and we changed pretty much everything. We changed the basic technologies, we embraced genomics to discover new targets, we embraced high-throughput technologies to be able to screen millions of compounds at a very fast pace, we changed the organization because R&D departments grew significantly with investment in R&D, and instead of 2,000 scientists organizing a very classic pyramid type set up, we ended up with 18,000 or 20,000 scientists. That became hugely bureaucratic, so we had to reinvent the model of organization. We created multiple centers of excellence — a center of excellence is targeting one or two critical diseases — and those groups of 300 or 400 scientists have tremendous autonomy, responsibility, and transparency. It started to make a big difference and we saw that bureaucracy was lifted, there was more of a

sense of purpose within those groups. They also had a heightened sense of accountability and were fully responsible without interference. There was a CEO at the top of the small organization. In a way, they had the best of both worlds — they had the “small is beautiful” structure of biotech, but they also had access to the very large support services, which in R&D are very important. The services were organized to be at the disposal of those therapeutic centers.

I feel that had we not adopted this model and made significant changes to the R&D process, we would be struggling to find molecules like most of our colleagues. At the time, we didn't have a great pipeline, so it was very important to us to be successful. If you look back six or seven years, the success has been undeniable. We now have the largest pipeline of drugs in the clinic — over 150 drugs. We have been rated by three different analysts this year as having the best pipeline in the industry.

Whether it is the depth, degree of innovation, quality of the molecules, or simply productivity — that is the number of molecules getting in the pipeline every year and staying in the pipeline — on every barometer you can think of, GlaxoSmithKline's R&D seems to be extremely successful. Ironically, I don't think we can claim victory yet because even though we might be best in class, it is hard to tell if it is good enough to propel the company forward in the years to come.

It is never finished business here, but we are very encouraged by the pace at which we are discovering drugs and putting them in the pipeline, and also by the fact that we are not suffering undue attrition. The attrition of the pipeline is about the same as for all the other companies. All in all, it has been a very successful re-engineering and major shift in the history of GlaxoSmithKline, and this has and will create substantial shareholder value.

Q: GlaxoSmithKline continues to be the leader in respiratory pharmaceuticals. What steps are being taken to ensure continued success in this area?

A: We look for new targets and do not go back to what already exists. Our center of excel-

lence in respiratory medicine is made up of some of the best scientists in the field, so those people should be the ones who pick the best targets for drug discovery. There is no magic solution. We have to pick the right targets that will allow us to discover a product that has a different mechanism of action and therefore might emerge as the world leader in terms of this particular application.

Ironically, there is a technology that is very important in drug discovery and drug development in respiratory medicine and we, of course, are very good at this. We have invented new delivery systems that are still to this day best in class. For example, the one that is used for Advair.

Q: How has GlaxoSmithKline redefined the business strategy and operating model of the Consumer Healthcare division?

A: Our Consumer Healthcare division is successful in the sense of financial results. It is the most profitable consumer health-care business if you compare and benchmark it to its direct competitors. The reason is very simple. We only have one infrastructure that serves those divisions, we do not duplicate business infrastructure. This structure allows us to have a very profitable Consumer Healthcare unit.

The way GlaxoSmithKline succeeds with its consumer health-care segment is by first, creating global brands. We are present in more than 130 countries with substantial infrastructure and the means to achieve the end. We are developing new products and new line extensions for major brands, and we internationalized them throughout the world. That is the key to success because the over-the-counter market in the United States and Europe is less than dynamic, so you have to make your growth come out of the rest of the world. That is what we have been doing.

The second factor is that occasionally there is a prescription to over-the-counter switch opportunity, particularly in the U.S. market. The prescription-to-OTC switch has been an enormous growth driver for GlaxoSmithKline as we have seen with our smoking-cessation brands. Out of nowhere we have created a business that is worth \$500 million

in revenue in the United States alone. We intend to do the same with Alli, which will be the first weight-loss product FDA approves for over-the-counter use. We cannot wait to see FDA give us the go-ahead with this product. We are still hoping for approval this year or early next year. This will be a substantial opportunity if the product is marketed in a very responsible way. Weight loss creates incredible expectations from patients, but if we manage it successfully, this will be a new franchise for us.

If you look back over the last 10 years, GlaxoSmithKline has been the key company in terms of successful prescription-to-OTC switches. We have certainly demonstrated our strength in this area. We hope to in-license products for prescription-to-OTC switches from other companies. We do not have access to the same kind of a marketing and selling organization and a clinical-development organization, which is important in that field.

Q: How is GlaxoSmithKline faring in markets other than the United States and Europe? For instance, in Japan, you have 10 product launches expected in the next three years.

A: Like everybody else, we have to be successful outside Europe and the United States. We made the appropriate investments way back when it was necessary. If you look at the markets in China, India, and Vietnam, GlaxoSmithKline is the No. 1 company. All of those booming markets are now helping us, and we are riding the wave. This is also true in South America where we have a very strong presence.

In Japan, the merger of Glaxo and SmithKline has helped tremendously because we did not have critical mass before that, and we were not ranked among the top 30 companies. Now we are already in the top 10 and growing rapidly because we have so many new product launches. The two key drivers for the company today — Avandia and Advair — have not even been introduced in Japan, so their introduction will propel our subsidiary in Japan to the very top of the class. We expect this to take place during the next several years.

Q: What steps has GlaxoSmithKline taken in pre-

paring the United States for the threat of a possible flu pandemic?

A: We are extremely well-positioned. We gambled last year by investing \$2 billion in extra manufacturing capacity in Canada by buying ID Biomedical and by buying the Marietta campus in Pennsylvania from Wyeth. We also doubled up on our plant in Germany because we were convinced that the pandemic was becoming more serious. We had a chance of discovering a vaccine that could be used in the case of a pandemic alert.

The plan we had has been executed successfully as you have seen. We have published extremely positive results on our pandemic vaccine. We hope to go into industrial production by Christmas or so, and therefore, we are in active discussions with many governments to sell our vaccine next year. The flu pandemic vaccine is a reality. The vaccine is extremely effective, extremely safe, and it has the advantage of necessitating a very tiny quantity of antigen, which means that we could manufacture large quantities of the vaccine if need be.

We have an antiviral drug, Relenza, which is a protective antiviral similar to Tamiflu, although Relenza is administered differently. It is not a pill. Relenza is administered like many of our asthma products. We have multiplied the capacity for producing Relenza by a factor of 40 in less than two years. We have done everything we could to help the company prepare itself and help the world in terms of the pandemic threat.

Q: How is GlaxoSmithKline investing in its vaccines business to assure success down the road?

A: We have had a very successful run with our vaccine business, which is currently booming. We have a spectacular pipeline with Cervarix, the meningitis program is very successful, and we have the only malaria vaccine that has shown proof of concept in the final stage of clinical trials in Africa. Anywhere you look, GlaxoSmithKline is on the cutting edge in the pandemic race because another 15 companies were trying to

accomplish the same thing, so our scientists are ahead of the curve. We are very pleased with the vaccine business. Vaccines will generate substantial value for our company.

Q: How has GlaxoSmithKline differentiated Cervarix from Merck & Co.'s Gardasil?

A: With Cervarix, we made a different choice from Gardasil. Gardasil tried to deal with the viruses responsible for cervical cancer, but also, at the same time, they added some antigens to cover the risk of certain sexual diseases which are not that frequent, ones that mostly occur with men. We decided to focus exclusively on females with a vaccine that is the most effective vaccine you can design for the prevention of cervical cancer. And that is exactly what we are going to deliver to FDA by year end.

If you compare the two products, you will notice that in the case of Cervarix, we have some cross-protection advantage. In other words, Gardasil is 100% effective on HPV 16 and HPV 18, which are the most common viruses that trigger the potential for cervical cancer. But there are other viruses, of course, that also can be responsible for the development of cervical cancer. And in that case, Cervarix in contrast to Gardasil seems to have some efficacy beyond HPV 16 and HPV 18 where we have also shown 100% efficacy. Cervarix is a broader-spectrum vaccine, which means that from a pure efficacy standpoint, we should have an advantage. Now, the jury is out to see if FDA will give us this claim, but the data are very suggestive at this point.

Because of the very innovative adjuvant that is part of the formulation of the vaccine, which is not available to Merck, we are showing very high antibody titers, much higher than if we had used the classic adjuvant that is generically available and used by Merck. When you show a higher antibody titer, it suggests that the degree of protection and the duration of protection will be superior with Cervarix as compared with Gardasil.

Q: In what ways have the legal issues with the Paxil franchise had an impact on GlaxoSmithKline?

A: Legal issues are the cost of doing business. In the United States, the legal system is kind of broken and unfortunately we have to defend ourselves against plaintiff lawyers and play in a field that is sometimes not entirely fair to us. However, we have managed to do so in the past and will continue to do so in the future.

Q: How will GlaxoSmithKline continue to address the uninsured population now that Medicaid Part D closed in May 2006?

A: GlaxoSmithKline has a policy that we are going to make every effort to make our new drugs and vaccines available to people beyond the ones who can afford them. In other words, we go to extremes to try to make those drugs available. If you look at our actions in the developing world, we have the largest donation program ever for lymphatic filariasis. We were the first company to sell HIV drugs at marginal cost, and this has allowed us to ship hundreds of millions of Combivir tablets this year when three or four years ago, there were none. We have out-licensed our technology for HIV. We have been doing this for about seven years. We have out-licensed to generic companies. We have shown the way in terms of being generous and trying to reach the population that unfortunately cannot afford to buy our medicines.

These efforts have not been solely in the developing world. We have programs in place in the United States as well. The first discount card, the so-called Orange Card, was an initiative started by GlaxoSmithKline to give the seniors a 30% to 40% discount on all medicines if they were having financial difficulties or were uninsured. That card was very successful and was then superseded by Together Rx, which was a similar type of approach for eight or nine companies, and of course, we were one of the sponsors of the Together Rx card. This card stays in effect even after Medicare Part D. We also have a patient-assistance program. We spent more than \$1 million a day giving away free drugs to people who cannot afford them. We are completely committed to these efforts and try to close the hole that still exists in the United States in the drug reimburse-

ment system.

Q: How is Medicare Part D expected to affect GlaxoSmithKline's future marketing strategies? Will the program also affect R&D strategies, as the company will have to convince formulary plans of the value of its drugs?

A: In terms of marketing before and after Medicare Part D, in my view, there really is no change for us because from way back, our company has always given out drugs while also demonstrating the drugs' efficacy and safety, not just in the clinical sense, but also in health economic models and experiments. For example, GlaxoSmithKline has a new drug called Entereg, which will hopefully be introduced later this year. Entereg takes patients who go through bowel surgery and allows those patients to leave the hospital faster. There is a direct cost saving to the health-care system. This is not unusual. Drugs tend to be the most cost-effective intervention in health care, much more cost effective than alternative methods such as surgery. But we have to demonstrate that. We can't just tell the world, we have to show the proof and do the clinical studies. And we are doing very large and expensive clinical studies to build up those claims and demonstrate to the payers that it is in their best interest to embrace our medicines and our vaccines. And we have had no trouble doing so for the great majority of our products.

We have been trying to get our medications reimbursed in Europe. The payer in Europe, in a way, has all the power. It's a single-payer system, in which you have only one customer per country. If you don't convince that customer that your medication is going to help save money or improve the public health, then your drug doesn't get through. It is not particularly difficult for us to apply those techniques to the situation in the United States. We have already considered that it is part of our mission to justify why our innovation is good for patients and the health-care system, and we will continue to do so in the future.

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