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MedAdNews

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TEVA PHARMACEUTICAL COMPANY OF THE YEAR

While the rest of the industry plays defense, no pharmaceutical company in the world has grown quite like Teva in the past decade.

26TH ANNUAL REPORT TOP 50 PHARMA COMPANIES

- Abbott Laboratories
- Actelion Pharmaceuticals Ltd.
- Allergan Inc.
- Amgen Inc.
- Astellas Pharma Inc.
- AstraZeneca plc
- Baxter International Inc.
- Bayer AG
- Biogen Idec Inc.
- Boehringer Ingelheim GmbH
- Bristol-Myers Squibb Co.
- Celgene Corp.
- Chugai Pharmaceutical Co.
- CSL Ltd.
- Daiichi Sankyo Co.
- Dainippon Sumitomo Pharma Co.
- Eisai Co.
- Endo Health Solutions Inc.
- Forest Laboratories Inc.
- Gilead Sciences Inc.
- GlaxoSmithKline plc
- Grifols S.A.
- Hospira Inc.
- Johnson & Johnson
- Kyowa Hakko Kirin Co.
- Eli Lilly and Co.
- H. Lundbeck A/S
- Merck & Co.
- Merck KGaA
- Mitsubishi Tanabe Pharma Corp.
- Mylan Inc.
- Novartis AG
- Novo Nordisk A/S
- Ono Pharmaceutical Co.
- Otsuka Holdings Co.
- Pfizer Inc.
- Ranbaxy Laboratories Ltd.
- F. Hoffmann-La Roche Ltd.
- Sanofi
- Shionogi & Co.
- Shire plc
- Stada Arzneimittel AG
- Taisho Pharmaceutical Co.
- Takeda Pharmaceutical Co.
- Teijin Ltd.
- Teva Pharmaceutical Industries Ltd.
- UCB S.A.
- Valeant Pharmaceuticals International Inc.
- Warner Chilcott plc
- Watson Pharmaceuticals Inc.

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BPA WORLDWIDE

inside

COMPANY OF THE YEAR

ANNUAL REPORT

CHARTS AND LISTS

PROFILES

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Climbing up the cliff

Several pharmaceutical companies in 2011 and 2012 are experiencing the ravages of patent expirations; but some experts believe that the worst may be over, and executives are more confident about the future.

by Christiane Truelove chris.truelove@ubm.com

2012 isn't going to be the end of the world for the pharmaceutical industry, but it does mark the continuation of the patent cliff for many blockbuster brands and some companies are going to find it very hard going indeed in the future. The cliff that emerged in 2009 peaked in 2011 and 2012, with the expirations of patents for Arimidex, Lipitor, Zyprexa, Diovan, Plavix, Seroquel, Lexapro, Actos, and Singulair all taking place during this time. The expirations of these product patents depressed sales for their marketers. But industry experts are seeing brighter times ahead, with more product approvals and a global rebound in spending on medicines.

According to IMS Health's Institute for Health Informatics, annual global spending on medicines will rise from $956 billion in 2011 to nearly $1.2 trillion in 2016, representing a compound annual growth rate of 3 percent to 6 percent. Growth in annual global spending is predicted to more than double by 2016 to as much as $70 billion, up from a $30 billion pace in 2012, driven by volume increases in emerging markets and an uptick in spending in developed nations.

Additionally, patent expiries, which will peak in 2012, as well as increased cost-containment actions by payers, will constrain branded medicine spending growth through 2016, at 0 percent to 3 percent. Developed markets are expected to experience their lowest annual growth this year, at less than 1 percent or $3 billion, and then rebound to $18 billion to $20 billion in annual growth in the 2014 to 2016 period.

"As health systems around the world grapple with macroeconomic pressures and the demand for expanded access and improved outcomes, medicines will play an even more vital role in patient care over the next five years," says Murray Aitken, executive director, IMS Institute for Healthcare Informatics. "The trillion-dollar spending on medicines we forecast for 2016 represents a rebound in growth that will accentuate the challenges of access and affordability facing those who consume and pay for healthcare around the world."

Despite the highest number of patent expiries in history, spending in the United States will grow by $35 billion to $45 billion over the next five years, representing an average annual growth rate of 1 percent to 4 percent, as newer medicines that address unmet needs are introduced and patient access expands in 2014 due to implementation of the Affordable Care Act.

Losers and winners

Perhaps the hardest hit of the top pharmaceutical companies during this period is **AstraZeneca**. In the first half of 2012, the company's sales dropped 15 percent as the patents for the cancer drug **Arimidex** and the antipsychotic **Seroquel** expired. The pain isn't over yet for AstraZeneca, as about half of the company's $33 billion in revenue is expected to be gone by 2016, including the heartburn drug **Nexium** and the cholesterol reducer **Crestor**. (For more information, see profile on page 34.)

As Arimidex and Seroquel sales were slipping away, the company also experienced several setbacks with highly anticipated drugs in its pipeline. For example, at the end of 2011, AstraZeneca announced that trials for **TC-5214**, an antidepressant, and **olaparib**, a cancer drug, did not meet their endpoints. By April 2012, Chief Executive David Brennan quit, rumored to be the victim of a shareholder-decreed shakeup of the top management levels.

One company that is claiming that it will emerge from the patent cliff period in a strong position is **Sanofi**. Chris Viehbacher, Sanofi's CEO, believes that despite the losses of Plavix, the heart drug **Avapro**, and the cancer drug **Eloxatin**, the company can grow back its business. ""We'll have one of the lowest exposures to patent expiry coming from that," he says. "So it'll be a challenging 2012, but most of us in management are now focused on growth post the patent cliff period."

Mr. Viehbacher says in looking at the patent exposure for small-molecule drugs in Europe, the United States, and Japan, only 6 percent of Sanofi's 2012 sales will be affected, making it one of the lowest exposures in the pharmaceutical industry. Meanwhile, Sanofi's growth platforms are performing strongly and are expected to continue to do so in the future. (For more information, please see the profile on page 76.)

IMS Health says health systems in developed economies will experience slow growth in medicine spending. Spending on medicines in developed nations will increase by a total of $60 billion to $70 billion from 2011 to 2016, following an increase of $104 billion between 2006 and 2011.

In Europe, growth will be in the -1 to 2 percent range due to significant austerity programs and healthcare cost-containment initiatives. The Japanese market for medicines is forecast to grow 1 percent to 4 percent annually through 2016, slightly lower than the rate during the prior five years and reflecting biennial price cuts scheduled for 2012, 2014, and 2016. Overall, patent expiries in developed markets will yield a five-year "patent dividend" of $106 billion, reflecting reduced brand spending of $127 billion offset by $21 billion in higher generics spending

Health systems in emerging markets will nearly double their medicine spending in five years. Annual spending on medicines in the emerging markets will increase from $194 billion in 2011 to $345 billion to $375 billion by 2016, or $91 in drug spending per capita. The increase will be driven by rising incomes, continued low cost for drugs, and government-sponsored programs designed to increase access to treatments – by limiting patients' exposure to costs and encouraging greater use of medicines. Generics and other products, including over-the-counter medicines, diagnostics, and non-therapeutics, will account for approximately 83 percent of the increase.

Even with all of this increased healthcare spending, pharma manufacturers will see minimal growth in their branded products through 2016. The market for branded medicines will experience flat to 3 percent annual growth through 2016 to $615-$645 billion, up from $596 billion in 2011. In the major developed markets, branded medicine growth will be severely constrained at only $10 billion over the five-year period due to patent expiries, increased cost-containment actions by payers, and modest spending on newly launched products. The pharmerging markets are expected to contribute $25 billion to $30 billion in branded product growth over the same period. Off-invoice discounts and rebates will offset about $5 billion of global branded medicine growth.

The big winners of the industry will be manufacturers of small molecule generics, which will be experience accelerating growth. Global generic spending is expected to increase from $242 billion in 2011 to $400 billion to $430 billion by 2016, fueled by volume growth in pharmerging markets and the ongoing transition to generics in developed nations. The impact of patent expiries primarily will be felt in the United States. In Europe, limited savings from expiring patents are prompting policy shifts to encourage greater use of generics and lower reimbursement for these products.

Med Ad News' 2012 Company of the Year, **Teva** Pharmaceutical Industries Ltd., exemplifies the power of generics. Teva leads the world in total prescriptions filled, thanks to its gigantic portfolio of generic products, which also leads the world – but it also boasts two blockbuster branded products, with others possibly on the way. Teva has held the leading generic position in the United States for almost a decade, and is the leading generic drug company in Europe, where the company boasts a balanced presence throughout the region. In addition, the company has significantly increased its presence in its "rest of the world" markets. Teva is now the third leading generics company in Japan and has experienced significant growth in Russia and Latin America.

In 2011, about 56 percent of Teva's revenue was generated from generic pharmaceuticals, including active pharmaceutical ingredients sold to third parties, and about 35 percent from branded products, which include **Copaxone** for multiple sclerosis, **Azilect** for Parkinson's disease, the company's respiratory and women's health products, and products from the newly-acquired Cephalon portfolio. With the acquisition of Cephalon in late 2011, Teva's branded portfolio was expanded to include, most significantly, **Provigil** for excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work disorder, and **Treanda** for chronic lymphocytic leukemia and indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. The company's remaining revenue was generated from its joint venture with P&G and other activities such as its Hungarian and Israeli distribution services to third parties. Company leaders expect the branded share of Teva's revenue to increase markedly in 2012 due to the effects of the Cephalon acquisition.

According to Jeremy Levin, Teva's new CEO, the true differentiator between pharma companies is how well companies adapt to change. "Over the last five years, Teva has faced significant changes in the differences in the markets it serves," he says. "These changes necessitate changes in the way we operate. Other large companies focus on developing and marketing medicines at higher prices with higher margins for smaller subsets of patients with significant diseases. Teva has a nearly unique circumstance in that our patients are in 120 countries, our portfolio consists of over 1300 medicines, and our cultural diversity is unparalleled. This sets the stage for us to develop solutions to take advantage of the market evolution adapted to our particular circumstances."

One way Teva is shaping itself to the changes in the pharmaceutical industry is by establishing one R&D division for the entire company, combining generic with branded R&D. "We deploy common technologies and remove an artificial barrier in the industry that implies there is 'innovation' only on one side of the business," Mr. Levin says. "We believe that through our focus on the patient and unmet medical need, in R&D we can achieve greater success for our patients."

Another winner in the future as envisioned by IMS Health will be biotech companies and large pharma companies with concentrations in biotech research, as biologics manufacturers will benefit from expanding market opportunity. IMS Health says biologics are expected to account for about 17 percent of total global spending on medicines by 2016, as important clinical advances continue to emerge from research. Seven of the top 10 global medicines by spending will be biologics within five years. Adoption of biosimilars as low-cost alternatives to the original biologic medicines will remain limited, as biologics remain protected by patents or market exclusivity in many countries.

The biotech pipeline is crowded with a new wave of possible billion-dollar brands and one-of-a-kind products expected to gain regulatory approval in 2012 or 2013. 2012 kicked off with FDA approval of a long-awaited diabetes drug, **Amylin** Pharmaceuticals Inc.'s **Bydureon**. This is the first once-weekly treatment for type 2 diabetes. Bydureon is an injectable, extended-release form of Amylin's older and market-successful diabetes product **Byetta**, which is injected twice per day. Byetta and Bydureon have the same active chemical, exenatide. Bydureon is designed to help the body produce more insulin, which can reduce high blood-sugar levels. Some industry analysts have projected that Bydureon annual sales could approach $2 billion before 2020, though the drug will compete in a crowded marketplace with other new medicines on the horizon.

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Another potential blockbuster medicine approved by FDA in January 2012 was **Erivedge**. The drug's first approval was for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. The first-in-class hedgehog-pathway inhibitor is part of a development program between the biotech companies **Curis** Inc and **Roche**/Genentech Inc. Some analysts expect the drug to exceed $1 billion in yearly sales for advanced basal cell carcinoma alone. Erivedge is also being developed in Phase II trials for operable basal cell carcinoma and is undergoing studies for other indications. (For more information about Roche and Erivedge, please see page 73.)

Several of the top pharmaceutical and biotech companies have acquired other biotech companies to shore up their biologics pipelines. Sanofi completed the acquisition of Genzyme and Teva purchased Cephalon in 2011.

GlaxoSmithKline (see profile on page 42) made an unsolicited bid for Human Genome Sciences Inc. in April 2012. Human Genome Sciences capitulated in July, agreeing that GlaxoSmithKline could buy the company for $3.6 billion. Human Genome Sciences markets the drug **Benlysta** with GlaxoSmithKline. Approved in March 2011, Benlysta is the first new drug in 56 years to treat lupus. The drug is a monoclonal antibody that inhibits B-cell activating factor. Analysts expect the drug to exceed $2.2 billion in sales by 2014. At the time of the acquisition, Human Genome Sciences was working on two other products with GlaxoSmithKline, the heart disease drug **darapladib** and the diabetes drug **albiglutide**. GlaxoSmithKline filed for approval of albiglutide in July 2012. The drug is an injectable GLP-1 inhibitor in the same class as Bydureon and Byetta.

AstraZeneca agreed in April to acquire Ardea Biosciences for $1.26 billion. The acquisition was completed in June, making the company a wholly owned subsidiary of AstraZeneca. The Ardea acquisition brought the drug **lesinurad**, which is in Phase III development as a potential treatment for the management of hyperuricemia in gout patients.

Amgen Inc. in April 2012 announced its acquisition of Kai Pharmaceuticals. Amgen, of Thousand Oaks, Calif., generated 2011 revenue of $15.58 billion. Privately held Kai is located in South San Francisco. The purchase price is $315 million in cash. Kai's lead product candidate is **KAI-4169**, which is undergoing Phase II stud-

NOTES AND METHODOLOGY

General notes: For this annual special report, which is in its 26th year of publication, *Med Ad News* editors rank and profile the world's top 50 companies that generate revenue from healthcare products. Companies that research, develop, manufacture, and sell healthcare products with a strong base in pharmaceuticals are eligible to be included in this special report. As defined by *Med Ad News*, healthcare products include human prescription and over-the-counter pharmaceuticals, generics, imaging agents, medical devices, medical equipment, medical/surgical supplies, raw pharmaceutical chemicals, diagnostics, and animal healthcare products.

To be considered for the top 50 company list, companies must be independent and publicly traded (or make their financials public) and must develop, manufacture, and market human prescription therapeutic drugs. The companies must have R&D programs that produce original products. Companies are ranked according to the name of the parent company. All companies are ranked in the main table by their worldwide 2011 healthcare revenue. This number was provided by the companies, unless otherwise noted. Unless otherwise stated, all other data in tables represent the group's consolidated financial figures.

Many companies reported on a calendar-year basis (year ended Dec. 31, 2011). These companies reported on a fiscal-year basis (year ended March 31, 2012): Astellas Pharma, Daiichi Sankyo, Dainippon Sumitomo Pharma, Eisai, Forest Laboratories, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Otsuka Holdings, Shionogi, Taisho Pharmaceutical, Takeda Pharmaceutical, and Teijin. CSL's fiscal year ended June 30, 2012. Although the charts and statistics report financial-statement and balance-sheet figures for 2011 and 2010, the information in the articles is as current as press time allows.

Companies that are new to this year's ranking are Grifols at No. 44 and Valeant Pharmaceuticals International at No. 45.

Companies that did not return to this year's top 50 list are Cephalon (ranked No. 42 on last year's list) and Nycomed Group (ranked No. 33 on last year's list).

Cephalon was acquired by Teva Pharmaceutical Industries effective Oct. 14, 2011. Teva ranks No. 14 in this year's top 50 listing.

Nycomed was acquired by Takeda effective Sept. 30, 2011. Takeda ranks No. 15 in this year's top 50 listing.

Any top 50 companies that are in the process of being acquired – but the acquisition has not been completed as of this publication's press time – are included in this year's listing.

Revenue: In tables that rank by revenue, each company is positioned according to worldwide revenue — either by healthcare or consolidated group, depending on the chart. The revenue figures include net sales of healthcare products, as well as interest, dividends, and other income when provided. Sales from discontinued operations have been included when they were available. In the percent-change column, the figures in parentheses indicate a loss.

Earnings: This number represents the net-income figure that appears in the income statement, after taxes and after nonrecurring and extraordinary charges. The net-income figure is based on the consolidated sales of the group. Figures in parentheses indicate a loss.

Earnings per share: The number for earnings per common share is taken directly from company financial statements. This figure, based on consolidated results of the group, is adjusted for stock splits and stock dividends. *Med Ad News* editors used the diluted earnings per share figure when provided. Figures in parentheses indicate a loss.

Research and development: In the chart that ranks each top 50 company according to the research and development expenditure of healthcare products, the numbers were provided by the companies. Also provided is each company's total R&D expenditure (consolidated) for all businesses. For some of the Japanese companies, the healthcare R&D was not provided and thus the consolidated figure was used in its place; in these instances, the difference between the healthcare and consolidated R&D was not a significant amount.

Assets: This number represents the company's year-end total assets.

Shareholders' equity: This number represents total shareholders' equity at year-end as reported in the company's balance-sheet statement, and is for the group.

Employees: This number represents the total number of employees for the year.

Market capitalization: The information that appears in this chart shows the market capitalization of companies. The information came from Yahoo! Finance and Google Finance, and reflects company market capitalization as of Sept. 24, 2012.

Exchange rates: For non-U.S. companies reporting in foreign currency, *Med Ad News* editors used exchange rates to convert income-statement and balance-sheet figures to U.S. dollars. The conversions have been made for the purpose of convenience and comparison only. *Med Ad News* editors used average exchange rates to calculate income-statement figures and balance-statement figures. The exchange rates are based on data made available by the U.S. Federal Reserve Board (federalreserve.gov) and certain company documents. Unless otherwise indicated, the editors used the average 2011 exchange rates. So that the percent change in financial-statement and balance-sheet information reflects the actual increase or decrease in the company's home-country currency, the editors used a constant rate of exchange for 2011 and 2010. This reflects the increase or decrease actually reported by the non-U.S. company. The same exchange rate was used for the income-statement and the balance-sheet figures.

For the companies that report in euros, *Med Ad News* translated U.S. dollar amounts from euros at the rate of €1.00 to $1.3931, the average rate of exchange in 2011. The top 50 companies that reported in euros were: Bayer, Boehringer Ingelheim, Grifols, Merck KGaA, Sanofi, Stada, and UCB.

For the companies that report in yen, *Med Ad News* translated U.S. dollar amounts from yen at the March 2012 rate of ¥82.4659 to $1.00, except for Chugai and Kyowa Hakko Kirin, whose numbers were translated at the 2011 average rate of ¥79.70 to $1.00. The top 50 companies that reported in yen were: Astellas, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Kyowa Hakko Kirin, Mitsubishi Tanabe, Ono, Otsuka, Shionogi, Taisho, Takeda, and Teijin.

For the company that reports in pounds sterling, *Med Ad News* translated U.S. dollar amounts from pounds sterling at the rate of £1.00 to $1.6043, the average rate of exchange in 2011. The top 50 company that reported in pounds sterling was GlaxoSmithKline.

For the companies that report in Swiss francs, *Med Ad News* translated U.S. dollar amounts from Swiss francs at the rate of SFr0.8862 to $1.00, the average rate of exchange in 2011. The top 50 companies that reported in Swiss francs were Actelion and Roche.

For the companies that report in Danish kroner, *Med Ad News* translated U.S. dollar amounts from the kroner at the rate of DKr5.3535 to $1.00, the average rate of exchange in 2011. The top 50 companies that reported in kroner were Novo Nordisk and Lundbeck.

For CSL, which reported in Australian dollars, *Med Ad News* translated U.S. dollar amounts from the Australian dollar at the rate of A$0.9986 to $1.00, the average rate of exchange in June 2012.

Selection criteria for Company of the Year

The criteria for selecting the company of the year are based on a model developed by the editors of *Med Ad News*. Each one of the top 50 companies is evaluated on a number of categories, including:

- Recent and projected future financial strength
- Number of billion-plus drugs on the market
- Number of potential billion-plus drugs in the pipeline
- Recent number of new drug introductions
- Number of new drugs to be launched in the near future
- Quality of new products
- Quality of management and vision
- Marketing ability and activity
- Strength of the product pipeline
- First-half current-year performance
- Formative events and actions
- Business strategy
- Corporate governance and ethics
- Wall Street standing
- Responsiveness to market forces
- Shareholder value
- Future direction and potential

Past companies of the year

2011: Novartis
2010: Roche
2009: AstraZeneca
2008: Novartis
2007: Roche
2006: GlaxoSmithKline
2005: Johnson & Johnson
2004: Novartis
2003: AstraZeneca
2002: Pfizer
2001: Novartis
2000: Pharmacia
1999: Lilly
1998: Pfizer
1997: Warner-Lambert
1996: Abbott Laboratories
1995: Pfizer
1994: SmithKline Beecham
1993: Schering-Plough

Best overall brand value of any full-line manufacturer on the road today.[1]
IntelliChoice

Longest lasting vehicles[2] and most fuel-efficient full-line automotive manufacturer.[3]
Polk

Awarded more Vincentric Best Fleet Value in America awards than any other manufacturer.[4]
Vincentric

More vehicles named to the American-Made Index's Top 10 than any other brand.[5]
Cars.com

Best retained value of any full-line car manufacturer on the road today.[1]
IntelliChoice

#1 selling brand of hybrid vehicles in America.[6]
MotorIntelligence

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Options shown. 1. 2012 IntelliChoice, www.IntelliChoice.com; Popular Brand. Based on 2012 model year study. 2. Longevity based on Polk U.S. Vehicles in Operation registration statistics MY 1987-2011 as of July 2011. Full-line manufacturer based on car, SUV, minivan, compact and full-size pickup. 3. Fuel efficiency based on NHTSA Final Industry MY10 CAFE data for Toyota Motor Sales. 4. Based on Vincentric Best Fleet Value in America awards from 2006-2012. 5. For more information about the 2012 American-Made Index, visit Cars.com 6. MotorIntelligence.com, CY 2011 sales.

ies. The novel agent is being initially studied for treating secondary hyperparathyroidism in patients with chronic kidney disease who are on dialysis.

In January 2012, Amgen agreed to purchase the biotech entity Micromet Inc. for $11 per share in cash. The deal valued Micromet at $1.16 billion. Founded in Germany, Micromet's R&D center is located in Munich. The company's headquarters is based in Rockville, Md. The acquisition includes **blinatumomab**, a bispecific T cell engager antibody in Phase II trials for acute lymphoblastic leukemia. Blinatumomab is additionally being studied for treating non-Hodgkin's lymphoma. The drug compound may have uses for other hematologic malignancies. (For more about Amgen, see profile on page 28.)

Revamping R&D

As every company continues to review its R&D organization, some will be reaping the results of tactics that aimed to anticipate the patent cliff. IMS Health predicts that global launches for new molecular entities will rebound during the next five years, as 32 to 37 new molecular entities are expected to be launched per year through 2016. Between 2011 to 2016, 160 to 185 new molecular entities are expected to launch, compared with 142 between 2007 and 2011. Experts predict that these will include drugs to treat Alzheimer's, autoimmune diseases, diabetes, and a number of cancer and orphan diseases. Treatments for global priority diseases, such as malaria, tuberculosis, and neglected diseases, are expected to improve, although gaps will remain.

But with pipelines thin throughout the industry, several companies have revamped their R&D organizations. For example, AstraZeneca announced a new program in February that executives said would "create a simpler and more innovative R&D organization with a lower and more flexible cost base." One of the areas bearing the cuts is the neuroscience therapy area. As a result, AstraZeneca created a "virtual" neuroscience Innovative Medicines unit made up of a small team of around 40 to 50 AstraZeneca scientists conducting discovery and development externally, through a network of partners in academia and industry globally. The team is based in major neuroscience hubs – Boston in the United States and Cambridge in the United Kingdom.

One of the first actions of Ian Read when he took over as CEO of **Pfizer** Inc. in 2010 was to refocus the company's R&D organization. The company's global R&D team was centralized under the leadership of Dr. Mikael Dolsten and an accelerated R&D strategy was introduced, focusing on neuroscience; cardiovascular, metabolic, and endocrine diseases; oncology; inflammation and immunology; and vaccines.

Early in 2011, Pfizer announced 1,100 job cuts at Groton laboratories in Connecticut to lower the company's R&D expenses by up to $2.9 billion. In June 2011, the company announced another $1 billion in cost reductions by 2012, most of which would target management positions. Over the past few years, tens of thousands of positions have been eliminated at Pfizer, including about 20,000 related to the Wyeth acquisition, according to published reports. "We expect that in five years many of our late-stage clinical trial starts will reflect a precision medicine R&D approach," Mr. Read says.

Some experts believe that revamping R&D organizations is not enough, and say for pipelines to improve, companies will have to cooperate and share noncompetitive data in early stage research. By sharing this data, researchers will be able to avoid repeating the pitfalls experienced by others in looking at the same problems.

In its annual report on the biotech industry, "Beyond Borders," Ernst & Young experts came up with the concept of "holistic open learning networks," or HOLnets, where academia, nonprofit groups, and industry can pool and share information.

In September 2012, Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Co., GlaxoSmithKline, Johnson & Johnson, Pfizer, Roche, and Sanofi announced that they are unveiling TransCelerate BioPharma Inc. The initiative is designed to identify and resolve common issues that can delay R&D.

By participating in TransCelerate, each of these companies will combine financial and other resources, such as personnel, to work out industry-wide challenges in a team work atmosphere. Members of TransCelerate have pinpointed clinical study execution as the initiative's initial focus area. Five projects have been selected by the group for funding and development. These areas include development of a shared user interface for investigator site portals, mutual recognition of study site qualification and training, development of risk-based site monitoring approach and standards, development of clinical data standards, and establishment of a comparator drug supply model. TransCelerate was incorporated in early August 2012 and was expected to file for non-profit status in the fall. The board of directors includes R&D heads of the 10 member companies. Membership in TransCelerate is open to all pharmaceutical and biotechnology companies who can contribute to and benefit from these shared solutions. TransCelerate's headquarters will be located in Philadelphia, Pa.

Glen Giovannetti, Ernst & Young Global Biotechnology, Leader, told the industry blog Pharmalot that the announcement is encouraging because it is unique.

"We haven't seen one quite like this before where 10 pharmaceutical companies paired up of sort of their own volition in a way," he says. "They join other consortia. This seems to be more of a real commitment of their resources and their effort. I think it's great. They're going to concentrate on getting some standardization around the clinical trial process. Perhaps more important in the long term, how data is gathered and assembled it really could move toward greater standardization of data so that trial results downstream could be more easily pooled and shared and investigated for insights." ■ MEDADNEWS

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TOP 50 COMPANIES RANKED BY HEALTHCARE REVENUE

Rank 2011	Company	Healthcare Revenue 2011	Healthcare Revenue 2010	Consolidated Revenue 2011	Consolidated Revenue 2010	Net Income/ (Loss) 2011	Net Income/ (Loss) 2010
1	Pfizer Inc.	$67,425,000,000	$67,057,000,000	$67,425,000,000	$67,057,000,000	$10,009,000,000	$8,257,000,000
2	Johnson & Johnson	65,030,000,000	61,587,000,000	65,030,000,000	61,587,000,000	9,672,000,000	13,334,000,000
3	Novartis AG	58,566,000,000	50,624,000,000	58,566,000,000	50,624,000,000	9,245,000,000	9,969,000,000
4	Merck & Co.	48,047,000,000	45,987,000,000	48,047,000,000	48,987,000,000	6,272,000,000	861,000,000
5	F. Hoffmann-La Roche Ltd.	47,992,552,471	53,569,171,745	47,992,552,471	53,569,171,745	10,769,577,973	10,032,723,990
6	Sanofi	46,514,215,900	45,090,467,700	46,514,215,900	45,090,467,700	7,930,918,300	7,616,077,700
7	GlaxoSmithKline plc	43,936,964,100	45,549,285,600	43,936,964,100	45,549,285,600	8,440,222,300	2,621,426,200
8	Abbott Laboratories	38,851,259,000	35,166,721,000	38,851,259,000	35,166,721,000	4,728,449,000	4,626,172,000
9	AstraZeneca plc	33,591,000,000	33,269,000,000	33,591,000,000	33,269,000,000	10,016,000,000	8,081,000,000
10	Eli Lilly and Co.	24,286,500,000	23,076,000,000	24,286,500,000	23,076,000,000	4,347,700,000	5,069,500,000
11	Bayer AG	23,918,133,900	23,561,500,300	50,887,156,800	48,881,092,800	3,440,957,000	1,812,423,100
12	Bristol-Myers Squibb Co.	21,244,000,000	19,484,000,000	21,244,000,000	19,484,000,000	3,709,000,000	3,102,000,000
13	Boehringer Ingelheim GmbH	18,348,520,100	17,533,556,600	18,348,520,100	17,533,556,600	2,056,215,600	1,237,072,800
14	Teva Pharmaceutical Industries Ltd.	18,312,000,000	16,121,000,000	18,312,000,000	16,121,000,000	2,759,000,000	3,331,000,000
15	Takeda Pharmaceutical Co.	17,266,361,005 (March 12)	16,138,816,165 (March 11)	18,297,647,876 (March 12)	17,211,780,869 (March 11)	1,505,616,261 (March 12)	3,005,702,963 (March 11)
16	Amgen Inc.	15,582,000,000	15,053,000,000	15,582,000,000	15,053,000,000	3,683,000,000	4,627,000,000
17	Baxter International Inc.	13,893,000,000	12,843,000,000	13,893,000,000	12,843,000,000	2,224,000,000	1,420,000,000
18	Otsuka Holdings Co.	13,172,462,800 (March 12)	12,826,052,950 (March 11)	14,000,611,162 (March 12)	13,673,397,125 (March 11)	1,117,722,598 (March 12)	998,824,969 (March 11)
19	Novo Nordisk A/S	12,393,013,916	11,352,573,083	12,393,013,916	11,352,573,083	3,193,611,656	2,690,389,465
20	Astellas Pharma Inc.	11,755,004,190 (March 12)	11,567,775,287 (March 11)	11,755,004,190 (March 12)	11,567,775,287 (March 11)	948,634,527 (March 12)	820,339,073 (March 11)
21	Daiichi Sankyo Co.	11,382,607,842 (March 12)	11,730,484,964 (March 11)	11,382,607,842 (March 12)	11,730,484,964 (March 11)	125,906,587 (March 12)	850,302,974 (March 11)
22	Merck KGaA	8,938,408,220	8,672,744,050	14,316,052,840	12,942,734,860	876,259,900	893,673,650
23	Gilead Sciences Inc.	8,385,385,000	7,949,420,000	8,385,385,000	7,949,420,000	2,803,637,000	2,901,257,000
24	Eisai Co.	7,361,539,739 (March 12)	8,852,883,434 (March 11)	7,857,502,313 (March 12)	9,324,023,627 (March 11)	709,517,510 (March 12)	817,234,760 (March 11)
25	Mylan Inc.	6,129,825,000	5,450,522,000	6,129,825,000	5,450,522,000	536,810,000	223,580,000
26	Allergan Inc.	5,419,100,000	4,919,400,000	5,419,100,000	4,919,400,000	934,500,000	600,000
27	Biogen Idec Inc.	5,048,634,000	4,716,423,000	5,048,634,000	4,716,423,000	1,234,428,000	1,005,273,000
28	Celgene Corp.	4,842,070,000	3,625,745,000	4,842,070,000	3,625,745,000	1,317,456,000	880,192,000
29	Mitsubishi Tanabe Pharma Corp.	4,820,889,604 (March 12)	4,853,266,623 (March 11)	4,937,264,979 (March 12)	4,966,173,897 (March 11)	473,092,515 (March 12)	457,728,588 (March 11)
30	Chugai Pharmaceutical Co.	4,686,537,014	4,761,731,493	4,686,537,014	4,761,731,493	442,095,358	519,861,982
31	CSL Ltd.	4,617,226,820 (June 12)	4,315,549,760 (June 11)	4,617,226,820 (June 12)	4,315,549,760 (June 11)	981,224,360 (June 12)	939,283,160 (June 11)
32	Forest Laboratories Inc.	4,586,044,000 (March 12)	4,419,700,000 (March 11)	4,586,044,000 (March 12)	4,419,700,000 (March 11)	979,058,000 (March 12)	1,046,770,000 (March 11)
33	Watson Pharmaceuticals Inc.	4,584,400,000	3,566,900,000	4,584,400,000	3,566,900,000	260,900,000	184,400,000
34	UCB S.A.	4,522,002,600	4,482,995,800	4,522,002,600	4,482,995,800	327,378,500	143,489,300
35	Shire plc	4,263,400,000	3,471,100,000	4,263,400,000	3,471,100,000	865,000,000	588,000,000
36	Hospira Inc.	4,057,100,000	3,917,200,000	4,057,100,000	3,917,200,000	(9,400,000)	357,200,000
37	Dainippon Sumitomo Pharma Co.	3,759,893,483 (March 12)	4,057,277,008 (March 11)	4,248,980,488 (March 12)	4,602,059,760 (March 11)	104,649,316 (March 12)	203,672,063 (March 11)
38	Taisho Pharmaceutical Co.	3,288,995,815 (March 12)	3,257,491,885 (March 11)	3,288,995,815 (March 12)	3,257,491,885 (March 11)	295,358,445 (March 12)	423,108,218 (March 11)
39	Shionogi & Co.	3,241,036,598 (March 12)	3,423,839,429 (March 11)	3,241,036,598 (March 12)	3,423,839,429 (March 11)	328,632,805 (March 12)	242,839,768 (March 11)
40	H. Lundbeck A/S	2,990,006,538	2,758,008,779	2,990,006,538	2,758,008,779	426,263,192	460,633,231
41	Kyowa Hakko Kirin Co.	2,877,528,231	2,639,422,836	4,312,697,616	5,191,191,970	321,304,893	278,506,901
42	Endo Health Solutions Inc.	2,730,121,000	1,716,229,000	2,730,121,000	1,716,229,000	187,613,000	259,006,000
43	Warner Chilcott plc	2,728,106,000	2,974,482,000	2,728,106,000	2,974,482,000	171,146,000	170,972,000
44	Grifols S.A.	2,501,468,470	1,380,185,963	2,501,468,470	1,380,185,963	69,972,627	160,578,458
45	Valeant Pharmaceuticals International Inc.	2,463,450,000	1,181,237,000	2,463,450,000	1,181,237,000	159,559,000	(208,193,000)
46	Stada Arzneimittel AG	2,389,718,168	2,266,540,266	2,389,718,168	2,266,540,266	30,698,352	95,332,619
47	Ranbaxy Laboratories Ltd.	2,141,883,426	1,835,696,222	2,141,883,426	1,835,696,222	(622,526,621)	321,329,111
48	Actelion Pharmaceuticals Ltd.	2,026,701,647	2,176,674,566	2,026,701,647	2,176,674,566	(165,108,328)	440,709,772
49	Ono Pharmaceutical Co.	1,767,748,851 (March 12)	1,640,132,467 (March 11)	1,767,748,851 (March 12)	1,640,132,467 (March 11)	295,406,950 (March 12)	293,721,405 (March 11)
50	Teijin Ltd.	1,734,037,948 (March 12)	1,654,562,674 (March 11)	10,360,282,250 (March 12)	9,890,815,476 (March 11)	145,260,041 (March 12)	305,362,580 (March 11)

Source: www.eKnowledgeBase.com

Notes: N/A = Not applicable; March 12 = fiscal year ended March 31, 2012; March 11 = March 31, 2011; June 12 = June 30, 2012; June 11 = June 30, 2011;
For more details about this information, please see the Notes and Methodology on page 8.

Earnings/(Loss) Per Share 2011	Earnings/(Loss) Per Share 2010	Total Assets 2011	Total Assets 2010	Shareholders' Equity 2011	Shareholders' Equity 2010	Company
$1.27	$1.02	$188,002,000,000	$195,014,000,000	$82,190,000,000	$87,813,000,000	Pfizer Inc.
3.49	4.78	113,644,000,000	102,908,000,000	57,080,000,000	56,579,000,000	Johnson & Johnson
3.78	4.26	117,496,000,000	123,318,000,000	65,940,000,000	69,769,000,000	Novartis AG
2.02	0.28	105,128,000,000	105,781,000,000	54,517,000,000	54,376,000,000	Merck & Co.
12.39	11.41	69,483,186,640	68,855,788,761	13,648,160,686	10,684,946,965	F. Hoffmann-La Roche Ltd.
5.98	5.82	139,539,861,500	118,781,278,400	78,318,688,900	73,969,430,700	Sanofi
1.66	0.51	65,904,644,000	67,749,589,000	12,885,737,600	14,257,414,100	GlaxoSmithKline plc
3.01	2.96	60,276,900,000	60,573,900,000	24,526,145,000	22,765,131,000	Abbott Laboratories
7.30	5.57	52,830,000,000	56,127,000,000	23,472,000,000	23,410,000,000	AstraZeneca plc
3.90	4.58	33,659,800,000	31,001,400,000	13,535,600,000	12,412,800,000	Eli Lilly and Co.
4.17	2.19	73,506,921,500	71,753,008,600	26,764,237,200	26,236,252,300	Bayer AG
2.16	1.79	32,970,000,000	31,076,000,000	15,956,000,000	15,713,000,000	Bristol-Myers Squibb Co.
N/A	N/A	25,992,459,800	22,614,192,300	10,400,884,600	9,018,929,400	Boehringer Ingelheim GmbH
3.09	3.67	50,142,000,000	38,152,000,000	22,195,000,000	21,947,000,000	Teva Pharmaceutical Industries Ltd.
1.91 (March 12)	3.81 (March 11)	43,375,868,086 (March 12)	33,788,535,625 (March 11)	24,396,035,210 (March 12)	25,363,077,345 (March 11)	Takeda Pharmaceutical Co.
4.04	4.79	48,871,000,000	43,486,000,000	19,029,000,000	23,944,000,000	Amgen Inc.
3.88	2.39	19,073,000,000	17,489,000,000	6,585,000,000	6,567,000,000	Baxter International Inc.
2.00 (March 12)	1.99 (March 11)	20,211,590,488 (March 12)	19,277,264,906 (March 11)	14,655,609,167 (March 12)	13,947,595,309 (March 11)	Otsuka Holdings Co.
5.60	4.60	12,085,177,921	11,469,505,931	6,995,049,967	6,904,828,617	Novo Nordisk A/S
2.05 (March 12)	1.78 (March 11)	16,984,341,407 (March 12)	16,189,612,919 (March 11)	13,962,462,06 (March 12)	13,710,903,537 (March 11)	Astellas Pharma Inc.
0.18 (March 12)	1.21 (March 11)	18,413,416,940 (March 12)	17,949,722,249 (March 11)	10,708,001,732 (March 12)	11,094,137,092 (March 11)	Daiichi Sankyo Co.
3.96	4.05	30,815,511,310	31,188,722,800	14,553,855,010	14,390,444,380	Merck KGaA
3.55	3.32	17,303,134,000	11,592,630,000	6,867,349,000	6,121,837,000	Gilead Sciences Inc.
2.49 (March 12)	2.87 (March 11)	12,182,732,499 (March 12)	12,687,559,343 (March 11)	5,134,570,774 (March 12)	4,976,238,663 (March 11)	Eisai Co.
1.22	0.68	11,598,143,000	11,536,804,000	5,393,212,000	5,168,168,000	Mylan Inc.
3.01	0.00	8,508,600,000	8,308,100,000	5,309,600,000	4,757,700,000	Allergan Inc.
5.04	3.94	9,049,604,000	8,092,493,000	6,425,499,000	5,396,506,000	Biogen Idec Inc.
2.85	1.88	10,005,910,000	10,177,162,000	5,512,727,000	5,983,973,000	Celgene Corp.
0.84 (March 12)	0.82 (March 11)	9,942,594,454 (March 12)	9,927,800,461 (March 11)	8,789,911,951 (March 12)	8,515,071,078 (March 11)	Mitsubishi Tanabe Pharma Corp.
0.81	0.96	6,693,638,645	6,374,102,886	5,884,542,033	5,736,110,414	Chugai Pharmaceutical Co.
1.89 (June 12)	1.73 (June 11)	5,811,152,980 (June 12)	5,060,901,804 (June 11)	3,423,500,380 (June 12)	3,639,257,896 (June 11)	CSL Ltd.
3.57 (March 12)	3.59 (March 11)	7,491,755,000 (March 12)	6,922,454,000 (March 11)	5,676,817,000 (March 12)	5,498,880,000 (March 11)	Forest Laboratories Inc.
2.06	1.48	6,698,300,000	5,686,600,000	3,563,600,000	3,281,700,000	Watson Pharmaceuticals Inc.
1.77	0.78	12,785,871,800	12,494,713,900	6,716,135,100	6,394,329,000	UCB SA
1.51	1.05	6,380,200,000	5,387,600,000	3,185,000,000	2,451,400,000	Shire plc
(0.06)	2.11	5,779,100,000	6,046,300,000	2,938,000,000	3,183,500,000	Hospira Inc.
0.26 (March 12)	0.51 (March 11)	6,783,531,132 (March 12)	7,152,871,672 (March 11)	4,162,629,644 (March 12)	4,144,707,085 (March 11)	Dainippon Sumitomo Pharma Co.
3.59 (March 12)	1.51 (March 11)	7,633,530,950 (March 12)	7,499,269,395 (March 11)	6,531,984,736 (March 12)	6,490,331,155 (March 11)	Taisho Pharmaceutical Co.
0.98 (March 12)	0.73 (March 11)	6,331,853,530 (March 12)	6,344,949,852 (March 11)	4,552,633,270 (March 12)	4,386,455,493 (March 11)	Shionogi & Co.
2.17	2.35	3,835,621,556	3,363,220,323	2,386,476,137	2,077,519,380	H. Lundbeck AS
0.57	0.49	8,266,913,425	8,731,016,311	6,961,806,775	6,940,677,541	Kyowa Hakko Kirin Co.
1.55	2.20	7,292,583,000	3,912,389,000	2,039,591,000	1,803,329,000	Endo Health Solutions Inc.
0.67	0.67	5,030,029,000	5,651,989,000	69,131,000	(65,642,000)	Warner Chilcott plc
0.26	0.75	8,090,731,946	2,631,540,824	2,319,503,141	985,465,009	Grifols S.A.
0.52	(1.06)	13,141,713,000	10,795,117,000	4,007,016,000	4,911,096,000	Valeant Pharmaceuticals International Inc.
0.52	1.59	3,900,464,070	3,492,129,742	1,189,582,021	1,196,374,777	Stada Arzneimittel AG
(1.48)	0.68	1,733,655,002	2,016,553,671	803,313,225	1,101,844,568	Ranbaxy Laboratories Ltd.
(1.39)	3.63	3,082,913,564	3,296,118,258	1,704,416,610	2,025,732,340	Actelion Ltd.
2.79 (March 12)	2.71 (March 11)	5,292,054,049 (March 12)	5,146,891,018 (March 11)	4,862,870,593 (March 12)	4,799,013,895 (March 11)	Ono Pharmaceutical Co.
0.15 (March 12)	0.31 (March 11)	9,241,613,806 (March 12)	9,234,532,091 (March 11)	3,541,221,281 (March 12)	3,446,709,488 (March 11)	Teijin Ltd.

TOP 50 COMPANIES RANKED BY HEALTHCARE R&D EXPENDITURE

Rank 2011	Company	Healthcare R&D 2011	Healthcare R&D 2010	Consolidated R&D 2011	Consolidated R&D 2010
1	Novartis AG	$9,583,000,000	$9,070,000,000	$9,583,000,000	$9,070,000,000
2	F. Hoffmann-La Roche Ltd.	9,395,170,390	11,313,473,257	9,395,170,390	11,313,473,257
3	Pfizer Inc.	9,112,000,000	9,392,000,000	9,112,000,000	9,392,000,000
4	Merck & Co.	8,467,000,000	11,111,000,000	8,467,000,000	11,111,000,000
5	Johnson & Johnson	7,548,000,000	6,844,000,000	7,548,000,000	6,844,000,000
6	Sanofi	6,702,204,100	6,346,963,600	6,702,204,100	6,346,963,600
7	GlaxoSmithKline plc	6,431,638,700	7,150,365,100	6,431,638,700	7,150,365,100
8	AstraZeneca plc	5,523,000,000	5,318,000,000	5,523,000,000	5,318,000,000
9	Eli Lilly and Co.	5,020,800,000	4,884,200,000	5,020,800,000	4,884,200,000
10	Abbott Laboratories	4,129,414,000	3,724,424,000	4,129,414,000	3,724,424,000
11	Bristol-Myers Squibb Co.	3,839,000,000	3,566,000,000	3,839,000,000	3,566,000,000
12	Boehringer Ingelheim GmbH	3,505,039,600	3,417,274,300	3,505,039,600	3,417,274,300
13	Takeda Pharmaceutical Co.	3,357,751,507 (March 12)	3,442,635,077 (March 11)	3,418,200,735 (March 12)	3,502,950,917 (March 11)
14	Amgen Inc.	3,167,000,000	2,894,000,000	3,167,000,000	2,894,000,000
15	Bayer AG	2,713,758,800	2,878,144,600	4,084,569,200	4,253,134,300
16	Astellas Pharma Inc.	2,302,042,420 (March 12)	2,635,331,695 (March 11)	2,302,042,420 (March 12)	2,635,331,695 (March 11)
17	Daiichi Sankyo Co.	2,243,982,058 (March 12)	2,356,489,167 (March 11)	2,243,982,058 (March 12)	2,356,489,167 (March 11)
18	Otsuka Holdings Co.	1,810,445,287 (March 12)	1,860,162,807 (March 11)	1,930,846,568 (March 12)	1,996,837,481 (March 11)
19	Novo Nordisk A/S	1,798,449,612	1,793,592,977	1,798,449,612	1,793,592,977
20	Merck KGaA	1,739,006,730	1,660,575,200	2,113,472,010	1,946,300,010
21	Celgene Corp.	1,600,264,000	1,128,495,000	1,600,264,000	1,128,495,000
22	Eisai Co.	1,517,499,961 (March 12)	1,758,666,309 (March 11)	1,517,499,961 (March 12)	1,758,666,309 (March 11)
23	Gilead Sciences Inc.	1,229,151,000	1,072,930,000	1,229,151,000	1,072,930,000
24	Biogen Idec Inc.	1,219,602,000	1,248,604,000	1,219,602,000	1,248,604,000
25	UCB S.A.	1,086,618,000	982,135,500	1,086,618,000	982,135,500
26	Teva Pharmaceutical Industries Ltd.	1,080,000,000	933,000,000	1,080,000,000	933,000,000
27	Baxter International Inc.	946,000,000	915,000,000	946,000,000	915,000,000
28	Allergan Inc.	902,800,000	804,600,000	902,800,000	804,600,000
29	Mitsubishi Tanabe Pharma Corp.	851,758,121 (March 12)	797,711,539 (March 11)	851,758,121 (March 12)	797,711,539 (March 11)
30	Forest Laboratories Inc.	796,932,000 (March 12)	715,872,000 (March 11)	796,932,000 (March 12)	715,872,000 (March 11)
31	Shire plc	770,700,000	661,500,000	770,700,000	661,500,000
32	Chugai Pharmaceutical Co.	700,840,652	686,361,355	700,840,652	686,361,355
33	Dainippon Sumitomo Pharma Co.	689,873,026 (March 12)	826,523,448 (March 11)	689,873,026 (March 12)	826,523,448 (March 11)
34	Shionogi & Co.	649,953,496 (March 12)	617,479,467 (March 11)	649,953,496 (March 12)	617,479,467 (March 11)
35	H. Lundbeck A/S	620,155,039	568,786,775	620,155,039	568,786,775
36	Kyowa Hakko Kirin Co.	558,343,789	501,882,058	601,769,134	554,705,144
37	Ono Pharmaceutical Co.	538,186,087 (March 12)	520,675,819 (March 11)	538,186,087 (March 12)	520,675,819 (March 11)
38	Actelion Pharmaceuticals Ltd.	516,464,681	546,466,937	516,464,681	546,466,937
39	CSL Ltd.	354,503,000 (June 12)	324,644,860 (June 11)	354,503,000 (June 12)	324,644,860 (June 11)
40	Watson Pharmaceuticals Inc.	295,400,000	296,100,000	295,400,000	296,100,000
41	Mylan Inc.	294,728,000	282,146,000	294,728,000	282,146,000
42	Taisho Pharmaceutical Co.	293,830,541 (March 12)	287,112,613 (March 11)	293,830,541 (March 12)	287,112,613 (March 11)
43	Hospira Inc.	258,800,000	300,500,000	258,800,000	300,500,000
44	Endo Health Solutions Inc.	182,286,000	144,525,000	182,286,000	144,525,000
45	Teijin Ltd.	135,813,712 (March 12)	150,365,181 (March 11)	386,159,613 (March 12)	381,769,919 (March 11)
46	Grifols S.A.	124,543,140	56,699,170	124,543,140	56,699,170
47	Warner Chilcott plc	107,796,000	146,506,000	107,796,000	146,506,000
48	Ranbaxy Laboratories Ltd.	100,946,114	106,889,223	100,946,114	106,889,223
49	Stada Arzneimittel AG	70,143,978	76,496,514	70,143,978	76,496,514
50	Valeant Pharmaceuticals International Inc.	65,687,000	68,311,000	65,687,000	68,311,000

Source: www.eKnowledgeBase.com

Notes: March 12 = fiscal year ended March 31, 2012; March 11 = March 31, 2011; June 12 = June 30, 2012; June 11 = June 30, 2011;
For more details about this information, please see the Notes and Methodology on page 8.

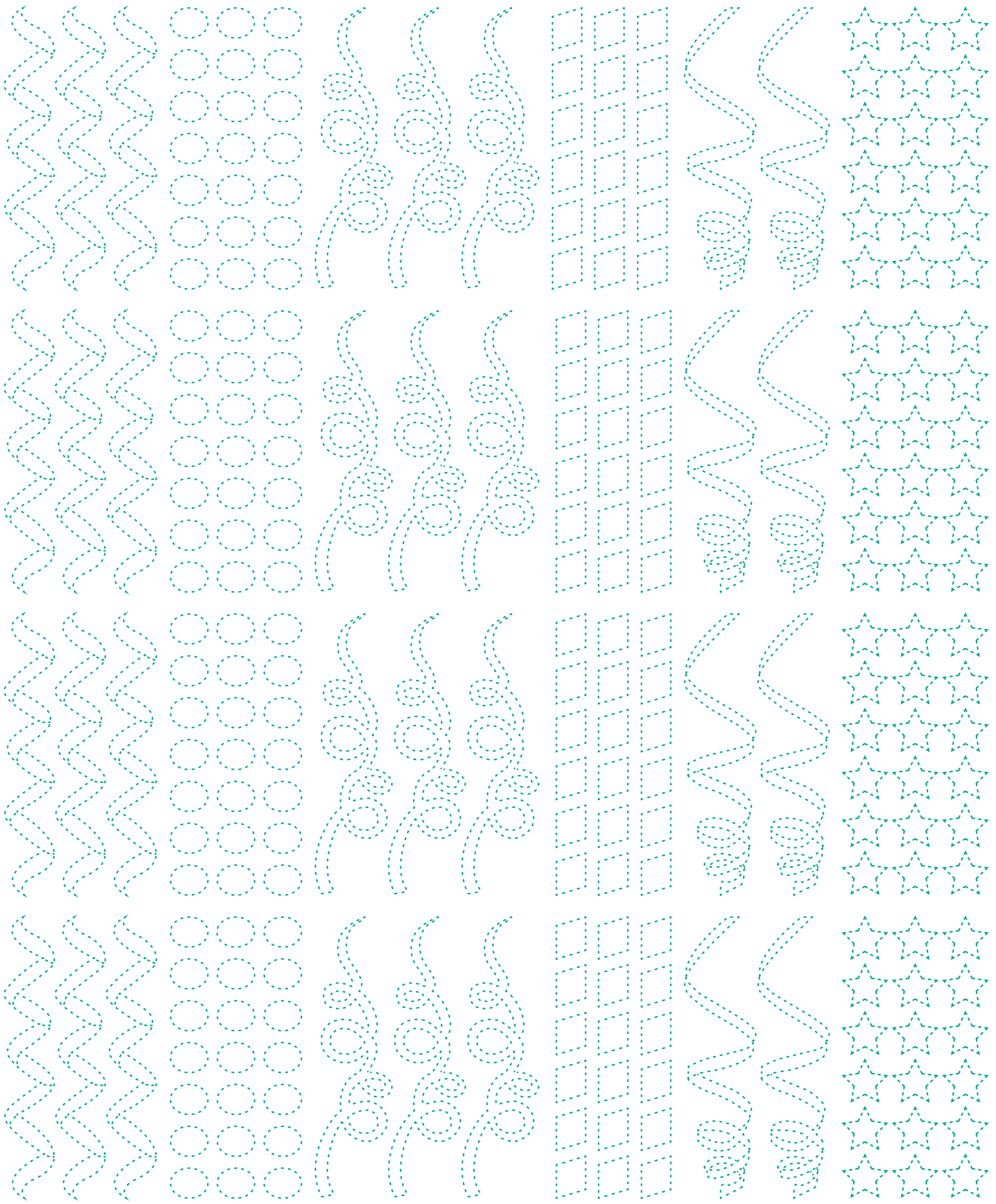
TOP 50 COMPANIES RANKED BY CONSOLIDATED REVENUE

Rank 2011	Company	Consolidated Revenue 2011	Consolidated Revenue 2010
1	Pfizer Inc.	$67,425,000,000	$67,057,000,000
2	Johnson & Johnson	65,030,000,000	61,587,000,000
3	Novartis AG	58,566,000,000	50,624,000,000
4	Bayer AG	50,887,156,800	48,881,092,800
5	Merck & Co.	48,047,000,000	48,987,000,000
6	F. Hoffmann-La Roche Ltd.	47,992,552,471	53,569,171,745
7	Sanofi	46,514,215,900	45,090,467,700
8	GlaxoSmithKline plc	43,936,964,100	45,549,285,600
9	Abbott Laboratories	38,851,259,000	35,166,721,000
10	AstraZeneca plc	33,591,000,000	33,269,000,000
11	Eli Lilly and Co.	24,286,500,000	23,076,000,000
12	Bristol-Myers Squibb Co.	21,244,000,000	19,484,000,000
13	Boehringer Ingelheim GmbH	18,348,520,100	17,533,556,600
14	Teva Pharmaceutical Industries Ltd.	18,312,000,000	16,121,000,000
15	Takeda Pharmaceutical Co.	18,297,647,876 (March 12)	17,211,780,869 (March 11)
16	Amgen Inc.	15,582,000,000	15,053,000,000
17	Merck KGaA	14,316,052,840	12,942,734,860
18	Otsuka Holdings Co.	14,000,611,162 (March 12)	13,673,397,125 (March 11)
19	Baxter International Inc.	13,893,000,000	12,843,000,000
20	Novo Nordisk A/S	12,393,013,916	11,352,573,083
21	Astellas Pharma Inc.	11,755,004,190 (March 12)	11,567,775,287 (March 11)
22	Daiichi Sankyo Co.	11,382,607,842 (March 12)	11,730,484,964 (March 11)
23	Teijin Ltd.	10,360,282,250 (March 12)	9,890,815,476 (March 11)
24	Gilead Sciences Inc.	8,385,385,000	7,949,420,000
25	Eisai Co.	7,857,502,313 (March 12)	9,324,023,627 (March 11)
26	Mylan Inc.	6,129,825,000	5,450,522,000
27	Allergan Inc.	5,419,100,000	4,919,400,000
28	Biogen Idec Inc.	5,048,634,000	4,716,423,000
29	Mitsubishi Tanabe Pharma Corp.	4,937,264,979 (March 12)	4,966,173,897 (March 11)
30	Celgene Corp.	4,842,070,000	3,625,745,000
31	Chugai Pharmaceutical Co.	4,686,537,014	4,761,731,493
32	CSL Ltd.	4,617,226,820 (June 12)	4,315,549,760 (June 11)
33	Forest Laboratories Inc.	4,586,044,000 (March 12)	4,419,700,000 (March 11)
34	Watson Pharmaceuticals Inc.	4,584,400,000	3,566,900,000
35	UCB S.A.	4,522,002,600	4,482,995,800
36	Kyowa Hakko Kirin Co.	4,312,697,616	5,191,191,970
37	Shire plc	4,263,400,000	3,471,100,000
38	Dainippon Sumitomo Pharma Co.	4,248,980,488 (March 12)	4,602,059,760 (March 11)
39	Hospira Inc.	4,057,100,000	3,917,200,000
40	Taisho Pharmaceutical Co.	3,288,995,815 (March 12)	3,257,491,885 (March 11)
41	Shionogi & Co.	3,241,036,598 (March 12)	3,423,839,429 (March 11)
42	H. Lundbeck A/S	2,990,006,538	2,758,008,779
43	Endo Health Solutions Inc.	2,730,121,000	1,716,229,000
44	Warner Chilcott plc	2,728,106,000	2,974,482,000
45	Grifols S.A.	2,501,468,470	1,380,185,963
46	Valeant Pharmaceuticals International Inc.	2,463,450,000	1,181,237,000
47	Stada Arzneimittel AG	2,389,718,168	2,266,540,266
48	Ranbaxy Laboratories Ltd.	2,141,883,426	1,835,696,222
49	Actelion Pharmaceuticals Ltd.	2,026,701,647	2,176,674,566
50	Ono Pharmaceutical Co.	1,767,748,851 (March 12)	1,640,132,467 (March 11)

Source: www.eKnowledgeBase.com

Notes: March 12 = fiscal year ended March 31, 2012; March 11 = March 31, 2011;
June 12 = June 30, 2012; June 11 = June 30, 2011;
For more details about this information, please see the Notes and Methodology on page 8.

1. Cut out shapes. 2. Color with vibrant hues. 3. Shower your TEVA colleagues.



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TOP 50 COMPANIES RANKED BY NET INCOME

Rank 2011	Company	Net Income/ (Loss) 2011	Net Income/ (Loss) 2010
1	F. Hoffmann-La Roche Ltd.	$10,769,577,973	$10,032,723,990
2	AstraZeneca plc	10,016,000,000	8,081,000,000
3	Pfizer Inc.	10,009,000,000	8,257,000,000
4	Johnson & Johnson	9,672,000,000	13,334,000,000
5	Novartis AG	9,245,000,000	9,969,000,000
6	GlaxoSmithKline plc	8,440,222,300	2,621,426,200
7	Sanofi	7,930,918,300	7,616,077,700
8	Merck & Co.	6,272,000,000	861,000,000
9	Abbott Laboratories	4,728,449,000	4,626,172,000
10	Eli Lilly and Co.	4,347,700,000	5,069,500,000
11	Bristol-Myers Squibb Co.	3,709,000,000	3,102,000,000
12	Amgen Inc.	3,683,000,000	4,627,000,000
13	Bayer AG	3,440,957,000	1,812,423,100
14	Novo Nordisk A/S	3,193,611,656	2,690,389,465
15	Gilead Sciences Inc.	2,803,637,000	2,901,257,000
16	Teva Pharmaceutical Industries Ltd.	2,759,000,000	3,331,000,000
17	Baxter International Inc.	2,224,000,000	1,420,000,000
18	Boehringer Ingelheim GmbH	2,056,215,600	1,237,072,800
19	Takeda Pharmaceutical Co.	1,505,616,261 (March 12)	3,005,702,963 (March 11)
20	Celgene Corp.	1,317,456,000	880,192,000
21	Biogen Idec Inc.	1,234,428,000	1,005,273,000
22	Otsuka Holdings Co.	1,117,722,598 (March 12)	998,824,969 (March 11)
23	CSL Ltd.	981,224,360 (June 12)	939,283,160 (June 11)
24	Forest Laboratories Inc.	979,058,000 (March 12)	1,046,770,000 (March 11)
25	Astellas Pharma Inc.	948,634,527 (March 12)	820,339,073 (March 11)
26	Allergan Inc.	934,500,000	600,000
27	Merck KGaA	876,259,900	893,673,650
28	Shire plc	865,000,000	588,000,000
29	Eisai Co.	709,517,510 (March 12)	817,234,760 (March 11)
30	Mylan Inc.	536,810,000	223,580,000
31	Mitsubishi Tanabe Pharma Corp.	473,092,515 (March 12)	457,728,588 (March 11)
32	Chugai Pharmaceutical Co.	442,095,358	519,861,982
33	H. Lundbeck A/S	426,263,192	460,633,231
34	Shionogi & Co.	328,632,805 (March 12)	242,839,768 (March 11)
35	UCB S.A.	327,378,500	143,489,300
36	Kyowa Hakko Kirin Co.	321,304,893	278,506,901
37	Ono Pharmaceutical Co.	295,406,950 (March 12)	293,721,405 (March 11)
38	Taisho Pharmaceutical Co.	295,358,445 (March 12)	423,108,218 (March 11)
39	Watson Pharmaceuticals Inc.	260,900,000	184,400,000
40	Endo Health Solutions Inc.	187,613,000	259,006,000
41	Warner Chilcott plc	171,146,000	170,972,000
42	Valeant Pharmaceuticals International Inc.	159,559,000	(208,193,000)
43	Teijin Ltd.	145,260,041 (March 12)	305,362,580 (March 11)
44	Daiichi Sankyo Co.	125,906,587 (March 12)	850,302,974 (March 11)
45	Dainippon Sumitomo Pharma Co.	104,649,316 (March 12)	203,672,063 (March 11)
46	Grifols S.A.	69,972,627	160,578,458
47	Stada Arzneimittel AG	30,698,352	95,332,619
48	Hospira Inc.	(9,400,000)	357,200,000
49	Actelion Pharmaceuticals Ltd.	(165,108,328)	440,709,772
50	Ranbaxy Laboratories Ltd.	(622,526,621)	321,329,111

Source: www.eKnowledgeBase.com

Notes: March 12 = fiscal year ended March 31, 2012; March 11 = March 31, 2011; June 12 = June 30, 2012; June 11 = June 30, 2011;
For more details about this information, please see the Notes and Methodology on page 8.

MOST PROFITABLE COMPANIES: RETURN ON REVENUE

Rank 2011	Company	Consolidated Revenue 2011	Net Income/ (Loss) 2011	Income/ (loss) as % of revenue 2011
1	Gilead Sciences Inc.	$8,385,385,000	$2,803,637,000	33.43%
2	AstraZeneca plc	33,591,000,000	10,016,000,000	29.82
3	Celgene Corp.	4,842,070,000	1,317,456,000	27.21
4	Novo Nordisk A/S	12,393,013,916	3,193,611,656	25.77
5	Biogen Idec Inc.	5,048,634,000	1,234,428,000	24.45
6	Amgen Inc.	15,582,000,000	3,683,000,000	23.64
7	F. Hoffmann-La Roche Ltd.	47,992,552,471	10,769,577,973	22.44
8	Forest Laboratories Inc.	4,586,044,000	979,058,000	21.35
9	CSL Ltd.	4,617,226,820	981,224,360	21.25
10	Shire plc	4,263,400,000	865,000,000	20.29
11	GlaxoSmithKline plc	43,936,964,100	8,440,222,300	19.21
12	Eli Lilly and Co.	24,286,500,000	4,347,700,000	17.90
13	Bristol-Myers Squibb Co.	21,244,000,000	3,709,000,000	17.46
14	Allergan Inc.	5,419,100,000	934,500,000	17.24
15	Sanofi	46,514,215,900	7,930,918,300	17.05
16	Ono Pharmaceutical Co.	1,767,748,851	295,406,950	16.71
17	Baxter International Inc.	13,893,000,000	2,224,000,000	16.01
18	Novartis AG	58,566,000,000	9,245,000,000	15.79
19	Teva Pharmaceutical Industries Ltd.	18,312,000,000	2,759,000,000	15.07
20	Johnson & Johnson	65,030,000,000	9,672,000,000	14.87
21	Pfizer Inc.	67,425,000,000	10,009,000,000	14.84
22	H. Lundbeck A/S	2,990,006,538	426,263,192	14.26
23	Merck & Co.	48,047,000,000	6,272,000,000	13.05
24	Abbott Laboratories	38,851,259,000	4,728,449,000	12.17
25	Boehringer Ingelheim GmbH	18,348,520,100	2,056,215,600	11.21
26	Shionogi & Co.	3,241,036,598	328,632,805	10.14
27	Mitsubishi Tanabe Pharma Corp.	4,937,264,979	473,092,515	9.58
28	Chugai Pharmaceutical Co.	4,686,537,014	442,095,358	9.43
29	Eisai Co.	7,857,502,313	709,517,510	9.03
30	Taisho Pharmaceutical Co.	3,288,995,815	295,358,445	8.98
31	Mylan Inc.	6,129,825,000	536,810,000	8.76
32	Takeda Pharmaceutical Co.	18,297,647,876	1,505,616,261	8.23
33	Astellas Pharma Inc.	11,755,004,190	948,634,527	8.07
34	Otsuka Holdings Co.	14,000,611,162	1,117,722,598	7.98
35	Kyowa Hakko Kirin Co.	4,312,697,616	321,304,893	7.45
36	UCB S.A.	4,522,002,600	327,378,500	7.24
37	Endo Health Solutions Inc.	2,730,121,000	187,613,000	6.87
38	Bayer AG	50,887,156,800	3,440,957,000	6.76
39	Valeant Pharmaceuticals International Inc.	2,463,450,000	159,559,000	6.48
40	Warner Chilcott plc	2,728,106,000	171,146,000	6.27
41	Merck KGaA	14,316,052,840	876,259,900	6.12
42	Watson Pharmaceuticals Inc.	4,584,400,000	260,900,000	5.69
43	Grifols S.A.	2,501,468,470	69,972,627	2.80
44	Dainippon Sumitomo Pharma Co.	4,248,980,488	104,649,316	2.46
45	Teijin Ltd.	10,360,282,250	145,260,041	1.40
46	Stada Arzneimittel AG	2,389,718,168	30,698,352	1.28
47	Daiichi Sankyo Co.	11,382,607,842	125,906,587	1.11
48	Hospira Inc.	4,057,100,000	(9,400,000)	-0.23
49	Actelion Pharmaceuticals Ltd.	2,026,701,647	(165,108,328)	-8.15
50	Ranbaxy Laboratories Ltd.	2,141,883,426	(622,526,621)	-29.06

Source: www.eKnowledgeBase.com

Note: For more details about this information, please see the Notes and Methodology on page 8.

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TOP 50 COMPANIES RANKED BY TOTAL ASSETS

Rank 2011	Company	Total Assets 2011	Total Assets 2010
1	Pfizer Inc.	$188,002,000,000	$195,014,000,000
2	Sanofi	139,539,861,500	118,781,278,400
3	Novartis AG	117,496,000,000	123,318,000,000
4	Johnson & Johnson	113,644,000,000	102,908,000,000
5	Merck & Co.	105,128,000,000	105,781,000,000
6	Bayer AG	73,506,921,500	71,753,008,600
7	F. Hoffmann-La Roche Ltd.	69,483,186,640	68,855,788,761
8	GlaxoSmithKline plc	65,904,644,000	67,749,589,000
9	Abbott Laboratories	60,276,900,000	60,573,900,000
10	AstraZeneca plc	52,830,000,000	56,127,000,000
11	Teva Pharmaceutical Industries Ltd.	50,142,000,000	38,152,000,000
12	Amgen Inc.	48,871,000,000	43,486,000,000
13	Takeda Pharmaceutical Co.	43,375,868,086 (March 12)	33,788,535,625 (March 11)
14	Eli Lilly and Co.	33,659,800,000	31,001,400,000
15	Bristol-Myers Squibb Co.	32,970,000,000	31,076,000,000
16	Merck KGaA	30,815,511,310	31,188,722,800
17	Boehringer Ingelheim GmbH	25,992,459,800	22,614,192,300
18	Otsuka Holdings Co.	20,211,590,488 (March 12)	19,277,264,906 (March 11)
19	Baxter International Inc.	19,073,000,000	17,489,000,000
20	Daiichi Sankyo Co.	18,413,416,940 (March 12)	17,949,722,249 (March 11)
21	Gilead Sciences Inc.	17,303,134,000	11,592,630,000
22	Astellas Pharma Inc.	16,984,341,407 (March 12)	16,189,612,919 (March 11)
23	Valeant Pharmaceuticals International Inc.	13,141,713,000	10,795,117,000
24	UCB S.A.	12,785,871,800	12,494,713,900
25	Eisai Co.	12,182,732,499 (March 12)	12,687,559,343 (March 11)
26	Novo Nordisk A/S	12,085,177,921	11,469,505,931
27	Mylan Inc.	11,598,143,000	11,536,804,000
28	Celgene Corp.	10,005,910,000	10,177,162,000
29	Mitsubishi Tanabe Pharma Corp.	9,942,594,454 (March 12)	9,927,800,461 (March 11)
30	Teijin Ltd.	9,241,613,806 (March 12)	9,234,532,091 (March 11)
31	Biogen Idec Inc.	9,049,604,000	8,092,493,000
32	Allergan Inc.	8,508,600,000	8,308,100,000
33	Kyowa Hakko Kirin Co.	8,266,913,425	8,731,016,311
34	Grifols S.A.	8,090,731,946	2,631,540,824
35	Taisho Pharmaceutical Co.	7,633,530,950 (March 12)	7,499,269,395 (March 11)
36	Forest Laboratories Inc.	7,491,755,000 (March 12)	6,922,454,000 (March 11)
37	Endo Health Solutions Inc.	7,292,583,000	3,912,389,000
38	Dainippon Sumitomo Pharma Co.	6,783,531,132 (March 12)	7,152,871,672 (March 11)
39	Watson Pharmaceuticals Inc.	6,698,300,000	5,686,600,000
40	Chugai Pharmaceutical Co.	6,693,638,645	6,374,102,886
41	Shire plc	6,380,200,000	5,387,600,000
42	Shionogi & Co.	6,331,853,530 (March 12)	6,344,949,852 (March 11)
43	CSL Ltd.	5,811,152,980 (June 12)	5,060,901,804 (June 11)
44	Hospira Inc.	5,779,100,000	6,046,300,000
45	Ono Pharmaceutical Co.	5,292,054,049 (March 12)	5,146,891,018 (March 11)
46	Warner Chilcott plc	5,030,029,000	5,651,989,000
47	Stada Arzneimittel AG	3,900,464,070	3,492,129,742
48	H. Lundbeck A/S	3,835,621,556	3,363,220,323
49	Actelion Pharmaceuticals Ltd.	3,082,913,564	3,296,118,258
50	Ranbaxy Laboratories Ltd.	1,733,655,002	2,016,553,671

Source: www.eKnowledgeBase.com

Notes: March 12 = fiscal year ended March 31, 2012; March 11 = March 31, 2011; June 12 = June 30, 2012; June 11 = June 30, 2011;
For more details about this information, please see the Notes and Methodology on page 8.

TOP 50 COMPANIES RANKED BY SHAREHOLDERS' EQUITY

Rank 2011	Company	Shareholders' Equity 2011	Shareholders' Equity 2010
1	Pfizer Inc.	$82,190,000,000	$87,813,000,000
2	Sanofi	78,318,688,900	73,969,430,700
3	Novartis AG	65,940,000,000	69,769,000,000
4	Johnson & Johnson	57,080,000,000	56,579,000,000
5	Merck & Co.	54,517,000,000	54,376,000,000
6	Bayer AG	26,764,237,200	26,236,252,300
7	Abbott Laboratories	24,526,145,000	22,765,131,000
8	Takeda Pharmaceutical Co.	24,396,035,210 (March 12)	25,363,077,345 (March 11)
9	AstraZeneca plc	23,472,000,000	23,410,000,000
10	Teva Pharmaceutical Industries Ltd.	22,195,000,000	21,947,000,000
11	Amgen Inc.	19,029,000,000	23,944,000,000
12	Bristol-Myers Squibb Co.	15,956,000,000	15,713,000,000
13	Otsuka Holdings Co.	14,655,609,167 (March 12)	13,947,595,309 (March 11)
14	Merck KGaA	14,553,855,010	14,390,444,380
15	Astellas Pharma Inc.	13,962,462,06 (March 12)	13,710,903,537 (March 11)
16	F. Hoffmann-La Roche Ltd.	13,648,160,686	10,684,946,965
17	Eli Lilly and Co.	13,535,600,000	12,412,800,000
18	GlaxoSmithKline plc	12,885,737,600	14,257,414,100
19	Daiichi Sankyo Co.	10,708,001,732 (March 12)	11,094,137,092 (March 11)
20	Boehringer Ingelheim GmbH	10,400,884,600	9,018,929,400
21	Mitsubishi Tanabe Pharma Corp.	8,789,911,951 (March 12)	8,515,071,078 (March 11)
22	Novo Nordisk A/S	6,995,049,967	6,904,828,617
23	Kyowa Hakko Kirin Co.	6,961,806,775	6,940,677,541
24	Gilead Sciences Inc.	6,867,349,000	6,121,837,000
25	UCB S.A.	6,716,135,100	6,394,329,000
26	Baxter International Inc.	6,585,000,000	6,567,000,000
27	Taisho Pharmaceutical Co.	6,531,984,736 (March 12)	6,490,331,155 (March 11)
28	Biogen Idec Inc.	6,425,499,000	5,396,506,000
29	Chugai Pharmaceutical Co.	5,884,542,033	5,736,110,414
30	Forest Laboratories Inc.	5,676,817,000 (March 12)	5,498,880,000 (March 11)
31	Celgene Corp.	5,512,727,000	5,983,973,000
32	Mylan Inc.	5,393,212,000	5,168,168,000
33	Allergan Inc.	5,309,600,000	4,757,700,000
34	Eisai Co.	5,134,570,774 (March 12)	4,976,238,663 (March 11)
35	Ono Pharmaceutical Co.	4,862,870,593 (March 12)	4,799,013,895 (March 11)
36	Shionogi & Co.	4,552,633,270 (March 12)	4,386,455,493 (March 11)
37	Dainippon Sumitomo Pharma Co.	4,162,629,644 (March 12)	4,144,707,085 (March 11)
38	Valeant Pharmaceuticals International Inc.	4,007,016,000	4,911,096,000
39	Watson Pharmaceuticals Inc.	3,563,600,000	3,281,700,000
40	Teijin Ltd.	3,541,221,281 (March 12)	3,446,709,488 (March 11)
41	CSL Ltd.	3,423,500,380 (June 12)	3,639,257,896 (June 11)
42	Shire plc	3,185,000,000	2,451,400,000
43	Hospira Inc.	2,938,000,000	3,183,500,000
44	H. Lundbeck A/S	2,386,476,137	2,077,519,380
45	Grifols S.A.	2,319,503,141	985,465,009
46	Endo Health Solutions Inc.	2,039,591,000	1,803,329,000
47	Actelion Pharmaceuticals Ltd.	1,704,416,610	2,025,732,340
48	Stada Arzneimittel AG	1,189,582,021	1,196,374,777
49	Ranbaxy Laboratories Ltd.	803,313,225	1,101,844,568
50	Warner Chilcott plc	69,131,000	(65,642,000)

Source: www.eKnowledgeBase.com

Notes: March 12 = fiscal year ended March 31, 2012; March 11 = March 31, 2011; June 12 = June 30, 2012; June 11 = June 30, 2011;
For more details about this information, please see the Notes and Methodology on page 8.

TOP 50 COMPANIES RANKED BY EMPLOYEES

Rank 2011	Company	Employees 2011	Employees 2010
1	Novartis AG	123,686	119,418
2	Johnson & Johnson	117,900	114,000
3	Sanofi	113,719	101,575
4	Bayer AG	111,800	111,400
5	Pfizer Inc.	103,700	110,600
6	GlaxoSmithKline plc	97,389	96,500
7	Abbott Laboratories	91,000	90,000
8	Merck & Co.	86,000	94,000
9	F. Hoffmann-La Roche Ltd.	80,129	80,653
10	AstraZeneca plc	59,800	61,700
11	Baxter International Inc.	48,500	48,000
12	Teva Pharmaceutical Industries Ltd.	45,754	39,660
13	Boehringer Ingelheim GmbH	44,094	42,224
14	Merck KGaA	40,676	40,562
15	Eli Lilly and Co.	38,080	38,350
16	Novo Nordisk A/S	32,632	30,483
17	Daiichi Sankyo Co.	31,929 (March 12)	30,488 (March 11)
18	Takeda Pharmaceutical Co.	30,305 (March 12)	18,498 (March 11)
19	Bristol-Myers Squibb Co.	27,000	27,000
20	Otsuka Holdings Co.	24,595 (March 12)	25,188 (March 11)
21	Mylan Inc.	18,000+	13,000
22	Amgen Inc.	17,800	17,400
23	Astellas Pharma Inc.	17,085 (March 12)	16,279 (March 11)
24	Teijin Ltd.	16,819 (March 12)	17,542 (March 11)
25	Hospira Inc.	15,000	14,000
26	Ranbaxy Laboratories Ltd.	14,000	13,420
27	Grifols S.A.	11,259	6,108
28	Eisai Co.	10,730 (March 12)	11,560 (March 11)
29	CSL Ltd.	10,515 (June 12)	10,411 (June 11)
30	Allergan Inc.	10,000	9,200
31	Mitsubishi Tanabe Pharma Corp.	9,180 (March 12)	9,198 (March 11)
32	UCB S.A.	8,506	8,898
33	Stada Arzneimittel AG	7,826	8,080
34	Dainippon Sumitomo Pharma Co.	7,601 (March 12)	7,746 (March 11)
35	Kyowa Hakko Kirin Co.	7,229	7,484
36	Valeant Pharmaceuticals International Inc.	6,900	4,300
37	Chugai Pharmaceutical Co.	6,779	6,709
38	Watson Pharmaceuticals Inc.	6,686	6,030
39	Shionogi & Co.	6,132 (March 12)	5,277 (March 11)
40	Taisho Pharmaceutical Co.	6,003 (March 12)	5,622 (March 11)
41	Forest Laboratories Inc.	5,700 (March 12)	5,600 (March 11)
42	H. Lundbeck A/S	5,690	5,689
43	Shire plc	5,251	4,183
44	Biogen Idec Inc.	5,000	4,850
45	Endo Health Solutions Inc.	4,566	2,947
46	Gilead Sciences Inc.	4,500	4,000
47	Celgene Corp.	4,460	4,182
48	Ono Pharmaceutical Co.	2,754 (March 12)	2,655 (March 11)
49	Actelion Pharmaceuticals Ltd.	2,570	2,462
50	Warner Chilcott plc	2,200	2,700

Source: www.eKnowledgeBase.com

Notes: N/A = Not applicable or available; March 12 = March 31, 2012; March 11 = fiscal year ended March 31, 2011; June 12 = June 30, 2012; June 11 = June 30, 2011;
For more details about this information, please see the Notes and Methodology on page 8.

TOP 50 COMPANIES: MARKET CAPITALIZATION

Rank 2011	Company	Market Capitalization as of Sept. 24, 2012 ($ in millions)	Ticker Symbols (not all global stock exchanges are listed)
1	Johnson & Johnson	$190,150	NYSE: JNJ
2	Pfizer Inc.	185,430	NYSE: PFE
3	Roche Holding Ltd.	165,340	SIX: ROG; PINK: RHHBY
4	Novartis AG	148,480	SIX: NOVZn; NYSE: NVS
5	Merck & Co.	137,750	NYSE: MRK
6	Sanofi	117,510	EPA: SAN; NYSE: SNY
7	GlaxoSmithKline plc	115,140	LSE: GSK.L; NYSE: GSK
8	Abbott Laboratories	109,350	NYSE: ABT
9	Novo Nordisk A/S	107,450	CPH: NOVO-B NYSE: NVO
10	Bayer AG	72,610	PINK: BAYRY; ETR: BAYN
11	Amgen Inc.	63,880	Nasdaq: AMGN
12	AstraZeneca plc	60,310	LON: AZN; NYSE: AZN
13	Bristol-Myers Squibb Co.	56,940	NYSE: BMY
14	Eli Lilly and Co.	55,070	NYSE: LLY
15	Gilead Sciences Inc.	50,810	Nasdaq: GILD
16	Takeda Pharmaceutical Co.	38,030	TYO: 4502; PINK: TKPYY
17	Biogen Idec Inc.	36,490	Nasdaq: BIIB
18	Teva Pharmaceutical Industries Ltd.	34,930	TLV: TEVA; NYSE: TEVA
19	Baxter International Inc.	33,460	NYSE: BAX
20	Celgene Corp.	33,170	Nasdaq: CELG
21	Allergan Inc.	28,220	NYSE: AGN
22	Merck KGaA	27,006	ETR: MRK; PINK: MKGAY
23	Astellas Pharma Inc.	23,560	TYO: 4503; OTC: ALPMY
24	CSL Ltd.	22,570	ASX: CSL; OTC: CMXHY
25	Otsuka Holdings Co.	16,990	TYO: 4578; OTC: OTSKY
26	Shire plc	16,810	LON: SHP Nasdaq: SHPG
27	Valeant Pharmaceuticals International Inc.	16,710	NYSE: VRX
28	Eisai Co.	13,110	TYO: 4523; OTC: ESALY
29	Daiichi Sankyo Co.	12,020	TYO: 4568; OTC: DSNKY
30	Watson Pharmaceuticals Inc.	10,640	NYSE: WPI
31	Chugai Pharmaceutical Co.	10,460	TYO: 4519; OTC: CHGCY
32	UCB S.A.	9,989	EBR: UCB; OTC: UCBJF
33	Mylan Inc.	9,820	Nasdaq: MYL
34	Forest Laboratories Inc.	9,700	NYSE: FRX
35	Mitsubishi Tanabe Pharma Corp.	8,460	TYO: 4508; OTC: MTZXF
36	Ono Pharmaceutical Co.	6,620	TSE: 4528; OTC: OPHLF
37	Taisho Pharmaceutical Co.	6,571	TYO: 4581; OTC: TSOPF
38	Kyowa Hakko Kirin Co.	6,485	TYO: 4151; OTC: KYKOF
39	Actelion Ltd.	6,320	SIX: ATLN; PINK: ALIOF
40	Hospira Inc.	5,650	NYSE: HSP
41	Shionogi & Co.	4,690	TYO: 4507; OTC: SGIOF
42	Dainippon Sumitomo Pharma Co.	4,402	TYO: 4506 PINK: DNPUY
43	Ranbaxy Laboratories Ltd.	4,130	BSE: 500359; NSE: RANBAXY; OTC: RBXZF
44	Endo Health Solutions Inc.	3,850	Nasdaq: ENDP
45	H. Lundbeck A/S	3,540	CPH: LUN; PINK: HLUKF
46	Warner Chilcott plc	3,330	Nasdaq: WCRX FRA: G3LA
47	Grifols S.A.	2,600	MCE: GRF.MC NasdaqGS: GRFS
48	Teijin Ltd.	2,292	OTC: TINLY.PK TYO: 3401
49	Stada Arzneimittel AG	1,360	ETR: SAZ; PINK: STDAF
–	Boehringer Ingelheim GmbH	N/A	N/A

Note: N/A = not applicable

Sources: Yahoo! Finance (finance.yahoo.com) and Google Finance (google.com/finance)

TOP 50 COMPANIES: HEADQUARTERS AND YEAR ESTABLISHED

United States		
Company	**Headquarters**	**Year Established**
Pfizer Inc.	New York, NY	1849
Eli Lilly and Co.	Indianapolis, IN	1876
Johnson & Johnson	New Brunswick, NJ	1887
Abbott Laboratories	Abbott Park, IL	1888
Merck & Co.	Whitehouse Station, NJ	1891
Endo Health Solutions Inc.	Chadds Ford, PA	1920
Baxter International Inc.	Deerfield, IL	1931
Allergan Inc.	Irvine, CA	1950
Forest Laboratories Inc.	New York, NY	1956
Mylan Inc.	Canonsburg, PA	1961
Amgen Inc.	Thousand Oaks, CA	1980
Celgene Corp.	Summit, NJ	1980
Watson Pharmaceuticals Inc.	Parsippany, NJ	1985
Gilead Sciences Inc.	Foster City, CA	1987
Bristol-Myers Squibb Co.	New York, NY	1989
Biogen Idec Inc.	Weston, MA	2003
Hospira Inc.	Lake Forest, IL	2003
Europe		
Company	**Headquarters**	**Year Established**
Merck KGaA	Darmstadt, Germany	1668
Bayer AG	Leverkusen, Germany	1863
Boehringer Ingelheim GmbH	Ingelheim, Germany	1885
Stada Arzneimittel AG	Bad Vilbel, Germany	1895
F. Hoffmann-La Roche Ltd.	Basel, Switzerland	1896
H. Lundbeck A/S	Ottiliavej, Denmark	1915
UCB S.A.	Brussels, Belgium	1928
Grifols S.A.	Barcelona, Spain	1940
Warner Chilcott plc	Dublin, Ireland	1968
Shire plc	St. Helier, United Kingdom	1986
Novo Nordisk A/S	Bagsvaerd, Denmark	1989
GlaxoSmithKline plc	Basel, Switzerland	1996
Actelion Pharmaceuticals Ltd.	Allschwil, Switzerland	1997
AstraZeneca plc	London, United Kingdom	1999
GlaxoSmithKline plc	Brentford, United Kingdom	2000
Sanofi	Paris, France	2004
Japan		
Company	**Headquarters**	**Year Established**
Ono Pharmaceutical Co.	Osaka	1717
Takeda Pharmaceutical Co.	Osaka	1781
Shionogi & Co.	Osaka	1878
Taisho Pharmaceutical Co.	Tokyo	1912
Teijin Ltd.	Osaka	1918
Chugai Pharmaceutical Co.	Tokyo	1925
Eisai Co.	Tokyo	1941
Otsuka Holdings Co.	Tokyo	1964
Astellas Pharma Inc.	Tokyo	2005
Daiichi Sankyo Co.	Tokyo	2005
Dainippon Sumitomo Pharma Co.	Osaka	2005
Mitsubishi Tanabe Pharma Corp.	Osaka	2007
Kyowa Hakko Kirin Co.	Tokyo	2008
Australia		
Company	**Headquarters**	**Year Established**
CSL Ltd.	Melbourne	1916
Canada		
Company	**Headquarters**	**Year Established**
Valeant Pharmaceuticals International Inc.	Montreal	2000
India		
Company	**Headquarters**	**Year Established**
Ranbaxy Laboratories Ltd.	Gurgaon	1962
Middle East		
Company	**Headquarters**	**Year Established**
Teva Pharmaceutical Industries Ltd.	Petach Tikva, Israel	1901

NOTES FOR TOP 50 COMPANY MERGERS & ACQUISITIONS THROUGHOUT THE DECADES

- Abbott completed the acquisition of Solvay Pharmaceuticals on Feb. 16, 2010.
- Astellas was formed by the April 1, 2005, merger of Fujisawa Pharmaceutical Co., founded in 1894, and Yamanouchi Pharmaceutical Co., founded in 1923.
- AstraZeneca was formed by the April 5, 1999, merger of Astra AB, founded in 1913, and Zeneca Group plc, founded in 1993.
- Bayer in June 2006 acquired a majority of the shares of Schering AG, which was subsequently renamed Bayer Schering Pharma AG and fully consolidated in the Bayer Group financial statements.
- Biogen Idec was formed by the 2003 merger of Biogen Inc., founded in 1978, and Idec Pharmaceuticals Corp., founded in 1985.
- Bristol-Myers Squibb was formed in 1989 through the merger of Bristol-Myers Co., formed in 1887, and Squibb Corp., founded in 1858.
- Daiichi Sankyo was formed by the Sept. 28, 2005, merger of Daiichi Pharmaceutical Co., founded in 1915, and Sankyo Co., founded in 1899.
- Dainippon Sumitomo was formed Oct. 1, 2005, through the merger of Dainippon Pharmaceutical Co., founded in 1897, and Sumitomo Pharmaceuticals Co., established in 1984 through the consolidation of the pharmaceuticals operations of Sumitomo Chemical Co. and the pharmaceuticals division of Inabata & Co.
- GlaxoSmithKline was formed in 2000 through the merger of Glaxo Wellcome plc and SmithKline Beecham plc. Glaxo Wellcome was formed in 1994 through the merger of Glaxo, founded in 1973, and Wellcome, founded in 1880. SmithKline Beecham was formed in 1989 through the merger of SmithKline Beckman Corp., founded in 1830, and Beecham Group plc.
- Kyowa Hakko Kirin was formed Oct. 1, 2008, via the merger of Kyowa Hakko Kogyo Co. and Kirin Pharma Co. Kyowa Hakko Kogyo was established in 1949 as a secondary company of Kyowa Sangyo Co. as part of industrial readjustment plans. Kirin Pharma was launched in 2007 to accompany the adoption by Kirin Brewery Co. of a pure holding-company system; Kirin Brewery was founded in 1885 under the original name of Japan Brewery Co.
- Merck & Co. merged Nov. 3, 2010, with Schering-Plough Corp. Merck was founded in 1891. Schering-Plough was formed in 1971 through the merger of Schering Corp., founded in 1928, and Plough Inc., founded in 1908.
- Mitsubishi Tanabe was formed Oct. 1, 2007, via the merger of Mitsubishi Pharma Corp. and Tanabe Seiyaku Co., which was established in 1678. Mitsubishi Pharma was formed in 2001 through the merger of Welfide Corp., founded in 1940, and Mitsubishi-Tokyo Pharmaceuticals Corp., founded in 1999.
- Novartis was formed in 1996 through the merger of Ciba-Geigy, founded in 1884, and Sandoz, founded in 1886. Novartis completed majority ownership of Alcon Inc. on Aug. 26, 2010.
- Novo Nordisk was formed in 1989 through the merger of Nordisk Gentofte AS, founded in 1923, and Novo Industri AS, founded in 1925.
- Pfizer merged Oct. 15, 2009, with Wyeth, which was founded in 1926. Pfizer merged June 19, 2000, with Warner-Lambert Co., which was founded in 1920. Pfizer merged April 16, 2003, with Pharmacia Corp. Pharmacia was formed by the March 31, 2000, merger of Pharmacia & Upjohn Inc. and Monsanto Co., founded in 1901. Pharmacia & Upjohn was founded in 1995 through the merger of Pharmacia, founded in 1911, and The Upjohn Co., founded in 1886. Pfizer completed the acquisition of King Pharmaceuticals Inc. on Feb. 28, 2011.
- Roche acquired Genentech Inc. on March 26, 2009. Roche was founded in 1896. Genentech was founded in 1976.
- Sanofi was previously known as Sanofi-Aventis SA until May 2011. Sanofi-Aventis was formed Aug. 20, 2004, through the merger of Sanofi-Synthelabo SA and Aventis SA. Sanofi-Synthelabo was formed in 1999 through the merger of Sanofi SA, founded in 1970, and Synthelabo SA, founded in 1973. Aventis was formed in 1999 by the merger of Hoechst AG, founded in 1863, and Rhone-Poulenc SA, founded in 1895. Sanofi-Aventis completed the acquisition of Genzyme Corp. on April 8, 2011.
- Takeda acquired Nycomed A/S on Sept. 30, 2011. Nycomed was founded in 1874.
- Teva acquired Cephalon Inc. on Oct. 14, 2011. Cephalon was founded in 1987.
- Valeant Pharmaceuticals International was acquired by Biovail Corp. on Sept. 28, 2010. Valeant survived as a wholly owned subsidiary of Biovail. In connection with the merger, Biovail was renamed Valeant Pharmaceuticals International Inc. Biovail was formed under the Business Corporations Act (Ontario) on Feb. 18, 2000, as a result of the amalgamation of TXM Corp. and Biovail Corporation International.

Source: www.eKnowledgeBase.com

TOP 50 COMPANIES: BUSINESS SEGMENTS	
Company	**Segment**
Abbott Laboratories	Pharmaceuticals, biologics, branded generics, devices, diagnostics, nutritional products, vascular products
Actelion Pharmaceuticals Ltd.	Biopharmaceuticals
Allergan Inc.	Pharmaceuticals, biologics, medical devices, over-the-counter products
Amgen Inc.	Human therapeutics
Astellas Pharma Inc.	Pharmaceuticals and related products, other businesses
AstraZeneca plc	Pharmaceuticals, biopharmaceuticals
Baxter International Inc.	Bioscience, medication delivery, renal
Bayer AG	Pharmaceuticals; consumer healthcare; animal health; devices and contrast agents; material science; crop science; business, technology and chemical-industry services
Biogen Idec Inc.	Biopharmaceuticals
Boehringer Ingelheim GmbH	Pharmaceuticals, consumer healthcare, biopharmaceuticals, biosimilars, contract manufacturing, animal health
Bristol-Myers Squibb Co.	Pharmaceuticals, biopharmaceuticals
Celgene Corp.	Biopharmaceuticals
Chugai Pharmaceutical Co.	Pharmaceuticals
CSL Ltd.	Plasma protein biotherapeutics, plasma collection, biological products, vaccines, prescription pharmaceuticals, donated plasma collection and testing, in vitro diagnostics, immunohematology
Daiichi Sankyo Co.	Pharmaceuticals, consumer health, generics
Dainippon Sumitomo Pharma Co.	Pharmaceuticals; food ingredients, food additives, and chemical product materials; animal health products; diagnostics and research materials
Eisai Co.	Pharmaceuticals, consumer healthcare, diagnostics, generics, food additives, chemicals, other
Endo Health Solutions Inc.	Branded and generic pharmaceuticals
Forest Laboratories Inc.	Pharmaceuticals
Gilead Sciences Inc.	Biopharmaceuticals
GlaxoSmithKline plc	Pharmaceuticals, vaccines, consumer healthcare
Grifols S.A.	Bioscience, diagnostic, hospital
Hospira Inc.	Specialty injectable pharmaceuticals (primarily generics), other pharmaceuticals (primarily large volume I.V. solutions, nutritionals and contract manufacturing services), medication management
Johnson & Johnson	Pharmaceuticals, medical devices and diagnostics, consumer healthcare
Kyowa Hakko Kirin Co.	Pharmaceuticals, bio-chemicals, chemicals, other
Lilly and Co., Eli	Pharmaceuticals, animal health
Lundbeck A/S, H.	Pharmaceuticals
Merck & Co.	Pharmaceuticals, vaccines, biologicals, consumer healthcare, animal health
Merck KGaA	Biopharmaceuticals, pharmaceuticals, OTC products, liquid crystals, pigments and cosmetics, bioscience, process solutions and lab solutions
Mitsubishi Tanabe Pharma Corp.	Pharmaceuticals, vaccines, OTC drugs, fine chemicals, real-estate leasing, information services, advertising, other
Mylan Inc.	Generics, active pharmaceutical ingredients, pharmaceuticals
Novartis AG	Pharmaceuticals, vaccines and diagnostics, generics, OTC medicines, animal health, eye care
Novo Nordisk A/S	Pharmaceuticals for diabetes, biopharmaceuticals
Ono Pharmaceutical Co.	Pharmaceuticals, diagnostics
Otsuka Holdings Co.	Pharmaceuticals, nutraceuticals, consumer products, chemical goods, pharmaceutical intermediates, logistics, electronic devices, other
Pfizer Inc.	Pharmaceuticals, biopharmaceuticals, vaccines, animal health, consumer healthcare, nutritionals
Ranbaxy Laboratories Ltd.	Generics, pharmaceuticals
Roche Ltd., F. Hoffmann-La	Pharmaceuticals, biotechnology, diagnostics
Sanofi	Pharmaceuticals, vaccines, generics, consumer healthcare, animal health
Shionogi & Co.	Pharmaceuticals, contract manufacturing, consumer healthcare, diagnostics, other businesses
Shire plc	Pharmaceuticals, biopharmaceuticals
Stada Arzneimittel AG	Generics, pharmaceuticals, active pharmaceutical ingredients
Taisho Pharmaceutical Co.	Pharmaceuticals, consumer healthcare, health foods, other
Takeda Pharmaceutical Co.	Pharmaceuticals, consumer healthcare, other
Teijin Ltd.	Healthcare; advanced fibers and composites; electric materials and performance polymer products; products converting; IT; other
Teva Pharmaceutical Industries Ltd.	Generics, active pharmaceutical ingredients, pharmaceuticals, animal health
UCB S.A.	Biopharmaceuticals
Valeant Pharmaceuticals International Inc.	Generic, branded, and OTC products
Warner Chilcott plc	Specialty pharmaceuticals
Watson Pharmaceuticals Inc.	Generics, pharmaceuticals
Source: www.eKnowledgeBase.com	

TOP 50 PHARMA COMPANIES

An enthusiastic divorce

In a few months Abbott Laboratories will become two companies—and the new research-based pharmaceutical half will boast the world's best-selling prescription product.

By Joshua Slatko joshua.slatko@ubm.com

Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064-6400
Telephone: 847-937-6100
Website: abbott.com

Abbott
A Promise for Life

BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Humira	$7,932	$6,548
Trilipix/ TriCor	$1,692	$1,582
Kaletra	$1,170	$1,255
Niaspan	$976	$927
Lupron	$810	$748
Synthroid	$638	$555

All sales are in millions of dollars

FINANCIAL PERFORMANCE

	2011	2010
Sales	$38,851	$35,167
Net income	$4,728	$4,626
EPS	$3.01	$2.96
R&D	$4,129	$3,724

	1H12	1H11
Sales	$19,264	$18,657
Net income	$2,967	$2,806
EPS	$1.85	$1.79
R&D	$2,017	$1,968

All figures are in millions of dollars, except EPS

Breaking up may usually be hard to do, but in Abbott's case company leaders are looking forward to the exercise. After years being the odd man out in big pharma – a top 10 research-based drug developer with an equally large portfolio in devices, diagnostics, nutrition, and other non-drug endeavors – the company has decided to split off its drug and non-drug businesses, with the portfolio of proprietary pharmaceuticals and biologics going to the to-be-born AbbVie spinoff entity. This new company, expected to launch by the end of the year, will enter the world with a formidable advantage: Humira, now the world's biggest-selling prescription pharmaceutical product.

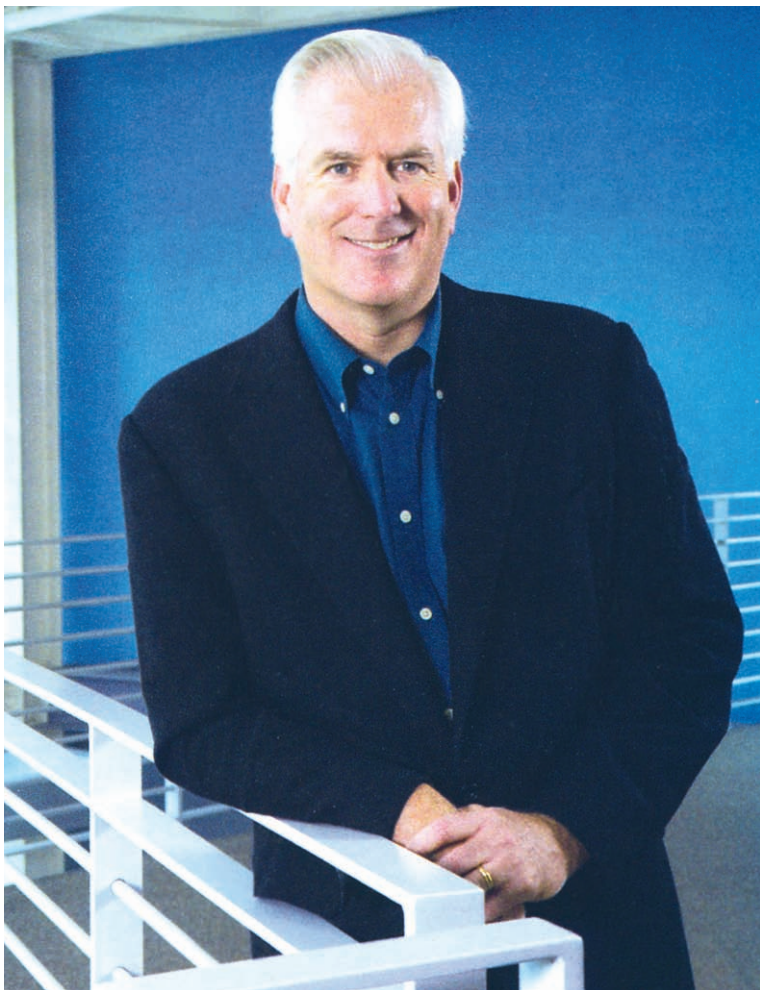
"This next large step in Abbott's evolution fits squarely in our company's long history of growth and success through continual strategic adaptation," says Miles D. White, CEO and chairman of Abbott. "We expect Abbott to be one of the fastest-growing large-cap diversified medical products companies, with a durable mix of products and a strong emerging-markets presence. The new, research-based pharmaceutical company will be a leader in its industry with a strong and sustainable portfolio of specialty medicines, as well as a promising pipeline."

Abbott's sales in 2011 totaled $38.85 billion, a 10.5 percent improvement over the previous year. The bottom line, though, grew more slowly, with net income up just 2.2 percent to $4.73 billion thanks to increased R&D and SG&A expenses. Earnings per share for the year rose five cents to $3.01. With separation approaching, the company's financial performance has remained stable in the first half of 2012, with sales growth of 3.3 percent to $19.26 billion, net earnings growth of 5.7 percent to $2.97 billion, and earnings per share up six cents to $1.85. Company leaders are projecting full-year earnings per share for 2012 at between $4.29 and $4.39.

Splitting up

In October 2011, Abbott announced plans to separate into two publicly traded companies, one in diversified medical products and the other in research-based pharmaceuticals. The diversified medical products company will consist of Abbott's existing diversified medical products portfolio, including its branded generic pharmaceutical, devices, diagnostic, and nutritional businesses, and will retain the Abbott name. The research-based pharmaceutical company will include Abbott's portfolio of proprietary pharmaceuticals and biologics. The transaction is intended to take the form of a tax-free distribution to Abbott shareholders of a new publicly traded stock for the new pharmaceutical company.

"Today's news is a significant event for Abbott, and reflects another dynamic change in our company's 123-year history, strengthening our outlook for strong and sustainable growth and shareholder returns," Mr. White said on the announcement of the separation plan.



"This next large step in Abbott's evolution fits squarely in our company's long history of growth and success through continual strategic adaptation," says Miles D. White, CEO and chairman of Abbott, about the company's upcoming split. "The new, research-based pharmaceutical company will be a leader in its industry with a strong and sustainable portfolio of specialty medicines, as well as a promising pipeline."

The research-based pharmaceutical company has nearly $18 billion in annual revenue and will have a considerable portfolio of brands, including Humira, Lupron, Synagis, Kaletra, Creon, and Synthroid. The diversified medical products company has about $22 billion in annual revenue and a mix of products balanced across four major businesses. Mr. White will remain chairman and CEO of Abbott, the diversified medical products company. Richard A. Gonzalez, currently executive VP, Global Pharmaceuticals, will become chairman and CEO of the research-based pharmaceutical company. Mr. Gonzalez is a more than 30-year Abbott veteran and was previously president and chief operating officer of Abbott.

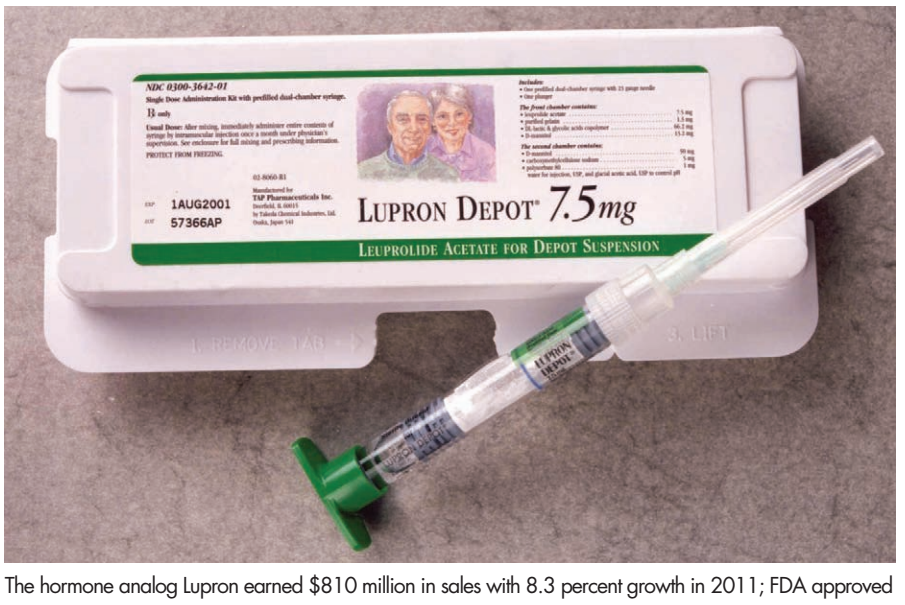
In March, Abbott announced that **AbbVie** (pronounced Abb-vee) will be the name of the new, independent research-based pharmaceutical company. The name is derived from a combination of Abbott and "vie," which references the Latin root "vi" meaning life. Company leaders expect the new company to launch by the end of 2012.

"The beginning of the name connects the new company to Abbott and its heritage of pioneering science," Mr. Gonzalez says. "The 'vie' calls attention to the vital work the company will continue to advance to improve the lives of people around the world."

In his annual letter to the company's shareholders, Mr. White laid out the reasoning behind Abbott's move.

"Our strategic actions of the past decade-plus have dramatically reshaped and strengthened Abbott," he wrote. "Most recently, we have expanded our presence in emerging markets and aggressively rebuilt our pharmaceutical pipeline. At the same time, the investment identities and operating models of our current medical products businesses and pharmaceuticals business evolved independently. They now represent two distinct and compelling investment opportunities for shareholders. This period also saw significant change in our operating environment, including the rise of emerging markets and their growing impact on global business. Abbott's sales outside the United States now exceed those within. At the same time, rising global regulatory standards have changed the landscape for new healthcare products."

These changes in the environment, Mr. White believes, essentially led each side of Abbott's business to pursue distinctly different business models. "Today, research-based pharmaceutical products have different approval and life cycles, research and development profiles, regulatory environments, and geographical market focuses than our other businesses. As a result, these two halves of today's Abbott



The hormone analog Lupron earned $810 million in sales with 8.3 percent growth in 2011; FDA approved two new strengths for one of the product's depot formulations in August and approved another supplemental NDA in October.

have moved in very different directions with equally different demands and priorities and are already functioning as separate, highly successful businesses. Acknowledging this, with the creation of two independent companies, helps clarify for investors each business' value, which we believe will be beneficial for both companies and both stocks."

Acquisitions and partnerships

In December, Abbott and **Reata** Pharmaceuticals entered into a worldwide collaboration to jointly develop and commercialize Reata's portfolio of second-generation oral antioxidant inflammation modulators. The agreement is in addition to the partnership between the two companies announced in September 2010 in which Reata granted to Abbott exclusive rights to develop and commercialize its lead AIM compound, **bardoxolone** methyl, outside the United States, excluding certain Asian markets. The collaboration includes a large number of molecules in a broad range of therapeutic areas, including pulmonary, central nervous system disorders, and immunology. Abbott and Reata will equally share costs and profits for all new AIMs in all newly licensed indications except for rheumatoid arthritis and select other autoimmune diseases, in which Abbott will take 70 percent of costs and profits and Reata will take 30 percent. The deal also includes a research agreement in which the companies will work together to discover new molecules that exhibit the same pharmacology as the AIMs already in Reata's pipeline. Abbott will make a one-time license payment of $400 million to Reata. The companies expect the first compound in this collaboration to enter into human clinical trials in 2012.

AIMs are potent activators of the transcription factor Nrf2. Activation of Nrf2 promotes the production of a wide range of antioxidant, detoxification, and anti-inflammatory genes. Activation of Nrf2 also inhibits NF-kB, a transcription factor that regulates many pro-inflammatory enzymes. Suppression of Nrf2 and activation of NF-kB have been associated with numerous chronic diseases, including multiple sclerosis, rheumatoid arthritis, chronic kidney disease, neurodegenerative disease and COPD. Therefore, agents that activate Nrf2 and inhibit NF-kB may be beneficial in the treatment of these chronic diseases.

"This partnership allows Abbott to enhance its promising research pipeline across multiple therapeutic areas," says John Leonard, M.D., senior VP, pharmaceuticals, research and development, Abbott. "Accumulating data has established the potential for antioxidant inflammation modulators in neuroscience and immunology, and we look forward to expanding our knowledge through further research."

Under an agreement reached in September 2010, Reata granted to Abbott exclusive rights to develop and commercialize its lead AIM compound, bardoxolone methyl, outside of the United States, excluding certain Asian markets. Reata retains U.S. development and commercialization rights. Reata and Abbott are currently conducting the BEACON study, a multi-national Phase III clinical trial of bardoxolone methyl in patients with stage 4 chronic kidney disease and type 2 diabetes.

In January, Abbott and the Drugs for Neglected Diseases initiative (DNDi) signed a four-year joint research and non-exclusive licensing agreement to undertake research on new treatments for several of the world's most neglected tropical diseases, including Chagas disease, helminth infections, leishmaniasis, and sleeping sickness. Through this collaboration, DNDi and Abbott scientists will focus initial efforts on discovering and advancing novel antimicrobial agents with activity against these neglected diseases.

Since 2009, Abbott has provided compounds for DNDi to screen for activity against neglected diseases. The new agreement expands this relationship, and provides DNDi access to selected classes of molecules and accompanying data generated by Abbott that are crucial for the development of effective and accessible new treatments for neglected diseases.

"Innovative product development partnerships have significant potential for addressing neglected diseases," Dr. Leonard says. "By combining the unique scientific expertise and resources of DNDi and Abbott, we look forward to accelerating research to find practical new treatment options for people affected by these diseases."

Equitable access to treatments for neglected diseases in all endemic countries, not only least-developed countries, is at the core of this agreement, and DNDi has committed to ensuring the lowest sustainable pricing for any products developed and distributed as a result of the agreement. Intellectual property related to this agreement, existing relevant Abbott IP and new IP generated by this collaboration will be subject to a principle of non-exclusive licensing to address neglected diseases in endemic countries. Under the agreement, Abbott has the right of first negotiation to become DNDi's development and distribution partner. DNDi is free to engage other partners if Abbott chooses not to serve as a development and distribution partner.

Humira is poised to crack the $8 billion sales mark and take over as the best-selling prescription drug in the world in 2012; the product has earned three new approvals in Europe in the past few months.

In February, Abbott and **Galapagos** entered into a global collaboration to develop and commercialize an oral, next-generation JAK1 inhibitor in Phase II development with the potential to treat multiple autoimmune diseases. **GLPG0634** is a highly selective JAK1 inhibitor that Galapagos is developing for the treatment of rheumatoid arthritis and other autoimmune diseases. The Janus kinases (JAK) are a family of enzymes that play a key role in the signaling mechanism used by a number of cytokines that are involved in autoimmune diseases. In previously reported results from a 4-week Phase IIa study, GLPG0634 demonstrated efficacy measures among the best reported in RA. All patients completed the study, and few experienced any side effects. No anemia, change in blood pressure or lipids were observed. An additional Phase IIa dose-range finding study with GLPG0634 was expected to begin shortly.

"The addition of this novel, oral compound offers patients the potential for advanced treatment options and an improved patient experience to address RA and other autoimmune diseases," Dr. Leonard says. "Abbott's expertise in immunology, combined with a robust portfolio of investigational treatments represents promising innovation across several areas of medical need."

Under the terms of the agreement, Abbott made an initial upfront payment of $150 million for rights related to the global collaboration. Upon successful completion of the RA Phase II studies, Abbott will license the program for a one-time fee of $200 million if the studies meet certain pre-agreed criteria. Abbott will assume sole responsibility for Phase III clinical development and global manufacturing. Pending achievement of certain developmental, regulatory, commercial, and sales-based milestones, Galapagos would be eligible to receive additional milestone payments from Abbott, potentially amounting to $1 billion, in addition to tiered double-digit royalties on net sales upon commercialization. Galapagos retains joint-promotion rights in Belgium, the Netherlands, and Luxembourg.

In May, Abbott agreed to acquire the compound **AP214** from **Action** Pharma A/S. AP214 is in development to prevent acute kidney injury associated with major cardiac surgery in patients at increased risk and has further potential in adjacent indications. The compound is a hormone analogue that targets both systemic inflammation and cellular death caused by hypoxia that can occur during surgery. In September 2011, Action Pharma announced positive Phase IIb top-line results evaluating the efficacy, safety, and tolerability of AP214. Abbott plans to conduct another Phase IIb study, expected to begin later this year.

This acquisition, company leaders say, will enhance Abbott's renal care pipeline. Abbott already has two investigational drugs in development for chronic kidney disease. **Bardoxolone**, a first-in-class anti-oxidant inflammation modulator that activates Nrf2, a pathway involved in the progression of chronic kidney disease, is in Phase III development with Reata Pharmaceuticals. **Atrasentan**, a compound discovered by Abbott scientists, is being evaluated in a Phase IIb study in patients with diabetic kidney disease.

"Clinical experience with AP214 in cardiac surgery patients suggests that it has the potential to be the first compound specifically approved to prevent acute kidney injury, a long-standing unmet need in the medical community," Dr. Leonard says. "This acquisition complements and broadens Abbott's late-stage renal care pipeline and builds on our existing experience in treating kidney disease."

Product performance

The **Humira** train kept rolling for Abbott in 2011 and early 2012. The company's prized autoimmune product brought in an impressive $7.93 billion in sales for 2011, a 21.1 percent improvement over the previous year, and appears poised to take over as the top-selling prescription product in the world this year, with $4.26 billion in sales through the first two quarters, another 16.9 percent jump. And the last few months have brought a number of new indications for Humira in Europe. In April, the European Commission approved Humira for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy. With this approval, Humira became the first and only self-injectable biologic therapy for the treatment of moderately to severely active ulcerative colitis in adults. In July, the EC approved Humira for the treatment of adults with severe axial spondyloarthritis who have no X-ray evidence of structural damage. Humira is now the first and only approved medication available for non-radiographic severe axial spondyloarthritis patients. Finally, in August, the European Commission approved Humira for the treatment of moderately active Crohn's disease in adult patients who have had an inadequate response to conventional therapy.

The onward rush of new indications for Humira won't be ending any time soon – in addition to its six present indications in the United States, Abbott has the product in development for at least six more. In March, the company announced the initiation of two Phase III clinical trials designed to evaluate the safety and efficacy of Humira in adult patients with moderate to severe hidradenitis suppurativa, a difficult-to-treat, chronic, inflammatory skin disease characterized by painful, recurrent abscesses, and nodules that primarily appear in the groin or under the armpits or breasts and start out as tender, swollen bumps. Over time, these lesions can fill with fluid, burst, and result in scars, leading to pain and discomfort.

"Ten years ago, Humira was approved for moderate-to-severe rheumatoid arthritis and since then has achieved five additional indications to treat millions of patients across a range of immune diseases," says John Medich, Ph.D., divisional VP, Clinical Development, Immunology, Abbott. "Abbott is committed to investigating adalimumab as a treatment option for patients with hidradenitis suppurativa, and these studies represent another important step in continuing this exploration."

Growth of the **TriCor/Trilipix** franchise slowed for Abbott in 2011. The franchise earned a total of $1.69 billion in sales for the year, an improvement of just 7 percent after 18.3 percent growth in 2010 and 14.6 percent in the first half of 2011. This second-half slowdown may have come due to a label change issued by FDA for Trilipix in November; the agency notified healthcare professionals that month that Trilipix may not lower a patient's risk of having a heart attack or stroke. FDA based its decision on data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial, which found no significant difference in the risk of experiencing a major adverse cardiac event between the group treated with Trilipix plus simvastatin compared with simvastatin alone. In the first half of 2012,

TriCor/Trilipix sales dropped 8.5 percent to $717 million. TriCor has three cholesterol-related indications in the United States; the follow-on Trilipix earned three more in December 2008.

Sales of the HIV drug **Kaletra** continued to fall in 2011, descending 6.8 percent to $1.17 billion. In the first half of 2012, Kaletra sales dropped another 15.2 percent to $496 million.

A variety of public health groups around the world are campaigning vigorously to either lower the price of Kaletra or break Abbott's patent on the product. Upon the launch of a global campaign in November 2011, groups in the United States, Vietnam, and Indonesia asked their governments to authorize generic competition under rules providing for the government use of patents. In Brazil and India, lawyers filed formal challenges to Abbott's patent claims, arguing that the company had not met national standards for patentability and therefore is not entitled to its patent monopoly.

Colombian health advocates are pursuing a lawsuit for a compulsory license authorizing generic competition, as the government of Ecuador and health advocates in Thailand seek to expand licenses already in effect. Peruvian groups have asked Abbott to abandon new patent applications. And treatment providers in Sint Maarten (Kingdom of the Netherlands) and Malaysia and health groups in China have filed request letters with Abbott seeking licenses to permit generic competition. More than 300 Vietnamese health groups have signed a similar letter to Abbott.

The cholesterol drug **Niaspan** continued to edge its way towards blockbuster status for Abbott in 2011, with sales growing 5.3 percent to $976 million. But this slow growth came to a sharp end in the first half of 2012, as Niaspan sales tumbled 15 percent to $402 million. In November 2011, final results were presented from the AIM-HIGH study, testing whether raising HDL "good" cholesterol by adding Niaspan to simvastatin would provide an additional 25 percent reduction in cardiovascular outcomes in patients with established cardiovascular disease and well-controlled LDL "bad" cholesterol levels. The study was stopped early following an interim analysis in May 2011 and found that combination therapy did not result in an additional reduction in cardiovascular events beyond treatment with simvastatin in this patient population with well-controlled LDL cholesterol and non-HDL-cholesterol (a measure of all plaque-causing particles).

"Niaspan remains an important treatment option to help patients reach their lipid treatment goals, many of whom require multiple medications to do so," Dr. Leonard says. "Even when looking only at the high-risk patient group evaluated in the AIM-HIGH study, epidemiologic data tell us that in clinical practice more than three-quarters of these patients do not reach their recommended goals for lipid therapy. Physicians should consider each patient's cardiovascular profile and the NCEP treatment guidelines when evaluating a patient for potential additional treatment with lipid lowering medicines such as Niaspan."

Sales of the hormone analog **Lupron** bounced back in 2011 after dropping the year before. The drug accumulated $810 million in sales for the year, up 8.3 percent. Sales have edged up a bit more in the new year, rising 2.6 percent in the first half of 2012 to an even $400 million. In August 2011, FDA approved two new strengths for three-month administration of Lupron Depot-PED for the treatment of children with central precocious puberty. Two months later, the agency approved a supplemental NDA for Lupron Depot-PED. The one-month formulation is the first product in its class to include long-term data in its label for the treatment of central precocious puberty. The prescribing information now contains 18 years of data, including pre-specified outcome results on puberty, height, and reproductive function.

TriCor/Trilipix sales have slowed of late after FDA notified healthcare professionals in November 2011 that Trilipix may not lower a patient's risk of having a heart attack or stroke.

"Guiding a child through puberty can be a challenge for any parent, but when things go awry in the body and this process happens too soon, it can be worrisome for everyone," Dr. Leonard says. "This study provides patients and physicians with important information to better understand Lupron Depot-PED for 1-month administration and its long-term impact, particularly on reproductive function and normalized adult height."

Synthroid, Abbott's drug for hypothyroidism, enjoyed a 15 percent jump in sales in 2011, earning $638 million for Abbott. In the first half of 2012, sales of Synthroid dropped slightly, falling 1.2 percent to $304 million.

In the pipeline

Abbott spent $4.13 billion on research and development in 2011, 10.9 percent more than the previous year. In the first half of 2012, R&D expenses rose by 2.5 percent to $2.02 billion.

In June 2011, Phase II clinical trial data showed that patients with moderate to severe chronic kidney disease and type 2 diabetes receiving bardoxolone methyl for 52 weeks experienced a sustained improvement in kidney function throughout the treatment period, as measured by estimated glomerular filtration rate (eGFR). The Phase II dose-finding clinical trial, known as the BEAM study, showed that in patients with moderate to severe chronic kidney disease – defined by an eGFR of 20 to 45 mL/min/1.73m2 – and type 2 diabetes, eGFR at 52 weeks was significantly improved with bardoxolone methyl treatment by up to 10.5 mL/min/1.73m2 in patients receiving 75 mg. Partner developers Abbott and Reata Pharmaceuticals Inc. initiated a Phase III study that same month.

"The Phase II data we have seen showing sustained improvements in eGFR are very encouraging," says Eugene Sun, M.D., VP, Global Pharmaceutical Research and Development, Abbott. "These results set the stage for our Phase III program for bardoxolone methyl, which will evaluate whether it is possible to delay or prevent progression to dialysis."

In August 2011, Abbott and partner developer **Biogen Idec** announced positive top-line results from SELECT, a global, registrational Phase IIb clinical trial designed to evaluate the investigational compound **daclizumab** high-yield process (DAC HYP) in people with relapsing-remitting multiple sclerosis over one year. Results showed that DAC HYP, administered subcutaneously once every four weeks, significantly reduced annualized relapse rate by 54 percent in the 150 mg dose arm and 50 percent in the 300 mg dose arm compared to the placebo arm at one year. DAC HYP also met key secondary endpoints for the 150 mg and 300 mg arms, respectively, providing a highly statistically significant reduction in the cumulative number of new gadolinium-enhancing lesions between weeks eight and 24 (69 percent; 78 percent); in the number of new or newly enlarging T2 hyperintense lesions at one year (70 percent; 79 percent); and in the reduction in the proportion of patients who relapsed (55 percent; 51 percent). DAC HYP also showed a trend toward improvement in quality of life measures at one year.

The SELECT trial also investigated DAC HYP's effect on disability progression as measured by the expanded disability status scale as a tertiary endpoint. Findings showed that DAC HYP reduced the risk of sustained disability progression at one year by 57 percent in the 150 mg dose arm and by 43 percent in the 300 mg dose arm compared to placebo. Additional analyses are ongoing.

"These results bring us one step closer in the development of a potential new treatment option for multiple sclerosis, an area of medicine where there continues to be a significant need for novel approaches for patients," Dr. Sun says. "We look forward to continued analysis of the SELECT data and the opportunity to present these results in full context at an upcoming scientific forum."

In April, complete data from the study known as "Pilot" – Abbott's initial interferon-free study of its direct-acting antiviral agents for the treatment of hepatitis C – showed that 91 percent of genotype 1 infected, treatment-naïve patients taking **ABT-450/r** and **ABT-072** combined with ribavirin administered for 12 weeks, achieved sustained viral response at 24 weeks (SVR24). 82 percent of patients achieved SVR36. This is among the first 12-week, interferon-free HCV regimen with 36-week post-treatment data in genotype 1 patients. That same month, Abbott and partner developer **Enanta** Pharmaceuticals announced data from "Co-Pilot," a second interferon-free, Phase II study of Abbott's direct-acting antiviral medicines for the treatment of HCV that found that more than 90 percent of patients new to HCV treatment achieved sustained viral response through 12 weeks.

In the three-arm "Co-Pilot" study, different doses of ABT-450/r, plus **ABT-333** and ribavirin administered for 12 weeks showed sustained virological response at 12-weeks post treatment (SVR 12) in 95 percent and 93 percent of treatment-naïve genotype 1 patients, with no post-treatment relapses. In these patients, response was independent of HCV subtype, host IL28B genotype or dose of ABT-450/r. In addition, SVR 12 was achieved in 47 percent of patients who were previous non-responders to past HCV treatment.

Current treatments for HCV remain interferon-based. A significant number of HCV patients are unable or unwilling to take interferon due to contraindications and/or side effects, which may include flu-like symptoms, depression and insomnia. Specifically targeted antiviral therapies for HCV, such as protease inhibitors and non-nucleoside polymerase inhibitors, may have the potential to increase the proportion of patients in whom the virus can be eradicated.

Also in April, Abbott announced results from a Phase III trial evaluating the company's investigational compound for advanced Parkinson's disease, **levodopa-carbidopa intestinal gel** (LCIG). The study showed that patients treated with LCIG for 12 weeks reported clinically meaningful and statistically significant improvements in "off" time compared to levodopa-carbidopa immediate release tablets, without increasing troublesome dyskinesia. "Off" time refers to the periods of poor mobility, slowness and stiffness experienced by patients with Parkinson's disease. Two months later, Abbott announced results from five abstracts evaluating LCIG. The abstracts included the results from the second interim analysis of a long-term safety and tolerability trial, as well as secondary endpoint analyses from the Phase III pivotal trial.

In a 54 week open-label safety and tolerability study of 354 patients with advanced Parkinson's disease, the primary endpoint of safety showed adverse events were mostly mild to moderate, were generally associated with the percutaneous endoscopic gastrostomy tube placement procedure and its complications, were transient, and resolved over time. In the secondary endpoint analysis from the open-label study, patients experienced an average daily "off" time of 6.7 hours, and 7.7 hours of "on" time without troublesome dyskinesia at baseline. At week 54, mean daily "off" time had decreased an average of 4.5 hours, and "on" time without troublesome dyskinesia had increased by 5.1 hours. "On" time with troublesome dyskinesia decreased an average of 0.6 hours

In June, Abbott and partner developer **Neurocrine** Biosciences Inc. announced the initiation of a pivotal Phase III clinical trial designed to evaluate the safety and efficacy of **elagolix** in female patients with endometriosis. Elagolix is an oral gonadotropin-releasing hormone (GnRH) antagonist. The trial, called M12-665, is a 24-week, multinational, randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of elagolix in 875 women, age 18 to 49, with moderate-to-severe endometriosis-associated pain. It will be conducted at approximately 160 sites in the United States, Puerto Rico, and Canada. A second pivotal Phase III study is also planned, with an NDA filing targeted in 2016.

"The investigation of elagolix for endometriosis is an important step in the exploration of potential treatments for this underserved patient population," says Rita Jain, M.D., divisional VP, Pain, Respiratory and Metabolic Development, Global Pharmaceutical R&D, Abbott. "We are pleased to announce that the Phase III trial has begun screening for enrollment." ■ MEDADNEWS

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TOP 50 PHARMA COMPANIES

Expansion mode

Amgen ended 2011 with good momentum that carried over into 2012, as revenue is on pace to increase by a double-digit percentage year over year; various acquisitions are helping build the biotechnology entity's global footprint and R&D program.

By Andrew Humphreys andrew.humphreys@ubm.com

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PRODUCT	2011 SALES	2010 SALES
Neulasta	$3,952	$3,558
Enbrel	$3,701	$3,534
Aranesp	$2,303	$2,486
Epogen	$2,040	$2,524
Neupogen	$1,260	$1,286
Sensipar/ Mimpara	$808	$714
Xgeva	$351	$8
Vectibix	$322	$288
Nplate	$297	$229
Prolia	$203	$33

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Revenue	$15,582	$15,053
Net income	$3,683	$4,627
EPS	$4.04	$4.79
R&D	$3,167	$2,894

	1H 12	1H 11
Revenue	$8,525	$7,665
Net income	$2,450	$2,295
EPS	$3.09	$2.45
R&D	$1,562	$1,555

All figures are in millions of dollars except EPS.

The world's largest independent biotech medicines company generated 3.5 percent revenue growth in 2011. Through the halfway mark of 2012, Amgen was on pace to produce impressive double-digit sales growth for the full year as the first-half total increased 11.2 percent versus the first six months of 2011. Amgen's long-standing blockbusters continue to grow or hold steady course, while a new generation of medicines are propelling toward eventual annual billion-dollar sales status.

The Thousand Oaks, Calif.-based company markets primarily recombinant protein therapeutics in supportive cancer care, inflammation, and nephrology. Amgen had five billion-dollar sales generators during 2011: the neutropenia drugs **Neulasta** and **Neupogen**, the autoimmune disorders medicine **Enbrel**, and the anemia products **Aranesp** and **Epogen**. These five products accounted for 87 percent of Amgen's total 2011 sales, versus 91 percent in 2010 and 93 percent for 2009. That annual percentage will continue to decrease as Amgen's current collection of growth-phase products continue to succeed in the global marketplace.

Amgen has been active on the acquisition front during 2012 (as was the case in 2011), including the purchase of the biopharma company **Micromet** Inc. The deal gives Amgen access to a novel cancer treatment technology, expanding its existing oncology pipeline and providing a broad validated technology platform. According to industry sources, this is the largest acquisition by Amgen since the company's $2.2 billion cash purchase of **Abgenix** during 2005.

Amgen has new product candidates in mid-stage to late-stage development in various therapeutic areas, including oncology, hematology, inflammation, bone health, nephrology, cardiovascular, and general medicine, which includes neuroscience. The company's research and development organization has expertise in multiple treatment modalities, including large molecules (such as proteins, antibodies, and peptibodies) and small molecules.

As of May 23, 2012, Amgen is operating under the guidance of a new CEO. Robert Bradway, previously president and chief operating officer of the company, took over the helm on that date from Kevin W. Sharer. Mr. Sharer will remain chairman of Amgen until he retires from the company at the end of 2012. Mr. Sharer had been CEO and chairman of Amgen since 2000. Under his leadership, Amgen grew from $3.6 billion in revenue with a presence in 17 countries to a company with revenue of nearly $16 billion and operations in 55 countries.

"I am very pleased with the performance of the business in the first half," noted Mr. Bradway on Amgen's results for the first six months of 2012. "I am excited about the growth opportunities in our research and development pipeline, particularly our biologic **AMG 145** for hypercholesterolemia."

Developed by Amgen scientists, the fully human monoclonal antibody AMG 145 inhibits proprotein convertase subtilisin/kexin type 9. PCSK9 is a protein that reduces the liver's ability to remove high LDL cholesterol (LDL-C) from the blood, resulting in an increase of bad cholesterol. AMG 145 binds to PCSK9 circulating in the blood and prevents the protein from binding to LDL receptors located in the liver. Without PCSK9 bound to them, the LDL receptors can take up and remove low-density lipoprotein cholesterol from the blood, recycle and remain available for binding more LDL-C. AMG 145's cholesterol-lowering effects thus far have been shown to be similar among patients on high doses of the world's two leading statins.

Robert Bradway took over as CEO of Amgen in May 2012.

Company performance

Amgen generated total revenue of $15.58 billion during 2011, versus $15.05 billion in 2010. Full-year 2011 adjusted earnings per share came in at $5.33 compared to $5.21 for the previous calendar term, growing 2.2 percent year over year. Adjusted net income for 2011 declined 3.3 percent versus 2010 to $4.86 billion. Amgen's reported GAAP diluted EPS for 2011 amounted to $4.04, down 16.9 percent in comparison to 2010. GAAP net income for 2011 fell 20.4 percent to $3.68 billion. GAAP diluted EPS and net income for 2011 were negatively impacted by a previously disclosed charge for a legal settlement.

Research and development expenses on a GAAP basis in 2011 totaled $3.17 billion, growing 9.4 percent compared to the 2010 amount. On an adjusted basis, the 2011 R&D budget rose 12.4 percent versus 2010, coming in at $3.12 billion. The change was mainly due to increased later-stage clinical-program support for various products.

For the first half of 2012 on a GAAP basis, total revenue amounted to $8.53 billion (first-half 2011 was $7.67 billion), net income totaled $2.45 billion (first-half 2011 was $2.3 billion) and diluted EPS reached $3.09 (first-half 2011 was $2.45). R&D expenses edged up 0.5 percent to $1.56 billion for January-June 2012 versus first-half 2011.

At the start of 2012, the company announced total revenue guidance for the year to be in the range of $16.1 billion to $16.5 billion. Management expected 2012 adjusted EPS to be in the range of $5.90 to $6.15. The adjusted EPS discounts certain expenses related to acquisitions, the non-cash interest expense associated with Amgen's convertible notes, stock-option expense, and certain expenses related to a cost-saving initiative.

Based upon Amgen's first-half 2012 performance, the company changed its guidance figures for the full year as announced in July 2012. For the whole of 2012, management revised the ranges to $16.9 billion-$17.2 billion for total revenue and $6.20-$6.35 for adjusted EPS.

In addition to the positive financial results, other first-half 2012 highlights included the company modifying its deal with **Takeda** Pharmaceutical Co. to grant exclusive global development rights for **motesanib**, recognizing income of $206 million in other revenue. Also, four AMG 145 Phase II studies were successfully completed and Amgen intends to begin Phase III clinical trials during early 2013. In addition, during 2Q 2012 the company generated $2.2 billion of free cash flow.

Product overview and performance

Amgen's top-selling product franchise consists of the neutropenia drugs Neulasta (pegfilgrastim) and Neupogen (Filgrastim). Both products stimulate production of neutrophils, a form of white blood cell that plays a significant role in the body's fight against infection. Treatments for various diseases can lead to extremely low amounts of neutrophils, a condition known as neutropenia. Myelosuppressive chemotherapy – a treatment option for patients with certain forms of cancers – targets cell types that grow rapidly, including tumor cells. Normal cells that divide rapidly, such as those in the bone marrow that turn into neutrophils, are vulnerable to the cytotoxic effects of myelosuppressive chemotherapy. That can lead to neutropenia with an increased risk of severe infection.

Prolia and Xgeva combined sales jumped from $41 million during 2010 to $554 million in 2011.

Filgrastim is a recombinant-methionyl human granulocyte colony-stimulating factor (G-CSF). Pegfilgrastim is a pegylated protein based on the filgrastim molecule. For pegfilgrastim, a polyethylene glycol molecule is added to the filgrastim molecule.

Because pegfilgrastim is eliminated via binding to its receptor on neutrophils and neutrophil precursor cells, the drug remains in the circulation until neutrophil recovery has taken place. This neutrophil-mediated clearance enables for administration as one dose per chemotherapy cycle. In comparison, Amgen's predecessor product to Neulasta – Neupogen – necessitates more frequent dosing.

Amgen markets Neulasta and Neupogen mainly in the United States and Europe. Filgrastim is additionally marketed under the trade name **Granulokine** in Italy. Amgen is granted an exclusive license to manufacture and market Neulasta and Neupogen in the United States, Europe, Canada, Australia and New Zealand through a licensing deal with **Kirin-Amgen** Inc.

Neulasta was launched in the United States and Europe during 2002 and is indicated to decrease the incidence of infection associated with chemotherapy-induced febrile neutropenia in cancer patients with non-myeloid malignancies. Administration of Neulasta in every cycle of chemotherapy is approved for patients receiving myelosuppressive chemotherapy associated with a clinically significant risk of febrile neutropenia.

Neupogen was introduced to the U.S. and European markets during 1991. The drug is indicated for reducing the incidence of infection as manifested by febrile neutropenia for patients with non-myeloid malignancies undergoing myelosuppressive chemotherapy; reducing the duration of neutropenia and neutropenia-related consequences for patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone-marrow transplantation; reducing the incidence and duration of neutropenia-related consequences in symptomatic patients with congenital neutropenia, cyclic neutropenia or idiopathic neutropenia (collectively, severe chronic neutropenia); mobilizing peripheral blood progenitor cells in cancer patients who have undergone myeloablative chemotherapy for stem-cell transplantation; and reducing the recovery time of neutrophils and the duration of fever following induction or consolidation chemotherapy treatment in adult patients with acute myeloid leukemia.

Combined global sales of Neulasta and Neupogen during 2011 totaled $5.21 billion, compared to the 2010 total of $4.84 billion. The 7.6 percent growth for 2011 was primarily fueled by an increase in the U.S. average net sales price and Neulasta unit growth. U.S. Neulasta and Neupogen sales for 2011 amounted to $3.97 billion versus the 2010 total of $3.59 billion. International sales for the two drugs combined to be $1.25 billion in 2011 versus $1.26 billion during the previous calendar term.

Neulasta sales in 2011 totaled $3.95 billion, compared to $3.56 billion for the prior year. For full-year 2011, the product's U.S. sales tallied at $3.01 billion compared with $2.65 billion in 2010. International sales came in at $946 million, up from $904 million in 2010.

During first-half 2012, Neulasta global sales amounted to $2.05 billion compared with $1.95 billion in first-half 2011. For the first six months of 2012, the product's U.S. sales came in at $1.61 billion compared with $1.48 billion in first-half 2011 and rest-of-world sales amounted to $446 million, up from $472 million in the same period for 2011.

Global 2011 sales for Neupogen came in at $1.26 billion compared to the 2010 amount of $1.29 billion. U.S. sales totaled $959 million during 2011 and $932 million in 2010. Internationally, Neupogen sales decreased from $354 million for 2010 to $301 million during 2011.

For the first six months of 2012, Neupogen worldwide sales reached $637 million compared to the first-half 2011 sum of $607 million. U.S. first-half 2012 sales amounted to $507 million versus the $450 million total during first-half 2011. Rest-of-world sales were reported to be $130 million in first-half 2012 and $157 million during January-June 2011.

Amgen's main European patent relating to G-CSF expired during August 2006. With the expiration of that patent, some companies received regulatory clearance to market products – including biosimilars – that compete with Neulasta and Neupogen in Europe.

As for U.S. competition for Neulasta and Neupogen, **Bayer** HealthCare Pharmaceuticals markets **Leukine** (sargramostim). Additionally, **Teva** Pharmaceutical Industries Ltd. won FDA clearance for its biologics license application for **tbo-filgrastim** (XM02 filgrastim) during August 2012. The filgrastim product is sold under the brand name **Tevagrastim** in some European countries. The drug is expected to be branded in the United States as **Neutroval**. Teva will market the product in the United States as early as November 2013, in accordance with a settlement reached with Amgen. Tbo-filgrastim represents the first new G-CSF to be FDA-approved in more than a decade.

According to Amgen reports, several companies have short-acting filgrastim product candidates in Phase III trials. At least two companies have long-acting filgrastim product candidates in Phase III studies.

Amgen's No. 2 best seller is the biologic Enbrel. The TNF receptor fusion protein inhibits the binding of tumor necrosis factor to its receptors. This can lead to a significant reduction in inflammatory activity. TNF is a chemical messenger that helps regulate the inflammatory process. When the body creates too much tumor necrosis factor, it overwhelms the immune system's ability to control inflammation of the joints or of psoriasis-affected skin areas. Enbrel binds certain tumor necrosis factor molecules before they can trigger inflammation.

Amgen acquired the rights to Enbrel during July 2002 upon its acquisition of **Immunex** Corp. The drug was introduced to the U.S. marketplace during November 1998 and in Canada during March 2001 for treating rheumatoid arthritis. Since that time, Enbrel has received indications for treating adult patients with the following conditions: moderate-to-severe active rheumatoid arthritis; chronic moderate-to-severe plaque psoriasis patients who are candidates for systemic therapy or phototherapy; active psoriatic arthritis; and active ankylosing spondylitis.

Amgen markets the blockbuster product under a collaboration deal with **Pfizer** Inc. in the United States and Canada, which expires during 4Q 2013. Pfizer holds the rights to market and sell Enbrel outside the United States and Canada. Takeda markets the drug in Japan.

Combining sales reported by Amgen, Pfizer and Takeda, Enbrel was one of the world's six best-selling prescription drugs in 2011 at about $7.87 billion. EvaluatePharma analysts issued a report in June 2012 projecting that Enbel will rank No. 4 worldwide among Rx brands in 2018 with global sales of $7.19 billion.

Amgen reported Enbrel total sales of $3.7 billion for 2011 and $3.53 billion during 2010. The 4.7 percent year-over-year growth was mainly spurred by an increase in the average net sales price. Enbrel remained the segment share leader in each of the rheumatology and dermatology segments. Amgen's U.S. sales for Enbrel came in at $3.46 billion during 2011 versus $3.3 billion for 2010. In Canada, the company's Enbrel sales rose from $230 million during 2010 to $243 million for 2011.

For January-June 2012, Enbrel global sales reported by Amgen reached $2 billion versus $1.83 billion during first-half 2011. U.S. sales increased from $1.72 billion in first-half 2011 to $1.87 billion for the first two quarters of 2012. Sales in Canada also advanced year over year, from $116 million in first-half 2011 to $127 million in first-half 2012.

Enbrel is subject to patent expiration as of October 2012 related to TNFR DNA vectors, cells and processes for making proteins. The product's aqueous formulation, however, accounts for the majority of the blockbuster's U.S. sales and is safe from expiration until 2023. The drug is additionally sold as an alternative lyophilized formulation that necessitates reconstituting before it can be administered to patients.

Amgen's top-selling product, the neutropenia drug Neulasta, closed in on $4 billion in sales in 2011.

The biologic's U.S. patent for fusion protein and pharmaceutical compositions is protected until November 2028.

On Nov. 22, 2011, Amgen announced the issuance of U.S. Patent No. 8,063,182 related to Enbrel. This patent is owned by **F. Hoffman-La Roche** Ltd. and exclusively licensed to Amgen. Immunex originally licensed this patent application from Roche in 1999. During 2004, Amgen gave Roche a one-time payment and obtained an exclusive, fully paid-up license to the application issued on Nov. 22 as the '182 patent. The patent describes and claims the fusion protein that is etanercept, and by statute, the '182 patent has a term of 17 years until Nov. 22, 2028.

Aranesp ranks as Amgen's third best-selling product. The drug is marketed by Amgen primarily in the United States and Europe. The company is granted an exclusive license by Kirin-Amgen to manufacture and market the medicine in the United States, all European countries, Canada, Australia, New Zealand, Mexico, all Central and South American countries, and some countries in Central Asia, Africa and the Middle East.

Aranesp was introduced during 2001 in the United States and Europe for treating anemia associated with chronic renal failure (both in patients on dialysis and patients not on dialysis). Aranesp is additionally indicated for treating anemia due to concomitant chemotherapy in patients with non-myeloid malignancies.

Global Aranesp sales totaled $2.3 billion for 2011 and $2.49 billion during 2010. The decrease of 7.4 percent was mainly attributed to a high-teens percentage point unit decline in the United States. The product's U.S. sales came to $986 million in 2011 and $1.1 billion for the prior year. International sales declined from $1.38 billion during 2010 to $1.32 billion for 2011.

Worldwide sales for Aranesp during first-half 2012 reached $1.05 billion compared to $1.17 billion for first-half 2011. The product's U.S. and rest-of-world sales declined during this time frame, with the first-half 2012 totals coming to $417 million (U.S.) compared with $491 million in first-half 2011, and $637 million (ROW) compared with $674 million in the same period in 2011.

Aranesp competes in the United States with Amgen's Epogen, mainly in the hospital dialysis clinic setting. Epogen was Amgen's fourth best-selling product in 2011 with sales of $2.04 billion, compared to $2.52 billion during the previous year (all sales were generated in the United States). The 19.2 percent sales drop-off resulted from a decline in dose use related to changes in reimbursement and the product label, offset partially by an increase in the average net sales price and patient population growth.

Amgen was granted an exclusive license to manufacture and market Epogen in the United States through a licensing accord with Kirin-Amgen. Amgen retained exclusive rights to market the medicine in the United States for dialysis patients. The company granted **Ortho Pharmaceutical** Corp. – a subsidiary of **Johnson & Johnson** (which has assigned its rights under the product license agreement to its **Janssen** subsidiary) – a license to commercialize recombinant human erythropoietin as a human therapeutic in the United States in all indications other than dialysis.

Amgen launched Epogen in the United States during 1989 for treating anemia associated with chronic renal failure in patients who are on dialysis. The brand is available in the United States for treating anemic adult and pediatric patients with chronic renal failure who are on dialysis. The product is indicated for elevating or maintaining the red blood cell level (as determined by hematocrit or Hb measurements) and decreasing the need for blood transfusions in these patients.

Epogen first-half 2012 sales totaled $971 million, a decrease versus the January-June 2011 figure of $1.08 billion. The drop-off was propelled by a reduction in dose utilization, offset largely by reductions in customer discounts and a change in accounting estimates.

Sensipar/Mimpara is a small-molecule medicine containing cinacalcet that is used in treating chronic kidney disease patients on dialysis who produce too much parathyroid hormone, a condition known as secondary hyperparathyroidism. Sensipar is the U.S. brand name and Mimpara is the trade name in Europe.

The product was approved during 2004 by health authorities in the United States and Europe for treating secondary hyperparathyroidism in chronic kidney disease patients on dialysis and for treating hypercalcemia in patients with parathyroid carcinoma. In 2008, Mimpara was cleared in Europe for the reduction of hypercalcemia in patients with primary hyperparathyroidism where a parathyroidectomy is not clinically appropriate or is contraindicated. During 2011, Sensipar was FDA-approved for treating severe hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy.

Global sales for Sensipar/Mimpara totaled $808 million during 2011 and $714 million for 2010. The 13.2 percent rise in sales was mainly spurred by worldwide unit growth during fourth-quarter and full-year 2011. Sensipar U.S. sales came in at $518 million in 2011, compared to $459 million for the previous year. Internationally, Mimpara produced sales of $290 million in 2011 and $255 million during 2010.

The Phase III EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events (E.V.O.L.V.E) study was launched during 2006. The 3,800-patient, multi-center, interna-

tional, randomized double-blind trial is assessing the effects of Sensipar/Mimpara on mortality and cardiovascular morbidity in patients with chronic kidney disease undergoing maintenance dialysis. The E.V.O.L.V.E study completed enrollment during January 2008, and Amgen expected data from the study in 2012.

Sensipar/Mimpara is on track to break the billion-dollar sales barrier in 2013. In the first half of 2012, global sales for the product totaled $451 million, with U.S. sales amounting to $290 million and rest-of-world sales equaling $161 million. For first-half 2011, worldwide sales came in at $386 million, with U.S. sales of $240 million and rest-of-world sales of $146 million.

The monoclonal antibody **Vectibix** is an antagonist of the epidermal growth factor receptor pathway. The drug is marketed for treating patients with epidermal growth factor receptor (EGFr) expressing metastatic colorectal cancer after disease progression on, or following fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy regimens. Epidermal growth factor receptor is a protein that has a significant role in cancer-cell signaling. EGFr is over-expressed in many types of human cancers. Vectibix binds with high affinity to epidermal growth factor receptors as well as interferes with signals that might otherwise activate growth and survival of the cancer cell.

Amgen obtained full ownership of Vectibix upon its acquisition of **Abgenix** Inc. during April 2006. Five months later, Vectibix gained FDA accelerated approval based upon clinical-trial data from a study showing a statistically significant improvement in progression-free survival. The FDA marketing clearance was granted with the condition that Amgen perform a confirmatory study to verify the clinical benefit of panitumumab via demonstration of an improvement in overall survival.

EU conditional approval of Vectibix was received during December 2007. The conditional approval was for the drug as monotherapy for treating patients with EGFr expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS genes after failure of fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy regimens. The EU conditional marketing authorization has been renewed annually with an additional specific obligation to carry out a clinical study in the approved monotherapy indication.

During 2010, Amgen started enrollment for this additional study that compares the effect of Vectibix versus the blockbuster brand **Erbitux** on overall survival for chemorefractory metastatic colorectal cancer patients with wild-type KRAS genes. KRAS is a protein present in every human cell. Certain colorectal cancers have mutations in the KRAS gene. Vectibix has been demonstrated to be ineffective in individuals whose tumors had KRAS mutations in codon 12 or 13.

Amgen announced in 2009 results from the '203 and '181 pivotal Phase III studies evaluating Vectibix in combination with chemotherapy (FOLFOX or FOLFIRI) as a first-line and second-line treatment for metastatic colorectal cancer, respectively. Each clinical trial showed that Vectibix administered with chemotherapy significantly improved progression-free survival in patients with wild-type KRAS metastatic colorectal cancer. The two studies demonstrated numeric improvements in median overall survival in the same patient population. The numeric improvements in median overall survival did not achieve statistical significance. There was a previous agreement with FDA that the '181 study would serve as the confirmatory study for establishing full approval for the metastatic colorectal cancer indication.

Amgen announced during July 2011 receipt of complete response letters from FDA on the first-line and second-line metastatic colorectal cancer supplemental BLAs that were submitted in late 2010. U.S. regulators did not request new clinical studies, but did ask for an updated safety analysis and additional analyses of the overall survival data in the '181 and '203 studies using more mature data sets. FDA informed Amgen that marketing clearance for the first-line and second-line metastatic colorectal cancer indications are contingent upon approval of the companion diagnostic device being developed in collaboration with **Qiagen** N.V. The device identifies an individual's KRAS gene status. Amgen has been working on addressing the U.S. regulatory agency's requests.

The EC approved during November 2011 a variation to the marketing authorization for Vectibix. The approved variation includes indications for treating patients with wild-type KRAS metastatic colorectal cancer in first-line and second-line in combination with chemotherapy.

Global Vectibix sales totaled $322 million during 2011 and $288 million for 2010. Amgen attributes the Vectibix sales rise of 11.8 percent mainly to worldwide unit growth during the 2011 fourth period and full year. In 2011, Vectibix U.S. sales amounted to $122 million ($115 million during 2010) and international sales came in at $200 million ($173 million for 2010).

The product's sales increased from $156 million for first-half 2011 to $180 million during January-June 2012. U.S. and rest-of-world sales improved in first-half 2012 compared to the 2011 comparable period. Sales in the United States went up $1 million to $62 million, and sales in the rest of the world advanced from $95 million to $118 million.

Nplate is a thrombopoietin receptor agonist marketed in various countries around the globe by Amgen via an exclusive license from Kirin-Amgen. The product gained U.S. approval during August 2008 for treating thrombocytopenia in splenectomized (spleen removed) and non-splenectomized adults with chronic immune thrombocytopenic purpura. The drug acts by increasing and sustaining platelet counts.

During February 2009, Amgen announced that the European Commission had granted marketing authorization for the drug as a treatment of splenectomized adult chronic immune thrombocytopenic purpura patients who are refractory to other treatment. In the European Union, Nplate may be considered as second-line treatment for adult non-splenectomized immune thrombocytopenic purpura patients where surgery is contraindicated.

Nplate global sales totaled $297 million during 2011 and $229 million in the previous year. The product's year-over-year total sales improvement of 30 percent was spurred primarily by worldwide unit growth during fourth-quarter and full-year 2011. During that fourth quarter, Amgen discussed FDA modification of the requirements of the Risk Evaluation and Mitigation Strategy Program. Prescribing physicians, patients and institutions no longer need to enroll in the safety monitoring program to prescribe or receive Nplate.

First-half 2012 sales for Nplate equaled $176 million, with the first-half 2011 amount totaling $140 million. U.S. sales were $104 million in first-half 2012 and $77 million from January to June 2011. Rest-of-world sales amounted to $72 million in the first half of 2012 and $63 million in the one-year-earlier period.

Amgen's most recent new product to reach the marketplace is denosumab, which occurred during 2010 under two different brand names: **Prolia** and **Xgeva**. Though the two medicines contain the same active ingredient, they are approved for different indications, patient populations, doses and frequencies of administration. Amgen has a collaboration arrangement with **GlaxoSmithKline** for the commercialization of denosumab in certain countries. In those countries, marketing applications are submitted by GSK. The denosumab franchise was projected by an EvaluatePharma June 2012 analyst report to be a $3.36 billion sales generator in 2018.

Prolia gained U.S. regulatory clearance on June 1, 2010, for treating postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. On Sept. 19, 2011, Amgen announced FDA approval of two more indications for Prolia: as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, and as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer. Another new indication for Prolia was cleared for marketing by U.S. regulators during September 2012: as a treatment to increase bone mass in men with osteoporosis at high risk for fracture.

Prolia represents the first FDA-approved RANK Ligand inhibitor. The protein RANK Ligand is an essential regulator of osteoclasts, which are the cells that break down bone. The drug is administered as a 60-mg subcutaneous injection by a health-care professional every six months.

Amgen estimates that the large majority of Prolia usage in the United States has been under Medicare Part B. Most potential U.S. Prolia patients additionally have coverage for the drug under Medicare Part D. Future U.S. product sales for Prolia will depend mainly on postmenopausal osteoporosis disease-state awareness, the willingness of primary-care physicians to prescribe the product, and the availability of reimbursement for and patient acceptance of the drug.

On May 25, 2010, the European Commission granted marketing authorization for Prolia as a treatment of osteoporosis in postmenopausal women at increased risk of fractures and for treating bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Since the initial reimbursement authority was obtained in Germany during July 2010, reimbursement authority approval has been granted in most of the European Union.

Prolia global sales amounted to $203 million for 2011 and $33 million in the previous year. Of the 2011 total, U.S. sales accounted for $130 million and international sales registered at $73 million.

During first-half 2012, Prolia sales reached $208 million versus the year-earlier same-period total of $71 million. First-half 2012 U.S. sales amounted to $129 million and rest-of-world sales came in at $79 million.

Xgeva gained FDA marketing clearance on Nov. 18, 2010, for preventing skeletal-related events in patients with bone metastases from solid tumors. Xgeva is the first RANK Ligand inhibitor approved in the United States for this indication. The product gained FDA approval after a six-month priority review.

This is the first novel bone metastases treatment for advanced cancer patients in almost a decade. Xgeva is administered as a once-monthly 120-mg subcutaneous injection. The drug provides a unique option for urologists and oncologists to prevent skeletal-related events in patients with bone metastases from solid tumors.

The fully human monoclonal antibody binds to RANK Ligand, which is essential for the formation, function and survival of osteoclasts. Xgeva prevents RANK Ligand from activating its RANK receptor on the surface of osteoclasts, resulting in decreased bone destruction.

Xgeva has been studied in more than 6,000 patients with cancer. In clinical studies, the product showed a clinically meaningful improvement versus the previous standard of care in preventing bone complications. The drug is additionally being investigated for the potential use to delay the onset of bone metastasis and disease-free survival in the adjuvant treatment of breast cancer.

Results of a pivotal Phase III trial (study '147) for Xgeva were announced by Amgen in May 2011. The study involved 1,432 men with castration-resistant prostate cancer that has not yet spread to bone. The study showed that Xgeva significantly improved median bone metastasis-free survival by 4.2 months versus placebo (primary endpoint) and significantly improved time to first occurrence of bone metastases (secondary endpoint). Overall survival was similar between the Xgeva and placebo arms (secondary endpoint), with adverse events and serious adverse events relatively similar. Hypocalcemia and osteonecrosis of the jaw were reported with increased frequencies in the Xgeva treated patients versus placebo. The annual rate of osteonecrosis of the jaw in the Xgeva arm was similar to previous study results for the drug. Back pain was the most common adverse event reported in the Xgeva arm of the study.

The filing of a supplemental biologics license application to U.S. regulators in June 2011 sought to expand the indication to treat men with castration-resistant prostate cancer to reduce the risk of developing bone metastases. On Feb. 8, 2012, FDA's Oncology Drug Advisory Committee panel voted 12-to-1 that the overall magnitude of benefit shown with Xgeva early treatment to delay bone metastases was insufficient to conclude a positive risk-benefit ratio in the absence of additional measures impacting quality of life or other disease outcomes. The U.S. regulatory agency targeted a PDUFA action date of April 26, 2012.

On that date, Amgen announced that FDA had issued a complete response letter for the supplemental biologics license application. The letter stated that FDA will not approve the Xgeva application in its present form. U.S. regulators determined that the effect on bone metastases-free survival was of insufficient magnitude to outweigh the risks (including osteonecrosis of the jaw) of the drug in the intended population. FDA requested data from an adequate and well-controlled trial(s) showing a favorable risk-benefit profile for Xgeva that is generalizable to the American population. Amgen is working with FDA to determine any next steps.

The European Commission granted marketing authorization for the drug for preventing skeletal-related events such as pathological fracture, radiation to bone, spinal-cord compression or surgery to bone in adults with bone metastases from solid tumors, as announced by Amgen in July 2011. One month later, Xgeva received reimbursement authority in Germany. The European Commission granted the product an extra year of data and market exclusivity in the EU since the indication was considered new for denosumab and based on the important clinical benefit of Xgeva versus existing therapies.

Xgeva global sales totaled $351 million in 2011 after the drug produced $8 million during its 2010 launch year. U.S. sales accounted for $343 million of the 2011 total.

First-half 2012 sales for Xgeva reached $332 million, with $295 million in U.S. sales and $37 million generated in the rest of the world. The 2011 first-half total was $115 million, all accounted for in the U.S. market.

M&A activity

In the first month of 2012, Amgen and fellow biotech company Micromet agreed on a definitive merger deal. Micromet was acquired for $11 per share in cash in a transaction valued at $1.16 billion. Micromet is the surviving

corporation in the merger and became a wholly owned subsidiary of Amgen upon finalization of the transaction during March 2012.

Micromet has concentrated on the discovery, development and commercialization of innovative antibody-based therapies for treating cancer. The company has been advancing a robust pipeline of novel therapeutics based on its proprietary BiTE technology. Micromet's head product candidate is the anti-cancer drug **blinatumomab**. The company has collaborated with leading pharma and biotech companies such as Amgen, Bayer HealthCare Pharmaceuticals, **Boehringer Ingelheim**, **MedImmune**, **Merck Serono**, **Nycomed** and **Sanofi**. Founded in Germany, Micromet's R&D center is located in Munich and headquarters is based in Rockville, Md.

The acquisition of Micromet further builds on Amgen's innovative oncology therapeutics pipeline and capabilities. Micromet's blinatumomab is a bispecific T cell engager (BiTE) antibody in Phase II trials for acute lymphoblastic leukemia. The product candidate is additionally in Phase I studies for treating non-Hodgkin's lymphoma and could have applications in other hematologic malignancies.

"The acquisition of Micromet is an opportunity to acquire an innovative oncology asset with global rights and a validated technology platform with broad potential clinical applications," noted Kevin Sharer, chairman and former CEO of Amgen. "Blinatumomab will serve as an important complement to our oncology pipeline and is representative of our corporate strategy, which is focused on developing and successfully commercializing therapeutics to treat patients with grievous illness."

In addition to blinatumomab, other assets gained through the acquisition include: proprietary BiTE antibody technology that provides an innovative, validated platform for future clinical research; potential milestone and royalty payments from existing licensees of BiTE and other technologies; unencumbered rights to **solitomab**, a BiTE antibody in Phase 1 for patients with advanced solid tumors; and Micromet's Munich site that is operating as an Amgen R&D center of excellence.

BiTE antibodies are designed to direct the body's cytotoxic (cell-destroying) T cells against tumor cells. The antibodies represent a new therapeutic approach to cancer therapy. Typically, antibodies are unable to engage T cells because they lack the appropriate receptors for binding antibodies. BiTE antibodies have been demonstrated to bind T cells to tumor cells, ultimately killing the tumor cells.

The acquisition of **KAI** Pharmaceuticals was completed by Amgen during July 2012. The acquisition was first announced on April 10, 2012. The privately held, clinical-stage biopharma company is located in South San Francisco, Calif. The purchase price was $315 million in cash.

KAI's lead drug compound is **KAI-4169**. The product candidate is administered intravenously while a patient is undergoing dialysis. The novel peptide is an agonist of the calcium sensing receptor, which affects calcium homeostasis by modulating the release of parathyroid hormone.

KAI-4169 is being studied initially for treating secondary hyperparathyroidism in patients with chronic kidney disease who are on dialysis. Secondary hyperparathyroidism is a component of chronic kidney disease mineral and bone disorder. SHPT is a common and serious complication for patients with chronic kidney disease who are on dialysis.

KAI previously reported compelling Phase IIa results for KAI-4169 in the secondary hyperparathyroidism indication. Phase IIa data showed that administration of KAI-4169 lead to sustained reductions in parathyroid hormone, phosphorus, calcium and FGF-23. Those are recognized markers of secondary hyperparathyroidism. The Phase IIa data demonstrated KAI-4169 to be well-tolerated.

Amgen acquired global rights to KAI-4169, excluding Japan. During September 2011, KAI agreed to a partnership through which **Ono** Pharmaceutical Co. will develop and commercialize KAI-4169 in Japan.

In another April 2012 acquisition, Amgen agreed to buy a leading, privately held, Turkish pharma company. Amgen acquired 95.6 percent of **Mustafa Nevzat** Pharmaceuticals at a value of $700 million. The all-cash deal significantly expands Amgen's presence in Turkey and the surrounding region, which represents large, fast-growing priority markets for the biotech leader.

Mustafa Nevzat is the leading supplier of pharmaceuticals to the hospital segment and a major supplier of injectable medicines in Turkey. The company has a successful and fast-growing export business and generated revenue of $200 million during 2011. Mustafa Nevzat has grown on average at double-digit rates in local currency during the past five years.

Amgen's concentration on Turkey and the surrounding area is part of a broad international expansion strategy. Amgen established an affiliate in Turkey during 2010 and markets two products. Amgen intends to develop its robust pipeline of clinical candidates for the benefit of patients in Turkey, as well as other markets around the world.

In the pipeline

Amgen is teaming up with one of the world's largest pharma companies to jointly develop and commercialize the biotech entity's clinical-stage inflammation portfolio. During early April 2012, the deal was announced in which **AstraZeneca** plc will jointly develop and commercialize five monoclonal antibodies from Amgen's clinical inflammation portfolio. The monoclonal antibodies are **AMG 139**, **AMG 157**, **AMG 181**, **AMG 557** and **brodalumab/AMG 827**.

Brodalumab is being investigated for psoriasis (completed Phase II and planned Phase III), psoriatic arthritis (Phase II) and asthma (Phase II). The drug compound binds to and blocks signaling through the IL-17 receptor. The IL-17 pathway has a significant role in inducing and promoting inflammatory disease processes. Amgen says brodalumab is the only investigational treatment in development that blocks the IL-17 receptor, thereby blocking several of the IL-17 ligands at once from sending signals to the body. By stopping IL-17 ligands from binding with the receptor, brodalumab prevents the body from receiving signals that may result in inflammation and other ailments.

AMG 139 is being developed in Phase Ib for treating Crohn's disease. AMG 181 is being investigated in Phase Ia and Phase Ib for treating ulcerative colitis and Crohn's disease.

AMG 557 binds to B7-related protein 1 (B7RP-1). The product candidate is undergoing Phase Ib studies for autoimmune diseases, including systemic lupus erythematosus.

AMG 157 blocks interaction of thymic stromal lymphopoietin with the TSLP receptor. The drug compound is being developed in Phase Ib for the treatment of asthma.

According to the companies, each molecule has novel profiles and offer the potential to deliver significant treatments across multiple indications in inflammatory diseases. The collaboration provides Amgen with more resources to optimally progress its portfolio. The biotech company will benefit from the strong respiratory, inflammation and asthma development expertise of MedImmune, AstraZeneca's biologics arm. The collaboration will capitalize on AstraZeneca's worldwide commercial reach in respiratory and gastrointestinal diseases. The deal excludes certain territories previously partnered by Amgen for brodalumab with **Kyowa Hakko Kirin** Co. and AMG 557 with Takeda.

AstraZeneca made a one-time $50 million up-front payment and the companies are sharing costs and profits. Based on current plans, 65 percent of costs for the 2012-2014 period will be covered by AstraZeneca. Thereafter, the companies will split costs 50/50. Amgen will book sales worldwide and will retain a low single-digit royalty for brodalumab as well as a mid single-digit royalty for the rest of the portfolio, after which the companies will equally share profits.

AstraZeneca is leading the development and commercial strategy of AMG 139, AMG 157 and AMG 181. Amgen heads the development and commercial strategy of brodalumab and AMG 557. Each development and commercialization lead is under the oversight of joint governing bodies. Brodalumab's commercial promotion will be split. Amgen will promote in dermatology indications in the United States and Canada, and in rheumatology indications in the United States, Canada and Europe. AstraZeneca will promote in respiratory and, initially, in dermatology indications of brodalumab throughout all territories outside the United States, Canada and those markets where Amgen has existing partnerships. Allocation of promotional rights for other territories, indications and molecules were to be determined at a later date between the companies.

The Phase III clinical-trial program for Amgen and **UCB**'s sclerostin antibody **AMG 785/CDP7851** for postmenopausal osteoporosis is under way as of April 2012. The two companies are collaborating on the development of AMG 785/CDP7851 for treating bone-related conditions, including postmenopausal osteoporosis and fracture healing.

This program includes a multicenter, international, randomized, double-blind, placebo-controlled, parallel-group two-year trial in 5,000-plus postmenopausal women with osteoporosis. The primary endpoint will evaluate the incidence of new vertebral fractures at one year. The first results from the Phase III program are expected by year-end 2015.

The humanized monoclonal antibody binds to and inhibits sclerostin, which is a protein secreted by bone cells that inhibits bone formation. By binding to and blocking sclerostin, AMG 785/CDP7851 is designed to raise the amount of skeleton bone. With 75-plus million people around the globe suffering from osteoporosis, there is a major patient need for therapeutics that help build bone.

As mentioned earlier, Amgen discovered and is developing a potential blockbuster, AMG 145. A Phase II program for the drug is enrolling 1,900 patients across six studies to evaluate the effects of the product candidate across multiple patient populations who may benefit from additional cholesterol-lowering treatment options. Phase II studies are evaluating AMG 145 in combination with statins in patients with or at risk for cardiovascular disease, in patients who cannot tolerate statins, as a stand-alone treatment in patients with low cardiovascular risk, and in patients whose cholesterol results from the genetic disorder heterozygous familial hypercholesterolemia.

Positive results from a Phase Ib study of AMG 145 in patients with high cholesterol who were taking statins were announced in March 2012. The study showed that multiple doses of the drug significantly reduced serum low-density lipoprotein cholesterol, also known as "bad" cholesterol, by up to 81 percent compared to placebo (maximum reduction) in subjects on low-to-moderate doses of statins ($p<0.001$). The cholesterol-lowering effects of AMG 145 were similar among patients on high doses of statins (80-mg atorvastatin and 40-mg rosuvastatin) as well as patients on low-to-moderate doses of statins. Atorvastatin and rosuvastatin are marketed as **Lipitor** and **Crestor** respectively, the world's best-selling cholesterol therapies. Additionally, no deaths or serious adverse events were reported in the study.

High LDL cholesterol is a major public health issue in most countries as LDL-C contributes to the risk of developing cardiovascular disease, the No. 1 cause of death among men and women. The majority of patients who are treated for high cholesterol take drugs called statins. Although statins are effective, many patients still have trouble reaching their cholesterol goals and others cannot tolerate statin therapy. AMG 145 inhibits PCSK9, a protein that reduces the liver's ability to remove LDL-C from the blood.

Phase III planning is under way for the gastric cancer drug **rilotumumab/AMG 102**. The investigational fully human monoclonal antibody is designed to inhibit the hepatocyte growth factor/scatter factor: MET pathway. According to Amgen, Phase II data announced in May 2012 demonstrated that the addition of rilotumumab to chemotherapy improved median overall survival in subjects with gastric tumors with high expression of MET. Based on these results, the company will conduct a Phase III study to confirm the efficacy of rilotumumab in advanced gastric and gastroesophageal cancer with high MET expression.

"These data are the first to demonstrate a potential biomarker for treatment with rilotumumab in gastric cancer, the second leading cause of cancer deaths worldwide," commented Michael Severino, M.D., senior VP of global development and corporate chief medical officer at Amgen. "Personalized medicine has the potential to transform cancer care, and by leveraging our understanding of biology and the mechanism of disease, we hope to identify safe and effective new treatments for patients who aren't well-served by current therapies."

Amgen and **Dako** agreed in February 2012 on a collaboration to develop and evaluate the use of a companion diagnostic test in the development of rilotumumab. This deal followed a January 2012 announcement by Dako regarding a collaboration agreement with Amgen to introduce a new business model that supports the concurrent development of drug and diagnostics for a rare but deadly cancer. Denmark-based Dako is a worldwide leader in tissue-based cancer diagnostics.

Amgen announced in August 2012 the company's decision to halt the **ganitumab/AMG 479** Phase III GAMMA (Gemcitabine and AMG 479 in Metastatic Adenocarcinoma of the Pancreas) trial. The investigational fully human monoclonal antibody ganitumab targets type 1 insulin-like growth factor receptor. Amgen also has discontinued a separate Phase II study for ganitumab in locally advanced pancreatic cancer.

GAMMA is a randomized, multicenter, double-blind Phase III study to determine if ganitumab plus gemcitabine improves overall survival – versus placebo with gemcitabine – in the first-line treatment of patients with metastatic adenocarcinoma of the pancreas. Amgen's decision followed the recommendation of an independent data monitoring committee overseeing the study. Based on the review of a pre-planned interim analysis, the data monitoring committee concluded that the addition of ganitumab to gemcitabine is unlikely to show a statistically significant improvement in the primary endpoint of overall survival versus gemcitabine alone. There were no safety concerns raised in the committee's review of the clinical study. Gemcitabine is the active ingredient in **Eli Lilly** and Co.'s former blockbuster **Gemzar** for various cancers. ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

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BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Crestor	$6,622	$5,691
Seroquel	$5,828	$5,302
Nexium	$4,429	$4,969
Symbicort	$3,148	$2,746
Atacand	$1,450	$1,483
Zoladex	$1,179	$1,115
Toprol XL/ Seloken	$986	$1,210
Prilosec/ Losec	$946	$986
Pulmicort	$892	$872
Arimidex	$756	$1,512

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Revenue	$33,591	$33,269
Net income	$9,983	$8,081
EPS	$7.33	$5.19
R&D	$5,523	$5,318

	1H 2012	1H2011
Revenue	$14,009	$16,722
Net income	$2,999	$5,340
EPS	$2.55	$3.60
R&D	$2,719	$2,360

All figures are in millions of dollars except EPS.

Shaken up

The abrupt retirement of David Brennan as chief executive this year highlights a tough time for AstraZeneca.

by Christiane Truelove (chris.truelove@ubm.com)

AstraZeneca leaders learned an important lesson in 2012 – if you're not performing to the shareholders' expectations, your company's drug portfolio is being swamped by patent expirations, and the pipeline of anticipated new drugs is not coming through, prepare to get pushed out. In April, CEO David Brennan quit after more than six years in the post. Though he claimed to have volunteered to retire to spend more time with his family and to take a new direction in healthcare leadership, rumors suggested that company shareholders called for a shakeup of the top management levels.

Just a week before stepping down, Mr. Brennan had dismissed suggestions that investors were unhappy with AstraZeneca's financial performance and were seeking a change. At the annual meeting of the Pharmaceutical Research and Manufacturers of America, Mr. Brennan had stated to Bloomberg News, "I'm plugged in, my role hasn't changed a bit ... I read and hear and see lots of things, but we're here trying to change policy, make good decisions, and execute our strategy."

In August, Pascal Soriot, the chief operating officer and head of Pharmaceuticals for **Roche** and the CEO of **Genentech**, was appointed as the new CEO; he was expected to take on his new responsibilities and join the AstraZeneca board by Oct. 1. Simon Lowth, who was acting as interim CEO, is expected to resume his responsibilities as chief financial officer.

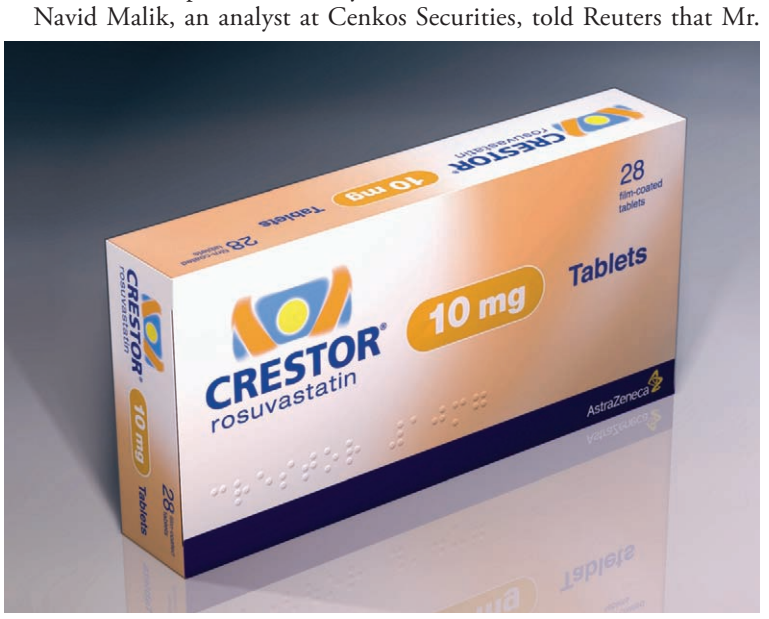
"I am excited and honored to have been asked to lead AstraZeneca," Mr. Soriot stated. "Throughout my career I have had enormous respect for the people of AstraZeneca and what they have achieved. No-one is blind to the challenges that confront the pharmaceutical sector and this company, but the underlying strengths of AstraZeneca in delivering on its strategy are clear. AstraZeneca will continue to make a positive difference to patients over the longer term and I'm looking forward to playing my part in shaping that future."

Leif Johansson, chairman of AstraZeneca, says Mr. Soriot's leadership qualities, strategic thinking, and relevant experience make him the right leader for the company. "I am confident that Pascal's approach and his track record of delivering results in innovation-driven businesses will be valued by shareholders and employees alike," Mr. Johansson says.

Mr. Soriot has his work cut out for him, industry observers agree. In February, the company announced that it was eliminating 7,000 jobs, with 3,750 jobs being slashed from sales and marketing and assorted administrative operations, another 2,200 positions being eliminated from R&D, and 1,300 coming from operations, as more supply chain outsourcing takes place.

The cuts, which are designed to save $1.6 billion annually by the end of 2014, underscore the fallout expected from patent expirations on some of AstraZeneca's biggest sellers, notably the cholesterol drug **Crestor**, the gastrointestinal drug **Nexium**, and the antipsychotic **Seroquel**, for which exclusivity has already ended. Nexium loses patent protection in 2014 and Crestor's patent runs out in 2016. The company has warned that profits will fall as much as 18 percent in 2012, but will buy back $4.5 billion in stock to appease investors. The layoffs are in addition to 21,600 positions already eliminated since 2007.

Navid Malik, an analyst at Cenkos Securities, told Reuters that Mr. Soriot's arrival was good news for AstraZeneca and could signal a step change towards greater involvement in fast-growing biotech medicine. "He will be looking to make significant changes, including reviewing the pipeline and doing more deals. He'll have to work fast because there's an uphill struggle now to grow sales in the face of major patent losses," Mr. Malik says.



Crestor sales were $6.62 billion in 2011, 16 percent more than in 2010, but the product will lose exclusivity in 2016.

"No-one is blind to the challenges that confront the pharmaceutical sector and this company, but the underlying strengths of AstraZeneca in delivering on its strategy are clear. AstraZeneca will continue to make a positive difference to patients over the longer term and I'm looking forward to playing my part in shaping that future," says Pascal Soriot, CEO.

In October, AstraZeneca announced that it is suspending the $4.5 billion share repurchase program with immediate effect. During 2012 the company has completed net share repurchases of $2.3 billion.

The company continued to maintain that its core earnings per share target range for 2012 is $6.00 to $6.30.

"As I assume my new responsibilities at AstraZeneca, I believe this is a prudent step that maintains flexibility while the board and I complete the company's ongoing annual strategy update." Mr. Soriot says.

According to news reports, the suspension will give the company more flexibility to do some large acquisitions. "It's a bit of a surprise that they changed course mid- year, but a new chief executive likes to take control and see what the options are," Brian Bourdot, an analyst at Barclays Plc'.s investment-banking unit in London, told Bloomberg News. "It would increase their ability to do a deal, that's something we have to bear in mind."

Mr. Brennan's departure raised certain financial questions about his compensation. An unconfirmed report in the *The Sunday Times* in April stated that he would receive a $65 million exit package that includes a pension of $1 million a year. The value of the pension was later estimated to be $23 million, with an additional $6.9 million in pay and key share awards. Responding to his critics, however, Mr. Brennan decided not to take a bonus for his final months of running AstraZeneca (his tenure ended June 1), forgoing as much as $5.4 million.

Company and product performance

In 2011, AstraZeneca's full-year revenue of $33.59 billion was down 2 percent at constant exchange rates but was up 1 percent on an actual basis as the result of the favorable impact of exchange rate movements. Sales were affected by government pricing interventions and generic competition, which combined to reduce revenue by some $3 billion. Revenue in the United States was down 2 percent to $13.43 billion. Revenue in Western Europe was down 11 percent to $8.5 billion, with mid-single digit declines in both volume and price. In Established Rest of World markets, revenue was up 4 percent to $5.9 billion. Revenue in Emerging Markets was up 10 percent for the full year, to $5.76 billion.

Core operating profit was $13.17 billion for the full year, down 4 percent. Executives say the decline was larger than the decline in revenue largely due to the higher intangible impairments charged to core R&D expense in the fourth quarter of 2011. The increase in R&D expense, together with lower core other income, combined to more than offset the benefits from lower core SG&A expense and a higher gross margin. Reported operating profit was up 10 percent to $12.7 billion, due to the disposal of Astra Tech assets in third-quarter 2011. Reported net profit was $9.98 billion, compared with $7.54 billion in 2010.

AstraZeneca's core earnings per share were up 7 percent to $7.28, which reflects the net adjustments to tax provisions previously disclosed and the benefit from share repurchases. Reported earnings per share were up 29 percent to $7.33, which includes the $1.08 non-taxable gain on the sale of Astra Tech.

Executives say revenue in 2012 will continue to be adversely affected by government interventions on pricing, and ongoing generic competition, including the anticipated loss of market exclusivity for Seroquel IR and Atacand in global markets, as well as for Crestor in Canada. AstraZeneca anticipates a constant currency revenue decline for 2012 in the low double-digit range.

Core pre-R&D operating margin is expected to be below 2011, but remain in the upper half of the company's planning range of 48 to 54 percent of revenue.

In the first half of 2012, revenue was $14 billion, down 15 percent at constant exchange rate and 16 percent on an actual basis from the same period last year. Executives say this is a result of the negative impact of exchange rate movements. Loss of exclusivity on several key brands accounted for 11 percentage points of the revenue decline, which included a $187 million returns reserve against U.S. trade inventories of Seroquel IR.

U.S. revenue was down 20 percent at a constant exchange rate and actual numbers to $5.26 billion; revenue in the Rest of World was $3.4 billion, down 20 percent at a constant exchange rate and 23 percent in actual numbers.

Reported operating profit in the first half was down 25 percent to $4.03 billion; reported earnings per share were down 16 percent to $3.34. The larger declines compared with the respective core financial measures are largely the result of higher restructuring costs in the first half 2012 of $907 million, compared with $281 million during the first half last year.

AstraZeneca's top selling product in 2011 was the cholesterol drug Crestor. The drug achieved sales of $6.62 billion, up 13 percent from 2010 on a constant exchange rate and 16 percent in actual numbers. Crestor total prescriptions increased by 4 percent while the overall statin market was flat. Although generic Lipitor, atorvastatin, became available in the United States at the end of November 2011, executives said average total prescription volumes for Crestor in the weeks following the launch of generic Lipitor were broadly in line with volumes before the launch.

In the first half of 2012, Crestor sales were $3.09 billion, down 2 percent at a constant exchange rate. In the United States, Crestor first-half sales were down 1 percent to $1.47 billion. Sales in the rest of the world were down 3 percent to $1.62 billion.

The second best-selling product was the CNS drug Seroquel, which had sales of $5.83 billion in 2011, 8 percent more than in 2010. The Seroquel franchise includes Seroquel IR and Seroquel XR. U.S. sales of Seroquel for the full year were $4.12 billion, 10 percent ahead of last year. U.S. sales for Seroquel XR were up 22 percent to $779 million. For the full year, Seroquel sales in the rest of the world increased by 4 percent to $1.71 billion. Sales of Seroquel XR were up 32 percent to $711 million.

For first-half 2012, AstraZeneca recorded Seroquel sales of $1.79 billion, 37 percent less than in first-half 2011. Seroquel IR sales plummeted 52 percent to $1.03 billion, but Seroquel XR sales rose 6 percent to $754 million. AstraZeneca lost exclusivity for Seroquel IR at the end of March. U.S. sales for Seroquel IR in the first half were down 59 percent to $668 million, but Seroquel XR sales rose 4 percent to $396 million. Sales in the rest of the world for Seroquel IR in the first half were down 28 percent to $363 million, reflecting the loss of exclusivity in many markets. Seroquel XR sales in the rest of the world for the first half were $358 million, an increase of 9 percent over last year.

AstraZeneca's third best-selling product in 2011 was Nexium, with sales of $4.43 billion, 12 percent less than in 2010 on a constant exchange rate and 11 percent in actual numbers.

In the United States, Nexium sales for the full year were down 11 percent to $2.4 billion. Sales in Emerging Markets increased by 24 percent. Nexium sales in other markets were down 13 percent for the full year to $2.03 billion. In the first half of 2012, sales were $1.9 billion, 15 percent less at a constant exchange rate than in the same period last year. Nexium sales in the United States in the first half were down 10 percent to $1.09 billion compared with first-half 2011. Nexium sales in other markets were down 21 percent in the first half to $813 million.

AstraZeneca's fourth highest selling product in 2011 was the respiratory drug **Symbicort**. The drug had sales of $3.15 billion, up 11 percent at a constant exchange rate and 14.6 percent in actual numbers. U.S. sales of Symbicort for the full year were $846 million, an increase of 17 percent. Symbicort sales in the rest of the world for the full year were up 9 percent to $2.3 billion.

In the first half of 2012, Symbicort sales were $1.52 billion, 1 percent more than in the same period last year. Symbicort sales in the United States in the first half of this year were up 16 percent to $466 million compared with the first half of last year, but sales in the rest of the world were $1.05 billion, 5 percent less than in first-half 2011.

The fifth best-selling product in 2011 was the cardiovascular drug **Atacand**, which generated $1.45 billion, 6 percent less than 2010 at a constant exchange rate. U.S. sales of Atacand were down 16 percent for the full year. Atacand sales in the rest of the world were down 4 percent for the full year. In the first half of 2012, the drug

had sales of $586 million, 18 percent less than in the same period of 2011. U.S. sales in the first half of 2012 were down 20 percent from first-half 2011 to $76 million, and sales in the rest of the world were $510 million, down 17 percent.

The sixth best-selling drug in 2011 was the cancer drug **Zoladex**, with sales of $1.18 billion, 3 percent more than in 2010 at a constant exchange rate. In first-half 2012, Zoladex sales were $548 million, 3 percent less than in first-half 2011.

Sales of Atacand in 2011 were $1.45 billion.

AstraZeneca's seventh best-selling product in 2011 was the cardiovascular drug **Toprol-XL/Seloken**, which had sales of $986 million, 20 percent less than 2010 at a constant exchange rate. U.S. sales of the Toprol-XL product range, which includes sales of the authorized generic, decreased by 25 percent in the fourth quarter to $89 million on declining prescription volume and lower prices. An additional generic product received regulatory approval in December 2011. U.S. franchise sales for the full year were down 41 percent to $404 million. Sales of Seloken in other markets were up 8 percent for the full year to $582 million, on a 15 percent increase in emerging markets.

The eighth best-selling drug in 2011 was the gastrointestinal drug **Prilosec/Losec**, with sales of $946 million, down 11 percent at a constant exchange rate. Prilosec sales in the US were down 21 percent for the full year to $38 million, and sales of Losec in the rest of the world were down 10 percent for the full year to $908 million. Prilosec/Losec sales in the first half of 2012 were $365 million, 22 percent less than the same period in 2011.

The ninth best-selling product for the company in 2011 was the respiratory drug **Pulmicort**. The drug generated sales of $892 million for the year, about the same as in 2010 at a constant exchange rate. U.S. sales of Pulmicort in fourth-quarter 2011 were down 10 percent to $61 million, where the brand share for budesonide inhaled suspension products has fallen to 11.5 percent. U.S. sales of Pulmicort for the full year were down 9 percent to $279 million. But sales of Pulmicort in the rest of the world for the full year were up 4 percent to $613 million.

In the first half of 2012, Pulmicort sales were $433 million, down 9 percent from first-half 2011 at a constant exchange rate. U.S. sales in the first half were down 30 percent to $116 million. Sales in the rest of the world were $317 million, 2 percent higher than the first half of 2011.

AstraZeneca's tenth best-selling drug was the cancer drug **Arimidex**. Sales of the drug, which has lost patent protection, declined 53 percent on a constant exchange rate basis from 2010, to $756 million. In the United States, sales of Arimidex were down 91 percent to $42 million. Generics now account for 97 percent of anastrozole prescriptions in the United States. Arimidex sales in other markets were down 34 percent to $714 million. Market exclusivity in many of these markets expired in February 2011. First-half 2012 sales of Arimidex were $291 million, 29 percent less than in first-half 2011.

Sales of the diabetes drug **Onglyza**, a collaboration with Bristol-Myers Squibb, totaled $211 million for the year, compared with $69 million in 2010. Alliance revenue in the United States was $53 million in the fourth quarter and $156 million for the full year. Prescriptions for DPP4 products increased by more than 25 percent in the United States in 2011. Over the course of the year, Onglyza's share of DPP4 prescriptions increased by 1.8 percentage points, and **Kombiglyze XR** added a further 4.7 percentage points to franchise share during its first year on the market. Combined franchise share reached 16.5 percent in December 2011. Worldwide alliance revenue in the first half was $151 million.

Onglyza's share of total prescriptions for DPP4 products in the United States was 11.5 percent in June 2012. Kombiglyze XR added a further 5.4 percent total prescription share to the franchise in the United States in June.

Sales of another new product, the blood thinner **Brilinta**, have been slow. In 2011, the drug generated $21 million. Executives say the sales reflect the fact that, based on the attainment of reimbursement, formulary acceptance, and protocol adoption achieved so far, the product is available to only about 12 percent of incident acute coronary syndrome patients.

"Where formulary and protocol adoption has been achieved, the early results are encouraging," executives say. "For example, the company's latest market research in Germany indicates that, in target hospitals where Brilique is on protocol, treatment with Brilique is being initiated in 31 percent of new ACS patients, second only to clopidogrel."

In the first half of 2012, sales were $27 million. Pricing negotiations have now been successfully concluded in Germany and also in France, supporting a launch in July 2012. In Germany, in the 85 percent of target hospitals where Brilique is on protocol, the drug continues to be the leading oral antiplatelet for incident ACS patients, ahead of prasugrel and clopidogrel. Brilique is now the No. 2 product in retail dynamic market share, accounting for 8.5 percent of oral antiplatelet therapy.

Sales in the United States in the second quarter were $3 million, as dispensed demand has begun to stimulate reorders now that launch stocks have been largely worked down in the trade channels. The company says it continues to make steady progress in terms of formulary access, protocol adoption, and product trial rates by interventional cardiologists.

"On balance, I think it is fair to say that – as the third brand into the market, and having to contend with generic clopidogrel – we are finding that penetrating the U.S. hospital market has been a real challenge," says Tony Zook, executive VP, commercial operations. "However, we remain confident that we can establish Brilinta's value in the world's largest market."

Executives say the company is making good progress in implementing the third phase of restructuring announced in February 2012. Restructuring charges of $205 million were taken in the second quarter, bringing the year to date total to $907 million.

The company anticipates that most of the estimated $2.1 billion programe cost will be taken in 2012, and is on track to deliver the $1.6 billion in annual benefits by the end of 2014.

In September, the company priced a $2 billion bond issue. The proceeds of the issue will be used for debt refinancing and general corporate purposes. The transaction consisted of two tranches: $1 billion of 7-year fixed rate notes with a coupon of 1.95 percent and $1 billion of 30-year fixed rate notes with a coupon of 4 percent.

Reforming R&D and the pipeline

AstraZeneca has struggled with its pipeline. In December 2011, the company announced that the second of four Phase III efficacy and tolerability studies of **TC-5214** as an adjunct therapy to an antidepressant in patients with major depressive disorder who do not respond adequately to initial antidepressant treatment, did not meet its primary endpoint. These results followed the recent announcement of top-line results of the RENAISSANCE flexible dose trial study 3, which also did not meet its primary endpoint. AstraZeneca stated that it would continue with the development of the two remaining fixed dose Phase III RENAISSANCE efficacy and tolerability studies and one long-term safety study.

Also in December 2011, the company announced that the investigational cancer drug **olaparib** would not continue into Phase III development for the maintenance treatment of serious ovarian cancer. The decision to discontinue olaparib's development in serous ovarian cancer was made following a review of an interim analysis of a Phase II study (study 19) which indicated that the previously reported progression free survival benefit is unlikely to translate into an overall survival benefit, the definitive measure of patient benefit in ovarian cancer. In addition, attempts to identify a suitable tablet dose for use in Phase III studies were not successful.

Blogger Derek Lowe of In the Pipeline, in taking note of these pipeline failures, stated "The problem is, these are two fields (cancer and depression) that have very high failure rates no matter who's doing the inlicensing. And while it's true that AZ seems to have had a lot of bad luck, some of that might just be the normal course of events if you're targeting these conditions. Having it happen while your other patents are expiring is bad, of course, but being in a position to have to depend on these therapeutic areas is a tough place to be to start with. (Not that there are a lot of safe places to work, true, but these are especially tricky)."

Symbicort's 2011 sales grew about 15 percent to $3.15 billion.

AstraZeneca spent $5.52 billion on R&D in 2011, compared with $5.32 billion in 2010. To get its R&D organization back on track, the company announced a new program in February that executives said would "create a simpler and more innovative R&D organization with a lower and more flexible cost base." In the first half of 2012, the company spent $2.72 billion on R&D, 27 percent more than in the first half of 2011.

One of the areas bearing the cuts is the neuroscience therapy area. "While the patient need for better medicines in neuroscience is huge and the science is promising, advances in treatments have proved elusive for the pharmaceutical industry in recent years, despite significant investment," executives say. "AstraZeneca believes that it will have the best chance of success in the future by combining the company's internal expertise with innovative external science."

As a result, AstraZeneca created a "virtual" neuroscience Innovative Medicines unit made up of a small team of 40 to 50 AstraZeneca scientists conducting discovery and development externally, through a network of partners in academia and industry globally. The team is based in major neuroscience hubs – Boston in the United States and Cambridge in the United Kingdom – and works closely with innovative partners such as the Karolinska Institute in Stockholm.

"We've made an active choice to stay in neuroscience though we will work very differently to share cost, risk, and reward with partners in this especially challenging but important field of medical research,"

Seroquel sales rose 10 percent to $5.83 billion in 2011, but sales in the first half of 2012 have steeply declined after the product's patent expired in the United States in March..

says Martin Mackay, president of research and development. "The creation of a virtual neuroscience iMed will make us more agile scientifically and financially – we will be able to collaborate flexibly with the best scientific expertise, wherever it exists in the world."

The formation of the new unit ended R&D activity and reduced numbers at two neuroscience-focused sites: Södertälje in Sweden and Montreal in Canada. As the location of the company's largest manufacturing site, and the base of the commercial business covering the Scandinavian markets, Södertälje remains open, but the Montreal facility will close. The restructuring is expected to affect 2,200 positions globally.

To also beef up the pipeline, AstraZeneca agreed in April to acquire Ardea Biosciences for $1.26 billion. The acquisition was completed in June., making the company a wholly owned subsidiary of AstraZeneca.

The Ardea acquisition brought **lesinurad**, which is in Phase III development as a potential treatment for the management of hyperuricemia in gout patients. "This attractive Phase III program is an excellent opportunity to leverage AstraZeneca's global specialty and primary care sales and marketing capabilities," Mr. Brennan said in a statement. "The Ardea team has done a great job developing lesinurad along with a promising next-generation gout program. These compounds have real potential to benefit patients."

AstraZeneca anticipates filing lesinurad for approval in the United States, the European Union, and emerging markets in the first half of 2014, and in Japan in the first half of 2016.

Ardea also has a cancer drug, **BAY 86-9766**, which is being jointly developed by **Bayer** in Phase II trials for primary liver cancer in conjunction with **Nexavar**, and in Phase I trials with gemcitabine for advanced pancreatic cancer. Another gout drug, **RDEA3170**, is in Phase I trials.

In another deal in June, AstraZeneca and Bristol-Myers Squibb announced an expansion of their diabetes alliance through Bristol-Myers Squibb's acquisition of Amylin Pharmaceuticals. As part of their collaboration, AstraZeneca agreed to make a payment to Amylin, as a wholly owned subsidiary of Bristol-Myers Squibb, of $3.4 billion. Profits and losses arising from the collaboration will be shared equally. In addition, AstraZeneca has the option, exercisable at its sole discretion, to establish equal governance rights over key strategic and financial decisions regarding the collaboration, upon the payment to Bristol-Myers Squibb of an additional $135 million.

Amylin's portfolio includes a GLP-1 franchise, including two treatments for type 2 diabetes, **Byetta** injection and **Bydureon**, and **Symlin**. The company also has a life-cycle management pipeline, including delivery devices and formulation improvements (including a once-monthly formulation of exenatide) under development. The pipeline also includes **metreleptin**, a leptin analogue under review by FDA for the treatment of diabetes and/or hypertriglyceridemia in patients with rare forms of inherited or acquired lipodystrophy.

In the first half of 2012, AstraZeneca claimed that its pipeline includes 90 projects, with 83 projects in the clinical phase of development and seven either approved or launched. There are nine new molecular entity projects in late stage development, either in Phase III or under regulatory review. In the first half of 2012, across the clinical portfolio, 22 projects had successfully progressed to their next phase (including seven projects entering first human testing); 10 projects have been withdrawn.

In June, AstraZeneca announced that the Committee for Medicinal Products for Human Use had adopted a positive opinion recommending the approval of **Zinforo**, an intravenous cephalosporin antibiotic for the treatment of adult patients with complicated skin and soft tissue infections or community-acquired pneumonia. Ceftaroline fosamil is the first monotherapy antibiotic to combine the established tolerability of the cephalosporin class, with effective coverage of a range of bacteria responsible for serious skin infections and pneumonia, including difficult-to-treat strains such as methicillin-resistant *Staphylococcus aureus* in complicated skin and soft tissue infections and *Streptococcus pneumoniae* in community-acquired pneumonia. The European Commission approved Zinforo in August.

"We are delighted that Zinforo has received regulatory approval across Europe and believe it will make a valuable contribution to addressing the significant unmet need for new antibiotics," Dr. Mackay says. "This is a key step in making Zinforo more widely available to patients across the globe and we will work with the appropriate health authorities, formulary and protocol reviews, and clinicians to bring this new antibiotic to patients as soon as possible."

In 2009, Forest Laboratories granted AstraZeneca exclusive worldwide commercial rights and co-exclusive development rights for ceftaroline fosamil, excluding the Unites States, Canada, and Japan. Forest launched ceftaroline fosamil with similar indications under **Teflaro** in the United States in March 2011. AstraZeneca plans further submissions in countries where it has rights in 2012.

Other products in Phase III development include **naloxegol**, an oral peripherally acting opioid antagonist for treating opioid-induced constipation; and **fostamatinib**, a spleen tyrosine kinase inhibitor for the treatment of rheumatoid arthritis. Filings for both drugs are expected in the second half of 2013 in the United States and the European Union.

Products in Phase II development include **AZD3241** for Parkinson's disease; **AZD3480** and **AZD5213** for Alzheimer's disease; **AZD4017** for glaucoma; **AZD6765** for major depressive disorder; **AZD9733** for severe sepsis; **CXL** for MRSA; and **tralokinumab** for ulcerative colitis. ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

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Bristol-Myers Squibb

BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Plavix	$7,087	$6,666
Abilify	$2,758	$2,565
Reyataz	$1,569	$1,479
Sustiva	$1,485	$1,368
Baraclude	$1,196	$931
Avapro/ Avalide	$952	$1,176
Orencia	$917	$733
Sprycel	$803	$576
Erbitux	$691	$662

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Sales	$21,244	$19,484
Net income	$5,260	$4,513
EPS	$2.16	$1.79
R&D	$3,839	$3,566

	1H12	1H11
Sales	$9,694	$10,445
Net income	$2,290	$2,674
EPS	$1.02	$1.10
R&D	$1,871	$1,858

All figures are in millions of dollars, except EPS.

Après Plavix le déluge

The leaders of Bristol-Myers Squibb are hoping that a group of fast-growing products and an aggressive strategy of acquisition and partnership can keep the company afloat after the loss of its most successful brand.

By Joshua Slatko joshua.slatko@ubm.com

"Without question, this is a very good moment in the life of Bristol-Myers Squibb," says Bristol-Myers Squibb CEO Lamberto Andreotti. "We see it in the numbers. We see it in the products. We see it in the engagement of our employees. We see it in the lives of the patients we serve. And I have every reason to believe that we can continue to see it - this year and in years to come."

After years of planning and preparation, the day of reckoning finally arrived for Bristol-Myers Squibb this past May when Plavix, responsible for a third of the company's revenue, lost its patent protection in the United States. It's too early to tell what a future without Plavix might bring for the company, but Bristol-Myers Squibb's decisionmakers have long tied their hopes to a strategy they call the String of Pearls – enriching the company's pipeline with a heavy dose of strategic alliances, partnerships, and acquisitions. The String of Pearls continued to grow both before and after Plavix's expiration – highlighted by the multibillion-dollar acquisitions of Inhibitex and Amylin – and has even developed an offshoot, Project Oyster, through which Bristol-Myers Squibb is seeding companies in key markets with promising investigational medicines from its early pipeline. On top of that, several of of the company's younger marketed products, including brands like Baraclude, Orencia, Sprycel, Onglyza, and Yervoy, are showing signs of great promise in the marketplace. Not every part of the strategy has worked out so well of late; Bristol-Myers Squibb's pipeline has endured a trying few months, with regulatory delays for two of its most promising late-stage products and bad study news for another. But the company's CEO, Lamberto Andreotti, remains confident in the path Bristol-Myers Squibb is following.

"Without question, this is a very good moment in the life of Bristol-Myers Squibb," Mr. Andreotti says. "We see it in the numbers. We see it in the products. We see it in the engagement of our employees. We see it in the lives of the patients we serve. And I have every reason to believe that we can continue to see it – this year and in years to come."

Bristol-Myers Squibb's sales were $21.24 billion in 2011, a 9 percent improvement over the previous year, which company leaders credited to higher volume, higher average net selling prices, favorable foreign exchange, and the continued growth of the company's younger key products. The company's bottom line was up by an even larger margin, rising 16.6 percent to $5.26 billion. Earnings per share for the year were $2.16, up 37 cents over the 2010.

The company's financial performance has dropped off in the first half of the new year with the Plavix expiration. Sales for the first six months of 2012 totaled $9.69 billion, a 7.2 percent decline, while earnings were down 14.4 percent to $2.29 billion and EPS dropped eight cents to $1.02. Company leaders are projecting full-year EPS at between $1.78 and $1.88.

Acquisitions and partnerships

In July 2011, Bristol-Myers Squibb signed an agreement to acquire privately held Amira Pharmaceuticals, a small-molecule pharmaceutical company focused on the discovery and early development of new drugs to treat inflammatory and fibrotic diseases. Under the terms of the agreement, Bristol-Myers Squibb acquired all of Amira Pharmaceuticals' issued and outstanding shares of capital stock and stock equivalents in an all-cash transaction for a purchase price of $325 million upfront and potential additional milestone payments totaling $150 million. The company secured Amira Pharmaceuticals' fibrosis program, including the lead asset **AM152**, an orally available lysophosphatidic acid 1 (LPA1) receptor antagonist which has completed Phase I clinical studies and is entering Phase IIa proof-of-confidence studies for the treatment of idiopathic pulmonary fibrosis and systemic sclerosis, or scleroderma. Bristol-Myers Squibb has also obtained Amira Pharmaceuticals' preclinical autotaxin program, which may be useful in the treatment of neuropathic pain and cancer metastases. The transaction was duly completed in September 2011.

"As part of the continued execution of our focused BioPharma strategy, Bristol-Myers Squibb has identified fibrotic diseases as an area of high unmet medical need that complements our research efforts in several of our therapeutic areas," says Elliott Sigal, executive VP, chief scientific officer, and president, Research and Development, Bristol-Myers Squibb. "The acquisition of Amira Pharmaceuticals represents the latest example of our String of Pearls strategy, a highly targeted set of transactions designed to enrich our innovative pipeline with potential medicines to help patients in need."

Also in July, Bristol-Myers Squibb and **Innate** Pharma S.A. announced a global agreement for the development and commercialization of **IPH2102**, a novel antibody in Phase I development for the treatment of cancer. Under the terms of the agreement, Innate Pharma will grant to Bristol-Myers Squibb exclusive worldwide rights to develop, manufacture, and commercialize IPH2102 and related compounds blocking KIR receptors. The agreement covers all potential indications for IPH2102. Innate Pharma will continue to develop IPH2102 in acute myeloid leukemia through to the end of Phase II, and will also provide pre-clinical support for the development of the compound. Bristol-Myers Squibb agreed to fund the development of IPH2102, make an upfront payment of $35 million, and additional payments of up to $430 million, depending on the achievement of pre-specified milestones during the development and commercialization period, as well as pre-specified tiered double-digit royalty payments on worldwide net sales.

"Bristol-Myers Squibb is dedicated to helping patients prevail over cancer," says Francis Cuss, M.D., senior VP, Research, Bristol-Myers Squibb. "To help us in this mission, we are very pleased to join forces with Innate Pharma which has developed a deep understanding of the immune system. Working together we have the opportunity to develop IPH2102, a potential first-in-class biologic that may be able to harness a patient's immune system in the fight against cancer."

In September, Bristol-Myers Squibb and **Ambrx** Inc. announced a collaboration under which Bristol-Myers Squibb will receive exclusive worldwide rights to research, develop, and commercialize biologics based on Ambrx's research surrounding the Fibroblast Growth Factor 21 (FGF-21) protein, for potential use in treating type 2 diabetes, and the Relaxin hormone, for potential use in treating heart failure. Derivatives of FGF-21 and Relaxin were developed using Ambrx's ReCODE platform technology to modify the native proteins with amino acid building blocks beyond the common 20 to engineer enhanced versions for investigation for therapeutic use. Under the terms of the agreement, Bristol-Myers Squibb made an upfront payment of $24 million to Ambrx. In addition, Bristol-Myers Squibb will make potential milestone payments and royalty payments on worldwide sales for both programs. Bristol-Myers Squibb and Ambrx will also enter research collaborations for both programs.

FGF-21 is a naturally occurring protein that has been characterized as a potent metabolic regulator, and has been shown to lower blood glucose, elevate

Plavix represented a third of Bristol-Myers Squibb's total revenue in 2011, the product's final full year under patent protection.

good cholesterol, and promote weight loss in preclinical studies. The lead compound in this program, ARX618, or PEG-FGF-21, is in the final stages of preclinical development. Relaxin is a naturally occurring hormone known for its role in pregnancy and childbirth. Preclinical studies suggest Relaxin may aid in the treatment of heart failure by improving cardiac function.

"Bristol-Myers Squibb has a strong heritage discovering, developing and delivering medicines to treat diabetes and cardiovascular disease," Dr. Cuss says. "As part of our String of Pearls strategy we seek to build relationships with companies that have innovative programs and capabilities that complement our own internal efforts. We are excited to be working with Ambrx, which has used its unique ReCODE technology to create precisely engineered investigational biologics in both of these therapeutic areas. Our combined expertise will provide the best chance of bringing these innovative medicines to patients."

Also in September, Bristol-Myers Squibb and **Ono** Pharmaceutical Co. announced an agreement to expand Bristol-Myers Squibb's territorial rights to develop and commercialize the anti-PD-1 antibody known as **BMS-936558/ ONO-4538**, and to create a strategic alliance for the joint development and cocommercialization of Orencia in Japan. BMS-936558/ONO-4538, a fully human anti-PD-1 antibody, is an investigational cancer immunotherapy generated under a research collaboration entered into in May 2005 between Ono and Medarex Inc. When Bristol-Myers Squibb acquired Medarex in 2009, it also acquired Medarex's rights to develop and commercialize the anti-PD-1 antibody in North America.

Under the terms of the new agreement, Ono will grant Bristol-Myers Squibb exclusive rights to develop and commercialize BMS-936558/ ONO-4538 in the rest of the world, except in Japan, Korea, and Taiwan, where Ono has retained all rights to develop and commercialize BMS-936558/ONO-4538. Also under the agreement, the companies will jointly develop and jointly commercialize Orencia, a biologic therapy for rheumatoid arthritis, in Japan. The agreement applies to both the currently approved intravenous formulation of Orencia and the subcutaneous formulation of Orencia, and includes all current and future indications. Orencia I.V. was launched in Japan in September 2010 by Bristol-Myers Squibb's Japanese subsidiary, Bristol-Myers K.K., and is indicated for use in patients for whom other therapies have failed. Orencia S.C. is currently in Phase III development in Japan. Bristol-Myers K.K. will distribute and book sales of Orencia I.V., while Ono will distribute and book the sales of Orencia SC. The companies will jointly promote both formulations, with Ono's participation beginning when the post-marketing surveillance period for Orencia I.V. has concluded, expected in 2013.

"Bristol-Myers Squibb is pleased to enter into this important collaboration with Ono Pharmaceutical that further enhances our position as a leader in immuno-oncology," Mr. Andreotti says. "Obtaining expanded rights to this anti-PD-1 antibody through our String of Pearls strategy will enable broader global development of this promising cancer immunotherapy as we continue to build our pipeline and understanding in this exciting area."

In November, Bristol-Myers Squibb and **Aslan** Pharmaceuticals Pte Ltd, a pharmaceutical company headquartered in Singapore, announced a strategic partnership allowing for the rapid development of **BMS-777607**, Bristol-Myers Squibb's investigational small molecule inhibitor of the MET receptor tyrosine kinase for treatment of solid tumors. This approach, company leaders say, will accelerate the delivery of clinical proof-of-concept by taking advantage of the complementary strengths of an Asia-based drug development company and a global biopharmaceutical company. Under the terms of the agreement, Aslan will receive exclusive rights to develop and commercialize BMS-777607 in China, Australia, Korea, Taiwan, and other selected Asian countries, while Bristol-Myers Squibb retains exclusive rights in the rest of the world. Aslan will run and fund development of BMS-777607 under a pre-agreed development program that will initially target gastric cancer and lung cancer.

"As part of our biopharma strategy, Bristol-Myers Squibb seeks to seed companies in key markets with promising investigational medicines of continued interest to Bristol-Myers Squibb," Dr. Cuss says. "Dubbed our Oyster strategy, under this type of agreement partners like Aslan run and fund early development, working closely with Bristol-Myers Squibb, to produce high-quality data that may be used to further develop and commercialize the medicine worldwide. We are pleased to be working with Aslan to quickly further our understanding of this oncology compound for use in treating solid tumors."

The leukemia drug Sprycel grew sales by just under 40 percent in 2011.

In December, Bristol-Myers Squibb and the Gladstone Institutes announced the formation of a discovery-based research collaboration to identify and validate novel targets in Alzheimer's disease. Under the agreement, Bristol-Myers Squibb will fund Gladstone's research efforts to identify targets that affect Tau dysfunction. Tau is a protein that binds the cell's internal skeleton and may help regulate the activity of brain cells. In Alzheimer's disease, Tau forms abnormal deposits called neurofibrillary tangles, a hallmark pathology of the disease. By identifying targets that prevent or reverse Tau dysfunction, Bristol-Myers Squibb and Gladstone hope to identify novel therapeutic strategies to modify the course of the disease.

"Bristol-Myers Squibb is committed to helping patients address the unmet medical need for effective treatments across the Alzheimer's disease continuum, from predementia to severe disease, by developing and studying a broad and diversified portfolio of compounds directed at multiple pathologies and different mechanisms," Dr. Cuss says. "By leveraging the cutting edge expertise of the Gladstone Institutes in Alzheimer's disease we are hoping that the scientific innovation in drug development that often happens at the crossroads of different disciplines will lead to a better understanding of the role of Tau in Alzheimer's disease and, potentially, lead to the identification of new therapies for the treatment of this serious disease."

In January, Bristol-Myers Squibb agreed to acquire Inhibitex Inc. for $26 per share in cash pursuant to a cash tender offer and second step merger, with an aggregate purchase price of about $2.5 billion. Inhibitex is a clinical-stage biopharmaceutical company dedicated to the development of innovative products that can treat or prevent serious infections, whose primary focus is on the development of nucleotide/ nucleoside analogs for the treatment of hepatitis C virus . The company's lead HCV asset is **INX-189**, an oral nucleotide polymerase (NS5B) inhibitor in Phase II development that has exhibited potent antiviral activity, a high barrier to resistance, and pan-genotypic coverage. The deal duly closed in February.

"The acquisition of Inhibitex builds on Bristol-Myers Squibb's long history of discovering, developing and delivering innovative new medicines in virology and enriches our portfolio of investigational medicines for hepatitis C," Mr. Andreotti says. "There is significant unmet medical need in hepatitis C. This acquisition represents an important investment in the long-term growth of the company."

In March, Bristol-Myers Squibb and Meso Scale Discovery reached an agreement to develop diagnostic assays that will measure cerebrospinal fluid biomarkers for use in Alzheimer's disease research. Under the terms of the agreement, the companies will develop these assays based on the Meso Scale Discovery MULTIARRAY technology platform. Meso Scale Discovery will commercialize the assays for Alzheimer's disease research and drug development, with plans to release the assays in the second quarter of 2012.

"The collaboration with Meso Scale Discovery demonstrates Bristol-Myers Squibb's commitment to advancing the science of Alzheimer's disease research," says Jane Tiller, VP, Global Clinical Research, Bristol-Myers Squibb. "These assays could provide the Alzheimer's disease research community with an important tool to help advance understanding of this complex and devastating disease and may lead to advances in the diagnosis and treatment of Alzheimer's disease."

In May, Bristol-Myers Squibb announced the formation of the International Immuno-Oncology Network, a global collaboration between industry and academia that aims to further the scientific understanding of immuno-oncology. Immuno-oncology focuses on the potential of harnessing the intelligence of the body's own immune system to fight cancer.

In addition to Bristol-Myers Squibb, the II-ON comprises 10 leading cancer-research institutions around the world, including Clinica Universidad Navarra, Dana-Farber Cancer Institute, the Earle A. Chiles Research Institute (Providence Health & Services), Institut Gustave Roussy, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G. Pascale," Johns Hopkins Kimmel Cancer Center, Memorial Sloan-Kettering Cancer Center, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, the Netherlands Cancer Institute, and the University of Chicago.

An objective of this collaborative forum is to facilitate the translation of scientific research findings into clinical trials and, eventually, clinical practice. It will also work to further advance innovation in drug discovery and development.

"The International Immuno-Oncology Network facilitates a public-private partnership that will leverage intellectual capabilities across a global network," says Elliott Sigal, M.D., Ph.D., executive VP, chief scientific officer and president, Research and Development, Bristol-Myers Squibb. "The shared commitment of all those participating in this collaboration is to evolve our understanding of immuno-oncology towards our ultimate goal of improving patient outcomes."

In June, Bristol-Myers Squibb made its big-

gest splash in the M&A department with the announcement that the company would acquire Amylin Pharmaceuticals Inc. for $31 per share in cash, pursuant to a cash tender offer and second step merger, or an aggregate purchase price of about $5.3 billion. The total value of the transaction, including Amylin's net debt and a contractual payment obligation to Eli **Lilly** & Company, totaled about $7 billion.

Simultaneously, Bristol-Myers Squibb and **AstraZeneca** announced that, following the completion of the Amylin acquisition, the companies would enter into collaboration arrangements, based on the framework of their existing diabetes alliance, regarding the development and commercialization of Amylin's portfolio of products. Following completion of the Amylin acquisition, AstraZeneca agreed to make a payment to Amylin, as a wholly owned subsidiary of Bristol-Myers Squibb, in the amount of about $3.4 billion in cash. Profits and losses arising from the collaboration will be shared equally.

In addition, AstraZeneca received the option, exercisable at its sole discretion following the closing of the acquisition, to establish equal governance rights over key strategic and financial decisions regarding the collaboration, upon the payment to Bristol-Myers Squibb of an additional $135 million. Bristol-Myers Squibb's tender offer for Amylin was completed in August; AstraZeneca made its initial payment and announced its intention to exercise the $135 million option that same month.

Amylin is dedicated to the discovery, development, and commercialization of innovative medicines for patients with diabetes and other metabolic diseases. The company's primary focus is on the research, development and commercialization of a franchise of GLP-1 agonists, for the treatment of type 2 diabetes.

"Amylin's innovative diabetes portfolio, talented people and state-of-the art manufacturing facility complement our long-standing leadership in metabolics," Mr. Andreotti said on announcement of the deal. "We are pleased to be able to strengthen the portfolio we have built to help patients with diabetes by building on the success Amylin has had with its GLP-1 franchise. The acquisition of Amylin by Bristol-Myers Squibb is also a unique way for Bristol-Myers Squibb and AstraZeneca to expand the alliance between the two companies, and it demonstrates Bristol-Myers Squibb's innovative and targeted approach to partnerships and business development."

Also in June, Bristol-Myers Squibb formed a strategic partnership with Emory University to conduct clinical trials involving the company's investigational compounds. Under the newly established Master Clinical Trial Agreement, investigators from Emory University and affiliated institutions will conduct Phase II, Phase III, and pediatric clinical trials in the metropolitan Atlanta area to support the ongoing development of investigational medicines from across

Baraclude, indicated for hepatitis B, cracked the blockbuster barrier for the first time in 2011 with $1.2 billion in sales and 28.5 percent growth.

Bristol-Myers Squibb's portfolio, particularly in oncology, metabolics, hepatitis C, and immunoscience. This agreement builds on recent experiences between the two organizations in conducting clinical trials in organ transplantation and cancer. In the first studies under the new agreement, researchers from the Winship Cancer Institute of Emory University will work with Bristol-Myers Squibb scientists on multiple clinical trial programs in oncology.

"This partnership is aligned with Bristol-Myers Squibb's strategy, which embraces the opportunity to selectively integrate the expertise of other organizations with our own to best meet the treatment needs of patients," says Brian Daniels, senior VP, Global Development & Medical Affairs, Bristol-Myers Squibb. "Our expectation is that the shared commitment of providing innovative solutions for patients, the world-class talent at both organizations and the clinical trial expertise at Emory, will result in important advancements in the understanding of Bristol-Myers Squibb compounds and their potential for treating patients with devastating diseases, such as cancer."

Product performance

In its last full year of patent protection, the cardiovascular drug **Plavix** rolled up $7.09 billion in sales for Bristol-Myers Squibb in 2011, about a third of the company's total revenue for the year, and 6.3 percent better than the previous year. After the end of Lipitor's patent protection, Plavix actually spent a short time as the best-selling prescription product in the world; according to Drugs.com, it was the top-selling drug of the first quarter of 2012. But with Plavix's patent protection expiring in May, the erosion has begun; the product's sales fell 31.2 percent in the first half of 2012 to $2.33 billion.

The antipsychotic **Abilify**, on the other hand, managed a solid increase in sales in 2012, rising 7.5 percent to $2.76 billion. Abilify's performance was actually even more impressive than that; Bristol-Myers Squibb's contractual share of sales recognized fell in 2011 from 58 percent to 53.5 percent based on the commercialization agreement with partner marketer **Otsuka** Pharmaceutical Co. Estimated U.S. prescription demand continued to grow as well, increasing by 5 percent for the second consecutive year. In the first half of 2012, Abilify sales edged up 0.2 percent to $1.33 billion.

Growth of the HIV product **Reyataz** continued apace in 2012, with the drug adding 6.1 percent to its annual sales to finish at $1.57 billion after 5.6 percent growth the previous year. In October, Bristol-Myers Squibb entered into a licensing agreement with **Gilead** Sciences Inc. to develop and commercialize a fixed-dose combination containing Reyataz and Gilead's **cobicistat**, a pharmacoenhancing or "boosting" agent that increases blood levels of certain HIV medicines to potentially allow for one pill once daily dosing. Gilead is currently studying Reyataz and cobicistat in Phase II and III studies in HIV-1 treatment-naïve patients. In the first half of 2012, Reyataz sales rose by 0.3 percent to $764 million.

In November, Bristol-Myers Squibb reached an agreement with the Brazilian Ministry of Health to expand access to Reyataz in Brazil. The agreement was designed to build the capacity and skills required for the Brazilian government to produce a sustainable, high quality supply of Reyataz and will enable the government to become, over time, the sole source of Reyataz in Brazil. The agreement transfers the manufacture and distribution of Reyataz 200 milligram and 300 milligram capsules in Brazil from Bristol-Myers Squibb to Farmanguinhos, a technical-scientific unit of Fundação Oswaldo Cruz and the largest official pharmaceutical laboratory of the Brazilian Ministry of Health, and to a to be named local manufacturer of active pharmaceutical ingredients.

"[Bristol-Myers Squibb]'s technology transfer agreement is an innovative evolution of a longstanding collaboration that will ensure a sustainable supply of atazanavir in the future for the many patients who can benefit from the therapy in Brazil," says Mark Pavao, president, Emerging Markets, Bristol-Myers Squibb. "The agreement also provides an opportunity to increase access to this medicine and supports the Brazilian government's interests in the further development of its local pharmaceutical manufacturing base."

Sustiva's growth also continued at a similar rate in 2011. Bristol-Myers Squibb's other blockbuster HIV product earned sales of $1.49 billion for the year, an improvement of 8.3 percent, after 7.1 percent growth the previous year. In the first half of 2012, Sustiva sales rose another 8.4 percent, to $774 million.

The **Avapro/Avalide** franchise suffered another tumble in sales in 2011, falling 19 percent to $952 million. Marketed jointly with **Sanofi**, Avapro/Avalide is indicated for the treatment of hypertension and diabetic nephropathy; company leaders blamed the product's loss of sales on market share losses subsequent to a supply shortage in the first quarter of 2011 associated with recalls. The franchise will have no opportunity for a comeback; after losing patent protection in the United States in March, first-half 2012 sales of Avapro/Avalide dropped 40.1 percent to just $324 million.

The hepatitis B drug **Baraclude** cracked the blockbuster barrier for the first time in 2011 with sales of $1.2 billion, an improvement of 28.5 percent compared with 2010. In November, Bristol-Myers Squibb announced 96-week results from the BE-LOWTM study, a Phase IIIb clinical trial comparing Baraclude monotherapy (0.5 milligrams once daily) with Baraclude (0.5 milligrams once daily) plus tenofovir (300 milligrams once daily) in treatment-naïve adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease. In this study, no statistically significant difference was observed between the two treatment arms in the primary efficacy endpoint. In the first half of 2012, Baraclude sales rose another 20.3 percent to $682 million.

The autoimmune drug **Orencia** took a step towards blockbuster status itself in 2011, with sales up 25.1 percent to $917 million. In the first half of 2012, Orencia sales were up another 27.4 percent to $544 million. In June, Bristol-Myers Squibb announced the results of AMPLE (Abatacept Versus Adalimumab Comparison in Biologic-Naïve rheumatoid arthritis Subjects With Background Methotrexate), a head-to-head clinical trial of 646 patients comparing the subcutaneous (SC) formulation of Orencia versus Humira, each on a background of methotrexate, in biologic naïve patients with moderate to severe RA. AMPLE met its primary endpoint (as measured by non-inferiority) and demonstrated that Orencia plus methotrexate achieved comparable rates of efficacy for the American College of Rheumatology criteria of 20 percent response at one year of 64.8 percent versus 63.4 percent Humira plus methotrexate.

The leukemia drug **Sprycel** is not far behind Baraclude and Orencia on Bristol-Myers Squibb's sales charts and may be catching up soon; the product earned $803 million in sales in 2010, a 39.4 percent improvement over the previous year. In the first half of 2012, Sprycel sales rose another 30.1 percent to $475 million. In August, Bristol-Myers Squibb and partner marketer Otsuka launched a number of patient management programs for Sprycel patients with a select group of specialty pharmacy providers. The specialty pharmacies include Accredo, CuraScript, Diplomat, Biologics, and Avella (formerly The Apothecary Shops). The distribution of Sprycel will remain open to other specialty and retail pharmacies.

"Bristol-Myers Squibb is committed to supporting Sprycel patients and empowering them to take an active role in managing their health," says John Tsai, VP, U.S. Medical, Bristol-Myers Squibb. "We are excited to introduce these additional patient-centric programs that help support appropriate medication management."

Sales of the cancer drug **Erbitux** halted a losing streak in 2011, with sales up 4.4 percent to $691 million. On top of that, the drug recently earned two new U.S. approvals. In November, FDA approved Erbitux in combination with platinum-based chemotherapy with 5-fluorouracil (CT), for the first-line treatment of recurrent locoregional or metastatic squamous cell carcinoma of the head and neck. The approval, based on data from the EXTREME trial, makes Erbitux plus CT the first treatment regimen approved in 30 years with extended overall survival in patients with recurrent locoregional or meta-

static SCCHN. Then, in July, FDA approved Erbitux in combination with the chemotherapy regimen Folfiri (irinotecan, 5-fluorouracil, leucovorin) for the first-line treatment of patients with KRAS mutationnegative (commonly known as KRAS wild-type), epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer. Concurrently, the agency also approved the first KRAS companion diagnostic test, the Therascreen KRAS diagnostic kit developed by Qiagen.

The good news continued for the diabetes drug **Onglyza** in 2011. In its second full year on the market, the product's sales tripled to $473 million. Sales for the first half of 2012 totaled $333 million, an improvement of 72.5 percent. In September 2011, results from an investigational Phase IIIb clinical study showed that the addition of Onglyza 5 milligrams to ongoing insulin therapy (with or without metformin) maintained reductions of blood sugar levels (glycosylated hemoglobin levels, or HbA1c) in adult patients with type 2 diabetes compared to the addition of placebo (with or without metformin) from 24 to 52 weeks. Two months later, Onglyza was approved by the European Commission for use as a combination therapy with insulin (with or without metformin) to improve blood sugar (glycemic) control in adult patients with type 2 diabetes. Then, in July, Bristol-Myers Squibb and partner marketer AstraZeneca announced the results of analyses showing that Onglyza 5 milligrams demonstrated improvements across key measures of blood sugar control (glycosylated hemoglobin levels, or HbA1c; fasting plasma glucose, or FPG and post-prandial glucose, or PPG) compared to placebo in adult patients with type 2 diabetes at high risk for cardiovascular disease. These results were from a pooled, post-hoc assessment of five, 24-week, Phase III studies encompassing 1,681 patients with type 2 diabetes and varying degrees of cardiovascular risk, characterized by the presence of known risk factors or a history of cardiovascular disease.

Starting from zero – the product was first approved by FDA in March 2011 – the melanoma drug **Yervoy** earned $360 million in sales for Bristol-Myers Squibb in 2011. The product may nearly double that number in 2012; through two quarters it had already rolled up $316 million in sales. Yervoy, the first child of the String of Pearls strategy to reach the market, remains in development for several other indications, including lung cancer and hormone-refractory prostate cancer.

In the pipeline

Bristol-Myers Squibb spent $3.84 billion on research and development in 2011, a 7.7 percent increase compared with the previous year. In the first half of 2012, R&D expenses were up slightly, rising 0.7 percent to $1.87 billion.

Much of the good news in Bristol-Myers Squibb's pipeline in the past year came from the company's hepatitis C portfolio. In January, the company reported results from a Phase II clinical trial in patients with hepatitis C virus genotype 1 who had not responded to prior therapy with PEG-interferon alfa and ribavirin ("null responders"). The study demonstrated that its primary endpoint of the achievement of sustained virologic response 12-weeks post-treatment (SVR12) is possible with a direct-acting antiviral (DAA)-only combination containing **daclatasvir** and **asunaprevir** (4/11 patients, including two of two patients infected with HCV genotype 1b). This study was the first study to demonstrate the possibility that hepatitis C can be cured (defined as sustained virologic response 48 weeks post-treatment or SVR48) without the use of interferon. The study also demonstrated that 100 percent (10/10) of these difficult-to-treat patients dosed with quadruple therapy containing daclatasvir and asunaprevir in combination with PEG-Interferon alfa and ribavirin achieved SVR12. Daclatasvir is the first NS5A replication complex inhibitor to be investigated in HCV clinical trials and is currently in Phase III development; asunaprevir is an investigational, oral, selective NS3 protease inhibitor.

The positive news for daclatasvir continued in April, when Bristol-Myers Squibb announced interim results from a Phase II open-label study of the compound alongside **GS-7977**, an NS5B polymerase inhibitor, in treatment-naïve patients with hepatitis C genotypes 1, 2, and 3. In this interim analysis, a combination of the two oral, once-daily investigational compounds taken for 24 weeks, with or without ribavirin, achieved a rapid and sustained viral response. Overall, 100 percent of patients with genotype 1, 2, or 3 HCV achieved viral load below the lower limit of quantification at Week 4 on treatment. Also in April, the company announced results from a Phase II study in which treatment with an all-oral, dual direct-acting antiviral regimen of daclatasvir and asunaprevir achieved undetectable viral load 24 weeks post-treatment (SVR24) in 77 percent (33/43) of difficult-to-treat genotype 1b hepatitis C (HCV) patients. And results from the Phase IIb EMERGE clinical trial in 118 treatment-naïve patients chronically infected with genotype 2 or 3 hepatitis C virus showed that the investigational compound **peginterferon lambda-1a** (Lambda) plus ribavirin achieved sustained virologic response rates 24 weeks post-treatment (SVR24) that were comparable to peginterferon alfa-2a (alfa) plus ribavirin.

Sales of the diabetes drug Onglyza tripled to $473 million for Bristol-Myers Squibb in 2011, the product's second full year on the market.

News in the rest of the late-stage pipeline, though, was not so positive. In January, FDA issued a complete response letter to Bristol-Myers Squibb and partner developer AstraZeneca regarding their NDA for the investigational compound **dapagliflozin** for the treatment of type 2 diabetes in adults. The complete response letter requests additional clinical data to allow a better assessment of the benefit-risk profile for the compound. This includes clinical trial data from ongoing studies and may require information from new clinical trials. In June the two companies released results from a Phase III clinical study that showed that dapagliflozin 10 milligrams demonstrated significant reductions in blood sugar levels (glycosylated hemoglobin levels, or HbA1c) compared with placebo at 24 weeks when either agent was added to existing sitagliptin therapy (with or without metformin) in adult patients with type 2 diabetes. The results were maintained over a 24-week extension and similar results were observed when the data were stratified by background therapy. The study also demonstrated significant reductions in total body weight and fasting plasma glucose (FPG) levels in patients taking dapagliflozin added to sitagliptin (with or without metformin), with results maintained throughout the duration of the study extension.

Dapagliflozin, an investigational oral compound, is a selective and reversible inhibitor of sodium-glucose cotransporter 2 (SGLT2), which works independently of insulin. The compound is being investigated to evaluate its safety and efficacy in improving glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise, for once-daily use as a monotherapy and in combination with other glucose-lowering drugs. If approved, dapagliflozin would potentially be the first in the new SGLT2 inhibitor class for the treatment of type 2 diabetes, a disease where high unmet medical need exists. In a comprehensive clinical trial program of 19 studies, dapagliflozin has been studied together with diet and exercise as a monotherapy, and as an add-on therapy to commonly prescribed diabetes medications, including metformin, sulfonylurea (glimepiride), thiazolidinedione (pioglitazone), and insulin (with or without other diabetes therapies).

In April 2012, the Committee for Medicinal Products for Human Use of the European Medicines Agency issued a positive opinion recommending the approval of dapagliflozin for the treatment of type 2 diabetes as an adjunct to diet and exercise, in combination with other glucose-lowering medicinal products including insulin, and as a monotherapy in metformin intolerant patients.

In June, Bristol-Myers Squibb and partner developer Pfizer received a complete response letter from FDA regarding their NDA for **Eliquis** for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The letter requests additional information on data management and verification from the ARISTOTLE trial. FDA has not requested that the companies complete any new studies. The drug has been available in Europe since May.

"There is a significant unmet need to reduce the risk of stroke in patients with atrial fibrillation," Dr. Sigal says. "We believe that the two large trials called ARISTOTLE and AVERROES have established the therapeutic profile for Eliquis and demonstrated a meaningful advance over the standard of care."

In July, Bristol-Myers Squibb reported the result of the Phase III BRISK-FL clinical trial of the investigational agent **brivanib** versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma (HCC; liver cancer). The study did not meet its primary overall survival objective based upon a non-inferiority statistical design. BRISK-FL is a randomized, double-blind, multi-center Phase III study of the investigational agent brivanib versus sorafenib in patients with advanced HCC who have not received prior systemic treatment. The company is considering options for the ongoing brivanib development program. Ongoing clinical trials of brivanib, which include hepatocellular carcinoma as well as other tumor types, will continue.

In August, Bristol-Myers Squibb discontinued development of **BMS-986094** (formerly known as INX-189), a nucleotide polymerase inhibitor that was in Phase II development for the treatment of hepatitis C. This decision was made based on an ongoing assessment of patients in a Phase II study that the company voluntarily suspended Aug. 1. FDA subsequently placed the compound on clinical hold.

The initial case of heart failure, which was the basis for halting the study, subsequently resulted in death. Bristol-Myers Squibb is working in collaboration with FDA and clinical study investigators to conduct ongoing, comprehensive assessments and close follow-up of all BMS-986094 study patients. To date, nine patients have been hospitalized, including the initial patient; two patients remain hospitalized. The cause of these unexpected events, which involve heart and kidney toxicity, has not been definitively established. ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

Strategic priorities

GlaxoSmithKline management is focused on growing a diversified global business, delivering products of value, and simplifying the company's operating model.

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BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Advair/ Seretide	$8,119	$8,224
Flovent/ Flixotide	$1,304	$1,290
Avodart	$1,200	$1,009
Infanrix, Pediarix	$1,107	$1,123
Hepatitis Vaccines	$1,104	$1,155
Augmentin	$1,028	$1,003
Epzicom/ Kivexa	$990	$890
Ventolin	$966	$837
Lovaza	$913	$850
Lamictal	$860	$809
Cervarix	$812	$388
Paxil/ Seroxat	$698	$773
Synflorix	$562	$355
Valtrex	$544	$853
Combivir	$517	$582

All sales are in millions of dollars and were translated using the Federal Reserve Board's average rate of exchange in 2011: £1.6043.

FINANCIAL PERFORMANCE

	2011	2010
Revenue	$43,937	$45,549
Net income	$8,440	$2,621
EPS	$1.66	$0.51
R&D	$6,432	$7,150
	1H12	**1H11**
Revenue	$21,020	$21,345
Net income	$4,137	$4,221
EPS	$0.82	$0.81
R&D	$3,037	$3,096

All figures are in millions of dollars except EPS, and were translated using the Federal Reserve Board's average rate of exchange in 2011: £1.6043.

Since 2008 GlaxoSmithKline has sought to create a more balanced business capable of addressing market challenges, delivering sustainable financial performance, and providing new value to patients and consumers. According to management, results in 2011 and first-half 2012 show that the company is succeeding in its efforts to create a more geographically balanced business with improving operational and financial efficiency results. GSK is also developing a substantial late-stage pipeline that is anticipated to serve as a material and significant organic growth opportunity for the Group.

The company business is concentrated on accomplishing three strategic priorities that are intended to generate growth, reduce risk, and improve GSK's long-term financial performance. The three priorities are growing a diversified global business, delivering more products of value, and simplifying the operating model. In the past few years GlaxoSmithKline has substantially increased its investment in "growth" areas including: Emerging Markets; Japanese pharmaceutical and vaccines businesses; and the company's worldwide vaccine and consumer healthcare operations.

GSK leaders believe that the ability of companies in the pharmaceutical sector to succeed in the current economic environment and in the future will be determined by how successful they are in accessing growth markets and delivering valuable new product flow on a sustainable basis. According to GSK, the organization is making progress on both of those fronts.

With more than 97,000 employees, GlaxoSmithKline has three primary business areas: Pharmaceuticals, Vaccines, and Consumer Healthcare. The Group's objective is to deliver sustainable growth across this portfolio. During 2011, GSK's total turnover came in at £27.39 billion ($43.94 billion). Of that amount, Pharmaceuticals accounted for 68 percent of 2011 Group revenue at £18.7 billion ($29.99 billion), Vaccines represented 13 percent at £3.52 billion ($5.61 billion), and Consumer Healthcare generated 19 percent at £5.2 billion ($8.33 billion).

The Pharmaceuticals business develops and markets medicines to treat a wide array of serious and chronic diseases. This portfolio consists of established brands and newer innovative patent-protected medicines. The main therapy areas are Respiratory, Anti-virals, Central Nervous System, Cardiovascular and Urogenital, Metabolic, Anti-bacterials, Oncology and Emesis, Dermatology, **ViiV** Healthcare, and Other.

ViiV Healthcare, a specialist HIV company co-founded with **Pfizer** Inc. during 2009, functions as a worldwide business unit. ViiV generated global sales of £1.57 billion ($2.52 billion) in each of 2011 and 2010. For 2011 sales, the United States improved 4 percent, Europe declined 3 percent, Emerging Markets rose 9 percent, and the Rest of World fell 4 percent.

GSK's Vaccines business is one of the largest worldwide, producing pediatric and adult vaccines to combat a range of infectious diseases. During 2011, GlaxoSmithKline distributed 1.1 billion doses to 173 countries, of which more than 80 percent were supplied to developing countries. EvaluatePharma's World Preview 2018 report issued in June 2012 forecasts that GlaxoSmithKline will be the leading vaccine entity in 2018 with sales of $8.77 billion.

GlaxoSmithKline and fellow top 50 company **Daiichi Sankyo** Co. agreed in March 2012 to form a joint venture that is anticipated to create the leading vaccines company in Japan. The joint venture will hold the development and commercial rights for already-existing preventative vaccines from each parent company. The venture will supply on a worldwide basis recommended vaccines to help protect people of all ages in Japan including human papillomavirus (HPV) vaccine, rotavirus vaccine, seasonal flu vaccine, mumps vaccine, diphtheria pertussis (DTP) vaccine, and measles rubella (MR) vaccine. The business will be expanded in the future as new vaccines in the joint-venture development pipeline are cleared for marketing.

GSK and Daiichi sold their respective vaccines into the joint venture at agreed-upon prices and expect sales synergies from the JV. The companies have an equal stake in the JV and will split the joint venture's profits 50/50, with a portion going toward funding continuing capital needs of the new business. A minimal total cash investment of 100 million yen ($1.3 million) was split equally between the two entities to cover the joint venture's start-up capital requirements. The JV transaction was expected to be completed during 3Q 2012.

GSK has divested non-core OTC brands in various markets during 2011 and 2012 (for more details, please see the Company Performance section). The product divestments are an example of the company's dedication to realize value and enhance returns to shareholders. GSK is doing so via the sale of low-growth or non-core businesses and concentrating on priority brands, products, and pipeline opportunities that have long-term growth potential.

During February 2011, GlaxoSmithKline announced its intention to divest non-core Consumer Healthcare OTC products predominantly in the United States and Europe with aggregate yearly sales of £500 million ($802 million), accounting for about 10 percent of the company's total Consumer Healthcare revenue. The products include the analgesics **Solpadeine**, **BC**, and **Goody's**; the vitamin and supplement product **Abtei**; the feminine hygiene treatment **Lactacyd**; and **alli** for weight management.

GlaxoSmithKline CEO Sir Andrew Witty

GSK says the divested brands have strong heritage and good prospects on an individual basis, but the company has lacked sufficient critical mass in some product categories and particular brands have lacked focus due to other worldwide priorities. Management at GlaxoSmithKline therefore believes that other companies are better suited to maximize the potential they offer. The goal was to divest the products by late 2011.

Following the divestment, GSK's Consumer Healthcare business is concentrated on three priority categories: Oral Health, Wellness/OTC, and Nutrition, in which the company has fast-growing leading brands such as **Sensodyne**, **Panadol**, and **Horlicks**. On a pro-forma basis, the retained business generated sales of £4.5 billion in 2010, and increased at 6 percent CAGR over the 2007-2010 period. The reconcentrated business holds market-leading positions in Smoking Control, Denture Care, Dental Sensitivity, Analgesics, and Nutrition.

In the past few years GSK has been reshaping the Group's business to capitalize on the higher growth potential of markets outside the United States and Europe. These territories represented 38 percent of GSK's total sales for 2011. At the same time, GlaxoSmithKline has restructured its developed markets business to reflect the challenging commercial environment in those markets. GSK has a significant worldwide manufacturing and R&D presence, with a network of 74 manufacturing sites and large R&D centres located in the United States, United Kingdom, Spain, Belgium, and China.

The company's commercial businesses are structured around regional units or focus areas. For Pharmaceuticals and Vaccines, GSK operates in geographical segments that combine both of these businesses. The Consumer Healthcare business operates as a worldwide unit, as does ViiV Healthcare. Other trading revenue includes Canada, Puerto Rico, central vaccine tender sales, and contract manufacturing sales.

Company performance

In 2011, GSK delivered underlying sales growth of 4 percent, strong cash generation, and important R&D progress. The company was able to increase shareholder returns via ordinary dividend growth of 8 percent, along with a supplemental dividend of 5 pence and £2.2 billion ($3.5 billion) of share buy backs. GSK distributed £5.6 billion ($9 billion) in cash to shareholders during 2011 – a 75 percent improvement over 2010.

Underlying sales growth for the group during 2011 came to 4 percent. Pharmaceuticals advanced 2 percent, Vaccines increased 11 percent, and Consumer Healthcare rose 5 percent. The underlying Pharmaceuticals growth reflected the contribution from new products, partly offset by generic competition to older products in the United States and Europe as well as the increased impact of European austerity measures. The full-year 2011 incremental impact on sales of European austerity price cuts and U.S. healthcare reform totaled £315 million ($505 million). The growth in underlying Vaccines sales mainly reflected strong performances from **Cervarix**, **Synflorix**, and **Rotarix**. In Consumer Healthcare, strong growth in Oral Healthcare and Nutritional Healthcare was partly offset by flat OTC sales during 2011.

Group sales during 2011 outside the United States and Europe represented 38 percent of turnover, with underlying sales growth of 14 percent reflecting strong growth across all three businesses and geographic regions. Underlying growth amounted to 15 percent in Emerging Markets, 10 percent in Asia Pacific, and 28 percent in Japan. U.S. underlying turnover was flat, and dropped off 4 percent in Europe for 2011.

Pharmaceuticals and Vaccines underlying turnover in the United States was flat during 2011, as the contribution from new products was offset by competition to older established products. In Europe, Pharmaceuticals and Vaccines underlying turnover fell 4 percent due to austerity price cuts and a mild flu season. In Emerging Markets, underlying growth of 15 percent was spurred by relatively consistent Pharmaceuticals growth (+14 percent). This performance in part reflected Dermatology acquisitions made in 2010 and 2011 as well as strong Vaccines growth (+17 percent), with quarterly volatility due to tender phasing. Political and economic uncertainties affected the performance in various territories in Emerging Markets. In Japan, the largest driver of the 30 percent increase was Cervarix (human papillomavirus bivalent (types 16 and 18) vaccine). In Asia Pacific, underlying growth of 9 percent mainly stemmed from Respiratory products and Vaccines. ViiV Healthcare sales rose 1 percent. Consumer Healthcare sales advanced 5 percent, with decreases in the United States of 1 percent and Europe of 2 percent. This result reflected difficult economic conditions, more than offset by consistent strong growth in the Rest of World markets of 14 percent.

Total Group turnover during first-half 2012 was flat as a 1 percent decrease in Pharmaceuticals and Vaccines turnover was offset by a 1 percent improvement in reported Consumer Healthcare revenue. Pharmaceuticals turnover fell 1 percent versus 1H 2011, largely due to continued pressures in mature markets. Vaccines turnover was flat as growth in EMAP and Japan was offset by U.S.

and European decreases. Excluding the non-core OTC brands divested during the first six months of 2012 and alli, Consumer Healthcare turnover rose 7 percent.

Group turnover outside the United States and Europe in 1H 2012 represented 40 percent of revenue, growing 5 percent over the comparable one-year-earlier period.

U.S. Pharmaceuticals and Vaccines turnover advanced 1 percent in the January-June 2012 period. Pharmaceuticals turnover fell 2 percent versus 1H 2011, with growth in Respiratory, Oncology, and CNS products. Growth additionally benefited from the net effect of the incremental revenue from the conclusion of the **Vesicare** joint-promotion deal during first-quarter 2012, but no sales occurred thereafter. Sales decreases affected various older products such as **Arixtra**, **Avandia**, and **Valtrex**. New products performed well, especially in oncology, which grew 29 percent over the first-half 2011 figure. Vaccines sales decreased 3 percent as adverse comparisons for hepatitis vaccines and Rotarix with first-half 2012, which benefited from important CDC stockpile purchases, more than offset sales growth of the **Infanrix/Pediarix** group and **Boostrix**.

Europe Pharmaceuticals and Vaccines revenue for January-June 2012 fell 7 percent versus the one-year-earlier period, mainly fueled by the effects of various government austerity measures on prices. This result represented adverse pricing effects of 7 percent as well as flat volume. Pharmaceuticals sales were down 7 percent and Vaccines sales dropped off 4 percent compared to 1H 2011.

EMAP Pharmaceuticals and Vaccines revenue rose 6 percent during the 2012 first half as strong growth in Latin America and China was tempered by the effect of price reductions – including in Turkey and Korea – and instability in the Middle East/Africa region. Pharmaceuticals revenue advanced 6 percent versus the first six months of 2011. The Vaccines business, where volatility is often fueled by tender sales, advanced 3 percent with strong growth in many developing countries partially offset by lower tender orders in Latin America.

First-half 2012 turnover for Japan Pharmaceuticals and Vaccines climbed up 5 percent despite the effect of the mandatory biennial price cuts. Pharmaceuticals revenue rose 3 percent, with strong growth coming from the recently launched products, **Lamictal**, **Avodart**, **Volibris**, and Rotarix. The Respiratory portfolio advanced 1 percent during 1H 2012 – led by a strong performance from **Xyzal** – offsetting declines in **Flixonase** and **Zyrtec** due to a weaker allergy season than in first-half 2011. Vaccines sales were up 21 percent, mainly because of the strength of Rotarix following the drug's November 2011 launch in Japan.

ViiV's first-half 2012 global sales dropped off 6 percent at constant exchange rates to £680 million ($1.09 billion). U.S. sales declined 18 percent, Europe was down 3 percent, and EMAP advanced 30 percent. U.S. generic competition to the HIV medicines **Combivir** and **Epivir** offset the 1H 2012 growth produced by **Epzicom** and **Selzentry**.

Consumer Healthcare 1H 2012 sales improved 1 percent YoY to £2.59 billion ($4.16 billion). Excluding the non-core OTC brands divested during first-half 2012 and alli, the business turnover increased 7 percent compared to January-June 2011. This performance reflected continued strong contributions from Oral Care, Nutrition and Wellness, partly offset by a decrease in Skin Health. Sales rose 6 percent in the United States, 3 percent in Europe, and 11 percent in the Rest of World segment. Excluding only the non-core OTC brands divested during first-half 2012 (but including alli), Consumer Healthcare revenue improved 5 percent versus January-June 2011.

Announced April 24, 2012, GSK agreed to divest previously identified non-core OTC brands in its international markets to **Aspen Pharmacare** Holdings Ltd. for £164 million ($263 million) in cash. The divested brands – including **Phillips MOM**, Solpadeine, **Dequadin**, **Cartia**, and **Zantac** – produced sales of £60 million ($96 million) during 2011.

GSK continued to divest products during August 2012. The company agreed to divest the majority of its "Classic Brands" (25 non-promoted and genericized products) in Australia to **Aspen Global** Inc. for £172 million in cash. The divested brands – including Valtrex, Lamictal, **Timentin**, **Amoxil**, and **Aropax** – produced total sales of £83 million ($133 million) in 2011 and £31 million ($50 million) during first-half 2012. GSK says revenue for these products has gradually decreased in recent years because of local market price reductions and generic competition. The divestment was expected to be completed during fourth-quarter 2012.

Other non-core OTC brands were divested in the United States and Canada during December 2011 to **Prestige Brands** Holdings Inc. for £426 million ($660 million) in cash. The divested brands – including BC, Goody's, **Beano**, **Ecotrin**, **Fiber Choice**, and **Tagamet** – produced sales of £134 million ($215 million) in 2010 and £98 million ($157 million) during the first nine months of 2011.

Acquisitions

GlaxoSmithKline is an active player on the acquisition front. The company is dedicated to using free cash flow to support bolt-on acquisitions that hold attractive return value. GSK's recent acquisition concentration has been in higher-growth areas such as emerging markets, vaccines, and consumer healthcare, focusing on smaller businesses with strong product portfolios.

GSK completed its acquisition of **Human Genome Sciences** Inc. during early August 2012 for $3.6 billion on an equity basis, or $3 billion net of cash and debt. Every outstanding share of HGS was acquired for $14.25 per share in cash. The deal was initially announced by the companies July 16, 2012.

According to GSK leaders, this acquisition is well-aligned with the company's long-term strategy of delivering sustainable growth, simplifying its business model, enhancing R&D returns, and deploying capital with discipline. Via complete ownership of **Benlysta**, **albiglutide**, and **darapladib**, GlaxoSmithKline can simplify and optimize R&D, commercial, and manufacturing operations to advance these products most effectively and efficiently while securing the full potential long-term value of the assets. GlaxoSmithKline expects to achieve at least $200 million in cost synergies to be fully realized by 2015, subject to appropriate consultation, with the transaction anticipated to be accretive to core earnings starting in 2013. GSK assessed the potential returns of this transaction relative to the company's long-term share buyback program. As part of this continuing program, GlaxoSmithKline continues to expect to repurchase £2 billion to £2.5 billion in shares during 2012.

Benlysta was approved by U.S. health regulators during March 2011 and by the European Medicines Agency in July 2011 to treat systemic lupus erythematosus (SLE). Benlysta (belimumab) was the first approved drug for systemic lupus in 56 years. As of early 2012, the drug was available in Canada and in a growing amount of European countries such as Germany, Spain, Austria, Denmark, Finland, Hungary, Norway, and Sweden.

Key goals for Benlysta in 2012 included enrolling Phase III studies of a subcutaneous form of the drug, with completed enrollment in 2013; initiating a Phase III trial in vasculitis; starting a Phase III study in active lupus nephritis; and enrolling a Phase III trial in East Asia.

Licensed to GSK during 2004, albiglutide has completed Phase III trials for type 2 diabetes. Darapladib is undergoing Phase III studies for treating atherosclerosis.

GSK agreed during May 2012 to acquire the shares that it did not already own in **Cellzome** for £61 million ($99 million) in cash. Cellzome is a leader in the development and advancement of proteomics technologies. The privately owned company has labs in Cambridge, UK, and Heidelberg, Germany. As a result of the deal, Cellzome became part of GlaxoSmithKline's R&D organization.

Cellzome's proteomics technologies can be employed throughout drug discovery, from screening to selectivity profiling of compounds in different cells as well as in patient samples. The technologies developed by Cellzome vary from other traditional methods used in early drug discovery by assessing drug interactions with target proteins in a setting that more closely represents that located in a whole biological system. This offers scientists the chance to observe how candidate drugs affect intended and non-desired targets in a close-to-physiological environment, and may pinpoint potential safety issues earlier in the process.

GSK and Cellzome have two active early-stage research collaborations using these discovery capabilities within the immune-inflammation therapy field. With the acquisition, the technologies could be leveraged across the entire portfolio of GlaxoSmithKline.

Before the mid-May 2012 transaction, GlaxoSmithKline owned a 19.98 percent equity interest in Cellzome. Now with full control of Cellzome, GlaxoSmithKline plans to create a spin-off company. The spin-off would hold the rights to certain assets and activities of Cellzome that GSK did not intend to move forward.

Five million newly issued shares of **Response Genetics** Inc. were acquired by GSK during September 2012. The common stock was purchased at price of $1.10 per share in cash. As a result, GlaxoSmithKline owns 15.2 percent of the expanded share capital of RGI. This transaction builds on the relationship the two companies formed throughout the years in the diagnostics field of oncology and vaccines.

Response Genetics performs companion diagnostic tests and other related activities for GlaxoSmithKline's immunotherapies and oncology pipeline candidates. Based in Los Angeles, RGI is a CLIA-certified clinical lab concentrated on the development and sale of molecular diagnostic testing services for cancer.

Stiefel Laboratories Inc. – acquired by GSK during July 2009 for £2.2 billion ($3.5 billion), agreed to a global deal in June 2012 to acquire **Toctino** (alitretinoin) from **Basilea** Pharmaceutica Ltd. The once-a-day oral retinoid is the first prescription medicine specifically approved for treating severe chronic hand eczema unresponsive to potent topical steroids in adults. As of mid-2012, the product was marketed in 14 countries and approved in 15 others. In the United States, the drug is undergoing Phase III development. For 2011, global sales of Toctino amounted to £22 million ($35 million).

Stiefel acquired all Toctino patent rights, trademarks, and product registrations owned by Basilea. The GSK company will license certain clinical information and product know-how from Basilea. Stiefel is responsible for the product's additional development, manufacture, and commercialization globally. Basilea was given an initial payment of £146 million ($234 million) in cash and is eligible to receive further payments of up to £50 million ($80 million) from Stiefel upon FDA clearance of the product. Basilea is eligible for double-digit success payments on U.S. net sales, starting three years after launch of the product in America.

Product performance

GSK's long-running best-selling product is the asthma and chronic obstructive pulmonary disease (COPD) treatment **Advair/Seretide**. One of the pharma industry's top-selling prescription medicines of all time, Advair/Seretide contains the synthetic trifluorinated corticosteroid fluticasone propionate and the beta 2 adrenergic agonist salmeterol xinafoate.

Global sales of Advair/Seretide during 2011 decreased 2 percent in pounds sterling to £5.06 billion ($8.12 billion). According to GSK, this sales decline followed the drop-off in the U.S. market for ICS/LABA combination products due to the revised class labeling implemented by FDA in 2010. The product's overall sales were flat in terms of constant exchange rates as growth in Japan and Asia Pacific offset small decreases in the United States and Europe.

During first-half 2012, Advair/Seretide global sales rose 1 percent to £2.52 billion ($4.04 billion), spurred by 3 percent U.S. growth to £1.27 billion ($2.04 billion) versus 1H 2011.

The U.S. patent for compositions containing the combination of active ingredients in Advair/Seretide expired in 2010. GSK says the outlook for the timing and impact of entry of "follow-on" competition is uncertain. As of early 2012, the company has not been notified of any acceptance by FDA of an application for a "follow-on" product that refers to Advair/Seretide and contains the same main chemicals.

The No. 2 seller in GSK's respiratory franchise is **Flovent/Flixotide** for asthma and COPD. In 2011, year-over-year worldwide growth improved 1 percent in pounds sterling and 3 percent at constant exchange rates to

Advair/Seretide remains GSK's top-selling product by far, but the drug's 2011 sales dropped 2 percent after revised class labelling was implemented by FDA in 2010; however, first-half 2012 sales improved 1 percent.


WORKS A
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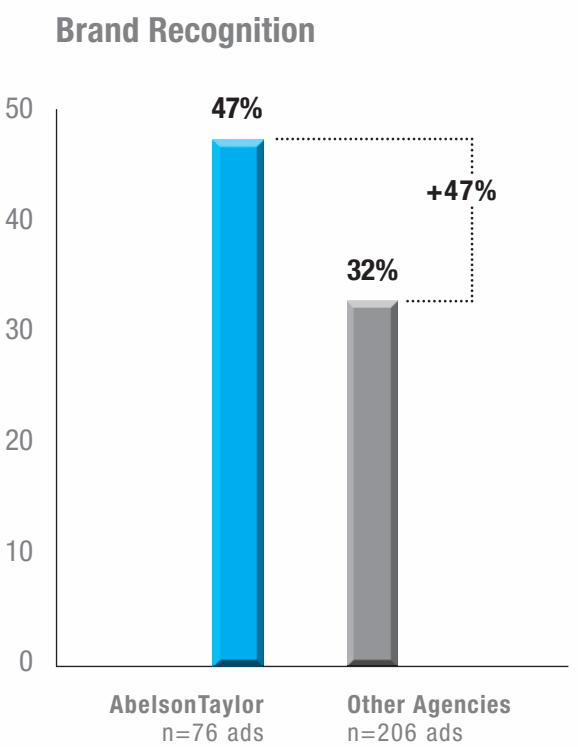
P SHUT DOWN ACID PUMPS

Branding more doctors recall seeing.



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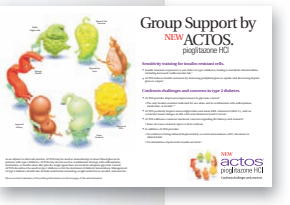

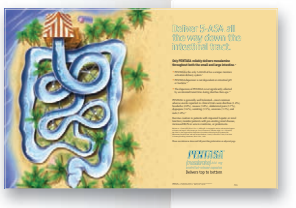

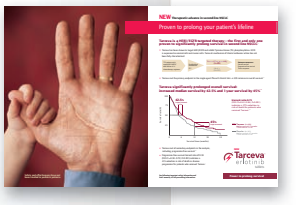

AbelsonTaylor
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£813 million ($1.3 billion). Flovent sales in the United States rose 8 percent versus 2010 to £447 million ($717 million). For January-June 2012, Flovent/Flixotide sales dropped off 3 percent compared to first-half 2011 to £388 million ($622 million).

Ventolin is another market success amongst GSK's respiratory portfolio. For 2011, Ventolin global sales increased 17 percent at constant exchange rates (CER) and 15 percent in pounds sterling to £602 million ($966 million), with U.S. sales advancing 39 percent in terms of CER to £239 million ($383 million). For the 2012 first-half period, Ventolin worldwide sales rose 3 percent CER versus 1H 2011 to £302 million ($484 million).

Among marketed cardiovascular and urogenital products for GSK, the 5-alpha reductase inhibitor Avodart/**Avolve** is the company's category leader. The benign prostatic hyperplasia treatment generated a 20 percent sales increase in 2011, coming in at £748 million ($1.2 billion). First-half 2012 global sales rose 9 percent to £383 million ($614 million). Product sales during 2011 and 2012 have been aided by Avodart's market launch in Japan.

Lovaza 2011 sales were up 12 percent compared to 2010, totaling £569 million ($913 million), with all sales generated in the United States and Puerto Rico. The lipid-regulating agent is indicated to reduce very high triglyceride levels. Lovaza sales for first-half 2012 advanced 10 percent CER to £308 million ($494 million) versus the one-year-earlier period.

GSK's flagship heritage medicine, the antibiotic **Augmentin**, has been on the market for 30 years. 2011 global sales increased 4 percent CER to £641 million ($1.03 billion). This performance was helped by 2011 growth of 11 percent in Emerging Markets and 2 percent in Asia-Pacific. In Singapore, a 45 percent price reduction for the antibiotic resulted in a threefold increase in volume sales. For January-June 2012, Augmentin global sales fell 4 percent YoY to £302 million ($484 million).

The leading product in GlaxoSmithKline's CNS category is the anti-epileptic drug Lamictal. The phenylpiperazine drug generated 2011 sales of £536 million ($860 million), up 8 percent CER and 6 percent in pounds sterling versus 2010. Product-line sales were bolstered by 66 percent CER growth to £109 million ($175 million) by **Lamictal XR**, which was launched in the United States during mid-2009 for treating epilepsy. In 2011, Lamictal received marketing clearance in Japan for a new indication, bipolar disorder.

Lamictal global sales for the first six months of 2012 rose 21 percent CER to £295 million ($473 million). U.S. sales during that period were up 31 percent versus 1H 2011 to £160 million ($257 million). The once-daily extended-release formulation for epilepsy continued to deliver strong volume growth and more than offset the decrease in the immediate-release (twice daily) version, which is facing generic competition.

Sales of the psychotherapeutic agent **Paxil/Seroxat** have been on the decline since patent expirations took effect years ago. During 2002 and 2003, global sales for the selective serotonin reuptake inhibitor exceeded $3 billion. In 2011, the product's sales fell 13 percent CER to £435 million ($698 million). GSK says Paxil remained a leader in the Japanese antidepressants market despite sales dropping off 7 percent versus 2010 due to the recent introduction of other depression medicines. In 1H 2012, worldwide Paxil/Seroxat sales declined 6 percent to £203 million ($326 million).

The Avandia franchise for type 2 diabetes suffered from a sharp sales decline, coming in at £123 million ($197 million) during 2011 versus £440 million ($706 million) in 2010. U.S. sales for Avandia products in 2011 plummeted 60 percent to £91 million ($146 million). Avandia product sales were not applicable for the first six months of 2012.

Valtrex sales have declined since 2009, when the nucleoside analog generated £1.29 billion ($2.08 billion) in sales. The amount dropped to £532 million ($853 million) for 2010 and £339 million ($544 million) during 2011. First-half 2012 sales came in at £129 million ($207 million), down 28 percent versus January-June 2011. The product's sales have been dropping in recent years due to generic competition in the United States and Europe.

GSK's Vaccines business experienced 19 percent growth loss during 2011, with global sales falling to £3.5 billion ($5.61 billion). The loss was due to a radical YoY change for flu pandemic sales, which went from £1.19 billion ($1.91 billion) in 2010 to £18 million ($29 million) during 2011. Excluding the effect of the flu pandemic vaccine sales, the category's underlying sales rose 11 percent.

The company's best-selling vaccine franchise is Infanrix and Pediarix, which generated combined 2011 sales of £690 million ($1.11 billion) compared to the 2010 figure of £700 million ($1.12 billion). Infanrix/Pediarix sales fared well in the United States by growing 16 percent compared to 2010. The 2011 U.S. growth was aided by CDC stockpile orders for Pediarix and **Kinrix**. Sales in Europe fell 7 percent to £403 million ($647 million), mainly due to price cuts. Sales in Emerging Markets dropped off 10 percent to £44 million ($71 million), primarily due to lower sales in China.

Global sales during first-half 2012 for the Infanrix/Pediarix franchise advanced 10 percent compared to January-June 2011 to £340 million ($545 million).

Hepatitis vaccines sales for GSK fell 3 percent in 2011 to £688 million ($1.1 billion). For first-half 2012, hepatitis vaccines declined 8 percent to £318 million ($510 million), mainly because of adverse comparison with 1H 2011 in the United States as well as austerity measures in Europe.

Cervarix had a strong 2011 with global sales of £506 million ($812 million) compared to £242 million ($388 million) during the prior calendar year. A majority of 2011 sales were generated in GlaxoSmithKline's ROW markets, coming in at £390 million ($626 million). First-half 2012 worldwide sales for Cervarix rose 2 percent to £181 million ($290 million).

Synflorix is approved for marketing in the European Union and 90 other countries for active immunization against invasive disease and acute otitis media caused by *Streptococcus pneumoniae* in infants and children 6 weeks old through 5 years old. Synflorix is not marketed in the United States. Worldwide sales rose from £221 million ($355 million) in 2010 to £350 million ($562 million) for 2011. Total sales of Synflorix improved 5 percent to £174 million ($279 million) during January-June 2012.

For 1H 2012, Epzicom sales rose 15 percent to £325 million ($521 million) and Selzentry improved 24 percent to £60 million ($96 million). The mature portfolio decreased 24 percent, with Combivir (lamivudine and zidovudine) global sales falling 39 percent versus first-half 2011 to £83 million ($133 million).

In the pipeline

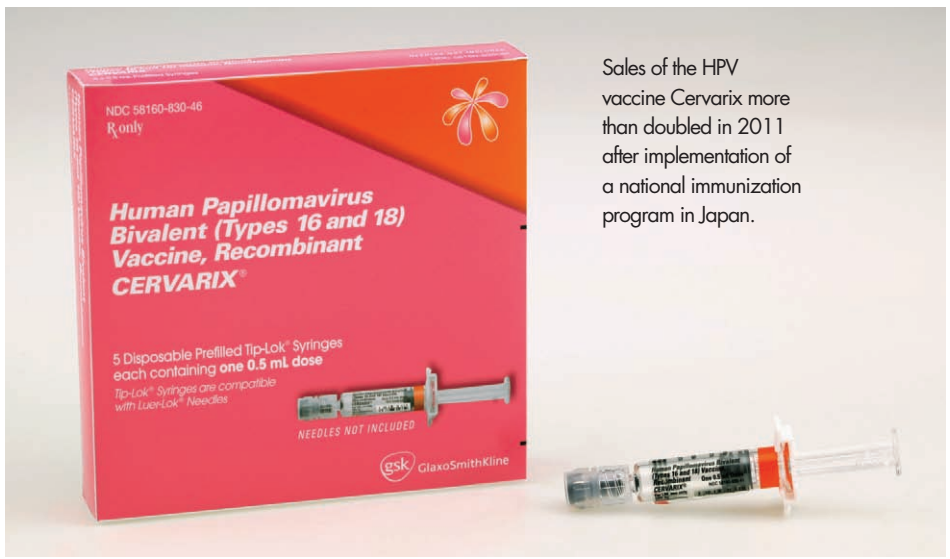
GSK says significant late-stage pipeline delivery supports the potential for multiple product launches and outlook for the Group. As of July 2012, in-house data supported the potential launch of eight new drugs and vaccines in the next two years across broad therapeutic categories, such as COPD, type 2 diabetes and HIV. The company's innovative oncology portfolio is expected to be bolstered with the eventual approval of MEK and BRAF inhibitors for melanoma.

The rare-disease drug **drisapersen** is undergoing Phase III trials in Europe for Duchenne muscular dystrophy. DMD is a recessive X-linked form of muscular dystrophy that affects roughly one in 3,600 boys, leading to muscle degeneration and eventually death.

GSK and **Theravance** Inc. in early July 2012 announced the completion of four pivotal Phase III trials for **UMEC/VI**, an investigational LAMA/LABA. Then on Aug. 24, 2012, the two companies announced the completion of the Phase III program involving 6,000 patients with chronic obstructive pulmonary disease. In addition to the four pivotal studies, the program includes a completed 52-week safety study. Two non-pivotal three-month crossover exercise studies also completed will be included in the registrational package. These recently completed studies support GlaxoSmithKline's plans to commence worldwide regulatory filings for UMEC/VI from the end of 2012. Data from these studies additionally will contribute to future regulatory submissions for UMEC as monotherapy, with worldwide submission for that use starting during 2013.

UMEC/VI combines two investigational bronchodilator molecules – the long-acting muscarinic antagonist (LAMA) GSK573719/umeclidinium bromide (UMEC), and the long-acting beta2 agonist (LABA) vilanterol (VI). UMEC/VI is a once-per-day investigational medicine for the maintenance treatment of COPD. The combination product is administered using the **Ellipta** inhaler.

The clinical registration package for the type 2 diabetes drug albiglutide was announced by GSK during July 2012. The package was completed after data was received from the Phase III Harmony 8 trial and from the event-driven meta-analysis for assessment of cardiovascular safety performed across the albiglutide clinical program. With completion of the chemistry and manufacturing package expected before the end of 2012, the company intends to commence global regulatory filings for the glucagon-like peptide-1 (GLP-1) receptor agonist during early 2013.



Sales of the HPV vaccine Cervarix more than doubled in 2011 after implementation of a national immunization program in Japan.

Albiglutide is an investigational biological, injectable formulation of human glucagon-like peptide-1. The peptide GLP-1 acts throughout the body to help maintain normal blood-sugar levels and control appetite. Generally, GLP-1 levels increase during a meal to help the body use and control the elevation in blood-sugar levels. But GLP-1 is rapidly degraded, thus the drug has a short duration of action. In type 2 diabetes patients, GLP-1 secretion in response to a meal is reduced. Albiglutide fuses human GLP-1 to human albumin. The drug is designed to extend the action of GLP-1.

Albiglutide has the potential to be administered as a weekly injection. The drug is being developed using a pen injector to enable reconstitution by the patient and a fine gauge needle for subcutaneous administration. A regulatory filing is anticipated for first-quarter 2013.

GSK announced during June 2012 detailed findings from a Phase III trial comparing albiglutide to prandial insulin (Lispro). The results demonstrated that the effect is maintained out to 52 weeks. In April 2012, results were announced from the Phase III Harmony 6 study. Albiglutide produced clinically significant reductions in HbA1c from baseline and non-inferiority compared to preprandial lispro insulin after 26 weeks of treatment, achieving the primary endpoint.

Regulatory filings in the United States and European Union for single-agent use of GSK's BRAF inhibitor **dabrafenib** and MEK inhibitor **trametinib** to treat patients with BRAF V600 mutation positive metastatic melanoma were announced by the company during early August 2012. New drug applications were submitted to FDA for dabrafenib and trametinib for treating patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA-approved test. The marketing authorization application to the European Medicines Agency was for dabrafenib as a treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The application for trametinib in BRAF V600 mutation positive metastatic melanoma could be filed by year-end 2012.

Shionogi-ViiV Healthcare LLC announced during early October 2012 that the Phase III data necessary for initial regulatory submissions of **dolutegravir** were in house. The investigational integrase inhibitor is being developed for treating adults infected with HIV in combination with other HIV medicines. The data from the two Phase III trials in treatment-experienced patients (VIKING-3 and SAILING) together with previously disclosed data from the SPRING-2 and SINGLE trials in treatment-naive patients support Shionogi-ViiV Healthcare's plans to commence worldwide regulatory filings for dolutegravir by year-end 2012.

Dolutegravir is being evaluated in clinical studies for safety and efficacy without an extra 'booster' drug being added to the regimen. Integrase inhibitors such as dolutegravir block HIV replication by preventing the viral DNA from integrating into the genetic material of human immune cells (T-cells). This process is essential in the HIV replication cycle and is responsible for establishing chronic infection.

Shionogi-ViiV announced SPRING-2 Phase III study results during July 2012 comparing dolutegravir to twice-daily raltegravir, the active ingredient in **Merck** & Co.'s HIV drug **Isentress**. The data offered compelling evidence for once-a-day dolutegravir as an option that does not necessitate a booster for first-line HIV treatment. Additionally, the efficacy was similar regardless of which dual NRTI therapy was used with the core dolutegravir regimen, according to a ViiV Healthcare spokesperson.

Also during July 2012, Shionogi-ViiV released initial results from the Phase III SINGLE (ING114467) study of dolutegravir in treatment-naïve adults with HIV-1. The study

showed superiority of the dolutegravir-based regimen versus the single-tablet regimen **Atripla**. At 48 weeks, 88 percent of trial participants on the dolutegravir regimen were virologically suppressed (<50 copies/mL) compared to 81 percent of participants on the single-tablet regimen Atripla [difference and 95 percent CI; 7.4 percent (+2.5 percent to +12.3 percent). The difference in the primary endpoint was statistically significant, p=0.003]. Differences in efficacy were mainly driven by a higher rate of discontinuation due to adverse events on the Atripla arm.

Shionogi-ViiV is a joint venture between **Shionogi** & Co. and ViiV Healthcare. Dolutegravir is the lead drug compound in the Shionogi-ViiV partnership. Shionogi-ViiV is additionally developing another integrase inhibitor that is in an earlier stage of development.

IPX066 (GSK product code 587124) is undergoing Phase III trials in the European Union for Parkinson's disease. GSK received from **Impax** Pharmaceuticals a product license to development and marketing rights for countries outside the United States and Taiwan. As of February 2012, IPX066 was awaiting U.S. approval for treating idiopathic Parkinson's disease. IPX066 is an investigational extended-release capsule form of carbidopa-levodopa (CD-LD). The drug candidate is intended to maintain consistent plasma concentration of levodopa for a longer duration compared to immediate-release levodopa, which may have an impact on fluctuations in clinical response.

MAGE-A3 is undergoing Phase III development in the United States and Europe for the treatment of melanoma and NSCLC. The recombinant therapeutic vaccine also is in Phase II trials for treating bladder cancer.

Migalastat is in U.S. and EU Phase III studies for treating Fabry disease. GSK received an exclusive global license to develop, manufacture and commercialize migalastat through an October 2010 deal with **Amicus** Therapeutics Inc. The orally administered pharmacological chaperone is expected to be branded as **Amigal**.

The pediatric vaccine **Mosquirix/RTS,S** is in Phase III trials for malaria prophylaxis (*plasmodium falciparum*). If clinical data are positive, GSK is expected to seek marketing approval of the vaccine in Europe.

Eltrombopag is approved in at least 88 countries as a treatment for thrombocytopenia in patients with chronic immune thrombocytopenia. The drug is branded as **Promacta** in the United States, and as **Revolade** in the European Union and other countries. During May 2012, regulatory applications were filed in the United States and European Union for Promacta/Revolade for use to increase platelet counts in patients with chronic hepatitis C virus infection and low platelets (thrombocytopenia). The U.S. submission for the thrombopoietin receptor agonist is being priority reviewed by FDA.

The registrational program for the once-a-day investigational medicine **FF/VI** (fluticasone furoate/vilanterol) was completed as of March 2012. As one of several late-stage assets in the GSK respiratory pipeline portfolio, the drug has been developed for the treatment of COPD and asthma. Also during September 2012, GSK filed the product candidate for marketing approval in Japan as a COPD and asthma treatment.

Lapatinib was initially approved for marketing use in combination therapy in the metastatic setting during 2007. The Her2 and EGFR dual kinase inhibitor is cleared for approval in at least 107 countries, including the United States, Europe, Australia, India, Brazil, Russia, Turkey, and South Korea.

Votrient was granted marketing authorization during August 2012 for treating patients with advanced soft tissue sarcoma (aSTS) who have received previous chemotherapy or have progressed within 12 months after (neo) adjuvant therapy. FDA gave Votrient the green light for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy during April 2012.

Soft tissue sarcomas make up a group of rare cancers stemming from mesenchymal cells. These cells typically give rise to soft tissues such as fat, muscle, nerve, blood vessels and other connective tissues. STS represents an estimated average of five out of 100,000 new cancer diagnoses in Europe per year. The incidence of STS during 2011 in the United States was 10,980 patients, according data from the American Cancer Society.

Votrient was initially FDA-approved for treating patients with advanced renal cell carcinoma (aRCC) during October 2009. The product received conditional marketing authorization in the EU during June 2010. Votrient has been cleared for approval in 75-plus countries.

In other GSK pipeline news, during August 2012 the company announced that dosing had commenced for **sirukumab** Phase III studies. The clinical program is evaluating sirukumab (CNTO 136) for treating patients with moderately to severely active rheumatoid arthritis (RA). The drug candidate is being developed by GlaxoSmithKline as part of a collaboration with **Janssen Biologics** (Ireland).

Sirukumab is an investigational human monoclonal IgG1 kappa antibody. The drug targets the cytokine interleukin (IL)-6, a naturally occurring protein believed to play a role in autoimmune conditions such as RA.

U.S. health regulators in June 2012 approved for marketing the first combination vaccine to help prevent meningococcal serogroups C and Y and Hib disease. GSK's **MenHibrix** is a vaccine indicated to prevent invasive disease caused by *N. meningitidis* serogroups C and Y and *Haemophilus influenzae* type b. MenHibrix can be used in children 6 weeks old through 18 months old.

The vaccination schedule for the vaccine is a four-dose series administered at 2, 4, 6, and 12 through 15 months of age. The first dose can be administered as early as 6 weeks of age and the last as late as 18 months old. MenHibrix was developed to align with the Centers for Disease Control and Prevention's recommended infant immunization schedule for Hib vaccination and to enable vaccination against meningococcal groups C & Y without adding more shots.

Another June 2012 FDA approval for a GlaxoSmithKline product occurred with the marketing clearance of **Horizant**. The extended-release tablet was FDA-approved for the management of postherpetic neuralgia in adults. Discovered and developed by **XenoPort** Inc., Horizant uses the body's nutrient transport mechanisms that are believed to facilitate its absorption into the body. Once absorbed, it is converted into gabapentin, which binds to a particular type of calcium channel but does not show affinity for other common receptors.

Stiefel's NDA for **Fabior** Foam 0.1% was FDA-approved during May 2012. Fabior is the only retinoid in a topical foam form for treating acne vulgaris in patients 12 years and older.

Nimenrix (Meningococcal group A, C, W-135 and Y conjugate vaccine) was granted European authorization during April 2012 for active immunization against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W-135 and Y. This is the first quadrivalent conjugate vaccine approved in Europe for active immunization of individuals from 12 months old against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W -135 and Y. The vaccine is provided as one dose and is generally well tolerated.

In other GSK vaccines news, the company filed regulatory applications for two different influenza vaccines as announced in March 2012. One is a **quadrivalent influenza vaccine** and the other is an **H5N1 influenza vaccine**.

GSK filed U.S. and EU regulatory submissions seeking approval of a quadrivalent influenza vaccine for the active immunization of adults and children from 3 years of age for the prevention of influenza disease caused by influenza virus types A and B contained in the vaccine. A supplemental BLA was filed with U.S. regulators and a new application was submitted to European health authorities. The quadrivalent influenza vaccine was not approved or licensed in any country for the prevention of influenza as of the submission filing.

As for the other vaccine, the BLA seeks marketing clearance of the active immunization for the prevention of disease in persons 18 years of age and older at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine, for use as directed by the U.S. government. GlaxoSmithKline's H5N1 pandemic influenza vaccine is manufactured in Quebec and approved in Europe under the trade name **Pumarix**. The H5N1 influenza vaccine program was backed by a development contract with the Biomedical Advanced Development and Research Authority of the U.S. Department of Health and Human Services.

Collaborations and partnerships

Glaxo Group Ltd. and Amicus Therapeutics announced in July 2012 an expansion of their collaboration to develop and commercialize the investigational pharmacological chaperone migalastat HCl for Fabry disease.

The expanded alliance consists of three components: one is joint development of all current and future forms of migalastat HCl for Fabry disease, including a co-formulation of the drug with GlaxoSmithKline and **JCR** Pharmaceutical Co.'s investigational enzyme replacement therapy for Fabry disease. Another component is commercialization arrangements for all future Fabry products. Amicus will have U.S. commercial rights to all Fabry products and GlaxoSmithKline will commercialize each product in the rest of world. For the third component, GSK increased its ownership in Amicus with an $18.6 million investment in common stock priced at $6.30 per share, bringing the total ownership stake in the biopharma company to 19.9 percent.

GlaxoSmithKline and **AstraZeneca** plc in May 2012 launched a collaboration regarded as a pioneering approach to antibiotic research in Europe. The pharma and biotech companies are working alongside public partners to tackle the increasing threat from antibiotic resistance and address some of the key barriers to the development of effective antibiotics.

The objective of the proposed research program is to improve the underlying scientific understanding of antibiotic resistance, design and implement efficient studies, and take novel drug candidates through clinical development. The innovative research program known as NewDrugs4BadBugs plans to boost the currently faltering discovery and development of new antibiotics. The program is part of the European Commission's "Action Plan against the rising threats from Antimicrobial Resistance," introduced during November 2011.

Supported by Europe's largest public-private initiative Innovative Medicines Initiative (IMI), the research program's first projects are being funded by a combined budget of up to €223.7 million: €109 million is provided by IMI and €114.7 million comes from contributions from the pharma and biotech companies involved. Other projects within the program, along with more funding, are expected to launch in 2012.

GlaxoSmithKline and **Yale University** announced the establishment of a drug discovery research collaboration during May 2012 to design a potential new class of medicines that degrade disease-causing proteins. The collaboration joins together GlaxoSmithKline's medicinal chemistry expertise with Yale's pioneering work on proteolysis targeting chimeric molecules (PROTACs). The PROTAC technology guides disease-causing proteins to a cell's "garbage disposal" where they can be destroyed. Mutant or higher-than normal amounts of these proteins typically drive disease progression in fields such as oncology, inflammation and infections; yet many cannot be tackled by traditional methods of making drugs. Under the agreement, a joint research team will work to show that PROTACs can be turned into future medicines. GSK will then have the right to use this technology for multiple disease-causing proteins across all therapy areas.

For each protein-degrading drug discovered and developed, Yale is eligible for milestone and royalty payments. Several collaborations between GSK and UK-based universities have been announced that entail such joint working towards common milestones, along with an element of risk sharing by the parties. The partnership with Yale differs via its scope around a potential new class of medicines and because of its association with a U.S. academic center.

GSK and the **University of Nottingham** in April 2012 formalized a collaboration to establish a new lab to accommodate the Centre of Excellence for sustainable chemistry and to build an innovative carbon neutral sustainable chemistry laboratory. This deal represents progress on GlaxoSmithKline's 'green chemistry' commitment initially announced during 2010. Company execs said the carbon neutral laboratory will help affirm the UK as a global hub for the future of the life-sciences industry.

GSK announced in January 2012 that the company joined forces with other worldwide pharma companies and leading organizations in a new united effort to support developing countries to defeat neglected tropical diseases (NTDs). The organizations include the World Health Organization (WHO), the Bill & Melinda Gates Foundation, the UK Department for International Development and the U.S. Agency for International Development (USAID). NTDs affect 1-plus billion people in developing countries, resulting in illness, disability and death, and increasing the burden on over-stretched health systems.

GSK says the coalition is supporting the ambitious goals set out during January 2012 by the WHO to control or eliminate 10 of the 17 diseases designated as NTDs by the end of this decade. This includes eliminating five diseases – lymphatic filariasis (elephantiasis), guinea worm, blinding trachoma, sleeping sickness and leprosy – and controlling another five: soil transmitted helminthes (intestinal worms), schistosomiasis, river blindness, Chagas and visceral leishmaniasis – by 2020.

In support of these goals, GlaxoSmithKline expanded its significant **albendazole** donation program that targets two neglected diseases and has bolstered its commitment to support research and development efforts. GSK in January 2012 pledged to extend by another five years the company's dedication to donate 400 million albendazole tablets per year to the WHO. This will allow for de-worming of school-age children in every endemic country. Expanding this program, which was originally intended to run until 2015, will equate to another 2 billion tablets of albendazole being donated up to 2020.

GlaxoSmithKline reaffirmed the company's commitment to supply all the albendazole necessary to eliminate lymphatic filariasis worldwide by 2020. The company donates 600 million tablets of albendazole every year to WHO to prevent transmission of lymphatic filariasis, and has donated more than 2 billion doses to the WHO as of January 2012. From 2000 to 2010, GlaxoSmithKline donated 2.6-plus billion albendazole treatments to 58 countries. The overall economic benefit of the lymphatic filariasis program in 2000-2007 is conservatively estimated at $24 billion. ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

Johnson & Johnson
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New Brunswick, NJ 08933
Phone: 732-524-0400
Website: jnj.com

Johnson & Johnson

BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Remicade	$5,492	$4,610
Procrit/ Eprex	$1,623	$1,934
Risperdal Consta	$1,583	$1,500
Velcade	$1,274	$1,080
Concerta/ Methyl-phenidate	$1,268	$1,319
Prezista	$1,211	$857
Aciphex/ Pariet	$975	$1,006
Stelara	$738	$393
Levaquin, Floxin	$623	$1,357
Duragesic/ Fentanyl Transdermal	$589	$748
Risperdal/ Risperidone	$542	$527

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Revenue	$65,030	$61,587
Net income	$9,672	$13,334
EPS	$3.49	$4.78
R&D	$7,548	$6,844

	1H12	1H11
Revenue	$32,614	$32,770
Net income	$5,318	$6,252
EPS	$1.91	$2.25
R&D	$3,411	$3,620

All figures are in millions of dollars, except EPS.

Looking to regroup

The world's largest and most diverse maker of healthcare products is seeking to improve manufacturing problems and capitalize on new drugs and indications; the Synthes acquisition is providing positive effects.

By Ed Silverman ed.silverman@ubm.com and
Andrew Humphreys andrew.humphreys@ubm.com

If the past year can be summed up in just three words for Johnson & Johnson, it would have to be recalls, **Risperdal**, and Alzheimer's. The healthcare giant may have notched $65 billion in sales through a slew of subsidiaries that sell a wealth of products – from contact lenses to joint replacements and prescription drugs to cough remedies – but 2012 will likely be remembered for a string of embarrassing setbacks that helped trigger top-level managerial changes, huge legal settlements, and gaping holes on store shelves.

Although investors may be heartened by various J&J strategic moves, the overall value of its many corporate assets and some pipeline products – the stock gained more than 13.5 percent for the 12-month period ended Oct. 1, 2012, not including dividends – J&J has suffered various blows to its credibility that pose challenges as the executive team looks to restore its image with customers of all sorts.

The year began with J&J continuing its struggle to recover from a string of manufacturing gaffes that led to a consent decree with FDA; highly publicized congressional hearings; government investigations; hundreds of job losses; the closure of a key plant; a reorganization of its consumer health unit; eroded consumer confidence; numerous lawsuits and hundreds of millions of dollars in lost sales.

Millions upon millions of over-the-counter products were recalled over the past three years, including such venerable names as **Tylenol** and **Motrin**. Nearly every month, in fact, J&J was issuing another product recall, many of which were traced back to quality control problems at a plant in Fort Washington, Pa., where its **McNeil Consumer Healthcare** unit is based.

Not surprisingly, the magnitude of the problem began taking a serious toll. In April 2011, one Wall Street analyst polled doctors and asked a simple question: Has Johnson & Johnson lost its way? A majority of 53 percent said no, but this was a glass-half-full scenario – the other 47 percent answered that the healthcare giant had gone astray.


William Weldon stepped down as Johnson & Johnson CEO effective April 2012 after a challenging run of scandals for the company; he remains chairman.

Meanwhile, the J&J executive team predicted its Fort Washington plant would be back on track during 2012. But that turned out to be corporate hubris – reopening was delayed to 2014. Unfortunately, investors wanted to believe the J&J team, which has usually displayed impressive skills for managing financial results as needed, would have the same ability to make facts on the ground go their way.

The extent of the remediation costs remains unclear, but J&J has had a small army of consultants on the premises for an extended period. Meanwhile, sales of the McNeil Consumer Healthcare business have been falling – a 1.9 percent drop in the United States was registered in the second quarter of 2012 and most product segments in the unit experienced revenue setbacks.

The chain of disastrous events led to increasing calls for J&J CEO Bill Weldon to resign. For months, he rebuffed criticism and insisted he would remain until an orderly succession was arranged. Ultimately, he announced his retirement in February 2012, signaling that he would leave the c-suite in the spring, although Mr. Weldon remains chairman for the moment.

By then, however, there were also embarrassing shortages of Tampons and certain shampoos, adding to the large spaces on store shelves that have been filled by rival brands, as well as increasingly negative publicity that the J&J **DePuy** unit had allegedly been aware that its all-metal hip replacement devices failed in significant numbers long before a recall was ordered.

Mr. Weldon's departure ended a 10-year reign at the top and occurred shortly after J&J made a disappointing showing in the coveted corporate reputation poll that is undertaken each year by Harris Interactive. The results showed J&J ranked 7th on the closely watched list. This was the first time that the healthcare giant did not rank in first or second place; last year, J&J placed second on the list.

Shortly afterwards, market-research data indicated that replacing J&J's lost stature on store shelves may prove more difficult than some may assume. Between the economy, which has trained consumers to look for private-label bargains, and the ongoing lack of some J&J products, shoppers may take some convincing before they again reach for Tylenol and Motrin, among other brands.

For instance, sales of private-label acetaminophen for adults rose nearly 14 percent last year from 2010, while Tylenol was often out of stock. In the children's pain category, sales of private-label acetaminophen rose more than 30 percent compared to 2010. And rival brands – **Pfizer** Inc.'s **Advil**, and **Bayer** AG's **Aleve** and **Bayer Aspirin** – rose 7.3 percent, 6 percent and 8.9 percent, respectively, in 2011 compared to the previous year.

Tylenol pain relievers declined 28.1 percent from 2008 to 2011 and J&J Cold brands, which include **Tylenol Cold** and **Sudafed** for adult and children markets, decreased 47.3 percent during the same period, according to Kline & Co. The market-research firm conducted the analysis by collecting online data from over 300 consumers during the winter of 2011/2012.

Overcoming such statistics will prove challenging for Alex Gorsky, who succeeded Mr. Weldon as CEO. However, the 53-year-old executive, who has worked for many years at the healthcare giant – with a spell in between at **Novartis** Pharmaceuticals – must prove that he is part of the solution, not the problem. And such concerns reflect his role in the marketing of Risperdal.

The antipsychotic Risperdal, of course, has been a legal boondoggle for the healthcare giant, although a profitable one. But J&J has been fending off a slew of civil and criminal charges that the pill was marketed illegally in various ways for more than a decade. In fact, a reported $2.2 billion settlement has been expected for months with the U.S. Department of Justice.

Over the past year, though, J&J has long cases against several states claiming they were misled about the drug's safety and risks and, as a result, their Medicaid programs overpaid. In April 2012, an Arkansas judge fined J&J $1 billion. In 2011, the company was ordered by a South Carolina judge to pay $327 million for deceptive marketing, which he called detestable.

The biggest defeat, though, came in Texas, where J&J agreed to a $158 million settlement after less than a week of blistering testimony that painted a highly unflattering portrait of its marketing efforts. The case actually paved the way for the numerous federal and state probes over the past several years and was begun by a former Pennsylvania state auditor, who was fired for his whistleblowing.

During August 2012, J&J paid $181 million to resolve claims by 36 states and the District of Columbia. The deal included various provisions, though, that some legal experts described as significant, especially one that restricts the ability of J&J to use sales and marketing personnel to distribute peer-reviewed reprints of journal articles that contain off-label information.

For his part, Mr. Gorsky has been silent – and for good reason. During 2012, the Justice Department sought to depose him in a case involving the **Omnicare** Inc. nursing home pharmacy. J&J denied claims in a whistleblower lawsuit charging Omnicare received kickbacks – in the form of rebates, educational grants and payments for marketing data – so Risperdal would be prescribed more often.

J&J argued that Mr. Gorsky "has no reasonable connection to the subject matter of the government's complaint and was not involved in the facts underlying this case." But the Justice Department also pointed out that he was, effectively, the go-to guy when it came to Omnicare and Risperdal, and no one else possessed the same level of knowledge.

Here is why: from October 1998 to October 2001, Mr. Gorsky was VP of marketing at the **Janssen Pharmaceutica** Inc. unit that marketed Risperdal, and from October 2001 to early 2003 he was the Janssen president. During that time, he was responsible for selling Risperdal, and Omnicare was the biggest Risperdal customer. Moreover, Mr. Gorsky instituted a Janssen compliance program for regulatory and legal issues.

He also regularly received monthly reports with details about Omnicare efforts to promote Risperdal prescribing. And Mr. Gorsky met repeatedly with senior Omnicare executives to discuss those efforts. Ultimately, the deposition was thwarted, but some damage was done. How so? The newest J&J chief executive may have played a role in yet another scandal hurting the healthcare giant.

Such issues helped investors win a so-called derivative shareholder lawsuit in which a group of J&J shareholders charged that the healthcare giant's board of directors breached their fiduciary duty, despite a series of red flags in the form of FDA warning letters; government subpoenas; a criminal plea to kickback charges; whistleblower lawsuits; the many product recalls and off-label marketing charges.

During the summer of 2012, J&J reached a settlement by agreeing to create a board-level committee to ensure that its numerous subsidiaries comply with FDA regulations. The healthcare giant also agreed to adopt companywide risk-management policies in hopes of catching problems before they mushroom into the sort of crises that have plagued its operations for the past few years.

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Shortly after striking the deal, Mr. Gorsky hired Bayer executive Sandra Peterson as a so-called group worldwide chairman and a member of the executive committee. Her responsibilities include overseeing the troubled consumer health unit and manufacturing operations, which have haunted the healthcare giant for nearly three years amid its startling series of managerial gaffes.

By hiring Ms. Peterson, Mr. Gorsky was trying to signal a new approach toward tackling these problems. Rather than promote someone from within the vast J&J ranks, he went outside for a key hire. To what extent Ms. Peterson can soon make a difference remains to be seen, but her arrival is meant to be symbolic, especially in the wake of the shareholder lawsuit that calls for beefing up internal oversight.

The hiring, which was the biggest personnel move Mr. Gorsky made since becoming chief executive, also seemed to dampen speculation that J&J may look to sell all or parts of its troubled consumer health unit, given its systemic and ongoing problems. Such a move, which has been touted by a few analysts, would dismantle the three-legged product strategy – drugs, devices and consumer health items.

Whether Mr. Gorsky would want to preside over such a radical move is unclear. J&J has long relied on consumer health to provide steady cash flow during times when its drug and device businesses – which are notoriously more cyclical – encounter slow stretches. For now, though, the consumer business is not in tip-top condition, suggesting such a step is unlikely, if only because its value has eroded.

Of course, Wall Street analysts correctly note that J&J – with more than 250 operating companies – is bigger than the sum of its parts. And the healthcare giant has scored some successes, notably with new pharmaceuticals over the past year, which have kept investor attention focused on product development instead of the courtroom or manufacturing plants. In their view, the litigation and quality-control problems are largely winding down.

Among the new medications that have given shareholders reason for optimism is the **Zytiga** prostate cancer treatment; the **Incivo** drug and follow-up in Phase III development for hepatitis C; and the **Xarelto** blood thinner, which was developed in conjunction with Bayer. All three medicines are competing in some of the fastest-growing therapeutic categories.

"These products are starting to help accelerate sales growth of J&J's pharmaceutical franchise," wrote Wells Fargo Securities analyst Larry Biegelsen in a recent investor note. "We believe J&J's business is starting to turn the corner from many of the challenges of 2011 and expect the pipeline to deliver accelerating growth."

Zytiga, for instance, was approved during 2011 by U.S. and EU health authorities in combination with prednisone to treat metastatic castration resistant prostate cancer (mCRPC) patients who have previously received docetaxel-based chemotherapy. In August 2012, FDA granted priority-review status for an application to use the medicine to treat mCRPC patients who have not undergone chemotherapy, which would significantly widen the market. Mr. Biegelsen expects more than $500 million in U.S. sales for the product during 2012.

Zytiga (abiraterone) is additionally under EU regulatory review to treat mCRPC prior to chemotherapy. The pending U.S. and EU applications are also intended to extend the use of Zytiga administered with prednisone to include treating patients with mCRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy.

Meanwhile, Xarelto is closing the gap with **Pradaxa**, a blood thinner that is marketed by **Boehringer Ingelheim** GmbH, and continues to benefit from delays that Pfizer and **Bristol-Myers Squibb** Co. have encountered in gaining FDA approval for their **Eliquis** blood thinner. These treatments were designed as a new generation of blood-clot treatments to supplant warfarin, which is the standard of care.

Xarelto, which was approved to prevent strokes in patients with atrial fibrillation, has also benefited from concerns about the rate of side-effect reports showing bleeding in Pradaxa patients. So far, though, the FDA has declined to endorse Xarelto for preventing heart attacks and strokes in patients with acute coronary syndrome. Just the same, Mr. Biegelsen forecasted $208 million in U.S. sales in 2012.

Unfortunately for J&J, some of the biggest headlines its pharma business generated during 2012 were about a disappointment – the failure of the **bapineuzumab** treatment for Alzheimer's disease to meet study goals. Although the results had largely been expected – a study of the same drug showed discouraging signs four years ago – the outcome marked a bet gone bad.

In short, the top-line results from a study in patients with mild-to-moderate Alzheimer's disease who do not carry the ApoE4 genotype filed to meet co-primary endpoints – a change in cognitive and functional performance compared to placebo. An earlier study, which involved patients who do carry this genotype, met a similar fate.

Just the same, the studies had little effect on shareholders, who were primed to expect failure given the difficulties in developing successful Alzheimer's treatments. For that reason, J&J escaped largely unscathed since anything resembling a positive outcome would have represented a huge upside victory for the company.

"While bapineuzumab had garnered much investor attention in recent months," Mr. Biegelsen correctly pointed out, "we note that the failed studies represent a small negative and that J&J's late-stage R&D pipeline remains quite robust." Of course, the pipeline may be filled with possibilities, but how many reach pharmacy and hospital shelves is another matter.

Company performance

J&J's global sales for full-year 2011 totaled $65.03 billion, an increase of 5.6 percent compared to the prior year. Operational sales for 2011 rose 2.8 percent and the positive impact of currency was 2.8 percent. Domestic sales declined 1.8 percent versus 2010. International sales for 2011 improved 12.4 percent, reflecting operational growth of 7 percent and a positive currency impact of 5.4 percent.

Net earnings and diluted EPS for 2011 came to $9.67 billion and $3.49. J&J reported that the 2011 net earnings reflect after-tax charges of $4.2 billion. The after-tax charges include product-liability expenses, the net impact of litigation settlements, a previously announced restructuring charge by **Cordis** Corp., costs associated with the DePuy **ASR Hip** recall program, and an adjustment to the value of a currency option and costs related to the planned acquisition of **Synthes** Inc. Full-year 2010 net earnings of $13.33 billion included a net after-tax gain of $55 million representing product-liability expenses, the net impact of litigation settlements, and costs associated with the DePuy ASR Hip recall program. Excluding these special items in both years, net earnings for 2011 amounted to $13.9 billion (+4.4 percent versus 2010) and diluted EPS were $5.00 (+5 percent).

"We delivered solid results for 2011, built on the strong growth of our recently launched pharmaceutical products, and continued the steady momentum of new product approvals across all our businesses," Mr. Weldon noted. "Our talented people are focused on bringing meaningful innovations to patients and customers to address significant unmet needs, positioning us well to deliver sustainable leadership and profitable growth in health care."

Global Consumer sales of $14.88 billion during 2011 marked year-over-year growth of 2 percent, consisting of an operational decrease of 0.7 percent and a positive impact from currency of 2.7 percent. Domestic sales for 2011 declined 6.7 percent compared to the prior year. International 2011 sales advanced 7.3 percent, which reflected an operational increase of 2.9 percent and a positive currency impact of 4.4 percent.

U.S. sales of OTC medicines were significantly affected by the suspended manufacturing at the McNeil Consumer Healthcare facility in Fort Washington and the impact on production volumes related to continuing efforts to enhance quality and manufacturing systems. Positive contributors to 2011 operational results were international sales of OTC medicines; **Neutrogena** skin-care products; baby-care products; and **Listerine** antiseptic mouthrinse.

Global Pharmaceutical sales of $24.37 billion in 2011 represented growth of 8.8 percent compared to 2010, with an operational increase of 6.2 percent and a positive impact from currency of 2.6 percent. Domestic sales dropped off 1.1 percent versus 2010. International 2011 sales rose 21.3 percent, which reflected operational growth of 15.5 percent and a positive currency impact of 5.8 percent. J&J's U.S. Pharmaceutical sales in 2011 were negatively impacted by generic competition for **Levaquin**, a bacterial infection treatment.

Remicade remained firmly atop J&J's sales chart in 2011, growing 19.1 percent to $5.49 billion.

In January 2012, J&J announced earnings guidance for full-year 2012 of $5.05 to $5.15 per share, excluding the impact of special items. The guidance reflects operational growth of 3.5 percent to 5.5 percent, partially offset by a projected negative currency impact of 2.5 percent. Upon announcing the company's first-half 2012 performance, J&J readjusted its earnings guidance for full-year 2012 to $5.00-$5.07 per share. The guidance excludes the impact of special items and reflects the negative effect of recent currency movements, partially offset by the positive contribution from the Synthes deal.

Through the first six months of 2012, J&J's total worldwide sales were down compared to the first half of 2011. Global sales totaled $32.61 billion for January-June 2012, decreasing 0.5 percent versus the corresponding one-year-earlier period.

Of the three major businesses, Pharmaceuticals was the only one to generate year-over-year worldwide sales growth for the first half of 2012, at 1.1 percent to $12.42 billion. International pharma sales lead the way with 11.3 percent growth over first-half 2011, coming in at $6.3 billion. The U.S. performance was a different story though as 1H 2012 sales fell 7.7 percent to $6.12 billion.

The Medical Devices & Diagnostics segment produced nearly flat growth during first-half 2012 at $12.98 billion (1H 2011 = $13 billion). U.S. global sales improved 1.6 percent to $5.83 billion for January-June 2012. International Medical Device & Diagnostics sales decreased by that same percentage to $7.15 billion for the 2012 first half.

The Consumer business generated worldwide decreases across the board for first-half 2012. Total sales fell 3.5 percent to $7.21 billion in comparison to the first six months of 2011. U.S. sales dropped 2 percent to $2.63 billion and international sales declined 4.3 percent to $4.59 billion.

Acquisitions

J&J in June 2012 completed the acquisition of Synthes for a total price tag of $19.7 billion in cash and stock. As a result, Synthes is being integrated with the DePuy franchise to establish the **DePuy Synthes** Companies of Johnson & Johnson. The definitive merger deal was originally announced in April 2011. West Chester, Pa.-based Synthes is regarded as a premier worldwide manufacturer of orthopaedic devices.

"The completion of the Synthes acquisition creates the world's most innovative and comprehensive orthopaedics business and reflects our long-standing strategy of leadership within attractive healthcare markets," Mr. Gorsky said. "The combination of these two respected leaders – Synthes and DePuy – will enable us to better serve clinicians and patients worldwide, bring new innovations to the marketplace in orthopaedics and neurologics, and strengthen our ability to compete in developing markets."

DePuy possesses one of the most diverse orthopaedics portfolios in the industry. Synthes is well-known for the company's innovations in trauma, spine, cranio-maxillofacial and power tools. Combined, the companies offer surgeons and patients a unique breadth and depth of technology and service around the globe to meet their orthopaedic needs.

J&J's **Janssen-Cilag** GmbH in June 2012 completed the acquisition of **Corimmun** GmbH, a privately held drug-development company based in Germany. Janssen-Cilag made an undisclosed up-front payment and is responsible for a contingent future clinical milestone payment. Corimmun's lead compound, **COR-1**, is a small cyclic peptide undergoing early clinical development for treating heart failure. The drug candidate has been demonstrated in preclinical studies to improve heart function by decreasing autoimmune, beta-1 receptor-simulating antibody effects. Janssen and its affiliates immediately assumed full development and worldwide commercialization responsibilities for COR-1.

Johnson & Johnson (China) Investment Ltd. announced in May 2012 the acquisition of **Guangzhou Bioseal** Biotech Co. The privately held biopharma company specializes in the design, development and commercialization of a porcine plasma-derived biologic product for controlling bleeding during surgery. Guangzhou Bioseal manufactures a porcine-derived fibrin sealant called **Bioseal**, the only porcine plasma-derived fibrin sealant approved for use in China as of May 2012. Fibrin sealants are utilized by surgeons as an adjunct to hemostasis for use in patients undergoing surgery, when control of bleeding by standard surgical techniques is not effective or practical.

Guangzhou Bioseal is working closely with Ethicon, which offers the world's most complete line of absorbable hemostats and is dedicated to advancing the future of biosurgery beyond hemostasis, to seal leaks, join structures and en-

hance healing. Ethicon biosurgery brands on the Chinese market include **Surgicel** and **Surgiflo**.

This acquisition is the first in the medical device arena for Johnson & Johnson (China). The corporation has been conducting business in China for 25-plus years. This includes the establishment of a new innovation center in China during 2011 to design and develop medical devices and diagnostic products specifically for Asia's emerging markets. The acquisition reinforces J&J's long-standing dedication to providing medical solutions in Asia that help to improve the standard of health care for millions of people in the region.

The Guangzhou Bioseal acquisition complements Ethicon's existing biosurgery portfolio. The acquisition enables the business to immediately enter the Chinese fibrin sealant market, broaden product offerings, and create an opportunity to increase worldwide reach by launching advanced biologic solutions that meet the various needs of more physicians and patients throughout Asia and worldwide.

Product performance

J&J's top-selling brand is **Remicade**, which treats various immune-mediated inflammatory diseases. With 2011 global sales of $5.49 billion for J&J, the biologic therapy generated 8.4 percent of the company's total revenue for that year. The sales figure represented a 19.1 percent increase over the 2010 amount of $4.61 billion. On a combined basis, Remicade's U.S. export and international sales for 2011 rose nearly 50 percent over the prior year due to the impact of a deal with **Merck** & Co., complemented by international market growth.

During April 2011, J&J and Merck struck a pact that included distribution rights to Remicade and **Simponi**. As a result, effective July 1, 2011, certain territories were relinquished to J&J that were previously supplied by Merck. At that time, the company started recording sales of the products – previously recorded by Merck – from particular territories such as Canada, Brazil, Australia, and Mexico.

Remicade was initially cleared by FDA for moderately to severely active Crohn's disease as well as fistulizing Crohn's disease indications in August 1998. The drug's most recent U.S. approval came during September 2011: for treating moderately to severely active ulcerative colitis in pediatric patients.

In first-half 2012, Remicade global sales for J&J grew 14.6 percent on a reported basis compared to January-June 2011 to $3.04 billion. J&J attributes the performance primarily to incremental sales from international territories included in the amended distribution deal with Merck. U.S. sales for the product in 1H 2012 rose 9.1 percent year-over-year to $1.77 billion.

J&J's second-best-selling prescription medicine is **Procrit/Eprex**, which stimulates red blood cell production. The U.S. version, Procrit, was initially approved by FDA regulators on June 1, 1989. The drug is indicated for treating anemia due to chronic kidney disease, including patients on dialysis and not on dialysis to decrease the need for red blood cell transfusion. Procrit is indicated for treating anemia in patients with non-myeloid malignancies where the condition results from the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy. The product is also approved by FDA to reduce the need for allogeneic red blood cell transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.

Global sales during 2011 amounted to $1.62 billion, representing a 16.1 percent drop-off from the 2010 figure. The sales decline for Procrit/Eprex continued in first-half 2012, falling 10.9 percent year over year to $777 million. Decreased sales were mainly due to a declining market for erythropoiesis stimulating agents and increased competition for Eprex overseas.

The Risperdal franchise has generated annual billion-dollar sales for J&J since the 1990s. Initially FDA-approved in December 1993, Risperdal continues to help patients around the globe who suffer from the debilitating effects of schizophrenia and bipolar mania. The long-acting formulation of the atypical antipsychotic drug – **Risperdal Consta** – entered the U.S. market in December 2003.

Risperdal/risperidone sales for 2011 increased 2.8 percent over the previous year to $542 million. Risperdal Consta produced 2011 sales of $1.58 billion, with growth of 5.5 percent versus 2010. Total U.S. sales of J&J's long-acting injectables, including Risperdal Consta and **Invega Sustenna**, rose by strong double digits over 2010 because of an increase in the company's combined market share in the antipsychotic market.

Invega was first approved by the U.S. regulatory agency during December 2006 for treating schizophrenia. The once-monthly formulation of the medicine, Invega Sustenna, was given the green light by FDA in July 2009. The overseas version of Invega Sustenna, **Xeplion**, was granted EU clearance during March 2011.

Invega 2011 global sales registered at $499 million, up 17.7 percent versus 2010. U.S. sales grew 5.6 percent to $285 million, and international sales climbed up 39 percent to $214 million for 2011.

For first-half 2012, J&J reported Risperdal Consta global sales of $716 million, which were down 11.4 percent compared to the one-year-earlier period. For the 2012 first-half reporting period, global Invega sales advanced 6 percent versus the first six months of 2011 to $263 million. Invega Sustenna/Xeplion worldwide sales rose from $142 million during first-half 2011 to $356 million during January-June 2012.

Velcade was introduced in the U.S. arena during May 2003 as an intravenous injection for treating multiple myeloma, a blood-based cancer. Velcade is the market leader for relapsed multiple myeloma with more than 300,000 patients treated around the globe. The product was jointly developed by **Millennium** Pharmaceuticals Inc. and Janssen Pharmaceutical Companies. Millennium is responsible for U.S. commercialization of Velcade, and Janssen mar-

kets the drug in Europe and the rest of the world. **Takeda** Pharmaceutical Co. and **Janssen Pharmaceutical** K.K. jointly promote the medicine in Japan.

Velcade 2011 sales (all generated internationally) for J&J tallied at $1.27 billion, with the 18 percent improvement over 2010 mainly due to strong growth in Asia and Latin America. The first-half 2012 amount reached $671 million, up 7 percent compared to the total produced during January-June 2011.

Containing the active ingredient methylphenidate HCl, **Concerta** is marketed for treating attention deficit hyperactivity disorder. Concerta's sales for 2011 totaled $1.27 billion, falling 3.9 percent versus the 2010 amount. According to J&J, all non-U.S. regions generated sales growth in 2011, with total international sales rising 14.4 percent to $446 million. U.S. sales decreased 11.5 percent compared to 2010, amounting to $822 million.

U.S. sales for Concerta/methylphenidate continued to decline during January-June 2012, dropping 29.7 percent from 1H 2011 to $343 million. International sales remained positive, rising 4.5 percent to $233 million. Total global sales for 1H 2012 came to $576 million, down 19 percent versus the first six months of 2011.

A U.S. supply and distribution deal with **Watson** Laboratories Inc. to distribute an authorized generic form of Concerta became effective May 1, 2011. In September 2012, J&J's **Alza** Corp. agreed to grant **Impax** Laboratories Inc. and **Teva** Pharmaceuticals USA Inc. a license to sell generic versions of Concerta on July 14, 2013, or earlier under certain circumstances.

The HIV treatment **Prezista** represents a newer-generation blockbuster for J&J. 2011 marked the first time Prezista topped the annual $1 billion mark, with sales rising 41.3 percent over 2010 to $1.21 billion. In 2011, the protease inhibitor generated U.S. sales of $529 million (+31.9 percent) and the international total reached $682 million (+49.6 percent).

The strong growth pattern continued in first-half 2012, with U.S. sales improving 28.3 percent to $326 million. International sales for Prezista climbed up 14.2 percent to $371 million. In total, the drug's global sales advanced 20.4 percent versus first-half 2011 to $697 million.

The drug was developed by **Tibotec** Pharmaceuticals Ltd. and is marketed by **Janssen Therapeutics**, a division of **Janssen Products** LP. Prezista was initially cleared for marketing by FDA during June 2006 as an accelerated approval. The initial indication was for Prezista, co-administered with 100-mg ritonavir and other antiretroviral agents, as a treatment for human immunodeficiency virus infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor. Prezista is available for once-a-day oral administration of 800mg, as two 400-mg tablets. The product is awaiting FDA approval for use as one 800-mg tablet.

Aciphex/Pariet global sales in 2011 dropped below the billion-dollar mark to $975 million, representing a 3.1 percent decrease. The drop-off for the proton-pump inhibitor was attributed to increased competition from generics in the category. For 2011, sales in the United States fell 12.8 percent to $414 million and international sales advanced 5.6 percent to $561 million versus 2010.

J&J's U.S. and international sales for Aciphex/Pariet decreased in first-half 2012 versus the one-year-earlier period. U.S. sales were down 4.8 percent versus January-June 2011 to $200 million; internationally, the figure fell 8 percent to $254 million. In total, global sales for first-half 2012 fell 6.6 percent to $454 million.

Pariet debuted in Japan during 1997. Launches followed during 1998 in Europe (as Pariet) and during 1999 in the United States (as Aciphex). The gastrointestinal disorders drug is jointly marketed with **Eisai** Co.

The human interleukin (IL)-12 and IL-23 antagonist **Stelara** is marketed for treating adult patients 18 years or older with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy. IL-12 and IL-23 are naturally occurring proteins believed to have a role in psoriasis.

Janssen Biotech discovered Stelara and has exclusive U.S. marketing rights. Janssen Pharmaceutical Companies hold exclusive global marketing rights to the drug, which is approved for treating moderate-to-severe plaque psoriasis in at least 65 countries.

Stelara generated worldwide 2011 sales totaling $738 million, increasing an impressive 87.8 percent versus its 2010 total. U.S. sales skyrocketed 84.6 percent to $443 million for 2011, and international growth was registered at 92.8 percent by reaching $295 million. The product in on its way to attaining blockbuster sales status by 2013. During 1H 2012, global sales amounted to $469 million, marking growth of 37.1 percent compared to the first six months of 2011. An EvaluatePharma June 2012 report projected Stelara sales of $2.54 billion for 2018.

Levaquin and **Floxin** have been marketed by J&J since the 1990s for treating bacterial infections. Levaquin lost U.S. market exclusivity during June 2011 and thus became subject to generic rivals. As a result, 2011 sales of Levaquin and Floxin in the United States fell 55.9 percent to $579 million. International sales during 2011 came to $44 million compared to $45 million one year earlier. Globally, 2011 sales amounted to $623 million versus $1.36 billion during 2010. The spiral continued during 1H 2012, as U.S. sales dropped from $571 million in January-June 2011 to $25 million, and worldwide sales plummeted from $593 million to $45 million.

Pipeline updates and recent product approvals

The investigational sodium glucose co-transporter 2 (SGLT2) inhibitor **canagliflozin** is awaiting U.S. and EU marketing approval for treating patients with type 2 diabetes. The kidneys of type 2 diabetes patients reabsorb greater amounts of glucose back into the body versus non-diabetic people, which may lead to elevated glucose levels. Canagliflozin blocks the reabsorption of glucose by the kidney, increasing glucose excretion and reducing blood-glucose levels.

The worldwide Phase III canagliflozin development program enrolled 10,285 patients in nine trials. This is the largest late-stage clinical program for an investigational pharmacologic product for treating type 2 diabetes that has been filed with health authorities. **Janssen Research & Development** LLC in early October 2012 announced that use of canagliflozin substantially lowered blood-glucose levels when used as add-on therapy in patients on insulin therapy for type 2 diabetes and who are considered to be at greater risk for cardiovascular disease.

Janssen and its affiliates have rights to canagliflozin via a license pact with **Mitsubishi Tanabe** Pharma Corp. **Janssen Pharmaceuticals** Inc. and its affiliates hold marketing rights in North America, South America, Europe, Middle East, Africa, Australia, New Zealand and parts of Asia.

Janssen Biotech and **Astellas** Pharma Inc. agreed during early October 2012 to globally develop and commercialize **ASP015K** (except in Japan). ASP105K blocks critical components of signaling mechanisms used by various inflammatory cytokines, including those that are believed to be significant to mediating disease in people with immune-mediated inflammatory diseases. The oral, small-molecule Janus kinase inhibitor is undergoing Phase IIb studies as a once-daily oral treatment for moderate-to-severe rheumatoid arthritis.

The European Commission during September 2012 approved the marketing authorization for **Dacogen** for treating adult patients (age 65 years and above) with newly diagnosed *de novo* or secondary acute myeloid leukemia – according to the World Health Organization (WHO) classification – who are not candidates for standard induction chemotherapy. The product additionally has Orphan Drug designation for treating acute myeloid leukemia.

The DNA hypomethylating agent Dacogen is approved for treating myelodysplastic syndromes in 35-plus countries, including the United States, Brazil, China, India, Korea, Russia and Turkey. **Janssen-Cilag International** NV and its affiliates hold Dacogen marketing and development rights in all markets except the United States, Canada and Mexico. Rights in those countries are maintained by Janssen's strategic partner Eisai Inc. and its affiliates.

A subcutaneous version of Velcade was approved by FDA for treating multiple myeloma and relapsed mantle cell lymphoma during January 2012. The subcutaneous form also was cleared for marketing for treating multiple myeloma by the European Commission during September 2012. Subcutaneous Velcade is regarded as a significant new option for multiple myeloma patients, especially those who may not be eligible or suitable for Velcade I.V. treatment.

Janssen Biotech announced in September 2012 the filing of a biologics license application to FDA for Simponi. The application requests approval of an investigational intravenous form of the anti-tumor necrosis factor-alpha drug for treating adults with moderately to severely active rheumatoid arthritis. In other Simponi news, a supplemental application was filed with U.S. and EU regulators during July 2012 for the drug to treat adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Xarelto is awaiting FDA approval for a new use: to reduce the risk of stent thrombosis in patients with acute coronary syndrome. The drug's supplemental new drug application was withdrawn by Janssen Research & Development on July 9, 2012. This action followed FDA's request in a letter issued to Janssen on June 21, 2012, that the application include more specific information. On Sept. 7, 2012, Janssen Research & Development announced that the company had submitted a complete response to the U.S. regulatory agency.

The oral anticoagulant is also awaiting FDA clearance to treat patients with deep-vein thrombosis and pulmonary embolism, and to prevent recurrent deep-vein thrombosis and pulmonary embolism. The supplemental new drug applications were subject to FDA priority review as of July 2012.

Xarelto is FDA-approved for three clinical uses: to reduce the risk of blood clots in the legs and lungs of people who have just had knee-replacement surgery, to reduce this risk in people who have just had hip-replacement surgery, and to reduce the risk of hemorrhagic and thrombotic strokes as well as other blood clots in people with atrial fibrillation not caused by a heart-valve problem.

Bedaquiline has received FDA priority review to treat pulmonary, multi-drug resistant tuberculosis in adults as part of combination therapy, according to a September 2012 announcement. One month earlier, the oral treatment was filed for approval in the European Union. Bedaquiline is a diarylquinoline drug discovered by Janssen scientists. If cleared for marketing, bedaquiline could be one of the first drugs with a new mechanism of action for tuberculosis in more than 40 years and one of the first ever to be specifically indicated for multi-drug resistant tuberculosis.

A supplemental new drug application was approved by U.S. regulators during August 2012 for **Nucynta ER** extended-release tablet. The twice-per-day oral analgesic was approved for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is necessary for an extended period of time. This is the first opioid FDA-approved for neuropathic pain associated with diabetic peripheral neuropathy. Nucynta ER was first cleared for U.S. marketing in August 2011 for the management of moderate-to-severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is required for an extended duration of time.

Nucynta ER is marketed in the United States by Janssen Pharmaceuticals and in Canada by Janssen Inc. **Grünenthal** GmbH discovered the drug's active chemical, tapentadol, and markets immediate-release and extended-release versions of it in several countries as **Palexia**.

Janssen Research & Development and Janssen Pharmaceutical K.K. are developing tapentadol in Japan. Janssen Pharmaceutical Companies have rights to develop and market immediate-release and extended-release forms of tapentadol in certain countries in Europe, Latin America, the Asia-Pacific region, Africa and the Middle East.

Janssen Biologics (Ireland) along with **GlaxoSmithKline** plc started the Phase III clinical program for **sirukumab** in August 2012. The human anti-interleukin (IL)-6 monoclonal antibody is being studied for treating adults with moderately to severely active rheumatoid arthritis. The investigational human monoclonal IgG1 kappa antibody targets the cytokine interleukin (IL)-6, a naturally occurring protein believed to have a role in autoimmune conditions such as RA. Janssen Biologics (Ireland) and GSK entered into a joint-development and co-commercialization license deal during December 2011 for sirukumab to treat rheumatoid arthritis. Before this deal, Janssen Research & Development was developing sirukumab for rheumatoid arthritis.

New five-year data released in June 2012 demonstrated a consistent efficacy and safety profile for Stelara in treating moderate-to-severe plaque psoriasis. These findings are from the only psoriasis clinical-study program for a biologic following patients continuously for five years. Also during June 2012, new Phase III data showed that Stelara significantly reduced signs and symptoms of active psoriatic arthritis. Treatment with the medicine additionally resulted in significant improvements in physical function, enthesitis and dactylitis, and plaque psoriasis.

Intelence gained FDA approval in March 2012 for a new indication. The drug now can be administered in combination with other antiretroviral medications for treating human immunodeficiency virus 1 in treatment-experienced pediatric patients, from 6 years to less than18 years old, who are experiencing virologic failure with HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretrovirals. This approval makes Intelence the first NNRTI indicated for this use in both treatment-experienced children and adults with resistance to an NNRTI and other antiretrovirals. ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

Eli Lilly and Co.
Lilly Corporate Center
Indianapolis, IN 46285
Website: lilly.com

BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Zyprexa	$4,622	$5,026
Cymbalta	$4,162	$3,459
Alimta	$2,461	$2,209
Humalog	$2,368	$2,054
Cialis	$1,876	$1,699
Humulin	$1,249	$1,089
Evista	$1,067	$1,024
Forteo	$950	$830
Strattera	$620	$577

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Sales	$24,287	$23,076
Net income	$4,348	$5,070
EPS	$3.90	$4.58
R&D	$5,021	$4,884
	1H12	**1H11**
Sales	$11,203	$12,092
Net income	$1,935	$2,253
EPS	$1.73	$2.02
R&D	$2,472	$2,385

All figures are in millions of dollars, except EPS.

After the flood

With the loss of Zyprexa and pending losses of Cymbalta and Humalog, leaders at Eli Lilly and Co. are buckling down for a bumpy ride.

By Joshua Slatko joshua.slatko@ubm.com

The so-called "patent cliff" over which much of big pharma must navigate of late is hitting Eli Lilly and Co. particularly hard. The company's long-standing best-seller Zyprexa, representing 19 percent of its total revenue in 2011, lost patent protection in October of last year; the multi-billion dollar seller Gemzar fell off-patent in 2010; and two more blockbuster products representing another 27 percent of 2011 revenue – Cymbalta and Humalog – will go off-patent in 2013. Lilly executives have even devised a name for this time of ill-fortune – they call it the YZ period – and they have been digging in to prepare for some time.

"Our strategy for YZ is to continue to grow sales volumes of our currently marketed products, harvest the fruits of our investments in our counter-cyclical growth engines, and supplement our internal growth with business development – while improving productivity," says John C. Lechleiter, Ph.D., Lilly's chairman, president, and CEO. "This will allow us to fund our innovation-based strategy and, specifically, a pipeline that can deliver long-term growth."

The counter-cyclical growth engines Dr. Lechleiter was talking about delivered in a big way in 2011. Elanco, Lilly's animal health business, grew its revenue by 21 percent for the year, while the company enjoyed 31 percent growth in both Japan and China. And the company appears to be meeting its productivity targets as well; since 2004, Lilly has doubled productivity as measured by sales per employee, and an organizational resizing for the post-Zyprexa era has reduced senior management by a quarter and cut projected expenses by more than $1 billion and staff by more than 5,500, excluding strategic additions from acquisitions and in high-growth emerging markets and Japan. Results from the pipeline, though, have been more mixed. While a number of compounds brewing in the Lilly-Boehringer Ingelheim diabetes partnership returned positive study results of late, this past August brought bad news for high-hope drugs in late-stage development in schizophrenia and Alzheimer's disease.

Lilly's sales for 2011 totaled $24.29 billion, up 5.2 percent compared with the previous year. As in 2010, the company's international growth exceeded its domestic performance, though this time the difference was much greater; U.S. sales rose just 1 percent to $12.98 billion after 5 percent growth in 2010, while ex-U.S. revenue was up 11 percent to $11.31 billion after 7 percent growth the previous year. Net income for the year dropped 14.2 percent to $4.35 billion, a circumstance which company executives blamed on a lower gross margin percentage; increased marketing, selling, and administrative costs; higher other expense; and the increased impact of collaboration costs, restructuring charges, and costs relating to U.S. healthcare reform. Earnings per share for the year dropped accordingly, from $4.58 to $3.90. Suffering from the growing impact of Zyprexa's loss, Lilly's sales for the first half of 2012 tumbled 7.4 percent to $11.2 billion, while net income dropped 14.1 percent to $1.93 billion and earnings per share were down 29 cents to $1.73. Company executives are estimating full-year earnings per share for 2012 at between $3.29 and $3.39, which would represent a decrease of between 13 percent and 15.6 percent.

Acquisitions and partnerships

In July 2011, Eli Lilly India and **Lupin** Ltd. entered into a strategic collaboration to promote and distribute Lilly's **Huminsulin** range of products, including Huminsulin R, Huminsulin NPH, Huminsulin 50/50, Huminsulin 30/70, and Humapen Ergo II. Lupin's India formulations business will promote and distribute the range of products in India and Nepal, virtually doubling the number of sales representatives behind the diabetes care product. This collaboration will double the current customer base; about 45,000 doctors will now be called on as a result of the new partnership.

According to Lilly leaders, caring for diabetes patients in India is a company priority. The country has an estimated 51 million people with diabetes currently and will have an estimated 85 million by 2030, or nearly one-fifth of all patients with diabetes globally. Lilly hopes to increase access to Huminsulin products through its relationship with Lupin India, bringing one of the most basic and proven therapies for diabetes treatment to more patients.

Lupin's India formulation business will deploy a sales force of medical representatives to provide education and resources to physicians and patients. Lupin has a significant presence in the Indian pharmaceuticals market and has over the past several years made major strides in expanding its therapy portfolio. The company also has a strong promotion and distribution setup along with a presence in various therapeutic areas, including the fast-growing diabetes market. This strategic collaboration, company leaders believe, will achieve synergy arising from the strength of the product portfolio of Lilly and the promotion and distribution capabilities of Lupin.

"Our strategy for YZ is to continue to grow sales volumes of our currently marketed products, harvest the fruits of our investments in our counter-cyclical growth engines, and supplement our internal growth with business development - while improving productivity," says John C. Lechleiter, Ph.D., Lilly's chairman, president, and CEO. "This will allow us to fund our innovation-based strategy and, specifically, a pipeline that can deliver long-term growth."

"As our highest priority, diabetes is a clear 'must win' for Lilly Emerging Markets," says Eberhard Ludewigs, VP, Emerging Markets, Lilly. "This partnership will allow us to change our game in India. We will have a stronger footprint with many more sales representatives promoting our diabetes brands, and this will become a foundation to expand our diabetes business not only for current products, but also for our future pipeline. Lupin is well-aligned with Lilly's goal of expansion in India and other emerging markets."

In January, Elanco, Lilly's animal health division, signed an agreement to acquire ChemGen Corp., a privately held bioscience company specializing in the development and commercialization of innovative feed enzyme products that improve the efficiency of poultry, egg, and meat production. Feed enzymes are naturally occurring digestive enhancers that can help animals unlock and better use nutrients in the feed that were otherwise unavailable. The acquisition, company leaders say, will provide Elanco with a portfolio of leading feed enzyme products, as well as a pipeline of innovative compounds in development. ChemGen will continue research and administrative operations at its location in Gaithersburg, Md., and manufacturing activities at its facility in Terre Haute, In., as well as its present sales and field service operations.

"Meeting the growing demand for food is one of the most critical issues of our time," says Jeff Simmons, senior VP of Lilly and president of Elanco Animal Health. "The acquisition of ChemGen and its premiere enzyme business further underscores Elanco's commitment to provide our customers with leading animal productivity solutions. This acquisition allows Elanco to leverage our expertise in developing trusted, science-based solutions into the enzyme space, which is an emerging field with significant growth potential. ChemGen's strong presence in the poultry and swine markets in North America and Asia is well-suited to Elanco's existing business, while Elanco's presence in Latin America and Europe represent growth opportunities. Given Elanco's global footprint, customer relationships, and market knowledge, we are well-positioned to continue to grow product sales, as well as expand to new customers and geographies."

In June, Lilly announced an increase of its network of manufacturing capabilities in China through an expanded collaboration with **Novast** Laboratories Ltd. Novast, a generic and specialty pharmaceutical company based in Nantong, China, has established high-quality systems and manufacturing facilities for the global and domestic Chinese markets. Lilly executives expect the company's expanded collaboration with Novast to greatly enhance efforts to build a portfolio of Lilly branded generic medicines in China. The collaboration may also ultimately result in Novast providing local and regional manufacturing capabilities for Lilly's own pipeline of potential new medicines in development.

As part of the agreement, Lilly will increase its equity position in Novast by $20 million. The company made an initial equity investment in Novast several years ago through the Lilly venture capital unit, Lilly Asian Ventures. Novast will set up a platform to support Lilly branded generic products and increase the manufacturing capacity at its Nantong site over the next several years, with Lilly providing technical support to enhance quality standards. The additional capacity will support the collaboration, but will not be solely dedicated to Lilly

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products. The two companies have selected an initial list of medicines across multiple therapeutic areas that will be manufactured by Novast once the facilities are operational.

"We are excited to expand our collaboration with Novast," says Jacques Tapiero, Lilly senior vice president and president of Emerging Markets. "As we develop a platform of high-quality Lilly branded generic medicines in China, we are supporting the Chinese governments' current five-year plan, which calls for significant improvement in the quality of medicines in the pharmaceutical industry. In Lilly's emerging markets business, we are focused on providing patients with innovative medicines from our own pipeline, as well as select Lilly-branded generic medicines that meet our quality standards. The additional manufacturing capabilities provided by Novast will allow us to better deliver on that strategy."

Product performance

The schizophrenia/bipolar disorder drug **Zyprexa** remained Lilly's top seller in 2011. But the drug's patent protection expired in several major European markets in September, followed by U.S. expiration in October, driving full year sales for 2011 down 8 percent to $4.62 billion. The effects of generic competition have been even more pronounced in the new year, with first-half sales of Zyprexa dropping by 65 percent to $942 million.

Now at the top of Lilly's sales charts, **Cymbalta** produced another year of solid growth for the company in 2011, with a 20.3 percent jump to $4.16 billion. In the first half of 2012, Cymbalta sales rose another 22.3 percent to $2.34 billion. In July, Lilly announced that the company has met FDA requirements for pediatric exclusivity for Cymbalta. Based on this decision by FDA, Lilly has gained an additional six months of U.S. market exclusivity for Cymbalta, which now will expire in December 2013. Cymbalta has earned five indications in the United States, including for the treatment of major depressive disorder, the treatment of generalized anxiety disorder, the management of diabetic peripheral neuropathic pain, fibromyalgia, and for the management of chronic musculoskeletal pain..

After a near-30 percent jump in 2010, sales growth for the cancer drug **Alimta** slowed down last year, with an increase of 11.4 percent to $2.46 billion. In October, the European Commission granted approval for the use of Alimta as a single agent for continuation maintenance therapy in patients with advanced nonsquamous non-small cell lung cancer. The approval was based on clinical trial results showing an improvement in progression-free survival, as well as a preliminary analysis showing a strong trend toward better overall survival, for non-small cell lung cancer patients treated first with Alimta plus cisplatin and then continue treatment with Alimta alone in the maintenance setting. Alimta is the first chemotherapy agent to be approved in Europe for continuation maintenance therapy. Sales of the drug in the first half of 2012 totaled $1.27 billion, an improvement of 6.1 percent.

In September, Lilly announced that the Phase III POINTBREAK trial did not meet its primary endpoint of improved overall survival for patients with nonsquamous non-small cell lung cancer who were randomized to receive a combination of Alimta with Avastin and carboplatin induction followed by Alimta plus Avastin maintenance compared to the combination of paclitaxel with Avastin and carboplatin followed by Avastin maintenance. The study did meet one of its secondary endpoints of improved progression-free survival for the Alimta arm.

"Phase II results with this combination were promising and we were hoping to demonstrate an improvement in survival for nonsquamous NSCLC patients, so we are disappointed with the results of this trial," says Allen S. Melemed, M.D., senior medical director, Lilly Oncology. "POINTBREAK did show an improvement in progression-free survival, though this did not translate to an overall survival advantage."

The diabetes product **Humalog**, crown jewel of Lilly's substantial endocrinology portfolio, enjoyed growth of 15.3 percent in 2011, with sales of $2.37 billion. In the first half of 2012, Humalog sales were up another 8.2 percent to $1.2 billion. **Humulin**, Lilly's other blockbuster diabetes product, grew sales by 14.7 percent in 2011 to $1.25 billion. The product's sales growth has slowed in the first half of the new year, though, rising just 1.5 percent to $611 million.

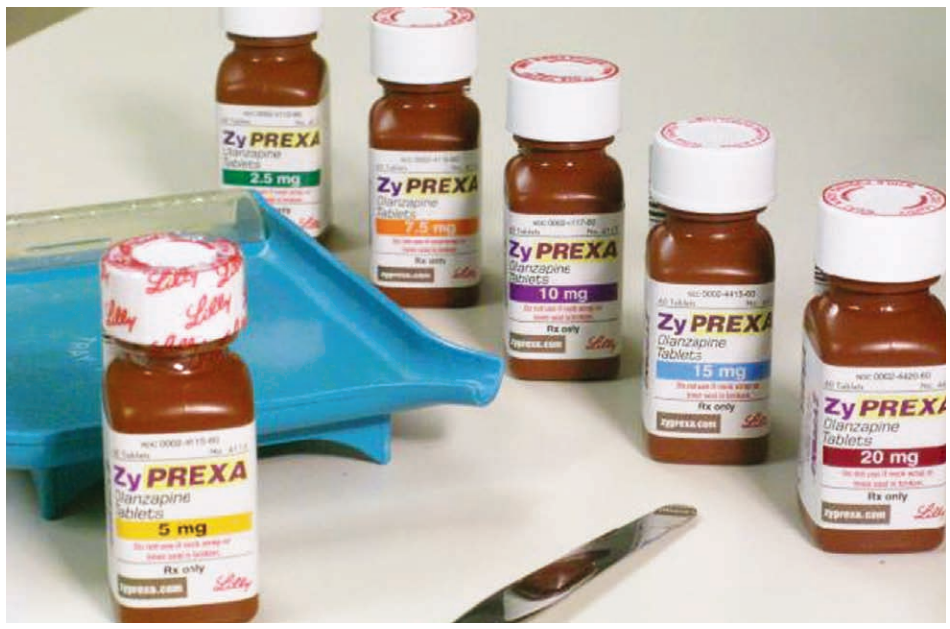
Returns are not yet in for the latest offerings in the Lilly diabetes stable. The company didn't report sales of **Tradjenta** (approved in May 2011) for the year, or in the first half of 2012. But results of several Phase III studies have offered positive signs. In May, Lilly and partner developer Boehringer Ingelheim announced study results for Tradjenta 5 milligrams once-daily which showed significant hemoglobin A1c (HbA1c or A1C) reduction of 0.88 percent compared to 0.24 percent in the placebo group at 24 weeks in black or African American adult patients with type 2 diabetes whose blood sugar was not adequately controlled. Then, in June, the partners presented results from two randomized Phase III clinical trials and a post-hoc analysis for Tradjenta. Interim results of the first study showed that adding Tradjenta to a background of basal insulin – alone or in combination with metformin and/or pioglitazone – demonstrated a placebo-adjusted reduction in hemoglobin A1c (HbA1c or A1C) of 0.65 percent from a baseline A1C of 8.3 percent at 24 weeks versus adding placebo to these background therapies in adult patients with type 2 diabetes. In the second study, Tradjenta showed a 0.64 percent placebo-adjusted reduction in A1C at 24 weeks from baseline (A1C=7.8 percent) in elderly patients (mean age 74.9 years) insufficiently controlled despite previous treatment with metformin and/or sulfonylurea and/or insulin therapy.

Less than a year after Tradjenta's launch, the product already has a franchise sibling. In January, FDA approved **Jentadueto** tablets, a new tablet combining Tradjenta and metformin. Jentadueto provides a new, single-tablet treatment option, taken twice-daily, for patients who need to control their blood sugar. The new combination product received European marketing authorization in June.

Cialis, Lilly's product for erectile dysfunction, continued to grow in 2011, with sales up 10.4 percent to $1.88 billion after 9 percent growth in the previous year. In October, the product earned a new approval from FDA, for once daily use for the treatment of men who have both erectile dysfunction and the signs and symptoms of benign prostatic hyperplasia. The agency also approved Cialis for once daily use for a separate indication for the treatment of the signs and symptoms of BPH. This means Cialis is now approved for three indications in the United States: ED, the signs and symptoms of BPH, and ED and the signs and symptoms of BPH in men who have both conditions. In the first half of 2012, Cialis growth has slowed, with the product earning $931 million in sales, up 2.2 percent.

Sales of Lilly's two osteoporosis drugs, **Evista** and **Forteo**, both improved in 2011. Evista sales rose 4.1 percent for the year to $1.07 billion, while Forteo sales jumped 14.4 percent to $950 million. In September 2011 Lilly released data from a study that assessed the effects of 18 months of treatment with Forteo on vertebral and proximal femoral strength, and the relationship of these effects to changes in the underlying volumetric bone mineral density of postmenopausal women with osteoporosis. Researchers concluded that Forteo increased vertebral and femoral strength in the spine and hip bones compared to baseline. In August, the company announced data from a Phase III trial comparing the effects of Forteo and risedronate on back pain in postmenopausal women with osteoporotic vertebral fractures. The study showed no difference between Forteo and risedronate on the primary endpoint of at least a 30 percent reduction in worst back pain from baseline to six months of therapy, as assessed by a numeric rating scale in each treatment group. However, there were statistically significant differences in favor of Forteo in some exploratory measures, including greater increases in bone mineral density and fewer patients with new vertebral fractures. With this new wind at its back, Forteo moved past Evista in the first half of 2012, with a 22.5 percent bounce to $548 million as Evista sales dropped 1.4 percent to $522 million.

The ADHD drug **Strattera** bounced back for Lilly in 2011 with sales growth of 7.5 percent to $620 million after a drop of 5.4 percent the previous year. In the first half of 2012, Strattera sales were up another 5.2 percent to $312 million.



After peaking at more than $5 billion in sales in 2010, the falloff for the antipsychotic Zyprexa began with the loss of its patent protection in late 2011.

Research and development

Lilly spent $5.02 billion on research and development in 2011, up 2.8 percent compared with the previous year. In the first half of 2012, R&D spending rose another 3.6 percent, to $2.47 billion.

In July 2011, Lilly presented data from the first of two Phase III trials of **semagacestat**, including data from a 32 week follow-up period after dosing was halted in August 2010. Semagacestat is a gamma secretase inhibitor that had been studied as a potential treatment for Alzheimer's disease. The dosing in both semagacestat trials was halted in August 2010 because preliminary results from the two Phase III trials showed semagacestat did not slow Alzheimer's disease progression and was associated with worsening of clinical measures of cognition and the ability to perform activities of daily living. Lilly continued to gather data, including cognitive scores, for 32 weeks after dosing was stopped. The study data confirmed preliminary results that showed that during the period of dosing, patients receiving semagacestat declined at a greater rate than patients taking placebo. During the follow-up period after dosing was halted, the cognitive and functional deficits of the patients initially treated with semagacestat remained worse than the deficits of patients initially treated with placebo. However, the course of the decline over time in the two groups did not diverge further after dosing was stopped.

"When we made the decision to halt dosing in the trials, we committed to collecting this data in an effort to benefit future Alzheimer's research and to provide safety follow-up for the patients," says Eric Siemers, M.D., senior medical director for the Alzheimer's Disease Team at Lilly. "We have a great deal of appreciation and respect for the dedication of the patients and caregivers who remained committed to the semagacestat trials from the beginning until these follow-up data were collected. By obtaining this information, future research efforts can be guided much more effectively."

In September, Lilly announced findings from a prospectively designed observational study that resulted in new ways to increase minority participation in clinical trials. The study assessed the impact of ethnicity on the second-line treatment of non-small cell lung cancer (NSCLC). As part of Lilly's goal to improve health outcomes for all patients, the company is working to increase enrollment of diverse populations in clinical trials, and making trials more accessible in minority communities.

"Our mission is to develop tailored therapies for some of the most difficult-to-treat tumors, in the populations that need them most," says Coleman Obasaju, M.D., Ph.D., senior medical director at Lilly Oncology. "Since lung cancer outcomes differ for different racial groups, it is imperative that these populations are represented in clinical trials."

When the study began, it had 19 percent minority representation, including 28 African Americans, seven Asian Americans, and 10 Hispanic Americans. Historically, there are a variety of reasons that minorities do not participate in clinical research, including lack of awareness of clinical trial research; economic factors; language and cultural barriers; and participant mistrust. Lilly then took steps to increase the number of underserved minority participants, including the selection of new trial sites likely to include more than 50 percent minority patient populations; providing patients with information regarding patient assistance programs that help them secure treatment; and on-site visits to trial sites to identify and address existing barriers. In addition, all patient materials were translated into Spanish.

Following the trial, Lilly began creating culturally competent patient tools, such as a Latino Toolkit that provided trial sites with information that supported efforts in recruiting and supporting Hispanic American patients in future trials, which were developed in partnership with the Education Network to Advance

Clinical Trials.

Lilly also sponsored multiple advisory boards and conducted a survey of 241 clinical trial investigators and coordinators to assess the impact of protocol design on minority participation. The results showed that certain improvements, such as the use of patient navigators who help guide a patient through the treatment process, and taking into account language and ethnic considerations of potential participants when designing trial protocols, were called for. With these enhancements in place, minority participation increased, with 43 percent of the remaining enrollees representing multicultural populations (37 African Americans, 30 Asian Americans, and 18 Hispanic Americans), with the trial ultimately not reaching critical mass on the Asian American and Hispanic American arms.

"While the study fell short of its planned patient accrual, with only 434 of 1,000 patients enrolled, it proved that minority participation in clinical trials can increase dramatically with targeted interventions," Dr. Obasaju says. "We will apply these learnings to future trials right from the start."

In December, Lilly announced that the company would be conducting the first major international, prospective observational study designed to understand the real-world obstacles that people with type 2 diabetes face that prevent them from reaching their ultimate treatment goals. The MOSA1c (A Multinational Observational Study Assessing Insulin use: Understanding the challenges associated with the progression of therapy) study will seek to determine why many people with diabetes who take daily insulin resist a progression of insulin therapy that could help them reach their ideal blood sugar target by gathering data on insulin use, interactions between people with and treating diabetes, and other factors involved in the progression of treatments used to manage diabetes.

MOSA1c – which company leaders call the first international study of its kind – is a part of Lilly Diabetes' broader commitment to improving the lives of people living with and treating diabetes by developing personalized solutions and support that complement its existing treatment portfolio. The company has partnered with Brigham and Women's Hospital and Harvard Medical School to conduct the study, which began enrolling patients in July 2011, following 4,500 people with type 2 diabetes taking insulin in the United States and 16 other countries for two years.

"At Lilly Diabetes, we understand that type 2 diabetes is influenced by behaviors that, if understood, could be adapted for improved management of the disease," says Robert Heine, M.D., VP, medical affairs, Lilly Diabetes. "The best way to achieve our goal is to understand not only how they respond to therapy but also what barriers exist in daily clinical practice that prevent the best care."

In March, Phase II data published in the *New England Journal of Medicine* showed that **ixekizumab**, an anti-IL-17 monoclonal antibody, met its primary endpoint in patients with moderate-to-severe plaque psoriasis, with significantly more patients achieving at least a 75 percent improvement in Psoriasis Area and Severity Index (PASI) scores from baseline (PASI 75) compared with placebo at week 12. PASI score represents a combined assessment of overall skin lesions ranging from 0 for no psoriasis to 72 for the worst possible psoriasis in a patient and is a standard measure of skin disease severity in clinical trials in psoriasis. A PASI 75 response in a patient represents a 75 percent reduction of PASI scores from baseline. In the 142-subject study, significantly more patients achieved a PASI 75 response in the 150 milligram (82 percent), 75 milligram (83 percent) and 25 milligram (77 percent) ixekizumab groups compared with placebo (8 percent, $p<0.001$) at week 12. The 10 milligram dose (29 percent) did not separate from placebo at week 12.

In May, Lilly announced that **dulaglutide**, the company's investigational, long-acting glucagon-like peptide 1 analog being studied as a once-weekly treatment for type 2 diabetes, met its primary endpoint of non-inferiority for mean 24-hour systolic blood pressure (SBP, or pressure while the heart contracts) after 16 weeks. The results came from a Phase II study that compared two doses of dulaglutide to placebo, using ambulatory blood pressure monitoring to characterize changes in blood pressure and heart rate. In addition, the 1.5 milligram dulaglutide dose significantly reduced mean 24-hour SBP compared to placebo.

"We are very encouraged by these clinical trial results, in addition to the rest of the clinical trial data we've seen to date for dulaglutide," says Gwen Krivi, Ph.D., VP, product development, Lilly Diabetes. "Dulaglutide is currently in Phase III clinical trials, where it will continue to be evaluated on its efficacy to lower blood glucose levels, overall safety, weight effects and effects on cardiovascular outcomes. We believe dulaglutide, if approved, can bring significant benefits to people with type 2 diabetes."

Cymbalta enjoyed a 20.3 percent sales bounce in 2011 and took over as Lilly's best-selling product in the new year, but the drug is due to lose patent protection at the end of 2013.

Also in May, Lilly announced the opening of the Lilly China Research and Development Center (LCRDC), a key component of the company's significant and sustainable commitment to China. The goal of the LCRDC, company leaders say, is to discover innovative diabetes medicines with novel mechanisms of action that can be tailored specifically for the Chinese population to delay the progression of the disease. Affecting nearly 90 million Chinese, diabetes is a significant national public health problem, due in part to longer life expectancies, dietary changes, and a sedentary lifestyle emerging in China. Differences in the genetic makeup of Asian patients may also play a role in diabetes development and progression, and exploring these differences is a priority for the LCRDC, which employs about 150 scientists and staff hired primarily from China.

"Conquering a devastating disease like diabetes requires innovation, collaboration and investment," says Jan M. Lundberg, Ph.D., executive VP, science and technology, and president, Lilly Research Laboratories. "The establishment of the Lilly China Research and Development Center demonstrates we are serious about discovering and developing desperately needed breakthrough medicines for Chinese people with diabetes. We will do this by looking at diabetes in new and different ways and through collaborations with local academic research centers and partners that enable us to link Lilly scientists with scientists in China. With an eagerness and optimism to explore new theories about disease development and progression and potentially translate this to tailored diabetes medicines, I believe we will make a difference for people with diabetes, in China and around the world."

Exploring the genetic profiles of Chinese, and eventually Asian, people with diabetes is a key area of research being conducted at the LCRDC. For example, Chinese people with diabetes have a significantly lower average body mass index than do Americans with diabetes. Chinese people with diabetes also tend to have a higher prevalence of abdominal obesity, fatty liver, and insulin resistance than non-Asians with diabetes. Research to better understand these characteristics may offer opportunities for discovering new medicines to treat diabetes. In the near term, the work at the LCRDC will focus on evaluating a pool of highly-selective targets with the potential to deliver robust candidates, helping to feed the Lilly portfolio with novel treatment opportunities.

In June, Lilly and partner developer **Boehringer Ingelheim** announced results from two Phase II studies of their investigational novel basal insulin analog **LY2605541**. Results of the type 1 diabetes study showed that LY2605541 was associated with greater improvements of glycemic control (lowering blood sugar levels) than insulin glargine. In the type 2 diabetes study, the primary measure showed that LY2605541 and insulin glargine had similar improvements in glycemic control.

"Lilly and Boehringer Ingelheim are excited to have the opportunity to share both the preclinical and clinical study data completed to date for LY2605541, and are pleased that these Phase II study results support the continued clinical development of this basal insulin," says David Kendall, M.D., distinguished medical fellow, Lilly Diabetes. "Based on the pre-clinical studies completed, compared to injected human insulin, LY2605541 appeared to work preferentially in the liver, which is more like the body's own insulin. We look forward to results from our ongoing Phase III clinical trials."

That same month, Lilly and Boehringer also announced results from a Phase IIb study of **empagliflozin** showing that the drug, alone or as an add-on to metformin, reduced hemoglobin A1c (HbA1c or A1C) levels, fasting plasma glucose (FPG) levels, and body weight when given to adults with type 2 diabetes for up to 90 weeks.

Also in June, Lilly and partner developer **Incyte** Corp. presented 12-week results from a Phase IIb study of **baricitinib**, an orally available janus kinase (JAK) inhibitor, in patients with active rheumatoid arthritis (RA). The Phase IIb randomized double-blind, placebo-controlled, dose-ranging study, known as JADA, involved a total of 301 patients with active RA on stable doses of methotrexate. Patients were randomized to receive either placebo or one of four once-daily doses of baricitinib (1 milligram, 2 milligram, 4 milligram, or 8 milligram) for 12 weeks. The trial achieved its primary endpoint by demonstrating a statistically significant difference in the American College of Rheumatology 20 response between the combined 4 milligram and 8 milligram baricitinib groups (76 percent) compared with placebo (41 percent) after 12 weeks of treatment. Statistically significant improvement was observed at the first assessment point after two weeks of treatment and was sustained through week 12.

Also in June, Lilly launched a searchable clinical trial mobile application for oncology healthcare professionals. The app – available for Apple iPad and iPhone, as well as RIM's BlackBerry and Google's Android platforms – allows healthcare professionals to search oncology trials that are enrolling new patients by disease state, molecule being studied, study phase, country, state, and keyword. Because the mobile app provides details on all global oncology trials, the app's functionality also provides a mechanism for the healthcare professional to contact Lilly Oncology for additional details on its trials, as well as a third-party contact for the non-Lilly clinical trials.

"Lilly Oncology created the Clinical Trial Resource mobile app to offer cancer care professionals an easy way to search for and identify details about all global oncology clinical trials – not just those sponsored by Lilly," says Anne White, senior director of portfolio management with Lilly Oncology. "The information will enable physicians to provide the most current study information – quickly – to patients who may be interested in participating in a clinical trial."

Directions for downloading the clinical trial app are available on a new website, LillyOncologyPipeline.com, an online resource that will house information on its pipeline of potential cancer and supportive care molecules. At LillyOncologyPipeline.com, healthcare professionals can search for information about Lilly Oncology's pipeline by drug discovery platform, cancer type, clinical trial phase, and molecular target. Specific information about each medicine includes illustrations of the target pathway and, when available, video of the pipeline compound's method of action.

The company suffered two pipeline disappointments in late August. On the 24th, Lilly announced that the primary endpoints, both cognitive and functional, were not met in either of the two Phase 3, double-blind, placebo-controlled **solanezumab** EXPEDITION trials in patients with mild-to-moderate Alzheimer's disease. However, a pre-specified secondary analysis of pooled data across both trials showed statistically significant slowing of cognitive decline in the overall study population of patients with mild-to-moderate Alzheimer's disease. In addition, pre-specified secondary subgroup analyses of pooled data across both studies showed a statistically significant slowing of cognitive decline in patients with mild Alzheimer's disease, but not in patients with moderate Alzheimer's disease. An open-label extension study, EXPEDITION-EXT, is fully enrolled and will continue as planned.

"We recognize that the solanezumab studies did not meet their primary endpoints, but we are encouraged by the pooled data that appear to show a slowing of cognitive decline," Dr. Lechleiter says. "We intend to discuss these data with regulatory authorities to gain their insights on potential next steps."

Then, on the 29th, Lilly decided to stop ongoing clinical studies investigating pomaglumetad methionil, also known as **mGlu2/3**, for the treatment of patients suffering from schizophrenia. The decision was made after a recently conducted independent futility analysis concluded that HBBN, the second of Lilly's two pivotal studies, was unlikely to be positive in its primary efficacy endpoint if enrolled to completion. The decision was not based on any safety signals. Additionally, the recently completed Phase II study, HBCO, which investigated pomaglumetad methionil as an adjunctive treatment with atypical antipsychotics, did not meet its primary endpoint.

"I'm disappointed in what these results mean for patients with schizophrenia who still are searching for options to treat this terrible illness," Dr. Lundberg says. "While there are many challenges in this complex field of research, neuroscience remains a core area of focus at Lilly. Our clinical development pipeline includes nearly a dozen neuroscience molecules being studied to treat illnesses such as depression, bipolar disorder and cognitive impairment associated with schizophrenia." ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

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BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Singulair	$5,479	$4,987
Januvia	$3,324	$2,385
Remicade	$2,667	$2,714
Zetia	$2,428	$2,297
Vytorin	$1,882	$2,014
Cozaar/ Hyzaar	$1,663	$2,104
Janumet	$1,363	$954
Isentress	$1,359	$1,090
Nasonex	$1,286	$1,219
Gardasil	$1,209	$988
Varivax	$1,202	$1,378
Temodar	$935	$1,065
Fosamax	$855	$926
PegIntron	$657	$737
RotaTeq	$651	$519
Cancidas	$640	$611
Maxalt	$639	$550
NuvaRing	$623	$559
Clarinex	$621	$623
Follistim AQ	$530	$528
Primaxin	$515	$610

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Sales	$48,047	$45,987
Net income	$6,392	$982
EPS	$2.02	$0.28
R&D	$8,467	$11,111

	1H112	1H11
Sales	$24,041	$23,732
Net income	$3,587	$3,125
EPS	$1.15	$0.98
R&D	$4,026	$4,094

All figures are in millions of dollars, except EPS.

Settling in

The new Merck's identity is coming into focus, as the company's latest generation of blockbuster products moves to the top of its sales charts and its list of partnerships continues to grow.

By Joshua Slatko joshua.slatko@ubm.com

Three years after its mega-merger with Schering-Plough, the new Merck is coming into view, and it isn't just a bigger version of the old Merck. The company is hanging its hat on a new series of blockbusters – the diabetes drug Januvia and its relatives being the most prominent example – alongside a burgeoning list of development and marketing partnerships with academia, non-profits, and other pharma companies. Company leaders boast that Merck's product portfolio is among the broadest in the industry, and they look forward to a number of high-profile new drug filings through the end of 2013. The company also made significant progress overseas in 2011, with sales in Japan up 29 percent, sales in China rising 37 percent, and overall emerging markets growth of seven percent. In 2011, 18 percent of the company's total pharmaceutical sales were in the emerging markets; company leaders expect this to grow to 25 percent by 2013. Meanwhile, company CEO Kenneth C. Frazier added the board chairmanship to his resume with the retirement of Richard T. Clark at the end of November 2011.

"We are competing amid a fast-changing healthcare environment and a complex global economy," Mr. Frazier wrote in his annual chairman's letter in April. "The differentiating factor that will allow a company to succeed over the long term is the ability to adapt to the powerful economic, technological, and political forces that are reshaping how healthcare is financed and delivered. For today's Merck, this means remaining focused on innovation that translates cutting-edge science into medically important products and services that address the evolving, real-world problems of our diverse customers around the world. This focus is the key driver of value for our shareholders, patients, and customers alike."

Merck's sales in 2011 totaled $48.05 billion, an improvement of 5.5 percent over the previous year. Company leaders credit this growth to the strength of a few key products – the Januvia franchise, Singulair, Isentress, and Gardasil in particular – as well as higher sales of Merck's animal health products and the launch of the hepatitis C product Victrelis. Net income for the year totaled $6.39 billion, up from $982 million in 2010. This shift, company executives say, came due to due to lower in-process R&D impairment charges (most such charges related to the Schering-Plough merger were posted in 2010) and amortization of inventory step-up, lower legal reserves, and the favorable impact of tax settlements. Earnings per share for the year jumped accordingly, from 28 cents in 2010 to $2.02 in 2011.

Restructuring continues

In July 2011, Merck announced the latest phase of its global restructuring program that was initiated in conjunction with the integration of the legacy Merck and legacy Schering-Plough businesses. This merger restructuring program, company leaders say, is intended to optimize the cost structure of the combined company. As part of this latest phase, Merck expects to reduce its workforce measured at the time of the merger by an additional 12 percent to 13 percent across the company worldwide. A majority of the workforce reductions in this phase of the program relate to manufacturing (including Animal Health), administrative, and headquarters organizations. Previously announced workforce reductions of about 17 percent in earlier phases of the program primarily reflect the elimination of positions in sales, administrative, and headquarters organizations, as well as from the sale or closure of certain manufacturing and research and development sites and the consolidation of office facilities. Merck will continue to hire employees in strategic growth areas of the business as necessary. The company will also continue to pursue productivity efficiencies and evaluate its manufacturing supply chain capabilities on an ongoing basis which may result in future restructuring actions. Merck recorded total pretax restructuring costs of $1.8 billion in 2011, $1.8 billion in 2010, and $1.5 billion in 2009 related to this program. The restructuring program is expected to be substantially completed by the end of 2013, with the exception of certain actions, principally manufacturing-related, which are expected to be substantially completed by 2015, with the total cumulative pretax costs estimated to be between $5.8 billion and $6.6 billion. Company leaders estimate that about two-thirds of the cumulative pretax costs relate to cash outlays, primarily related to employee separation expense. The remaining pretax costs are non-cash, relating primarily to the accelerated depreciation of facilities to be closed or divested. Merck expects the merger restructuring program to yield annual savings by the end of 2013 of between $3.5 billion and $4 billion, and annual savings upon completion of the program of between $4 billion and $4.6 billion.

Sales of the HPV vaccine Gardasil enjoyed a healthy bounce in 2011 after the product received a new indication to prevent anal cancer at the end of 2010.

"The differentiating factor that will allow a company to succeed over the long term is the ability to adapt to the powerful economic, technological, and political forces that are reshaping how healthcare is financed and delivered," says Merck CEO and chairman Kenneth C. Frazier. "For today's Merck, this means remaining focused on innovation that translates cutting-edge science into medically important products and services that address the evolving, real-world problems of our diverse customers around the world."

Acquisitions and partnerships

In July 2011, Merck and **Roche** signed a new non-exclusive agreement for the global promotion, upon appropriate marketing approvals, of **Victrelis** as part of a triple combination therapy regimen with peginterferon alfa and ribavirin (peg/riba). Victrelis had just been approved by FDA in May 2011 for the treatment of chronic hepatitis C.

"Reaching physicians with important information about the use of Victrelis in combination with peg/riba is essential as we enter this new era in the field of chronic hepatitis C," says Adam H. Schechter, executive VP and president, Global Human Health, Merck. "We're pleased to work with Roche to help physicians help patients with chronic hepatitis C around the world."

Under the terms of the agreement, Roche and Merck will work together in global markets, including Europe, Asia and Latin America, to educate physicians and patients about hepatitis C virus. The companies had previously announced an agreement to promote Victrelis in the United States and collaborate to explore new treatment regimens for patients with chronic HCV.

In December, Merck and Roche followed up their Victrelis agreement by announcing the initiation of the first of a series of planned clinical trials to examine novel combinations of marketed and investigational medicines to expedite the availability of potential new treatment regimens for patients with chronic hepatitis C virus genotype 1 infection. This clinical development collaboration is part of the overarching strategic agreement between Merck and Roche to improve treatment, diagnosis, and awareness of chronic HCV in developed and emerging markets.

"Victrelis is the first in a new class of medicines for the treatment of chronic HCV genotype 1 infection, and when used in combination with peginterferon alfa, can significantly increase a patient's chance of achieving undetectable levels of the virus," says Eliav Barr, M.D., VP, Infectious Diseases Project Leadership and Management, Merck Research Laboratories. "The start of this new study is an important milestone in our collaboration with Roche as we work to build on the innovative platform Victrelis provides by evaluating it in combination therapy with new investigational medicines for the treatment of chronic HCV genotype 1 infection, and also emphasizes our ongoing commitment to seeking novel treatment options for patients with chronic HCV."

The first trial is designed to provide clinical data on the use of Victrelis in combination with **mericitabine** (RO5024048), Roche's investigational oral HCV NS5B nucleoside polymerase inhibitor, **Pegasys** (pegylated interferon alfa-2a), and **Copegus** (ribavirin), in adult patients with chronic HCV genotype 1 infection who had a null response to prior peginterferon alfa and ribavirin therapy. The Phase II study, called DYNAMO 1, plans to recruit patients at 25 sites globally.

Also in July, Merck and China's **Simcere** Pharmaceutical Group signed a framework agreement to establish a joint venture focused on serving China's rapidly expanding healthcare needs by providing significantly improved access to quality medicines in major therapeutic areas. The partnership aims to combine the extensive resources and expertise of a global healthcare company and a leading Chinese pharmaceutical company in support of Merck and Simcere's goal of building a strategic partnership with development, registration, manufacturing, and sales capabilities. The initial focus of the partnership will be branded pharmaceutical products for cardiovascular and metabolic diseases.

Specifically, in the area of cardiovascular disease, the partnership will offer a combined portfolio of selected medicines from both companies, including Zocor, Cozaar, and Renitec by Merck, and Xinta and Shufutan by Simcere. In the metabolic disease area, the partnership will work to maximize access in China to sitagliptin, a DPP-IV inhibitor for the treatment of type 2 diabetes, which

Januvia, *Med Ad News'* most recent Medicine of the Year, grew sales by nearly 40 percent in 2011 to $3.32 billion, while sales of the Januvia-metformin combination product Janumet rose another 42.9 percent to $1.36 billion.

Merck sells worldwide as Januvia. Type 2 diabetes is increasingly recognized as a significant public health threat in China.

"Merck is proud to partner with Simcere, one of China's leading pharmaceutical companies and an organization that shares Merck's commitment to enhancing health care in China," Mr. Schechter says. "This partnership is another step forward in Merck's strategy to grow our business in China and is fully aligned with the Chinese government's goal to increase access to quality products."

In September, Merck and BGI, the world's largest genomics center, established a collaboration to focus on the discovery and development of biomarkers and genomic technologies. Under the agreement, scientists from Merck and BGI will work closely together to identify and characterize biomarkers with an emphasis on drug discovery, drug development and diagnostics applications across a range of therapeutic areas.

"This strategic collaboration combines BGI's genomic sequencing and analytic capabilities with Merck's expertise and experience in drug development," says Dr. Jeffrey Chodakewitz, VP, Late Stage Development, Merck Research Laboratories. "By working together we hope to apply BGI's comprehensive next-gen sequencing solutions to develop important new tools to aid drug development and enable effective tailoring of medicines to those patients most likely to respond."

Under the terms of the agreement, Merck and BGI will each be permitted to propose projects to be undertaken under the collaboration. Both Merck and BGI will provide resources, expertise, samples, and other research material as needed for the collaboration.

"We welcome this opportunity to bring extensive genomics experience to our collaboration with Merck, as well as our expertise in transcriptomics, proteomics and bioinformatics," says Ye Yin, president of the Research and Cooperation Division at BGI. "Through this close collaboration with Merck, we are confident that we will achieve more important breakthroughs to accelerate disease genomics research and drug R&D to facilitate improved healthcare. This collaboration will bring mutual benefits to BGI and Merck in the next few years, but also support the development of new techniques that will benefit the medical and pharmaceutical industries as a whole."

The BGI-Merck agreement follows the signing, in September 2010, of a statement of intent to initiate and develop a working relationship to explore areas of mutual interest in healthcare research and discovery with the common goal of creating value from the massive output of genomic information enabled by next-generation, high-throughput DNA sequencing and analysis technologies.

In February, Merck announced the formation of a new joint venture with **Supera Farma** Laboratorios SA, a Brazilian pharmaceutical company jointly owned by **Cristália** and **Eurofarma**. The new venture will market, distribute, and sell a portfolio of innovative pharmaceutical and branded generic products from Merck, Cristália, and Eurofarma solely in the Brazilian retail sector.

"Merck is pleased to partner with two of Brazil's leading pharmaceutical companies – organizations that share our commitment to enhancing healthcare for the people of Brazil," Mr. Frazier says. "This venture is an important step forward in our strategy to grow our business in key markets and improve global access to our medicines and vaccines."

By establishing the venture with Supera, Merck leaders expect to gain additional local expertise, an expanded portfolio of products, and a strong distribution network to help provide wider access to medicines for the people of Brazil. The initial portfolio of the venture will include about 30 products across a range of therapeutic areas.

The venture will have its own dedicated sales force separate from Merck, Cristália, and Europharma, but will take advantage of the parent companies' infrastructures for activities such as sales force training. The parent companies will continue to maintain separate businesses in Brazil. Merck, through a subsidiary, will own 51 percent of the venture, and Cristália and Eurofarma will collectively own 49 percent.

The venture will be managed by a joint board and leadership team consisting of members of senior management from the three companies.

Also in September, Merck sold its 50 percent interest in the Johnson & Johnson/Merck Consumer Pharmaceuticals Co. joint venture (JJMCP) to **Johnson & Johnson** affiliates. The venture between Merck and J&J was formed in 1989 to develop, manufacture, market, and distribute certain over-the-counter consumer products in the United States and Canada.

According to company leaders, Merck decided to sell its interest in the joint venture to enable the company to fully focus on building the long-term growth prospects of the wholly-owned consumer products division that had been part of Schering-Plough Inc. prior to the 2009 merger. Under the agreement, Merck received a one-time payment of $175 million. Merck's rights to the Pepcid brand outside the United States and Canada are not affected by this transaction. Termination of the JJMCP venture also gives Merck greater freedom to operate in the OTC consumer sector, allowing the company to fully exploit its pipeline of Rx-to-OTC switches as well as actively pursue OTC licensing activities in the U.S. and Canada.

Following the transaction, J&J now owns the venture's assets which include the exclusive rights to market OTC Pepcid, Mylanta, Mylicon, and other local OTC brands where they are currently sold in the United States and Canada. The partnership assets include a manufacturing facility in Lancaster, Pa.

That same month, Merck launched "Merck for Mothers," a long-term effort with global health partners to create a world where no woman has to die from complications of pregnancy and childbirth. The launch included a 10-year, half-billion-dollar initiative that will apply the company's scientific and business expertise to making proven solutions more widely available, developing new game-changing technologies, and improving public awareness, policy efforts, and private sector engagement for maternal mortality. Mr. Frazier made the launch announcement during the UN's Every Woman Every Child event.

In September 2010, United Nations Secretary-General Ban Ki-moon launched the Global Strategy for Women's and Children's Health supported by Every Woman Every Child – a global effort to improve the health of women and children. Merck, in concert with the UN and its partners, has committed to help tackle Millennium Development Goal (MDG) 5, which aims to reduce the maternal mortality ratio by 75 percent and create universal access to reproductive health.

"We are joining the fight to save women who risk their lives giving birth and making it part of Merck's mission," Mr. Frazier says. "'Merck for Mothers' will help us make a difference in the lives of more people in more parts of the world. By helping to address one of the world's oldest and most preventable global health tragedies, we believe 'Merck for Mothers' will have an important impact on society. We also believe it will provide valuable learnings to our business. We are in this fight for the long term."

Based on input from more than 100 experts in the field, Merck developed a strategic framework identifying where the company will focus its people and resources. "Merck for Mothers" will focus on the two leading causes of maternal mortality: excessive and uncontrolled bleeding after childbirth, known as post-partum hemorrhage, and life-threatening high blood pressure during pregnancy, known as preeclampsia, as well as family planning, which is known to play an important role in reducing maternal mortality. The initiative will be guided by input from both an internal steering committee and an external advisory board. The company will hold itself accountable for the initiative's programs and outcomes by ensuring that an independent organization will monitor and evaluate its efforts.

In March, Merck announced a collaboration to create the California Institute for Biomedical Research, or Calibr, an independent, not-for-profit organization established to accelerate the translation of basic biomedical research into innovative, new medicines to treat disease. Calibr will be led by Peter G. Schultz, Ph.D., a well-known chemist and biotechnology entrepreneur. The Institute is designed to offer academic scientists around the world a streamlined, efficient, and flexible path for translating their biomedical research into novel medicines.

"Calibr represents a new paradigm for early-stage translational research," Dr. Schultz says. "By leveraging the drug discovery expertise and resources of Calibr, academic researchers will have the opportunity to maximize the potential therapeutic value of their research."

Calibr investigators will work collaboratively with academic scientists to advance new discoveries to preclinical proof of concept, at which stage commercial partnerships will be sought for further development. Merck will provide funding to Calibr of up to $90 million over a period of seven years. The company has an option to obtain an exclusive commercial license to any proteins or small molecule therapeutic candidates derived from work conducted by Calibr. For any projects not licensed by Merck, Calibr will be free to seek alternative sources of funding for further development. In addition, the Institute plans to access funds from government and non-government sources. Revenue derived from licenses will be shared between Calibr and the collaborating institutions.

Project proposals from the scientific community will be chosen on the basis of novelty, biomedical impact, and technical feasibility and reviewed by a scientific advisory board headed by Christopher T. Walsh, Ph.D., Hamilton Kuhn Professor, Department of Biological Chemistry and Pharmacology, Harvard University. In addition, an independent board of directors headed by John D. Diekman, Ph.D., founder and managing partner of 5AM Ventures, will oversee the activities of the Institute.

"Effective translation of basic biomedical research is essential to advancing the next generation of novel therapies," said Peter S. Kim, Ph.D., president, Merck Research Laboratories and a member of Calibr scientific advisory board. "Calibr will provide an important venue where basic research and drug discovery scientists may leverage each others' strengths in the fight against disease."

Calibr will be located in San Diego, Calif., in close proximity to The Scripps Research Institute, Salk Institute, University of California, San Diego, and Sanford-Burnham Medical Research Institute. The institute will be equipped with the latest high through-put screening and imaging, medicinal and protein chemistry, and preclinical sciences capabilities.

In April, Merck and and **Endocyte** Inc. entered into an agreement to develop and commercialize Endocyte's novel investigational therapeutic candidate **vintafolide** (EC145). Vintafolide is being evaluated in a Phase III clinical trial for platinum-resistant ovarian cancer, and a Phase II trial for non-small cell lung cancer; both studies are also using Endocyte's investigational companion diagnostic agent, etarfolatide (EC20).

"Vintafolide is a promising and innovative late-stage cancer drug candidate," Dr. Kim says. "In addition to pursuing the lead indication of platinum-resistant ovarian cancer, Merck plans to further evaluate its potential for treatment of multiple other cancer types. This agreement underscores our strategy of building a portfolio of oncology therapeutics that employ a companion diagnostic to facilitate selection of those patients most likely to respond to treatment."

Under the agreement, Merck, through a subsidiary, will gain worldwide rights to develop and commercialize vintafolide. Endocyte will receive a $120 million upfront payment and is eligible for milestone payments of up to $880 million based on the successful achievement of development, regulatory, and commercialization goals for vintafolide for a total of six cancer indications. In addition, if vintafolide receives regulatory approval, Endocyte will receive an equal share of the profit in the United States as well as a double digit percentage royalty on sales of the product in the rest of the world. Endocyte has retained the right to co-promote vintafolide with Merck in the United States, and Merck has the exclusive right to promote vintafolide in the rest of world.

Endocyte will be responsible for the majority of funding and completion of the present Phase

III trial, while Merck will be responsible for all other development activities and costs and have all decision rights for vintafolide. Endocyte remains responsible for the development, manufacture, and commercialization worldwide of etarfolatide, a non-invasive companion diagnostic imaging agent that is used to identify folate receptor positive tumor cells.

Endocyte has completed three single-arm studies of vintafolide in patients with advanced platinum resistant ovarian cancer, non-small cell lung cancer, and solid tumors. In a randomized Phase II clinical trial comparing vintafolide plus pegylated liposomal doxorubicin versus PLD alone in women with platinum-resistant ovarian cancer, vintafolide demonstrated a statistically significant delay in disease progression or death in the overall population, with the largest improvement observed in patients with all tumors imaged as positive for folate receptor expression utilizing etarfolatide. Vintafolide in combination showed limited additional toxicity versus standard therapy with PLD alone. Common adverse events observed with this combination were neutropenia, fatigue, mouth sores, and redness/swelling/pain on the hands and feet. In March 2012, Endocyte announced that the European Union had granted orphan drug status to vintafolide, and that the company planned to file a marketing authorization application in the third quarter of 2012.

In June, Merck and **AstraZeneca** amended the option agreement related to their partnership known as AstraZeneca LP (AZLP). The updated agreement provides that AstraZeneca will not exercise its option to acquire Merck's remaining interest in AZLP in 2012 and provides AstraZeneca a new option to acquire Merck's partnership interest in June 2014. This amended agreement, company leaders say, will benefit both companies and provides clarity around the valuation process at the conclusion of the partnership.

As a result of the amended agreement, Merck will continue to record supply sales and equity income from the partnership for the remainder of 2012 and 2013. In 2014, AstraZeneca will have the option to purchase Merck's remaining interest in AZLP based in part on an agreed-upon calculation of the value of Merck's interest in Prilosec and Nexium. AstraZeneca's option is exercisable between March 1, 2014 and April 30, 2014. If AstraZeneca chooses to exercise this option, the closing date is expected to be June 30, 2014.

Under the amended agreement, the agreed-upon valuation for Merck's interest in Nexium and Prilosec for the 2014 exercise is a fixed sum of $327 million, subject to a true-up in 2018 based on actual sales from closing in 2014 to June 2018. Also, the exercise price will include an additional amount equal to a multiple of ten times Merck's average one percent annual profit allocation in the partnership for the three-years prior to exercise. The exercise price calculation also could include the net present value of up to five percent of future U.S. sales of Vimovo, subject to a sales threshold that has not yet been achieved plus certain additional amounts.

Merck previously assumed it would record sales and earnings contributions from AZLP only through Sept. 2012. The continuation of the partnership is expected to contribute about $200 million to Merck's revenue and about $0.03 to $0.05 in earnings per share in 2012 and does not change Merck's prior full-year guidance for 2012.

Also in June, Merck and Geisinger Health System and Merck launched a new multi-year collaboration designed to improve patient health outcomes by focusing on innovative solutions that facilitate shared decision making between patients and physicians and improve adherence to treatment plans and clinical care processes. Teams from Geisinger and Merck will work together to improve patient adherence, increase the role of patients in making decisions to help manage their conditions, share information among extended care teams, and improve clinical care processes. The first tool being developed is an interactive web application designed to help primary care clinicians assess and engage patients at risk for cardiometabolic syndrome.

Sales of the HIV drug Isentress grew by nearly a quarter to $1.36 billion in 2011; the product earned a pediatric indication from FDA in January 2012.

"When you have two leading healthcare companies that share a commitment to improve health outcomes and are focused on fundamental problems that have plagued the healthcare system for years, the results have the potential to be transformative," says Mark Timney, Merck's president of Global Human Health – U.S. Market. "We're excited about the opportunity to work with Geisinger to address these critical areas."

The Web application and other care management solutions that Merck and Geisinger develop will initially be tested within the Geisinger system. Geisinger has been at the forefront of the development of innovative healthcare delivery models focused on improving adherence and developing methods to better engage patients. Merck has conducted scientific research to better understand the drivers of non-adherence and develop evidence-based interventions.

In July, Merck signed two licensing agreements for investigational HIV drug candidates. The company signed a deal with **Chimerix** Inc., based in Research Triangle Park, N.C., for **CMX157**, an investigational oral nucleoside reverse transcriptase inhibitor currently in Phase I clinical development. Under the agreement, Merck will receive an exclusive worldwide license and will be responsible for development and commercialization of CMX157. Separately, Merck agreed with **Yamasa** Corp., based in Choshi, Japan, to develop **EFdA** (4'-ethynyl-2-fluoro-2'-deoxyadenosine), a novel nucleoside reverse transcriptase inhibitor candidate in preclinical studies that has shown antiviral activity toward highly resistant HIV strains. As part of the agreement, Merck will pay an up-front fee and future milestone payments in return for exclusive worldwide license rights. This candidate was discovered in collaboration with a group led by the world renowned HIV research scientist Dr. Hiroaki Mitsuya of Kumamoto University's Center for AIDS Research in Japan.

Product performance

Sales of the asthma/allergy drug **Singulair**, Merck's best-selling product, rose 9.9 percent in 2011 to $5.48 billion, driven by favorable pricing in the United States and volume growth in Japan and in emerging markets, as well as the beneficial impact of foreign exchange. The company's top seller is reaching the end of the line, though, as its patent protection expired in the United States in August and is due to expire in February 2013 in Europe. In the first half of 2012, before the bell rang on its patent protection, Singular's sales were up 3.3 percent to $2.77 billion.

Januvia, Merck's first-in-class DPP-IV inhibitor for diabetes, moved past Remicade to become Merck's second-best seller in 2011, and the product's growth continuing apace. Januvia generated sales of $3.32 billion for the year, an improvement of 39.3 percent; the product generated another $1.98 billion in sales in the first half of 2012, up 30.2 percent. Meanwhile, **Janumet**, a combination of Januvia with metformin, rolled up $1.36 billion in sales on its own in 2011, an improvement of 42.9 percent. First-half 2012 sales of Janumet were up another 28.1 percent to $802 million. The Januvia franchise was named *Med Ad News*' Medicine of the Year in the July 2012 issue, and analysts with EvaluatePharma have projected it to top all prescription products in worldwide sales by 2018.

That franchise is continuing to grow in ways other than sales. In October 2011, FDA approved approved Juvisync, a new treatment for type 2 diabetes that combines the glucose-lowering medication sitagliptin, the active component of Januvia, with the cholesterol-lowering medication Zocor (simvastatin). Juvisync is the first treatment option for healthcare providers to help patients who need the blood sugar-lowering benefits of a DPP-4 inhibitor and the cholesterol-lowering benefits of simvastatin, with the convenience of a single tablet once daily. Also, in February, FDA approved Janumet XR tablets, a new once-daily formulation of Janumet.

"Although clinical guidelines put people with type 2 diabetes who need glycemic and lipid therapy at the same risk level as those with coronary heart disease, nearly 40 percent of eligible patients do not receive statin treatment," says Barry J. Goldstein, M.D., Ph.D., VP, Diabetes and Endocrinology, Merck. "We are proud to bring forward a treatment option that can help these patients who need both glycemic and lipid therapy."

Not all the news has been good of late for Januvia, however, In February, FDA sent a warning letter to Merck stating that the company had not fulfilled a post-marketing requirement for a three-month pancreatic safety study in a diabetic rodent model treated with sitagliptin. The post-marketing requirement was included by FDA as part of its February, 2010 approval of supplemental new drug applications for Januvia and Janumet; the required study was to have been completed and submitted to FDA by June 15, 2011.

Merck has been providing information to FDA on the company's efforts. These efforts included the submission of a manuscript to the FDA with data from a 12-month study in mice that was conducted by an independent researcher. However, FDA informed Merck that what the company has submitted does not satisfy the post-marketing requirement, and directed Merck to conduct a new 3-month rodent study. The company is committed to complying with FDA's requirement, and company leaders are confident that Merck will complete the requirement within the time frame outlined in the agency's letter.

Merck's portion of the sales of the autoimmune drug **Remicade** actually fell in 2011, dropping 1.7 percent to $2.67 billion. This drop, company leaders say, was due to the new distribution rights agreement covering Remicade and its follow-on, **Simponi**, reached in April 2011 between Merck and Johnson & Johnson, under which Merck relinquished marketing rights for those products in territories including Canada, Central and South America, the Middle East, Africa, and Asia Pacific. Sales of Remicade in the retained territories actually rose 13 percent for the year. In the first half of 2012, this agreement effect was even more prominent – the first half of 2011 was the last full pre-agreement period – as Remicade sales fell by 35 percent to $1.04 billion.

Sales of the cholesterol drugs **Zetia** and **Vytorin** were again net stagnant in 2010, with Zetia up 5.7 percent to $2.43 billion while Vytorin dropped 6.6 percent to $1.88 billion. Both products have followed a similar path in the first half of 2012, with Vytorin sales down 5.3 percent to $889 million and Zetia sales up 6.1 percent to $1.25 billion.

In January, FDA approved an updated label for Vytorin that includes results from the Study of Heart and Renal Protection (SHARP). In SHARP, Vytorin 10/20 milligrams lowered LDL cholesterol in patients with moderate to severe chronic kidney disease, and major vascular events were reduced in the treatment group compared to placebo. The trial therefore demonstrated that treatment with Vytorin 10/20 milligrams versus placebo reduced the risk for major vascular events in this chronic kidney disease population. Because SHARP studied the combination of simvastatin and ezetimibe compared with placebo, it was not designed to assess the independent contributions of each drug to the observed effect; for this reason, FDA did not approve a new indication for Vytorin or for Zetia, and the study's efficacy results have not been incorporated into the label for Zetia.

"Merck is committed to supporting clinical research that helps to address important questions in medicine," says Michael Mendelsohn, M.D., senior VP and head, atherosclerosis and cardiovascular research, Merck Research Laboratories. "The results of SHARP as described in the new label for Vytorin can help the medical community understand the role of lowering lipids with Vytorin in managing cardiovascular risk in patients with CKD."

The HIV drug **Isentress** continued to grow impressively for Merck in 2011, with sales up by 24.7 percent to $1.36 billion. In the first half of 2012, Isentress sales were up another 16.9 percent to $735 million.

In January 2012, FDA approved the use of Isentress in combination with other antiretroviral medicines, for the treatment of HIV-1 infection in pediatric patients two years of age and older and weighing at least 10 kilograms. This new indication was based on the evaluation of safety, tolerability, pharmacokinetic parameters, and efficacy of Isentress through at least 24 weeks in a multicenter, open-label, non-comparative study, in HIV-1-infected children and adolescents two to 18 years of age. FDA also has approved a chewable tablet formulation of Isentress for the treatment of children two to less than 12 years of age.

"Isentress is now a new treatment option as part of a regimen for children ages two years and older living with HIV-1 in the U.S.," says Hedy Teppler, senior director, Clinical Research, Merck. "This advancement underscores Merck's longstanding commitment to help in the fight against HIV, which spans more than 25 years."

In May, FDA approved a labeling update for Isentress Film-coated Tablets to include 156-week data from the STARTMRK study with Isentress in combination therapy compared to efavirenz in combination therapy in previously untreated (treatment-naive) adult HIV-1-infected patients. The analyses showed that the regimen containing Isentress demonstrated long-term viral suppression, a greater immunologic response, and a proven safety and tolerability profile at 156 weeks. Isentress is the first and only integrase inhibitor indicated for the treatment of HIV-1 in adult treatment-experienced and treatment-naïve patients as part of a combination treatment regimen.

Sales of the HPV vaccine **Gardasil** made a comeback in 2011 after three consecutive years of decline, jumping 22.4 percent to $1.21 billion. Company leaders credit this improvement to increased vaccination of males 9 to 26 years of age in the United States (the vaccine was approved by FDA to prevent anal cancer in males and females 9 to 26 in December 2010), higher

sales in conjunction with the launch in Japan, and growth in emerging markets In the first half of 2011, Gardasil sales rose another 24.1 percent to $608 million.

In October 2011, data from a sub-study of the pivotal Phase III clinical trial with Gardasil in males were published in the *New England Journal of Medicine*. In this study of 602 healthy men who have sex with men, ages 16 to 26 years, Gardasil was 77.5 percent effective in the per-protocol efficacy population in reducing the rates of anal intraepithelial neoplasia associated with human papillomavirus types 6, 11, 16 and 18. The efficacy of Gardasil against HPV-related anal disease was studied in a population of men who have sex with men because of the known high risk of anal infection and disease that occurs in this group.

In the pipeline

Merck spent $8.47 billion on research and development in 2011, down 23.8 percent from the previous year. This drop, company executives say, came primarily as a result of the $2.4 billion in impairment charges due to the abandonment or revision in value of various compounds recorded in 2010 after the Schering-Plough merger. In the first half of 2012, R&D expenses appear to have stabilized, dropping 1.7 percent to $4.03 billion.

Merck has earned several regulatory approvals in the past few months. In August 2011, **Zoely**, an oral contraceptive, was granted marketing authorization by the EC for use by women to prevent pregnancy. Zoely is a combined oral contraceptive tablet containing a unique monophasic combination of two hormones: nomegestrol acetate, a highly selective progesterone-derived progestin, and 17-beta estradiol, an estrogen that is similar to the one naturally present in a woman's body. The company then earned two eye care approvals in February: for **Zioptan**, a preservative-free prostaglandin analog ophthalmic solution for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension; and for **Cosopt PF**, Merck's preservative-free formulation of Cosopt ophthalmic solution, indicated for the reduction of elevated intraocular pressure in appropriate patients with open-angle glaucoma or ocular hypertension.

The news has been bad of late, though, for one of Merck's greatest sources of hope, the cancer drug **ridaforolimus**. An NDA for the compound, in development for the treatment of metastatic soft-tissue or bone sarcomas in patients who had a favorable response to chemotherapy, was accepted by FDA in October. But in March, FDA's Oncologic Drugs Advisory Committee voted 13 to 1 against the use of ridaforolimus as maintenance therapy for patients with metastatic soft-tissue sarcoma or bone sarcoma whose disease has not progressed after at least four cycles of chemotherapy. Then, in June, FDA issued a complete response letter stating that the agency could not approve the application for ridaforolimus in its present form, and that additional clinical trials would need to be conducted to further assess safety and efficacy. Merck is in ongoing discussions with health authorities in Europe and other countries as part of their application procedures for ridaforolimus for the treatment of metastatic soft-tissue or bone sarcomas in patients who had a favorable response to chemotherapy. Additionally, Merck is studying ridaforolimus in combination with other mechanisms in several tumor types.

"Merck remains confident in the potential of ridaforolimus," says Eric Rubin, M.D., VP, Clinical Research Oncology, Merck. "We will continue to work closely with FDA to define potential paths forward for this investigational therapy."

Zolinza, already approved in the United States for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies, also suffered a development setback in 2011. In September, Merck announced that a Phase III study of the drug for use in patients with advanced malignant pleural mesothelioma who previously have been treated with systemic chemotherapy containing pemetrexed did not meet its primary endpoint of demonstrating an improvement in overall survival. Three months later, though, another Phase III study of Zolinza, for investigational use in combination with bortezomib in patients with progressive multiple myeloma, met its primary endpoint, demonstrating a 23 percent reduction in the risk of progression compared to the standard therapy of bortezomib.

Another Merck drug in development, **vorapaxar**, has also earned a split decision of late. In November, the results of the TRACER trial of vorapaxar in acute coronary syndrome showed that the compound did not meet its primary endpoint. In March, however, researchers presented data from the TRA-2P study of vorapaxar in patients with a prior history of cardiovascular events or disease showing that the addition of the drug to standard of care (e.g. aspirin, or thienopyridine, or both) resulted in a significantly greater reduction in the risk of the composite of cardiovascular death, heart attack, stroke, or urgent coronary revascularization. This was the first time that an anti-thrombotic medicine added to the standard of care, including aspirin, has been shown to provide an additional, significant reduction in cardiovascular events in the secondary prevention setting, defined as patients who previously experienced a heart attack, an ischemic stroke, or who had documented peripheral arterial disease.

"Despite all of the advances made in cardiovascular medicine, significant residual risk for recurrence of cardiovascular events remains, and that is why Merck is committed to developing medicines like vorapaxar that are intended to provide incremental, additional reductions in residual risk," says Francis Plat, M.D., VP, clinical research, therapeutic area head Atherosclerosis and Cardiovascular Disease, Merck Research Laboratories. "The results from this study showed that the addition of vorapaxar to standard of care, including aspirin, provided an additional reduction in risk. We plan to continue our discussions with the investigators and other outside experts to help define the role of this investigational compound in secondary prevention."

In October, Merck announced results from two 26-week investigational Phase III clinical studies evaluating the efficacy and safety of two dose strengths of **Dulera** in adults 40 years and older with moderate to very severe chronic obstructive pulmonary disease. The two dose strengths evaluated in the studies were Dulera 100 mcg/5 mcg and Dulera 200 mcg/5 mcg, both administered as two inhalations twice daily. In both studies, Dulera 200 mcg/10 mcg and Dulera 400 mcg/10 mcg significantly improved lung function as measured by forced expiratory volume in one second (FEV1) area under the curve over 0 to 12 hours (AUC0-12hr) at Week 13 (one of the co-primary endpoints) compared to treatment with mometasone furoate 400 mcg (administered as two inhalations of mometasone furoate 200 mcg twice daily), the primary treatment comparison for this endpoint, or placebo alone.

"This is the first presentation of data from these Phase III investigational studies evaluating the efficacy and safety of Dulera in patients 40 years and older with moderate to very severe COPD," says Dr. Dennis E. Doherty, M.D., professor of medicine in the Division of Pulmonary, Critical Care and Sleep Medicine at the University of Kentucky in Lexington, Ky., and a study investigator. "It's important that the scientific community continue evaluating potential treatment options for our patients with COPD."

Dulera is already indicated in the United States for the treatment of asthma in patients 12 years and older. It is not indicated for the relief of acute bronchospasm or for the treatment of COPD. A supplemental new drug application for Dulera for the treatment of COPD has been accepted for standard review by FDA.

In March, Merck announced the results from a Phase III clinical study of the company's investigational allergy immunotherapy tablet (**AIT**) for ragweed pollen. The study results showed that the use of ragweed AIT significantly reduced the total combined score that measured nasal and eye symptoms and use of rescue allergy medicines, compared to placebo, in ragweed-allergic adults with or without asthma. The study was conducted during peak ragweed pollen season.

Merck's AIT is an investigational, dissolvable oral tablet designed to treat the underlying cause of allergies, and is being studied to determine whether AIT may help to prevent allergy symptoms by generating an immune response to protect against targeted allergens. The company is investigating disease-modifying AITs for the treatment of allergies caused by ragweed pollen, grass pollen, and house dust mites. Merck has partnered with ALK-Abello to develop AITs to treat these allergens in North America and plans to file new drug applications for its ragweed and grass AITs with FDA in 2013.

"Merck is pleased that patients who took its AIT in this study experienced a significant reduction in the nasal and eye symptoms caused by ragweed allergies, and these positive results are an important step in the development of this investigational therapy," says Rupert Vessey, M.D., Ph.D, senior VP and franchise head, Respiratory & Immunology, Merck Research Laboratories. "We are committed to providing physicians and patients with a broad range of treatment options for allergies and other respiratory diseases."

In June, Merck revealed new data from two pivotal Phase III efficacy trials for **suvorexant**, an investigational medicine for the treatment of insomnia. In the studies, suvorexant significantly reduced the time it took patients to fall asleep and increased the time that patients stayed asleep as early as the first night and at the three-month time point compared to placebo. The investigational medicine met statistical significance for all primary endpoints except for one measurement at Month 3 in one of the trials. Other data presented included results that demonstrated the effects of suvorexant after daily dosing for at least a year. Additional data released in September showed that, after daily use of a consistent dose of suvorexant for one year, patients who stopped taking the medicine experienced a return of their sleeping difficulties to levels similar to those reported by patients who received placebo over the course of the trial. Patients who continued to receive suvorexant for the additional two months experienced mean improvements in their ability to fall asleep and stay asleep that were consistent with those seen over the first 12 months compared to placebo.

The company plans to file an NDA for suvorexant with FDA in 2012. If approved, suvorexant would be the first medicine approved in a new class of medicines, called orexin receptor antagonists, for use in patients with difficulty falling or staying asleep.

"We specifically focused our research efforts on insomnia because it is an area of significant unmet medical need," says Darryle D. Schoepp, Ph.D., senior VP and head of the Neuroscience and Ophthalmology franchise, Merck Research Laboratories. "Suvorexant approaches insomnia differently than other medicines because it helps patients to sleep by targeting and blocking orexins, which play a role in keeping people awake. We're excited about the Phase III results and the potential of suvorexant to become the first in a new class of medicines to help patients with insomnia."

In July, Merck announced an update on the Phase III trial assessing fracture risk reduction with **odanacatib**, the company's investigational cathepsin K (cat-K) inhibitor. The data monitoring committee for the study completed its first planned interim analysis for efficacy and recommended that the study be closed early due to robust efficacy and a favorable benefit-risk profile. As a result, Merck will begin taking steps to close the trial. The data monitoring committee noted that safety issues remain in certain selected areas and made recommendations with respect to following up on them. Merck's previously announced plan to conduct a blinded extension trial will allow further monitoring of the issues. The extension trial will also continue to measure efficacy. Merck anticipates submitting regulatory applications for approval of odanacatib in the United States, European Union, and Japan in the first half of 2013.

"We are encouraged by the data monitoring committee's recommendation to close the trial early, and look forward to reviewing the data with the scientific community to bring forward this innovation," Dr. Kim says.

The Phase III randomized, placebo-controlled trial with more than 16,000 patients was designed to assess the safety and efficacy of odanacatib in reducing fracture risk in postmenopausal women with osteoporosis. This trial started in 2007 and was expected to continue until hip fractures had been reported in a total of 237 patients. The interim analysis was conducted by the data monitoring committee as planned when about 70 percent of the targeted number of hip fractures had been reported.

Merck expects the process of closing the trial to take a number of months. Trial investigators will schedule final assessments for trial participants at 387 sites in 40 countries. Data from these visits will be collected and reviewed to allow a full and complete analysis, and final results of the study will be submitted for presentation and publication in 2013 once the analysis is complete.

In December, Merck announced the establishment of an Asia Research & Development headquarters for innovative drug discovery and development located in Beijing, China. The new facility is part of a $1.5 billion commitment the company has made to invest in R&D in China over the next five years.

"The establishment of the MSD Asia R&D headquarters represents an important milestone as we implement our strategy of building capabilities, and relationships to succeed in fast growing geographic regions," Dr. Kim says. "By strategically locating in China, we are able to complement our existing R&D capabilities, and facilitate new collaborations with scientists in the region and across emerging markets."

Located in Wangjing Park, one of Beijing's rapidly expanding science and technology parks, the facility will consist of 47,000 square meters of office and laboratory space. The first phase of construction, scheduled to be completed by 2014, will provide capacity for about 600 employees working in the areas of drug discovery, translational research, clinical development, regulatory affairs, and external scientific research programs.

In other late-stage R&D developments, Merck is continuing to advance plans for four additional major regulatory filings by end of 2013. These include **Bridion**, a neuromuscular blocker reversal agent; **V503**, a nine-valent vaccine for HPV; **Tredaptive**, a novel candidate for multiple lipid parameters; and **vintafolide**, a small molecule drug conjugate for ovarian and other cancers to be filed for approval in Europe. ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

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NOVARTIS

BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Diovan, Diovan HCT	$5,665	$6,053
Gleevec/ Glivec	$4,659	$4,265
Lucentis	$2,050	$1,533
Zometa	$1,487	$1,511
Sandostatin	$1,443	$1,291
Exforge	$1,209	$904
Exelon, Exelon Patch	$1,067	$1,003
Femara	$911	$1,376
Neoral, Sandimmun	$903	$871
Exjade	$850	$762
Voltaren Group	$794	$791
Tasigna	$716	$399
Galvus	$677	$391
Comtan, Stalevo	$614	$600
Reclast/ Aclasta	$613	$579
Tekturna/ Rasilez	$557	$438
Ritalin, Focalin	$550	$464
Myfortic	$518	$444

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Sales	$58,566	$50,624
Net income	$9,245	$9,969
EPS	$3.78	$4.26
R&D	$9,583	$9,070

	1H12	1H11
Sales	$28,038	$28,942
Net income	$5,060	$5,547
EPS	$2.07	$2.33
R&D	$4,520	$4,585

All figures are in millions of dollars, except EPS.

Post-Diovan growth prospects

After generating company-record sales in 2011, to help offset the patent-protection loss of its top-selling product, Novartis is capitalizing on growth from other billion-dollar brands and the Alcon business while awaiting a new generation of drug and vaccine blockbusters.

By Andrew Humphreys andrew.humphreys@ubm.com

"Novartis achieved eight significant regulatory milestones in the second quarter, including CHMP recommendation for Afinitor in advanced breast cancer, further enhancing our future growth prospects," says CEO Joseph Jimenez on the company's first-half 2012 performance. "Pharmaceuticals and Alcon delivered solid financial performance and operating leverage in the second quarter, underpinned by our continued focus on portfolio rejuvenation, with recently launched products now representing 29 percent of Group net sales compared to 25 percent last year."

Recognized as *Med Ad News*' Company of the Year in the magazine's September 2011 edition, Novartis had a strong 2011 indeed. Revenue growth for the year registered at 15.7 percent, an impressive increase for a company generating more than $50 billion in annual sales. But growth during 2012 has significantly fallen off that pace as Novartis' best-selling product franchise, the anti-hypertensive agent **Diovan**, has lost U.S. and EU patent protection. Though with an arsenal of still-growing blockbuster brands, one of the industry's strongest pipelines and a successful diversification of other healthcare businesses, Novartis' future growth prospects are very promising. The Swiss company has been projected by analysts to pace the industry in healthcare revenue by 2018 ahead of current leaders **Pfizer** Inc. and **Johnson & Johnson**.

Novartis announced in January 2012 a restructuring of the company's U.S. business to bolster its competitive position. The U.S. restructuring is anticipated to result in yearly savings of $450 million for the company by 2013. The decision reflects the loss of Diovan patent exclusivity in United States during September 2012 as well as the expected effect on global sales of **Tekturna/Rasilez** after the ALTITUDE study termination. The study ended following the recommendation from the data monitoring committee overseeing the clinical trial investigating Tekturna/Rasilez in a high-risk population of patients with type 2 diabetes and renal impairment. The hypertension drug Tekturna/Rasilez generated $557 million in 2011 sales for Novartis.

"We recognize that the next two years will be challenging in the Pharmaceuticals Division and we are proactively making these changes to further focus our pipeline on the best opportunities and align our market position on our growth brands," noted David Epstein, division head of Novartis Pharmaceuticals, in early 2012. "These are difficult but necessary decisions that will free up resources to invest in the future of our business which we view as well suited to bring new valuable therapies to patients and payors."

A significant element of the plan is a restructuring of the General Medicines business in the important U.S. market, where Novartis Pharmaceuticals will continue to concentrate on expanding its presence in specialty businesses aligned with the product portfolio and pipeline. As a result, the field force is intended to be reduced by 1,630 positions and headquarters functions will realign to support the new organization, resulting in another reduction of 330 positions. The changes took effect during second-quarter 2012.

Novartis' strategy for long-term sustainable growth is rooted in the concentrated diversification of the company's portfolio across high-growth segments of the healthcare arena. Novartis says it is well-positioned to deliver future growth as the only healthcare company with leading positions in pharmaceuticals, eye care, generics, vaccines and diagnostics, OTC medicines, and animal health.

Underpinning the company's strategy is a deep dedication to innovation, growth and productivity across Novartis' diversified portfolio. "Continued execution on this commitment has allowed us to expand and improve our offerings for patients with unmet medical needs while providing long-term value for our investors," executives say.

Company performance

For 2011, Novartis net sales jumped up 16 percent (12 percent more in constant currencies) to $58.6 billion. Recently launched products fueled growth across the expansive healthcare portfolio, with medicines introduced since 2007 accounting for one-quarter of group sales, rising from 19 percent in 2010. Sales for products launched since 2007 increased 38 percent to $14.4 billion. Since 2007, Novartis says it has received approvals for more innovative medicines in Europe and the United States than any other company.

Novartis achieved 15 major regulatory pharmaceutical approvals during 2011 in the United States, European Union and Japan. Included were new indications for the cancer drug **Afinitor/Votubia** in the United States and European Union, the first oral multiple sclerosis therapy **Gilenya** in Europe and Japan, two new indications for **Lucentis** in the EU, and the COPD product **Arcapta Neohaler** in the United States. New approvals for the **Alcon** Division included **Dailies Total1** – a daily disposable contact lens with silicone hydrogel technology – in the EU, and **WaveLight EX500 Excimer Laser** gained FDA clearance.

Net sales in Novartis' top six emerging markets increased 17 percent in constant currencies during 2011, accounting for 10 percent of the group's net sales. Novartis says China was a major success story, with net sales rising 38 percent in constant currencies. A new local management team leading the Pharmaceuticals Division focused on marketing and sales skills, and the new decentralized organization was launched during 2011 covering inland provinces in China.

Expanding its presence in China – as well as in other fast-growing nations such as Brazil, Russia and India – is critical to Novartis' long-term growth strategy, with several milestones attained in 2011. The company's completed purchase of an 85 percent holding in **Zhejiang Tianyuan** Bio-Pharmaceutical Co. is anticipated to enable Novartis to deliver a wide range of vaccines in China. Zhejiang Tianyuan is one of China's largest privately held vaccine companies.

In 2012, Novartis first-half net sales reached $28.04 billion, down 3 percent in U.S. dollars and representing flat growth at constant currencies. Currency depressed net sales by 3 percentage points. Products introduced since 2007 continued to perform strongly with 12 percent growth versus first-half 2011, reaching $7.9 billion. These recently launched products made up 28 percent of first-half 2012 group net sales, up from 24 percent during January-June 2011.

Pharmaceuticals net sales in first-half 2012 rose to $16.1 billion (representing flat growth in U.S. dollars; up 4 percent in constant currencies) with nine percentage points of volume growth partly offset by the affects of generic entrants of five percentage points. Excluding the impact of the mega-blockbuster Diovan and other patent expirations, the division increased 8 percent in constant currencies. Recently launched products contributed $5.5 billion to net sales, accounting for 34 percent of total net sales for the division versus 27 percent in the first half of 2011.

Growth in recently launched products during January-June 2012 offset the sales loss from Diovan patent expiration. The Diovan franchise generated 2011 sales of $5.67 billion in 2011, with peak sales exceeding $6 billion in each of 2010 and 2009. Novartis says generic erosion of Diovan is in line with expectations, with the outlook for the valsartan family remaining at more than $2 billion sales in 2014.

"Novartis achieved eight significant regulatory milestones in the second quarter, including CHMP recommendation for Afinitor in advanced breast cancer, further enhancing our future growth prospects," commented Novartis CEO Joseph Jimenez on the company's first-half 2012 performance. "Pharmaceuticals and Alcon delivered solid financial performance and operating leverage in the second quarter, underpinned by our continued focus on portfolio rejuvenation, with recently launched products now representing 29 percent of Group net sales compared to 25 percent last year."

Following the CHMP recommendation in June 2012, one month later Afinitor was approved for a new indication in combination with exemestane for advanced breast cancer by EU as well as U.S. health regulators. The drug represents the first major advance in HR+ advanced breast cancer in 15-plus years and the first mTOR inhibitor approved to treat women with this disease. Afinitor tablet is approved in 80-plus countries including the United States and throughout the European Union in advanced renal cell carcinoma following progression on or after vascular endothelial growth factor-targeted therapy. The product is available in the United States and EU for locally advanced, metastatic or unresectable progressive neuroendocrine tumors of pancreatic origin.

First-half 2012 net sales in Novartis' Emerging Growth Markets – which include all regions except the United States, Canada, Western Europe, Australia, New Zealand and Japan – advanced 6 percent at constant currencies in second-quarter 2012, contributing $3.4 billion or 24 percent to group net sales. Pharmaceuticals sales in Emerging Growth Markets increased 5 percent in the quarter. Alcon Emerging Growth Markets generated another very strong quarter, rising 14 percent versus April-June 2011. In China, net sales performance was strong across divisions, with 23 percent growth in second-quarter 2012. Further bolstering Novartis' growth prospects in the Chinese market, marketing approval was gained during the period for **Onbrez Breezhaler** as a once-a-day treatment for COPD.

Healthcare leader in five fields

When Novartis was created in 1996, 45 percent of the company's net sales came derived from healthcare. Since then, the company has transformed its business concentration to purely fast-growing areas of healthcare. Novartis is considered the only company with leading positions in each of these key fields: Pharmaceuticals, with innovative patent-protected medicines; Alcon, a worldwide leader

in eye care with surgical, ophthalmology and consumer products; **Sandoz**: with affordable, high-quality generic medicines and biosimilars; Consumer Health, with self-medication products and treatments for animals; and Vaccines and Diagnostics, with vaccines and diagnostic tools to protect against life-threatening diseases

The Pharmaceuticals division researches, develops, manufactures, distributes and sells patented prescription medicines in various therapeutic fields and was reorganized as of Jan. 1, 2012. The therapeutic areas are Oncology; Primary Care, consisting of Primary Care medicines and Established Medicines; and Specialty Care, consisting of Ophthalmology, Neuroscience, Integrated Hospital Care, and Critical Care medicines.

During 2011, this division accounted for $32.5 billion, or 56 percent, of group net sales, and for $8.3 billion, or 71 percent, of group operating income (excluding corporate income and expense, net). The division contained 80 affiliated companies that combined employed 60,527 full-time equivalent associates as of year-end 2011, selling products in 140 countries.

During first-half 2012, Pharmaceuticals net sales totaled $16.09 billion, versus $16.04 billion in January-June 2011. Operating income for the first two quarters of 2012 amounted to $5.14 billion, representing 32 percent of net sales.

Novartis completed in April 2011 its acquisition of Alcon, the world leader in eye care. Alcon represents the second-largest division in Novartis' diversified healthcare portfolio. In 2011, the division generated $10 billion, or 17 percent, of group net sales, accounting for $1.5 billion, or 13 percent, of Group operating income (excluding Corporate income and expense, net). As of Dec. 31, 2011, Alcon had 22,987 full-time equivalent associates in 75 countries.

The division discovers, develops, manufactures, distributes and sells eye-care products. Alcon is the worldwide leader in eye care with product offerings in Surgical, Ophthalmic Pharmaceuticals and Vision Care. In Surgical, the business develops, manufactures, distributes and sells ophthalmic surgical equipment, instruments, disposable products and intraocular lenses. In Pharmaceutical, the division discovers, develops, manufactures, distributes and sells medicines to treat chronic and acute diseases of the eye, as well as OTC medicines for the eye. In Vision Care, the business develops, manufactures, distributes and sells contact lenses and lens-care products.

Alcon first-half 2012 net sales increased 3 percent (up 6 percent in constant currencies) to $5.19 billion over first-half 2011. The performance was fueled by strong Surgical growth of 6 percent (up 9 percent in constant currencies) and solid Ophthalmic Pharmaceuticals growth of 2 percent (up 5 percent in constant currencies), overcoming the effect of a mild U.S. ocular allergy season. Alcon's operating income in January-June 2012 came in at $782 million, representing 15.1 percent of the division's net sales.

Sandoz is a global leader in developing, manufacturing and marketing generic pharmaceutical products, follow-on biopharma products and drug substances that are not protected by valid and enforceable third-party patents. As of year-end 2011, affiliates of the Sandoz Division employed 24,377 full-time equivalent associates in 130 countries. The division generated 2011 consolidated net sales of $9.47 billion, accounting for 16.2 percent of Novartis total net sales.

Sandoz is the No. 2 company in worldwide generic sales, trailing only **Teva** Pharmaceutical Industries Ltd. Sandoz is also a leader in biosimilars, with three marketed medicines accounting for about half of the total biosimilar market segment in the combined regions of North America, Europe, Japan and Australia. The acquisition of **EBEWE** Pharma in 2009 and the launch of generic **enoxaparin sodium** (branded by **Sanofi** as **Lovenox**) in the United States during 2010 has helped Sandoz attain a worldwide leadership position in generic injectables. Sandoz also is a leading global manufacturer of antibiotics.

The division's first-half 2012 net sales declined 12 percent (down 7 percent in constant currencies) to $4.27 billion. The decline was spurred by decreases in the United States (down 23 percent in constant currencies) and Germany (down 8 percent in constant currencies), which were partly offset by double-digit sales growth in Western Europe (up 10 percent in constant currencies) and Asia (up 21 percent), as well as growth in Central and Eastern Europe (up 3 percent in constant currencies) in declining markets, and continued strong results from biosimilars (up 46 percent in constant currencies). Total sales volume was flat due to competition on U.S. sales of enoxaparin, lost U.S. authorized generics of **gemcitabine** and **lansoprazole** in the previous year, and lower sales in Germany. Price erosion was seven percentage points during first-half 2012.

Novartis Consumer Health is a leader in the R&D, manufacturing and marketing of a broad range of competitively differentiated products that restore, maintain or improve the health and well-being of consumers, as well as pets and livestock. The business is carried out by affiliated companies globally. Consumer Health consists of two divisions: OTC and Animal Health.

As of Dec. 31, 2011, the Consumer Health affiliates employed 8,290 full-time equivalent associates. Consolidated net sales for 2011 totaled $4.63 billion, accounting for 7.9 percent of Novartis net sales.

In first-half 2012, Consumer Health sales dropped off 22 percent (down 18 percent in constant currencies) year-over-year to $1.84 billion. The decrease was primarily attributed to the effect of the suspension of production at Lincoln, Neb. OTC's net sales decreased sharply versus first-half 2011 mainly because of the impact of the manufacturing suspension. Animal Health generated a sales decrease in January-June 2012 versus first-half 20111 due to limited sales of companion animal products manufactured at the Lincoln facility, which mainly affected the United States and Canada.

The Vaccines and Diagnostics division is a leader in the R&D, manufacturing and marketing of vaccines and diagnostic tools used worldwide. Novartis Vaccines products consist of influenza, meningococcal, pediatric, adult and travel vaccines. Novartis Diagnostics is committed to preventing the spread of infectious diseases via the development and marketing of nucleic acid technology blood-screening products. Novartis Diagnostics is creating innovative diagnostics to detect, prevent, and predict disease and improve medical outcomes.

The Vaccines and Diagnostics division's product portfolio consists of 20-plus marketed products. The portfolio of development projects includes more than 15 potential new products in different stages of clinical development.

As of year-end 2011, the business employed 6,122 full-time equivalent associates throughout 30 countries. For 2011, the division had consolidated generated net sales of $2 billion, representing 3.4 percent of group net sales.

First-half 2012 net sales for Vaccines and Diagnostics totaled $648 million, compared to $670 million during the one-year-earlier period. The first six months of 2011 were affected by the release of bulk pediatric shipments that had been delayed from fourth-quarter 2010 because of production issues. Excluding the effect of these shipments, the underlying business generated solid growth – fueled by **Menveo** and the Diagnostics business – partially offset by higher late-season northern hemisphere flu sales in first-half 2011.

Product performance

Novartis' portfolio of billion-dollar medicines in 2011 consisted of the Diovan franchise for hypertension; the leukemia drug **Gleevec/Glivec**; the wet age-related macular degeneration product Lucentis; the hypercalcemia medication **Zometa**; the acromegaly drug **Sandostatin**; the **Exforge** family of antihypertensive agents; and the **Exelon** product line for Alzheimer's disease.

Diovan ranked No. 13 among global Rx medicine sales during 2011 at $5.67 billion after generating $6.05 billion in 2010. The angiotensin II receptor antagonist Diovan gained initial FDA marketing approval in December 1996. **Co-Diovan** (valsartan and hydrochlorothiazide) U.S. clearance came in October 1997. The Diovan product line eventually became the best-selling hypertension franchise worldwide. Patent expirations started in the majority of EU nations in November 2011, took effect in the United States during September 2012, and will occur in Japan during 2013.

Sales of the wet age-related macular degeneration drug Lucentis cracked the $2 billion mark for the first time in 2011.

Diovan global sales for first-half 2012 amounted to $2.46 billion, down 16 percent in U.S. dollars and 15 percent in constant currencies compared to January-June 2011. Global sales for Diovan during first-half 2012 dropped off due to the loss of exclusivity in the EU and Canada. U.S. sales for the product franchise in January-June 2012 improved 5 percent in constant currencies year-over-year to $1.25 billion. During first-half 2012, Diovan sustained performance in emerging growth markets such as China, and in select countries in Latin America, Asia Pacific, Middle East and Africa.

Taking the place of Diovan as Novartis' best-selling medicine by 2013 will be the tyrosine kinase inhibitor Gleevec/Glivec. The signal transduction inhibitor is marketed for treating patients with certain forms of chronic myeloid leukemia and gastrointestinal stromal tumors. First introduced to the marketplace during 2001, the drug is available in more than 110 countries.

Gleevec/Glivec is indicated for treating newly diagnosed adult and pediatric patients with a form of chronic myeloid leukemia. The product is marketed in the United States, EU, and Japan to treat Philadelphia chromosome positive acute lymphoblastic leukemia, which is a rapidly progressive form of leukemia. The medicine is additionally available in the United States and EU to treat dermatofibrosarcoma protuberans, a rare solid tumor; hypereosinophilic syndrome and myelodysplastic/myeloproliferative diseases; and other rare blood disorders. Gleevec is also FDA-approved for aggressive systemic mastocytosis. The drug has been cleared for marketing as a post-surgery (adjuvant setting) therapy for KIT+ gastrointestinal stromal tumors in 60-plus countries, including the United States and European Union. During February 2012, EU and U.S. health regulators approved that the Glivec label be updated to include three years of adjuvant treatment for patients with resected KIT+ gastrointestinal stromal tumors.

Gleevec/Glivec sales for 2011 reached $4.66 billion compared to $4.27 billion in 2010. First-half 2012 sales improved 2 percent in U.S. dollars and 5 percent in constant currencies to $2.32 billion. During second-quarter 2012, Novartis submitted marketing authorizations with the EMA and FDA for Gleevec/Glivec in pediatric Philadelphia chromosome–positive acute lymphoblastic leukemia.

The patent on Glivec/Gleevec is due to expire in 2015 in the United States, during 2016 in the major EU countries, and 2014 in Japan (in each case including extensions).

Lucentis was the other Novartis medicine to exceed $2 billion in 2011 sales ($2.05 billion), increasing from $1.53 billion during 2010. Lucentis is developed in collaboration with **Genentech** Inc., which holds the product's U.S. marketing rights. **Roche**, which owns Genentech, reported Lucentis 2011 sales of SFr1.52 billion ($1.72 billion).

The recombinant humanized high-affinity antibody fragment, which contains the active chemical ranibizumab, binds to vascular endothelial growth factors. Lucentis is the first VEGF inhibitor specifically designed for use in the eye to bind to and inhibit VEGF-A, which is a protein believed to have a critical role in the formation of new blood vessels (angiogenesis) and the hyperpermeability of the vessels. Lucentis is the first approved drug for wet age-related macular degeneration that has been demonstrated to improve vision and vision-related quality of life. Lucentis is the only therapy of its kind to significantly improve vision in patients with wet age-related macular degeneration, diabetic macular edema and macular edema secondary to retinal vein occlusion.

Lucentis 0.5 mg once monthly was initially approved by U.S. regulators for treating wet age-related macular degeneration in 2006 and for macular edema following retinal vein occlusion in 2010. In August 2012, Genentech announced that the drug became the first FDA-approved medicine for diabetic macular edema, a condition for which the standard of care has not changed significantly in 25-plus years.

Lucentis is regarded as the standard of care for treating wet age-related macular degeneration. The product was first approved in the EU during 2007 and is available in 100-plus countries. During January 2011, the European Commission granted a new indication for Lucentis: treating visual impairment due to diabetic macular edema. Lucentis has gained regulatory approval for this indication in 75-plus countries. During May 2011, the European Commission approved another indication: treating visual impairment due to macular edema secondary to retinal vein occlusion. Lucentis is available for

this indication in more than 70 countries.

In first-half 2012, Lucentis sales for Novartis increased 25 percent at constant currencies versus first-half 2011 to $1.2 billion. During 2012, two-year study data was announced confirming the drug's safety profile. Novartis says the CATT (Comparison of Age-related macular degeneration Treatment Trials) data adds to the growing body of evidence suggesting that the overall risk of serious systemic adverse events is higher with unlicensed intravitreal bevacizumab (marketed by Roche as the blockbuster medicine **Avastin**) compared to Lucentis in patients with wet age-related macular degeneration. Novartis believes that Lucentis, with more than 1 million patient treatment years underpinning its safety profile, is the best treatment option for patients with wet age-related macular degeneration.

Other research presented at the 2012 Association for Research in Vision and Ophthalmology Annual Meeting reinforced the long-term efficacy and well-characterized safety profile of Lucentis, as well as the benefits of an individualized treatment regimen, across multiple retinal disease fields. The RESTORE extension study demonstrated that a low amount of Lucentis injections are necessary to achieve and maintain vision gains over three years in diabetic macular edema patients.

Lucentis has been rigorously studied in multiple retinal diseases in 27 clinical trials involving 10,500-plus patients around the globe. There are more than 1 million patient-treatment years of exposure for the medicine.

EvaluatePharma analysts project that Lucentis will be the No. 15 best-selling prescription drug worldwide in 2018 with combined sales of $4.15 billion generated between Novartis and Roche. Patent protection for the main chemical in Lucentis expires in 2018-22 in the EU and Japan, some of the major territories where Novartis markets the medicine.

Zometa (zoledronic acid for injection/zoledronic acid 4 mg) is a leading product to reduce or delay skeletal-related events. These SREs include pathologic fracture, spinal cord compression, and/or requirement of radiation therapy or surgery to bone in patients with bone metastases (cancer that has spread to the bones) from solid tumors and multiple myeloma.

Initially FDA-approved in during 2001 for treating hypercalcemia of malignancy (tumor-induced excessive levels of calcium), the drug is approved in 100-plus countries for this indication as well as for treating patients with multiple myeloma and patients with bone metastasis from solid malignancies. These malignancies include prostate, breast and lung cancer. A new ready-to-use (RTU) form of Zometa was cleared by U.S. regulators during June 2011. Launched to market in September 2011, the RTU form offers improved convenience of use. The EMA approved this form during August 2011 and the product was introduced two months later in countries such as Germany, Austria, the UK, Ireland, Sweden, Denmark, Norway, Finland, Netherlands, Portugal, and Slovenia.

Zometa sales declined from $1.51 billion in 2010 to $1.49 billion during 2011. The sales decline for the leading bisphosphonate treatment continued during first-half 2012. Sales in January-June 2012 came in at $663 million, down 11 percent in U.S. dollars and 9 percent in constant currencies versus 1H 2011.

The patent on zoledronic acid is set to expire during 2013 in the United States, and during 2012 and 2013 in other major markets. Zoledronic acid is additionally the main chemical in Novartis' **Reclast/Aclasta** for use in non-oncology indications. Zometa and Reclast/Aclasta face significant competition from denosumab, an **Amgen** Inc. drug approved for treating post-menopausal osteoporosis (marketed as **Prolia**) and cancer treatment-induced bone loss in the oncology setting, for SRE reduction or delay in patients with advanced malignancy involving bone (branded as **Xgeva**). Denosumab is not approved for marketing in the multiple myeloma setting.

Sandostatin SC and LAR (octreotide acetate) are indicated for treating patients with acromegaly, a chronic disease caused by over-secretion of pituitary growth hormone in adults. The drug is indicated for treating patients with certain symptoms associated with carcinoid tumors and other forms of gastrointestinal and pancreatic neuroendocrine tumors. Also, Sandostatin LAR is approved in 25-plus countries for the delay of tumor progression in patients with midgut carcinoid tumors.

The product was first introduced during 1988 and is marketed in 100-plus countries. Sandostatin SC is experiencing worldwide generic competition. Formulation patents covering Sandostatin LAR expired during July 2010 in all countries except the United States, where the expiration starts by year-end 2014. The expiration of the last U.S. formulation patent is set for January 2017. As of early 2012, there were no equivalent versions of Sandostatin LAR approved in any markets.

Sandostatin sales improved from $1.29 billion for 2010 to $1.44 billion during 2011. During 1H 2012, product sales advanced 5 percent in U.S. dollars and 9 percent at constant currencies year-over-year to $740 million. In 2011 and 2012, the drug has benefited from the rising use of Sandostatin LAR in treating symptoms of patients with neuroendocrine tumors as well as approvals in 30-plus countries for the delay of tumor progression in patients with midgut carcinoid tumors. As of July 2012, more than 20 other countries are reviewing for approval Sandostatin for the delay of tumor progression in patients with midgut carcinoid tumors. Also, at least 14 countries have approved a new presentation of Sandostatin LAR. This includes a new diluent, safety needle and vial adapter improving the mixing and administration of Sandostatin LAR. Other regulatory filings are under way, according to Novartis.

Exforge (valsartan and amlodipine besylate) is a single-pill combo of Novartis' angiotensin receptor blocker (ARB) Diovan and the calcium channel blocker (CCB) **Lotrel**. Initially approved for treating high blood pressure in Switzerland during 2006, and in the United States and EU in 2007, the drug is marketed in 80-plus countries. During 2008, U.S. regulators approved Exforge for the first-line treatment of hypertension in patients likely to require multiple drugs to achieve their blood-pressure goals. During January 2010, the medicine was approved in Japan and introduced in China.

Exforge HCT (valsartan, amlodipine besylate and hydrochlorothiazide) is a pill that combines three widely prescribed high blood pressure treatments: an ARB (valsartan), CCB (amlodipine) and the diuretic HCT (hydrochlorothiazide). Exforge HCT was approved in the EU and the United States during 2009. The product is marketed in over 40 countries and more launches were expected in 2012.

Sales for Exforge came in at $1.21 billion during 2011, compared to $904 million for the previous calendar term. The strong global growth was spurred by continued prescription demand in the EU, United States and other key regions, as well as ongoing Exforge HCT market introductions in Europe, Asia and Latin America. The growth continued throughout 1H 2012, increasing by double digits versus January-June 2011 to $655 million.

Novartis has regulatory exclusivity for Exforge in Europe until 2017 and in Japan until 2014. There remains a risk that generic manufacturers may circumvent regulatory exclusivity and obtain approval of a combination valsartan-amlodipine product in Europe before 2017. In the United States, under a license deal with a generics manufacturer, the medicine is expected to face generic competition as of October 2014.

Marketed since 1997 for treating mild-to-moderate Alzheimer's disease dementia, Exelon (rivastigmine) capsule is available in 90-plus countries. In 2006, the drug became the only cholinesterase inhibitor to be approved for mild-to-moderate Parkinson's disease dementia in addition to AD in the United States and EU.

Exelon Patch (rivastigmine transdermal system) was cleared for marketing during 2007 in the United States and EU. The drug is available in 80-plus countries for mild-to-moderate AD dementia and more than 20 nations for Parkinson's disease dementia. The once-a-day medication has demonstrated comparable efficacy to the highest recommended doses of Exelon capsules, with significant improvement in cognition and overall functioning versus placebo.

During September 2012, Novartis announced FDA clearance for a higher dose of Exelon Patch for treating mild-to-moderate AD. The new 13.3 mg/24-hour dosage strength of Exelon Patch provides doctors with another treatment option for patients who are experiencing a decline in overall function and cognition. The drug also is available in 4.6 mg/24 hours and 9.5 mg/24 hours dosages.

Total Exelon sales amounted to $1.07 billion for 2011, compared to $1 billion for 2010. First-half 2012 sales reached $529 million, up 3 percent in U.S. dollars and 7 percent at constant currencies compared to the corresponding year-earlier period. The majority of sales are for the patch formulation.

Patent protection for rivastigmine tartrate expired during 2011 in most major markets and during 2012 in the United States. Novartis holds a patent on a specific isomeric form of the active ingredient used in Exelon, which expires during 2012-14 in major markets. Exelon Patch is also covered by a formulation patent that runs out in 2019 in major markets.

On track to join Novartis' billion-dollar product club in 2012 is the relapsing multiple sclerosis drug Gilenya (fingolimod). Gilenya represents the first in a new class of multiple sclerosis (MS) therapies known as sphingosine 1-phosphate receptor modulators. The drug is the first approved oral disease-modifying treatment for multiple sclerosis in the United States. Gilenya is a major advance for people with relapsing multiple sclerosis, the most common forms of the disease.

Gilenya is available for use in more than 55 countries. Gilenya is marketed as a first-line treatment for relapsing forms of multiple sclerosis in the United States, with FDA approval occurring in September 2010. In the European Union, the drug was cleared for approval in March 2011 as a disease-modifying therapy in patients with highly active relapsing-remitting multiple sclerosis (RRMS) despite treatment with **beta interferon**, or in patients with rapidly evolving severe RRMS.

During September 2011, Gilenya gained regulatory clearance in Japan for the prevention of relapse and delay of progression of physical disability in adults with MS. Gilenya is licensed from **Mitsubishi Tanabe** Pharma Corp., a top 50 pharma company based in Osaka, Japan.

The product has demonstrated superior efficacy by reducing relapses by 52 percent at one year ($p < .001$) compared to interferon beta-1a IM, which is a current standard of care. A two-year, placebo-controlled clinical trial showed that Gilenya significantly reduced the risk of disability progression. The medicine has a well-studied safety and tolerability profile with more than 2,600 MS clinical-trial patients part of the FDA regulatory review, with some patients in their seventh year of treatment.

Following a safety review by the FDA and CHMP during first-quarter 2012, Novartis announced during June that new long-term data for Gilenya demonstrated a sustained efficacy benefit and consistent safety profile with up to 4.5 years of continuous treatment. These results, from an extension of the Phase III head-to-head TRANSFORMS trial, additionally demonstrated improved efficacy for patients switched to Gilenya from another commonly prescribed MS treatment. Data revealed in April 2012 from seven-year Phase II extension trials showed sustained improvements in patients with relapsing MS who continued Gilenya treatment.

As of July 2012, 41,000 patients had been treated with Gilenya in clinical studies and in the post-marketing setting, with 42,000 patient years of exposure. A pediatric clinical trial in MS and a Phase II/III study in patients with chronic inflammatory demyelinating polyradiculoneuropathy were planned to begin in 2012.

The once-a-day oral therapy has produced rapid sales growth in 2012. Gilenya generated sales of $283 million in 2Q 2012 and $530 million during first-half 2012. As of July 2012, Gilenya was cleared for marketing in 60-plus countries.

Patent protection for fingolimod is scheduled to expire during 2019 in the United States and 2018 in Europe (including a five-year patent term extension for both territories). In Europe, Novartis has regulatory exclusivity for the data generated for Gilenya until 2021, which could potentially be extended by a year. Patent protection for the commercial form of Gilenya is due to run out during 2024 in most major markets, including the EU and Japan. A U.S. patent application is awaiting clearance for the commercial formulation of Gilenya which, if granted, would expire in 2024.

According to EvaluatePharma analysts, Novartis secured the largest one-day market-cap gain of 2011 amongst pharma companies thanks to Gilenya. Positive Phase III study results for Gilenya announced on Dec. 15, 2011, added $4.98 billion to the company's market cap, reflecting a 4 percent share price gain.

In the years to come, Gilenya is expected to challenge Teva's **Copaxone** as the leading MS therapy. Copaxone (glatiramer) is predicted to produce 2012 global sales of about $4 billion.

Pipeline updates and recent product approvals

Novartis has one of the pharma arena's leading pipelines with 130-plus products in development. The company's R&D expenditure for 2011 totaled $9.6 billion ($9.2 billion excluding impairment and amortization charges), representing 15.8 percent of Novartis net sales. More than 20 percent of the company's pharmaceutical sales were invested in R&D during 2011, consistent with previous years. For first-half 2012 the R&D budget amounted to $4.52 billion, compared to the January-June 2011 total of $4.59 billion.

Novartis' robust pipeline includes products for treating certain cancers, respiratory diseases, metabolic disorders, infections, as well as autoimmune and ophthalmic diseases. Significant investment, concentrating on areas of greatest patient need and scientific promise at **Novartis Institutes for BioMedical Research**, is targeted at discovering novel therapies. Biologics represent a growing proportion of the company's exploratory pipeline.

Potential blockbuster candidates in the Novartis pipeline include **Bexsero**, an investigational multicomponent meningococcal serogroup B vaccine. Bexsero has demonstrated the potential to be the first vaccine to provide broad coverage against meningococcal B disease.

During June 2011, Novartis released new data from a pivotal Phase III clinical trial in 1,800-plus infants demonstrating that Bexsero induced a robust immune response against meningococcal serogroup B when given alone or when co-administered with other routine vaccines. These data are included in the comprehensive clinical program with Bexsero in 8,000-plus infants, toddlers, adolescents and

adults that served as the basis of the registration file submitted to the EMA in December 2010. Bexsero has additionally been filed for marketing clearance to health authorities in Canada, Brazil and Australia.

Phase III trial results also showed that Bexsero can fit into various vaccination schedules in the first year of life when the likelihood of contracting this often-deadly disease is at its peak. The clinical trial additionally showed that the vaccine has an acceptable tolerability profile.

Meningococcal is easily misdiagnosed and can kill within 24 hours of onset as well as cause serious, life-long disabilities. The majority of cases in some of the developed world result from serogroup B (MenB), with a disproportionate disease burden in infants. One in 10 people who contract meningococcal disease will die despite appropriate treatment of the survivors.

Additionally known as 4CMenB, Bexsero was developed using a pioneering approach known as "reverse vaccinology." This was needed because the approach used to produce a conjugate meningococcal vaccine against serogroups A, C, W-135 and Y could not be used for MenB. The capsular polysaccharide of MenB is identical to a polysaccharide component found in the human body and is therefore not immunogenic. In contrast to conventional methods of developing vaccines, reverse vaccinology was used to decode the genetic makeup (genome sequence) of MenB and choose those proteins that were most likely to be broadly effective vaccine candidates. Bexsero contains multiple components that are highly immunogenic independently, and when taken together have the ability to protect against a wide range of disease-causing MenB strains. More than 8,000 infants, toddlers, and adults have been enrolled in clinical trials of Bexsero.

Novartis Pharmaceuticals has gained significant regulatory milestones in 2012. These milestones include U.S. and EU approval for Afinitor in advanced breast cancer, EU marketing clearance of **Jakavi** in myelofibrosis, and CHMP recommendations for **Seebri Breezhaler** in COPD.

Afinitor was approved by FDA in July 2012 for its fifth indication: in combination with exemestane after failure of treatment with letrozole or anastrozole for treating postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer. The European Commission also granted approval of Afinitor during July in combination with exemestane for advanced breast cancer. The approvals marked the first major advance for U.S. and EU women with hormone receptor-positive advanced breast cancer since the introduction of aromatase inhibitors 15-plus years earlier.

Afinitor tablet gained FDA clearance during April 2012 for treating adult patients with kidney tumors known as renal angiomyolipomas and tuberous sclerosis complex, who do not require immediate surgery. This represents the first approval of a medical treatment in this patient population. Kidney tumors affect up to 80 percent of patients with tuberous sclerosis complex – a genetic disorder that may lead noncancerous tumors to form in vital organs – and growing tumors may result in life-threatening complications.

Everolimus is also awaiting EU clearance for treating adult patients with renal angiomyolipoma associated with TSC who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors), but who do not need immediate surgery. If the drug is approved in the European Union for this patient population, the trade name will be Votubia. This would be the first medication/non-surgical treatment option in the European Union for kidney tumors associated with tuberous sclerosis complex.

The JAK 1 and JAK 2 inhibitor Jakavi (ruxolitinib) was approved for marketing in August 2012 by the European Commission. The drug was cleared for treating disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

Myelofibrosis is an uncommon, life-threatening blood cancer characterized by bone-marrow failure; enlarged spleen (splenomegaly); debilitating symptoms including extreme fatigue, night sweats and intractable pruritus (itching); poor quality of life and weight loss; as well as shortened survival. Jakavi directly targets the underlying mechanism of the disease, significantly reducing splenomegaly and improving symptoms regardless of JAK mutational status, disease subtype or any previous treatment, such as hydroxyurea.

Novartis licensed ruxolitinib from the biopharma company **Incyte** Corp. for development and potential commercialization outside the United States. Incyte retained rights for the U.S. development and marketing of ruxolitinib (product code INC424). The European Commission and FDA granted ruxolitinib orphan-drug status for myelofibrosis. Incyte received U.S. clearance for ruxolitinib in November 2011 under the name **Jakafi** for treating patients with intermediate or high-risk myelofibrosis.

Seebri Breezhaler 44 mcg delivered dose (50 mcg glycopyrronium per capsule) was recommended for approval by CHMP as a once-daily inhaled maintenance bronchodilator treatment for patients with chronic obstructive pulmonary disease. Novartis says the positive opinion was underpinned by data from three of the company's Phase III GLOW studies. If cleared for marketing, Seebri Breezhaler will offer patients an alternative once-a-day therapy in the long-acting muscarinic antagonist (LAMA) class with the potential to reduce breathlessness, increase the capacity to exercise and help improve quality of life.

Glycopyrronium was licensed to Novartis during April 2005 by the product-development company **Vectura** Group plc and its joint-development partner **Sosei** Co., a Tokyo-based biopharma company. The drug compound was filed for regulatory approval in Europe during 3Q 2011 and in Japan during 4Q 2011.

Among other Novartis products, **Signifor** (pasireotide) was granted European Commission approval for treating adult patients with Cushing's disease during April 2012. This endocrine disorder results from excessive cortisol in adults. Signifor is available to patients for whom surgery is not an option or has failed. This is the first pituitary-targeted medicine for Cushing's disease to gain EU approval.

For treating Cushing's disease, Signifor has been studied as a twice-per-day subcutaneous injection. The drug is being evaluated as a long-acting release, once-per-month intramuscular injection as part of a worldwide Phase III program. The multireceptor targeting somatostatin analog (SSA) binds with high affinity to four of the five somatostatin receptor subtypes – 1, 2, 3 and 5.

Novartis announced in June 2012 new data from two studies with **canakinumab** (ACZ885). One is a pivotal Phase III trial in patients with systemic juvenile idiopathic arthritis. The other is a Phase II trial in patients with tumor necrosis factor receptor-associated periodic syndrome. Both conditions are rare and serious autoinflammatory diseases that typically begin during childhood. The two studies met their primary endpoints.

In the Phase III trial, 62 percent of systemic juvenile idiopathic arthritis patients treated with ACZ885 were symptom-free at the end of the placebo-controlled period. Also, 33 percent patients treated with ACZ885 were able to completely discontinue corticosteroids within a five-month period. In the Phase II trial, 90 percent of tumor necrosis factor receptor-associated periodic syndrome patients treated with ACZ885 experienced clinical remission after only a week of treatment.

The rare systemic interleukin-1 beta (IL-1 beta)-mediated autoinflammatory disease SJIA is characterized by daily spiking fevers, rash, chronic pain, and arthritis that may cause joint destruction, functional disability and impaired growth. The rare auto-inflammatory disease tumor necrosis factor receptor-associated periodic syndrome can affect children and adults. The genetically inherited disease is characterized by long and intermittent attacks that can include fever, rash, abdominal pain, conjunctivitis, severe skin infection, inflammation around the eyes and severe joint pain.

By year-end 2012, eight Phase III trials are expected to have reached completion for **QVA149** (indacaterol 110 mcg/glycopyrronium bromide 50 mcg) in treating COPD. At the end of August 2012, Novartis announced that the fifth study, SPARK, met its primary endpoint of a reduced rate of moderate-to-severe COPD exacerbations versus glycopyrronium bromide (Seebri Breezhaler). SPARK is the final study intended for initial regulatory submissions of QVA149 in Europe and Japan, which are anticipated during fourth-quarter 2012. The FDA submission for QVA149 is expected at the end of 2014. The first five studies (ILLUMINATE, SHINE, BRIGHT, ENLIGHTEN and SPARK) of the IGNITE Phase III program met their primary endpoints of efficacy, safety, exercise endurance, and reduction of exacerbations.

QVA149 is an investigational inhaled, once-a-day, fixed-dose combo of the long-acting beta2-adrenergicagonist (LABA) indacaterol maleate and the investigational LAMA glycopyrronium bromide. QVA149 is being developed for treating COPD in the Phase III IGNITE clinical-study program. IGNITE is one of the largest international clinical-trial programs in COPD, consisting of 10 studies with 7,000-plus patients across 42 countries. Five studies were completed by August 2012, with three others (BLAZE, ARISE, BEACON) expected to end during the remainder of 2012. The studies are designed to investigate efficacy, safety and tolerability, exercise endurance, exacerbations, breathlessness as well as quality of life.

In addition to QVA149, the Novartis COPD portfolio includes Onbrez Breezhaler and Seebri Breezhaler. The QD LABA Onbrez Breezhaler is the only COPD treatment available to offer clinically relevant 24-hour bronchodilation combined with a rapid onset of action of five minutes at first dose. The product was first introduced in the EU in 150-mcg and 300-mcg once-a-day doses. More recently, Novartis introduced the 75-mcg once-daily dose in the United States as Arcapta Neohaler. In Japan, the product is available as 150-mcg once-daily doses known as **Onbrez Inhalation Capsules**.

Each of the Novartis COPD products are being developed for delivery via the Breezhaler device. The single-dose dry-powder inhaler has low air-flow resistance, making it particularly suitable for patients with airflow limitation, including COPD patients.

Phase II data released by Novartis in 2012 demonstrated that **LCZ696** may provide clinical benefits in patients with a difficult-to-treat form of heart failure. The PARAMOUNT clinical study showed that the drug candidate reduced a key predictor of morbidity and mortality in patients with a common form of heart failure known as HF-PEF (heart failure with preserved ejection fraction). The first-in-class angiotensin receptor neprilysin inhibitor has demonstrated evidence of superiority over the Novartis ARB valsartan in its ability to lower blood pressure with a favorable safety and tolerability profile.

LCZ696 works differently than existing heart-failure treatments by inhibiting an enzyme – neprilysin – in order to promote the body's protective mechanisms, and blocking receptors involved in blood-vessel narrowing (angiotensin receptors). The drug compound therefore acts simultaneously on two important pathways in the development of the disease.

Up to 50 percent of the 20 million Europeans and Americans diagnosed with heart failure have HF-PEF, resulting in reduced life expectancy and frequent hospitalization. There are no marketed therapies to reduce morbidity and mortality in patients with HF-PEF.

LCZ696 is one of several product candidates being developed by Novartis across the spectrum of heart failure. In addition to HF-PEF, LCZ696 is being investigated for treating heart failure with reduced ejection fraction (HF-REF) in the Phase III PARADIGM-HF study. A Phase II study demonstrated that LCZ696 is more effective than valsartan in reducing blood pressure. A Phase III study is under way for the first-line treatment of hypertension in Asia.

Three Alcon products were granted regulatory clearance during second-quarter 2012. EU approval was granted to **AcrySof IQ ReSTOR +2.5D Toric Multifocal** intraocular lenses, and Dailies Total1 and a new indication for **Durezol** received FDA clearance.

AcrySof IQ ReSTOR +2.5D Toric Multifocal intraocular lens gained a CE mark in the EU. The 2.5 diopter lens builds on Alcon's existing portfolio of intraocular lenses. The product provides enhanced distance vision and improved functional near vision while correcting for astigmatism. As a toric multifocal lens, it serves as an improved option for cataract patients with astigmatism who need presbyopia correction.

FDA approved Durezol for a new indication: treating inflammation in the uvea near the middle of the eye. If untreated, uveitis can result in other eye disorders such as cataracts and glaucoma. The product initially was approved for use as an anti-inflammatory following eye surgery.

Dailies Total1 – Alcon's first silicone hydrogel daily disposable contact lens – gained FDA clearance after the product's EU launch during late 2011. Dailies Total1 is the industry's first watergradient silicone hydrogel contact lens. The product increases water content at the core of the lens from 33 percent to more than 80 percent, marking a major advancement in patient comfort. The new lens has the highest oxygen transmissibility of any daily disposable lens.

Sandoz has a pipeline of eight to 10 biosimilar molecules, including monoclonal antibodies at various development stages. This pipeline includes the biosimilar **rituximab**, which is marketed globally by Roche under the brand names **Rituxan** and **MabThera**. Rituxan/MabThera was the 10th best-selling prescription drug in 2011 with sales of about $5.97 billion. U.S. Phase III clinical development for rheumatoid arthritis patients for biosimilar rituximab is under way.

Another biosimilar undergoing U.S. Phase III studies by Sandoz is **filgrastim**, which is marketed as the prescription product **Neupogen** by biotech leader **Amgen** Inc. The granulocyte-colony stimulating factor generated 2011 global sales of $1.26 billion.

Phase III results published in the *New England Journal of Medicine* during August 2012 demonstrated that **ocriplasmin** could be the first pharmacological eye treatment for vitreomacular adhesion patients.

Vitreomacular adhesion is an age-related progressive, debilitating eye disease often resulting in blindness; the standard of care is "watchful waiting" or surgery. Ocriplasmin significantly ($p<0.001$) resolved vitreomacular traction and closed macular holes versus placebo. For the majority of patients with resolution of vitreomacular adhesion after ocriplasmin administration, the resolution was attained within one week. Alcon acquired the non-U.S. commercialization rights to ocriplasmin from **ThromboGenics** Inc. ■ MEDADNEWS

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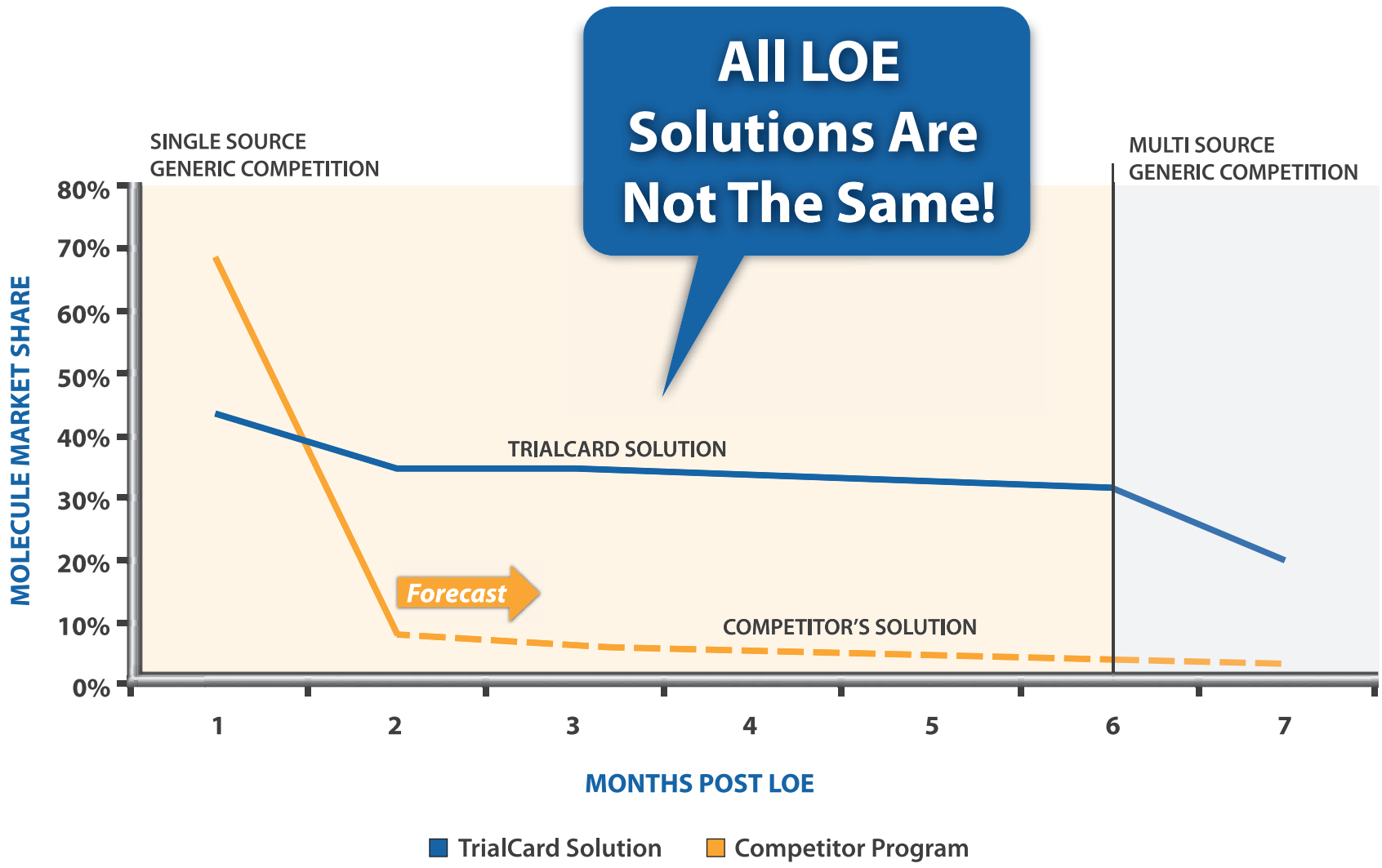

**Source: IMS's Vector One®: National (VONA) November 2011 – June 2012*
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BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Lipitor	$9,577	$10,733
Lyrica	$ 3,693	$3,063
Prevnar 13/ Prevenar 13	$3,657	$2,416
Enbrel	$3,666	$3,274
Celebrex	$2,523	$2,374
Viagra	$1,981	$1,928
Norvasc	$1,445	$1,506
Zyvox	$1,283	$1,176
Xalatan/ Xalacom	$1,250	$1,749
Sutent	$1,187	$1,066
Geodon/ Zeldox	$1,022	$1,027
Premarin family	$1,013	$1,040

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Sales	$67,425	$67,057
Net income	$10,009	$8,257
EPS	$1.11	$1.02
R&D	$9,112	$9,392
	1H12	**1H11**
Sales	$29,942	$32,509
Net income	$5,047	$4,832
EPS	$0.65	$0.58
R&D	$3,753	$4,311

All figures are in millions of dollars except EPS.

Hitting targets

In 2011, Pfizer revamped its R&D program to a "precision medicine" approach and prepared for the patent expiry of Lipitor; the company also launched an innovative new cancer drug and met its revenue goals.

by Christiane Truelove chris.truelove@ubm.com

In 2010, Pfizer CEO Ian Read promised shareholders that "we would create value in the short and long term by improving the performance of our innovative core, making the right capital allocation decisions, earning respect from society, and continuing to promote an ownership culture of confidence and trust." In 2011, Mr. Read said the company has achieved all its targets.

"Our financial performance in 2011 was strong," Mr. Read says. "We met or exceeded every component of our full-year financial guidance, despite the headwinds from a challenging global business environment and the reality of absorbing about $5 billion in revenue declines due to changes in the patent status of some products, most notably Lipitor in the United States. We also made substantial progress in our nonfinancial performance indicators, including access to medicines, environmental stewardship, and other measures of our social responsibility."

2011 was Mr. Read's first full year as leader. Pfizer ended 2010 with the sudden departure of former CEO Jeffrey Kindler, who resigned in December after four-and-a-half years on the job. Mr. Kindler was quickly replaced by Mr. Read, who has worked at Pfizer for 32 years and had served as senior VP and group president of the worldwide Biopharmaceutical businesses prior to taking over as president and CEO.

Once in place, Mr. Read set to work, narrowing the company's R&D focus to diseases with big sales potential or few existing treatment options and trimming the research budget significantly in the process. By reducing operating expenses and taking steps to allocate capital in ways that resulted in greater shareholder value, Pfizer claims to have returned more than $15 billion in capital to shareholders through dividend payments of more than $6 billion and stock repurchases of about $9 billion.

Additionally, Mr. Read has explored options for selling or spinning off Pfizer's nutrition and animal health businesses, and has boosted sales in emerging markets. In August 2012, the company announced an initial public offering of about $100 million in shares of its animal health business, newly named **Zoetis**. The name derives from zoetic, which means pertaining to life. The offering is for a 20 percent ownership stake in Zoetis, which sells the dog and cat antibiotic **Convenia**, the anti-flea and heartworm medication **Revolution**, and **Palladia**, a cancer drug for dogs. The money from the offering, which is expcted to take place in the first half of 2013, will be used to reduce Pfizer's debt. In 2011, the animal health business had sales of $4.18 billion, almost 37 percent more than in 2010.

The company has already sold its infant nutrition business to Nestle SA and its Capsugel business to a private investment company. The nutrition business generated $2.14 billion in 2011, 14.5 percent more than in 2010.

With the separation of the animal health and nutrition businesses, Pfizer will be concentrated on its prescription drug business, with a portfolio of innovative products as well a portfolio of unpatented products for emerging markets, and a Consumer Healthcare business. "Together, I believe that these elements will position Pfizer to generate strong cash flow and steady growth in earnings per share over time," Mr. Read says.

Lipitor was still Pfizer's best selling product in 2011, but the loss of its patent and thr entry of generic competition in May 2012 has unseated the drug from the top.

The Pfizer board was pleased with Mr. Read's performance in 2011 and nearly tripled his compensation, according to an AP report in March. The AP reported that Mr. Read received $18.12 million in 2011, compared with $6.42 million in 2010. The compensation includes a $1.7 million salary, stock awards and options totaling about $12.5 million, a $3.5 million incentive award, and about $319,000 in other compensation.

In his letter to shareholders, Mr. Read promised that Pfizer will stay the course. "We will work to increase our momentum by continuing to maximize the value of our in-line portfolio, accelerate our R&D strategy, advance our pipeline, effectively allocate our capital, operate efficiently to create a more flexible cost base, meet our financial commitments, and maintain high standards of corporate governance and business ethics – all while embracing an ownership culture," he says.

"We met or exceeded every component of our full-year financial guidance, despite the headwinds from a challenging global business environment and the reality of absorbing about $5 billion in revenue declines due to changes in the patent status of some products, most notably Lipitor in the United States. We also made substantial progress in our nonfinancial performance indicators, including access to medicines, environmental stewardship, and other measures of our social responsibility," says Ian Read, CEO.

Company and product performance

In 2011, Pfizer generated revenue of $67.43 billion, about the same as in 2010. Net income was $10.01 billion, a 21.2 percent improvement. Diluted earnings per share were $1.27, an increase of 27 percent.

For the first half of 2012, revenue was $29.94 billion, 7.9 percent less than first-half 2011. Net income was $5.05 billion, 4.4 percent more than in the same period the previous year. Diluted earnings per share were 67 cents, 9.8 percent more than in the first half of 2011.

Pfizer's Primary Care unit in 2011 generated revenue of $22.67 billion, 2.8 percent less than in 2010. In the first half of 2012, the Primary Care Unit recorded revenue of $8.12 billion, 28.3 percent less in comparison with the same period last year, Most of the decrease came after Lipitor lost exclusivity in the United States in November 2011 and the entry of many generic competitors in May 2012. U.S. Lipitor sales are now reported by the Established Products unit. Beginning in January U.S. branded Lipitor revenues decreased to $296 million, from $1.4 billion reported by the Primary Care unit in second-quarter 2011.

The Specialty Care segment reported $15.25 billion in sales in 2011, 1.5 percent more than 2010. In the first half of 2012, Specialty Care sales were $7.08 billion, 7.9 percent less than in the same period of 2011. For the second quarter, Specialty Care unit sales were affected by the U.S. losses of exclusivity of the antibiotic **Vfend** in February and the glaucoma drug **Xalatan** in March 2011, and the resulting shift in the reporting of Vfend and Xalatan U.S. sales to the Established Products unit beginning Jan. 1, 2012. Additionally, there was the loss of exclusivity of Xalatan in Europe in January 2012 and the antipsychotic **Geodon** in the United States in March 2012. Collectively, these developments reduced Specialty Care unit sales by about $265 million, or 7 percent, in comparison with second-quarter 2011.

In 2011, the Established Products unit generated $9.21 billion, 8.8 percent less than 2010. The decrease was mainly due to the loss of exclusivity of the antidepressant **Effexor XR**, the gastric medicine **Protonix**, and the antibiotic **Zosyn** in the United States. But sales of this unit increased 17 percent to $5.48 billion in the first half of 2012. Second-quarter 2012 revenue increased 18 percent operationally in comparison with the prior year period, primarily reflecting $433 million of U.S. and Japan branded Lipitor sales, contribution from the sales of the authorized generic version of Lipitor in the United States by Watson Pharmaceuticals Inc,. and launches of generic versions of other Pfizer branded primary care and specialty care products.

The Emerging Markets unit reported 2011 sales of $9.3 billion, 7.3 percent more than in 2010. Executives attribute the increase to higher operational revenue of 5 percent, as well as a 2 percent favorable impact

Lyrica generated sales of $3.69 billion in 2011, an increase of 20.6 percent.

of foreign exchange. Operational revenue growth was due to increases in the sales of certain key innovative brands, primarily the **Prevenar** vaccine franchise, the epilepsy and pain drug **Lyrica**, the rheumatoid arthritis drug **Enbrel**, the inflammation and pain drug **Celebrex**, Vfend, and the antibiotc **Zyvox**. Emerging Markets revenue in the first half of 2012 grew to $4.92 billion, 7 percent more than in the same period last year.

Pfizer's best-selling product in 2011 was once again Lipitor, which generated $9.58 billion, 10.8 percent less in 2010. For the first half of 2012, the drug had sales of $2.62 billion, 47.4 percent less than in the first half of 2011.

The second best-selling product in 2011 for the company was Lyrica. The drug had sales of $3.69 billion, 20.6 percent more than in 2011. Lyrica's first-half 2012 sales were $1.99 billion, 14.8 percent more than the same period last year.

Pfizer's No. 3 product in 2011 was Enbrel, generating sales outside the United States of $3.67 billion, about 12 percent more than the previous year. The drug had sales of $1.89 billion in the first half of 2012, 5.8 percent more than in first-half 2011.

The fourth best-selling drug for the company in 2011 was the pneumoccocal vaccine **Prevnar 13**/Prevenar 13, which generated $3.66 billion, growth of 51.4 percent from 2010. Prevnar 13 sales in the first half of 2012 were $1.86 billion, 2.2 percent more than in the same period in 2011.

The company's fifth best seller was Celebrex, with sales of $2.52 billion, 6.3 percent more than in 2010. In the first half of 2012, the drug recorded sales of $1.29 billion, 6.6 percent more than the same period of 2011.

The sixth best-selling product in 2011 was the erectile dysfunction drug **Viagra**, which had sales of $1.98 billion, 2.7 percent more than in 2010. During the first half of 2012, the drug posted sales of $981 million, 1.7 percent more than in first-half 2011.

The seventh best-selling drug for Pfizer in 2011 was the hypertension product **Norvasc**, with sales of $1.45 billion, 4.1 percent less than in 2010. Norvasc had first-half 2012 sales of $682 million, 6.7 percent less than the same period last year.

The company's eighth best-selling product in 2011 was the antibiotic Zyvox, which generated $1.28 billion, 9.1 percent more than in 2010. For the first six months of 2012, Pfizer recorded Zyvox sales of $668 million, an increase of 3.7 percent from the first half of 2011.

The ninth best-selling product in 2011 was the glaucoma drug Xalatan/Xalacom, which had sales of $1.25 billion, 28.5 percent less than in 2010. The first half of this year, sales of the product were $436 million, 36.2 percent less than in the same period last year.

The cancer drug **Sutent** was Pfizer's tenth best-selling product in 2011, with sales of $1.19 billion, 11.4 percent more than in 2010. Sutent sales in the first half of 2012 were $619 million, an increase of 8.2 percent from first-half 2011.

Pfizer's two other billion-dollar brands in 2011 were the schizophrenia drug Geodon/Zeldox, and the **Premarin** family of hormone replacement products.

Geodon/Zeldox sales were $1.02 billion, about the same as in 2010. First-half 2012 sales of the drug were $265 million, 45.9 percent less than the same period last year.

Premarin sales in 2011 were $1.01 billion, 2.6 percent less than the previous year. In first-half 2012, sales were $535 million, 9.2 percent more than in the first half of 2011.

Acquisitions and partnerships

Over the course of 2011, Pfizer continued to pursue business development opportunities and form external collaborations to play up to the company's strengths, build its portfolio, and strengthen its geographic presence. Pfizer signed a framework agreement with **Zhejiang Hisun** Pharmaceuticals in China to establish a joint venture in the branded generics area and a memorandum of understanding with **Shanghai** Pharma to explore potential business opportunities in China. The company also completed the acquisition of King Pharmaceuticals Inc., which strengthened its portfolio, and acquired Icagen Inc., a biotech company specializing in new pathways for the treatment of pain. With the acquisitions of Alacer Corp. and the Ferrosan Holding A/S consumer healthcare business, the company expanded the portfolio of Pfizer Consumer Healthcare's brands and entered new markets.

Enbrel had sales of $3.67 billion last year, 12 percent more than 2010.

In September 2012, Pfizer announced the launch of a joint venture with China's Zhejiang Hisun Pharmaceuticals. Called Hisun-Pfizer Pharmaceuticals, the venture will develop, manufacture, and commercialize off-patent pharmaceutical products in China and global markets. Executives say the creation of the joint venture strengthens the ability of both companies to reach more patients with high-quality and low-cost medicines in the branded generics arena. The joint venture is one of the first between a multinational pharmaceutical company and a local leading pharmaceutical company in branded generic medicines in China, and is also one of the largest pharmaceutical joint venture projects in Zhejiang province.

Hisun-Pfizer will take advantage of Hisun's strong product portfolio, broad market outreach, and experience with the production and commercialization of branded generic medicines. The joint venture will also benefit from Pfizer's research and development, manufacturing quality management, international market promotion, and operational capabilities. The joint venture will focus on R&D and the production and commercialization of high-quality branded generic medicines, and the broader commercialization of existing medicines through a local and global sales and marketing infrastructure. The partnership also paves the way for Hisun to transition from being an active pharmaceutical ingredients manufacturer to an established branded generics company.

For Pfizer, off-patent medicines, including branded generics, represent one of the fastest-growing segments in the global pharmaceutical market. This is especially true in emerging markets, where cost and access are primary drivers of off-patent medicine growth. In China, branded generics account for 70 percent of the domestic pharmaceutical market.

"We are confident that our joint venture will allow both companies to build upon existing core capabilities and our respective areas of expertise to address the needs of more patients than ever before," says Olivier Brandicourt, president and general manager of Pfizer's Emerging Markets and Established Products Business Units. "This partnership further supports the government of China's goals for improved access to medicines and treatments for the patients of China."

Hisun-Pfizer has an aggregate investment of $295 million and a registered capital of $250 million. Hisun holds 51 percent of the share and Pfizer holds 49 percent. The registration facilities and production plants of the joint venture will be located in Fuyang, Zhejiang province, while the management center will be in Shanghai and the R&D center in Hangzhou. The parties will contribute select existing products to the joint venture, which will have a broad portfolio covering cardiovascular disease, infectious disease, oncology, mental health, and other therapeutic areas. The parties will also contribute manufacturing sites, cash, and other relevant assets. The joint venture aims to build a robust sales network that covers most areas and hospitals in China and to enter the international market by leveraging on Pfizer's global business networks.

R&D revamp, and in the pipeline

One of Mr. Read's first actions when he took over as CEO in 2010 was to refocus the Pfizer's R&D organization. The company's global R&D team was centralized under the leadership of Dr. Mikael Dolsten and an accelerated R&D strategy was introduced, focusing on neuroscience; cardiovascular, metabolic, and endocrine diseases; oncology; inflammation and immunology; and vaccines.

With sales of $3.66 billion in 2011, 51.4 percent more than in the previous year, Prevnar 13 is expected to be one of the leading growth areas of Pfizer's portfolio.

The company continued on the path of reducing costs and improving productivity throughout 2011. Early in the year, Pfizer executives announced 1,100 job cuts at Groton laboratories in Connecticut to lower R&D expenses by up to $2.9 billion. In June, the company announced another $1 billion in cost reductions by 2012, most of which would target management positions. Over the past few years, tens of thousands of positions have been eliminated at Pfizer, including about 20,000 related to the Wyeth acquisition, according to published reports.

"We expect that in five years many of our late-stage clinical trial starts will reflect a precision medicine R&D approach," Mr. Read says.

Throughout 2011, the company saw a steady cadence of late-stage pipeline progress, including positive clinical data presentations, regulatory submissions, regulatory approvals, and new product launches, as well as the emergence of a promising mix of early to mid-stage compounds.

The company identified Prevnar 13/Prevenar 13 Adult, **Eliquis, tofacitinib**, **Xalkori**, and **Inlyta** as the near-term and mid-term drivers for its business units

In December 2011, Pfizer received FDA approval for the use of Prevnar 13 by adults 50 years of age and older. The drug is now approved in more than 40 countries, including markets within the European Union, and represents a significant expansion of the Prevnar/Prevenar franchise for preventing pneumococcal disease.

In 2011, Pfizer and its development partner **Bristol-Myers Squibb** received approval in the European Union for Eliquis, a twice-daily oral anticoagulant, for the treatment of blood clots in patients after elective hip-replacement or knee-replacement surgery. In addition, in late 2011, FDA and the European Medicines Agency accepted for review the applications for Eliquis for an indication in a larger patient population, to prevent strokes in patients with atrial fibrillation. The companies also have submitted that indication for review in Japan.

In September 2012, the Committee for Medicinal Products for Human Use of the European Medicines Agency adopted a positive opinion recommending that Eliquis be granted approval for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation and one or more risk factors for stroke. The CHMP's positive opinion will now be reviewed by the European Commission, which has the authority to approve medicines for the European Union. The final decision will be applicable to all

Celebrex generated $2.52 billion in 2011 sales, 6.3 percent more than in the previous year.

Viagra sales in 2011 were $1.98 billion, 2.7 percent more than in the previous year.

Sutent remained on its upward trend in 2011, generating sales of $1.19 billion, 11.4 percent more than in 2010.

27 European Union member states plus Iceland and Norway.

Tocafatinib is in development for the treatment of rheumatoid arthritis. If approved, tofacitinib would be the first rheumatoid arthritis treatment in a new class of medicines known as JAK inhibitors and the first new oral disease-modifying antirheumatic drug for rheumatoid arthritis in more than 10 years. FDA and the European Medicines Agency have accepted for review the company's new drug applications for adult patients with moderately to severely active rheumatoid arthritis, and that indication has been submitted for review in Japan as well.

Pfizer plans to present 14 abstracts for tocafatinib at the American College of Rheumatology/Association of Rheumatology Health Professionals 2012 Annual Meeting in November in Washington, D.C. The results being presented are for the Phase III studies ORAL Start and ORAL Scan. In addition, long-term safety and efficacy data of up to 48 months will be presented.

In 2011, Pfizer launched Xalkori in the United States. The drug, crizotinib, treats a certain type of lung cancer marked by a specific gene mutation. Xalkori is the first new drug approved by FDA for lung cancer in six years and represents Pfizer's first entry into precision medicine, an R&D approach that defines the molecular and biologic predictors of efficacy and then groups patients based on the unique molecular or genetic characteristics of their disease. With this approach, Pfizer executives say medicines can be developed for better defined populations of patients, often with superior efficacy when compared to medicines that are developed through non-precision approaches

Early in 2012, Pfizer received FDA approval for Inlyta for patients with previously treated advanced renal cell carcinoma. With the approval of Inlyta and with other medicines such as Sutent and Xalkori, as well as the work under way in finding new treatments in hematology and lung cancer, executives say Pfizer is building a leading oncology business.

The oncology success continued in September 2012, when FDA approved **Bosulif** for the treatment of patients with previously treated Philadelphia chromosome-positive chronic myelogenous leukemia. The drug is a kinase inhibitor that limits cancer cell growth by inhibiting the Abl and Src signaling pathways. Bosulif is the third cancer drug from Pfizer's pipeline to be approved in the last 13 months.

"By focusing our pipeline on those compounds best positioned for advancement, we have been able to bring yet another important therapy to patients who urgently need it," says Garry Nicholson, president and general manager, Pfizer Oncology Business Unit.

Pfizer executives say behind these new therapies is a next wave of new molecules in development aimed at significant unmet medical needs, including Alzheimer's disease, Crohn's disease, a range of cancers, severe pain, and cardiovascular and metabolic diseases. The company is also investing in several promising vaccine candidates aimed at preventing life-threatening infectious diseases, such as meningitis.

"I am encouraged by the depth and breadth of our current pipeline and believe it positions us well for the future," Mr. Read says.

Improving its image

Pfizer took steps in 2011 and 2012 to move away from events that damaged its public image. Such events included a government investigation of the company's international sales practices. In August 2011, Pfizer voluntarily provided the U.S. Department of Justice and the SEC with information about "potentially improper payments" made by the company and Wyeth employees with regard to overseas sales activities. Pfizer made the disclosure in an SEC filing, noting that the company was discussing a resolution with SEC and DOJ officials. The filing also states that the improper payments are being investigated by officials overseas, including in Germany, over tax matters involving a Pfizer subsidiary.

A year later, Pfizer announced a resolution with the Department of Justice and the SEC over the payments. To resolve those issues, a Pfizer indirect subsidiary, Pfizer H.C.P. Corp., will enter into a deferred prosecution agreement with the DOJ, and pay a fine of $15 million. Under the terms of a civil settlement with the SEC, Pfizer agreed to a disgorgement of profits of $16 million and prejudgment interest of $10.3 million. The DOJ declined to bring a criminal action against Pfizer.

In a separate civil settlement with the SEC, Pfizer's Wyeth subsidiary has agreed to a disgorgement of profits of $17.2 million and prejudgment interest of $1.66 million to resolve issues involving certain improper payments in the operations of four subsidiaries outside the United States. Pfizer's post-acquisition due diligence review of Wyeth identified certain improper payments in China, Saudi Arabia, Indonesia, and Pakistan.

The DOJ settlement with Pfizer H.C.P. Corp. covers improper conduct in Bulgaria, Croatia, Kazakhstan, and Russia. The Pfizer SEC civil settlement covers improper conduct in all of these countries as well as in Italy, China, the Czech Republic, and Serbia.

"The actions which led to this resolution were disappointing, but the openness and speed with which Pfizer voluntarily disclosed and addressed them reflects our true culture and the real value we place on integrity and meeting commitments," says Amy Schulman, executive VP and general counsel for Pfizer. "We expect every colleague across Pfizer to adhere to the highest standards of conduct, and we will continue to hold ourselves and our colleagues accountable for maintaining these standards. We are grateful that the DOJ and the SEC specifically recognized our extensive proactive compliance efforts and cooperation with the investigation, which demonstrates the hard work of many colleagues throughout the world and underscores the ongoing productive work we have done in this area."

In 2011, the company took new approaches to connect with customers. For example, Dr. Freda Lewis-Hall, chief medical officer, shared health and medical information in ways that encourage people to take charge of their healthcare, in areas such as stroke prevention, smoking cessation and the early diagnosis of cancer. Dr. Lewis-Hall spoke at conferences and has been interviewed on CNN about health problems of black Americans.

The company continued this outreach in June 2012 with"Get Old," a multi-year initiative supported by nearly a dozen advocacy organizations. The goal of Get Old is to amplify the conversation on aging and learn more about how Americans at all ages are tackling aging for themselves, their family, and society. At the center of the initiative is a first-of-its-kind online community, GetOld.com, where people can get and share information, add to the dialogue, and contribute to the growing body of knowledge about this important topic. This critical information is intended to help inform the unmet needs related to aging and what role Pfizer and its partners can play to help people live longer and better lives.

"We all have one thing in common – each day we get older," Dr. Lewis-Hall says. "At every age and stage of our lives, we can make choices and take actions that will help us live longer and better. There are so many positive role models today who are changing how people think about aging. There's a huge opportunity to support the shift that's underway. At GetOld.com, we want to hear what people want and need to live better and healthier and create a forum for dialogue on what it means to 'get old' today."

In September, Pfizer launched, in conjunction with Waste Management's WM Healthcare Solutions Inc. a new, free-of-charge, online pharmaceutical disposal guide for healthcare providers and facilities called the "Pfizer Responsible Disposal Advisor." Pfizer is the first pharmaceutical company to make this resource available to healthcare professionals to help guide them through sometimes complex waste disposal requirements.

Pfizer enlisted the technology of WM Healthcare Solutions' patented PharmE Waste Wizard, an online search engine that provides waste categorization and disposal information for healthcare facilities, including physician practices, clinics, ambulatory surgery centers, and walk-in clinics. The Waste Wizard information found on Pfizer's Responsible Disposal Advisor informs healthcare professionals whether the Pfizer drug to be disposed will be a hazardous waste based on the federal Environmental Protection Agency's regulations. In addition to any relevant waste codes, the Pfizer Responsible Disposal Advisor recommends disposal options for full, partial, and empty containers, and provides U.S. Department of Transportation shipping descriptions.

"Healthcare facilities often face complicated requirements to manage their waste streams," says Tom Polton, senior director, Product Stewardship, Pfizer. "The Pfizer Responsible Drug Advisor offers an easy-to-use online resource to help hospitals, long-term care facilities, medical clinics, and doctors' offices determine the disposal recommendations for unused medicines."

To prevent compliance problems in the future, Pfizer in 2011 developed and implemented an enhanced set of anti-corruption policies and procedures; designed an anti-corruption internal audit program used throughout the world to detect potential misconduct; pioneered annual proactive market reviews that scrutinize commercial practices in a risk-based sample of non-U.S. markets to ensure compliance with company policies; formed a mergers and acquisitions compliance function designed to support due diligence reviews of complex business transactions and to help ensure the integration of new businesses into Pfizer's compliance program; established other processes by which it closely monitors its relationships with non-U.S. healthcare providers and government officials; and implemented global mandatory training for all appropriate colleagues on its anti-corruption program and the need to maintain compliance in the area.

Developing these programs was part of Pfizer's actions to develop an "ownership culture," executives say. "In 2011, we thoroughly explored what our culture is and how it needs to evolve," Mr. Read says. "We engaged with leaders across the business and sought the candid input of approximately 11,000 colleagues globally. We concluded that we need a culture where colleagues behave like they are owners of the business, are not afraid to take thoughtful risks, deliver on their commitments, treat each other with trust and respect and work with integrity each and every day. Developing this ownership culture will be key to our success." ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

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BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Rituxan/ MabThera	$6,766	$7,172
Avastin	$5,972	$7,291
Herceptin	$5,928	$6,126
Lucentis	$1,719	$1,645
Pegasys	$1,623	$1,856
Xeloda	$1,528	$1,609
CellCept	$1,118	$1,456
Neo-Recormon/ Epogin	$1,011	$1450
Boniva/ Bonviva	$785	$1143
Actemra/ RoActemra	$697	$448
Xolair	$680	$723
Valcyte/ Cymevene	$642	$683
Pulmozyme	$555	$579
Activase/ TNKase/ CathFlo Activase	$511	$519

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Revenue	$47,993	$53,569
Net income	$10,769	$10,033
EPS	$12.39	$11.41
R&D	$9,395	$11,313

	1H12	1H11
Revenue	$25,302	$19,205
Net income	$4,928	$5,934
EPS	$5.63	$5.35
R&D	$5,594	$4,497

All figures are in millions of dollars except EPS.

Time to refocus

Roche is rejiggering its R&D organization to focus on key therapeutic areas, shutting down its N.J. research facility to better allocate resources for a strong cancer pipeline.

by Christiane Truelove chris.truelove@ubm.com

For Roche in 2011, the year was marked by the deepening debt crises in Europe and the United States, turbulent currency markets and slower global economic growth, and increasing pressure on government budgets as many countries have sought to ease their deficits by imposing substantial price cuts on pharmaceuticals along with other measures aimed at controlling or reducing healthcare expenditure. Despite these challenges, executives say Roche posted very strong results for the year, and the company's pipeline advanced, with 17 out of 20 clinical trials for major new medicines posting positive results. The company also launched **Zelboraf**, a novel skin cancer for treatment, in the United States.

"For a research-based company like ours, recent developments in healthcare policy and policymakers' short-term focus on costs are a major cause for concern," says Franz Shumer, chairman of the Roche Group. "Of course I understand that Roche as a leading pharmaceutical and diagnostics company – and indeed, our industry as a whole – must play its part in efforts to overcome the current financial and debt crises. We are prepared to do that. Through constructive dialogue we aim to contribute to finding a fair and sustainable balance between health policy and industrial policy – a balance that encourages and rewards the type of innovation from which society as a whole will benefit."

Mr. Humer has expressed great optimism for the medium-term to long-term outlook for research-based, innovation-driven companies such as Roche. "The fundamental trends point in the right direction: a growing, ageing global population; increasingly affluent emerging markets; rapid scientific and technological advances that are paving the way for more targeted, cost-effective treatments; and an undiminished need for medical progress, since many diseases are still not effectively treated," he says.

Roche remains the world's leading supplier of cancer medicines and the No. 1 *in vitro* diagnostics company. The company's combined strengths in pharmaceuticals and diagnostics and expertise in molecular biology, company leaders believe, position Roche to be the leader in the development of personalized medicine. "Cost-effective, targeted medicines and diagnostics have a key role to play in overcoming the healthcare sector's current difficulties," Mr. Humer says. "As pricing pressures increase, payers will shift resources to products and services offering the greatest incremental benefit to patients. As a company focused on developing medicines and tests that create real value for patients and physicians, we are well equipped to compete successfully in an increasingly challenging healthcare market. The strengths that serve us well today will be even more important tomorrow."

Company and product performance

"Given the significantly harsher market conditions we faced, 2011 was no easy year for the company, but it was nevertheless a successful one," says Severin Schwan, Roche's CEO.

According to Roche, group sales fell 10.4 percent to SFr42.53 billion ($47.99 billion) from SFr47.47 billion ($53.57 billion) in 2011. But earnings performance improved significantly faster, with net income rising 7 percent to SFr 9.54 billion ($10.77 billion). Diluted earnings per share were SFr10.98 ($12.39), 8.6 percent more than in 2010.

In the first half of 2012, the company generated sales of SFr22.42 billion ($25.30 billion), 3.5 percent more than in the first half of last year. Net income was SFr4.37 billion ($4.93 billion), almost 17 percent less than in first-half 2011. Diluted earnings per share were SFr4.99 ($5.63), compared with SFr6.04 ($5.35 in first half 2011.

Roche's Pharmaceuticals Division generated sales of SFr34.25 billion ($38.64 billion) in 2011, 11.3 percent less than in 2010. The Diagnostics Division had sales of SFr9.87 billion ($11.13 billion), a drop of 6.7 percent from 2010. In the first half of 2012, Roche posted sales of SFr22.43 billion ($25.30 billion) 3.5 percent more than in the first half of last year. Pharmaceuticals Division sales were SFr17.41 billion ($19.64 billion), 3.5 percent more than the same period last year. For the Diagnostics Division, first-half 2012 sales were SFr5.01 billion ($5.66 billion), 3.3 percent more than in first-half 2011.

"Given the significantly harsher market conditions we faced, 2011 was no easy year for the company, but it was nevertheless a successful one," says Roche CEO Severin Schwan.

Roche's best-selling product in 2011 was **Rituxan/MabThera**. In its combined sales for cancer and for inflammatory diseases such as rheumatoid arthritis, the drug generated sales of SFr6.23 billion ($6.77 billion), about 2 percent less than in 2010. Sales in the first half of 2012 were SFr3.31 billion ($3.74 billion), 9 percent more than the same period last year.

The company's second best seller was the cancer medicine **Avastin**. The drug had sales of SFr5.29 billion ($5.97 billion), 18 percent less than the previous year. Executives say the significant decline in overall sales was mainly due to regulatory and reimbursement uncertainty in the United States, beginning in 2010, regarding the use of Avastin for metastatic breast cancer. This led to lower sales in the United States throughout 2011 and also affected uptake for breast cancer in certain European and Latin American markets. In the first half of 2012, Avastin sales were SFr2.81 billion ($3.17 billion), 3 percent more than first-half 2011.

The product with the third-highest amount in sales was the cancer drug **Herceptin**. The drug generated SFr5.25 billion ($5.93 billion) in 2011, 3.2 percent less than in 2010. In the first half of 2012, Herceptin sales were SFr2.95 billion ($3.33 billion), 11 percent more than in the same period last year.

No. 4 in 2011 sales was the eye drug **Lucentis**, which brought in SFr1.52 billion ($1.72 billion), 4.5 percent more than in 2010. Sales in the first half of 2012 were SFr745 million ($840.7 million), 5 percent less than in the same period last year.

Avastin's 18 percent sales decrease to SFr5.29 billion ($5.97 billion) was attributed to regulatory and reimbursement uncertainty for the use of the drug in treating metastatic breast cancer.

The fifth best-selling pharmaceutical product for Roche in 2011 was the hepatitis drug **Pegasys**, which generated SFr1.44 billion ($1.62 billion), 12.6 percent less than in 2010. In the first half of 2012, Pegasys sales were SFr903 million ($1.02 billion), 31 percent more than in the first half of 2011. Executives say the increase can be attributed to Pegasys being a key component of the new triple combination regimens for hepatitis C that were launched in the United States and key Western Europe markets, such as France, Germany, and Switzerland. Pegasys has established itself as the foundation of this new treatment regime and has gained additional market share.

No. 6 in 2011 sales for Roche was the cancer drug **Xeloda**, generating SFr1.35 billion ($1.53 billion), 5 percent less than in 2010. First-half 2012 sales were SFr763

million ($861 million), 14 percent more than in the same period last year.

Roche's seventh best-selling drug in 2010 was **CellCept**, which posted SFr991 million ($1.12 billion). CellCept's first-half 2012 sales were SFR454 million ($512.3 million), 15 percent less than in first-half 2011.

The eighth best-selling drug for Roche in 2011 was the renal anemia and oncology product **NeoRecormon/Epogin**, which had sales of SFr896 million ($1.01 billion), 29.2 percent less than in 2010. First-half 2012 sales were SFr351 million ($396.1 million), 28 percent less than in first-half 2011.

Ranking No. 9 for Roche in 2011 was the osteoporosis drug **Boniva/Bonviva**, which had sales of SFr696 million ($785 million), 31.3 percent less than in 2010. First-half 2012 sales were SFr207 million ($235.6 million) 46 percent less than in the same period last year.

Roche's tenth best-selling medicine in 2011 was the rheumatoid arthritis drug **Actemra/RoActemra**, which generated SFr618 million ($697 million), 55.7 percent more than in 2010. First-half 2012 sales were SFr385 million ($434.4 million), 39 percent more than in the first half of 2011.

No. 11 for Roche was the asthma drug **Xolair**, which posted sales of SFr608 million ($680 million) in 2011, 5.9 percent less than in 2010. Xolair's sales in the first half of 2012 were SFr345 million ($389.3 million), 12 percent more than in first-half 2011.

Roche's No. 12 drug in 2011 sales was the antiviral **Valcyte/Cymevene**, which posted SFR569 million ($642 million), 6 percent less than in 2010. First-half 2012 sales were SFr307 million ($346.4 million), 9 percent more than in the same period last year.

No. 13 in 2011 sales was the respiratory drug **Pulmozyme**, which generated SFr492 million ($555 million), 4.1 percent less than in 2010. Sales in the first half of 2012 were SFr257 million ($290 million), 4 percent more than in the first half of 2011.

No. 14 for Roche in 2011 was the cardiac drug **Activase/TNKase/CathFlo Activase**, which had sales of SFr453 million ($511 million), 1.5 percent less than the previous year. Sales in the first half of 2012 were SFr285 million ($321.6 million), 21 percent more than in the first half of 2011.

Roche executives say they expect low-single-digit to mid-single-digit sales growth at constant exchange rates for the company and the Pharmaceuticals Division in 2012. Pharmaceuticals sales growth is expected to accelerate about 4 percent, driven by the strength of its established product portfolio as well as planned new product launches. Sales by the Diagnostics Division are expected to again outpace the market at about 5 percent.

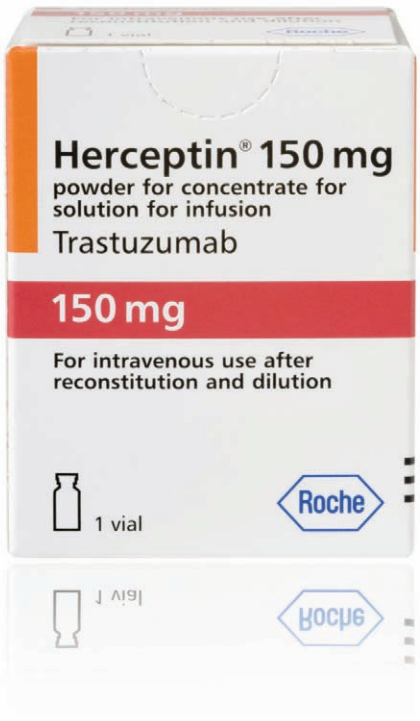
The company is planning to optimize value streams in 2012. To reallocate R&D resources into expanding the pipeline, Roche will be closing its Nutley, N.J., R&D site and focusing on its portfolio in its reorganization of the Pharma Research and Early Development organization. The resulting annual savings of SFr370 million ($417.5 million) will be largely reinvested in the expanding clinical product pipeline. Associated site closure costs amounted to SFr858 million ($968.2 million) in June. To sustain the long-term profitability of the Diagnostics business, Roche will reposition Applied Science and address the tougher environment in diabetes care. Roche incurred costs of SFr289 million ($326.1 million) for these initiatives. In looking at its cost structure, Roche will finalize the remaining part of its operational excellence plan and optimize the IR infrastructure to cope with business needs. And in focusing on net working capital, the company will be reducing receivables in Southern Europe.

Pegasys sales were SFr1.44 billion ($1.62 billion) in 2011, and sales are expected to increase in 2012 as the drug is now a key component of a new triple combination therapy for hepatitis C.

A failed takeover

Roche attempted to expand its diagnostic empire in 2012 by launching an offer for **Illumina** Inc. in January. The company offered to acquire Illumina for $44.50 per share in cash, or an aggregate of about $5.7 billion on a fully diluted basis. The offer represented a premium of 64 percent over Illumina's closing stock price on Dece. 21, 2011 – the day before market rumors about a potential transaction between Roche and Illumina drove Illumina's stock price significantly higher – a 61 percent premium over the one-month historical average and a 43 percent premium over the three-month historical average of Illumina's share price, both as of Dec. 21.

However, Illumina's board recommended that its shareholders not accept the offer, saying it was inadequate. "It is the board's unanimous belief that Roche's offer dramatically undervalues Illumina and fails to reflect the value of the company's unique leadership position and future growth prospects," said Jay Flatley, president and CEO. "Illumina has established itself as the innovation and market leader in tools for genetic analysis, with a proven track record of profitability and outperformance, resulting in significant value creation. Our industry is nascent, with the promise and potential to experience extraordinary growth in the years ahead as genetic information becomes broadly applied beyond molecular biology research, and into medical diagnostics, reproductive health, and cancer management. As the growth of this industry accelerates, Illumina is singularly positioned to expand its market leadership, and to deliver value to our stockholders that is far superior to Roche's offer."



Sales of the breast cancer drug Herceptin were SFr5.25 billion ($5.93 billion) in 2011.

In response, Roche extended the tender offer into March, and extended it again into April, raising the tender offer to $51 a share.

The Illumina board again rejected the offer. "Our board remains of the opinion that Roche has made an opportunistic offer, fully aware that even the revised offer does not reflect the intrinsic strength or future prospects of Illumina," Mr. Flatley said in a letter to Roche. "We are committed to acting in the best interests of all our stockholders and believe that Illumina's strategic plan, executed independently, will create stockholder value significantly greater than what you have proposed."

Illumina shareholders later in April rejected Roche's proposed nominees for the board and an expansion of the board, also proposed by Roche.

In the pipeline

Roche continued to invest heavily in R&D in 2011, although less than in 2010. The company spent SFr8.37 billion ($9.4 billion) in 2011, compared with SFr11.31 billion ($10.03 billion) in the previous year.

Still, this is more than competitors spent, Roche executives say. "Unlike some of our competitors, we intend to continue investing heavily in research and development, particularly in those areas where we have competitive advantages: oncology, diabetes, inflammatory and autoimmune diseases, and neuroscience," Mr. Humer says. "At the same time, we will maintain our strong focus on the optimal use of resources and continued productivity improvements." Executives say most of Roche's R&D activity continues to be located at the company's headquarters in Switzerland because of the country's competitive advantage.

In June 2012, Roche decided to streamline its R&D activities by closing its Nutley, N.J., site and consolidating some of these activities in Switzerland and Germany. The Nutley closure was expected to result in a reduction of about 1,000 positions. Along with the closure, Roche announced that Jean-Jacques Garaud, head of Roche Pharma Research and Early Development, was leaving the company at the end of the month. He was succeeded by Mike Burgess as acting head.

"Our R&D programs were exceptionally successful over the last 18 months, with 24 out of 28 late-stage clinical trials delivering positive results," Mr. Schwan says. "The overall number of programs in clinical development has grown substantially. The planned consolidation of our research and early development organization and the refocusing of R&D activities in Switzerland and Germany will free up resources that we can invest in these promising clinical programs while also increasing our overall efficiency."

Nutley's R&D activities will be consolidated at existing sites in Germany and Switzerland, focusing on oncology, virology, metabolism, and neuroscience.

As of September 2012, executives say as many as 19 late-stage clinical trials are expected to read out over the next 18 months, 12 of which are investigating new molecular entities. In addition, three NME projects could reach the lifecycle investment point to move into late-stage development later this year. Despite the promising increase of late–stage projects, Roche intends to keep its R&D budget stable by implementing continued productivity improvements and rigorous portfolio prioritization.

Executives say 2011 was a landmark year for Roche's efforts in personalized healthcare, due to advances in molecular diagnostics that allow the company's therapies to be targeted at particular patient populations.

"Already, roughly half the new molecular entities in our late-stage portfolio are tailored to subsets of patients who can be identified using specific diagnostic tests," Mr. Schwan says.

The prime example of this strategy is Zelboraf, Roche's personalized therapy for metastatic melanoma, the most aggressive form of skin cancer. FDA approved Zelboraf and its companion diagnostic test in August 2011, followed late in the year by a recommendation for approval from the European Medicines Agency. This marked the first time Roche has simultaneously launched a new medicine and a companion diagnostic.

The European Commission approved Zelboraf in February 2012. The cobas 4800 BRAF V600 Mutation Test, a diagnostic test jointly developed by Roche to identify patients eligible for treatment, was approved simultaneously with Zelboraf in the United States, and is CE-marked and commercially available in the European Union.

"We expect that approvals in many additional markets over the course of 2012 will make Zelboraf and its companion diagnostic available to patients worldwide," Mr. Schwan says.

In 2011, Roche also filed for regulatory approval its novel biologic pertuzumab for the treatment of breast cancer. FDA approved **Perjeta** for people with HER2-positive metastatic breast cancer in June 2012. The compound was approved in combination with Herceptin and docetaxel chemotherapy for the treatment of people with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Perjeta is a personalized medicine that targets the HER2 receptor, a protein found in high quantities on the outside of cells in HER2-positive cancers. Perjeta is believed to work in a way that is complementary to Herceptin,

MabThera/Rituxan was Roche's leading product in 2012, generating sales of SFr6.23 billion ($6.77 billion).

as the two medicines target different regions on the HER2 receptor. The combination of Perjeta, Herceptin, and chemotherapy is the only regimen to have shown a significant improvement in progression free survival compared to Herceptin plus chemotherapy in people with previously untreated HER2-positive metastatic breast cancer.

Roche has also submitted a marketing authorization application to the European Medicines Agency for Perjeta in combination with Herceptin and docetaxel for the treatment of previously untreated HER2-positive metastatic breast cancer or locally recurrent, unresectable breast cancer, in patients who have not received previous treatment or whose disease has returned after treatment in the early-stage setting. This application is currently under review by the EMA.

"Zelboraf and pertuzumab are tangible examples in the field of cancer of how we deliver significant benefits to patients through excellence in science," Mr. Schwan says. "We intend to build on successes like these in oncology, and in other therapeutic areas, by developing more effective, targeted strategies for fighting serious diseases."

The company also launched **Erivedge**, which was approved in February for the treatment of advanced basal cell carcinoma. The drug is also the first in a new class of anti-cancer treatments called hedgehog pathway inhibitors. Roche has submitted Erivedge for marketing approval in the EU, Australia, Mexico, Israel, and Canada.

In addition to new cancer therapies, Roche is working on personalized medicines for hepatitis C, for asthma, and drugs to alleviate or cure various disorders of the central nervous system, including Alzheimer's disease, schizophrenia, and depression.

"We currently have more than 200 drug development projects in which we are also doing research that could lead to a companion diagnostic," Mr. Schwan says. "Molecular biology is ushering in a new era in medicine. Our clear strategic advantages in this field will figure more and more prominently in our R&D successes going forward. As our understanding of the underlying biology of diseases grows, so will our ability to develop targeted medicines and companion diagnostics. We are increasingly making personalized healthcare a reality. This holds tremendous potential for patients and healthcare systems – and for Roche."

More than 60 percent of Roche's pharmaceutical pipeline projects are coupled with the development of companion diagnostics. Additionally, executives say Roche is at the forefront in developing antibody–drug conjugates that combine the specificity of antibodies with the power of chemotherapy and may result in improved efficacy and fewer adverse events. **T–DM1** is an investigational antibody–drug conjugate that attaches trastuzumab to the chemotherapy agent DM1 via a stable linker. It is designed to target and inhibit HER2 signaling and deliver the chemotherapy directly inside HER2-positive cancer cells. Pivotal Phase III data for T–DM1 showed significant and clinically meaningful improvements in progression-free and overall survival in pretreated patients with advanced HER2-positive breast cancer compared with lapatinib plus Xeloda chemotherapy.

In October, Roche announced that updated survival results from the Phase III EMILIA study showed that people with previously treated HER2-positive metastatic breast cancer survived significantly longer when treated withT-DM1 compared to those who received the combination of lapatinib and Xeloda. Results showed the risk of death was reduced by 32 percent for people who received trastuzumab emtansine compared to those who received lapatinib plus Xeloda. People in the study treated with trastuzumab emtansine survived a median of 5.8 months longer than those who received lapatinib and Xeloda

Lucentis posted U.S. sales of SFr1.52 billion ($1.72 billion) in 2011.

Roche has a total of nine antibody-drug conjugates in its development pipeline. These include **RG7593**, a humanised IgG1 anti-CD22 monoclonal antibody conjugated to an anti-mitotic agent that is being tested in Phase I in hematological cancers. The data indicate very promising anti-tumor activity in patients with relapsed or refractory disease following treatment with anti-CD20 containing therapies.

Roche is also developing combination therapies for cancer. For example, **onartuzumab**, a unique monovalent antibody, is being studied in combination with Tarceva in patients whose tumours overexpress MET in METLUNG, a Phase III study in second/third line non-small cell lung cancer. Results from METLUNG are expected in 2014. Onartuzumab is also being studied in combination with a paclitaxel regimen with or without Avastin in several further cancer types, such as breast and colon. New Phase II studies in squamous and non-squamous non-small cell lung cancer, as well as in gastric cancer and glioblastoma, began enrolment in 2012. A companion diagnostic test to identify people with MET-positive tumors is in development.

Roche is also focusing on neurodegenerative and psychiatric disorders such as Alzheimer's disease and schizophrenia, as well as on autoimmune and metabolic diseases.

The company is running a global Phase III program of six studies exploring two indications for **bitopertin**, an investigational first-in-class glycine reuptake inhibitor. The program is designed to optimize data quality by conducting three studies for negative symptoms and three studies for sub-optimally controlled symptoms in schizophrenia in parallel at the same clinical sites. A companion diagnostics assay is in development to validate the hypothesis for an exploratory biomarker predicting response to therapy with bitopertin. Data are expected in late 2013.

In Alzheimer's disease, Roche is pursuing a number of projects covering a broad range of approaches such as preventing the production of amyloid, removing amyloid plaque, and protecting tissue and blood vessels in the brain from oxidative stress. **Gantenerumab**, which is furthest advanced in clinical development, is a human IgG1 monoclonal antibody with low potential for immunogenicity and a high binding affinity towards aggregated forms of amyloid beta. Data from a Phase I study showed that gantenerumab reduced amyloid beta amyloid plaque in the brains of patients with Alzheimer's disease. A Phase II/III study called SCarlet RoAD in patients with prodromal Alzheimer's disease was recently expanded to recruit 770 patients. To identify prodromal Alzheimer's patients eligible for recruitment into SCarletRoAD, cerebrospinal fluid Tau/amyloid beta levels are determined and companion diagnostics assays based on cerebrospinal fluid Tau/amyloid beta are in development. Data read-out for SCarlet RoAD is expected in 2015.

A second anti-amyloid beta monoclonal antibody, **crenezumab**, targeting oligomeric and fibrillar forms of amyloid, is in Phase II testing to evaluate efficacy and safety in patients with mild to moderate Alzheimer's disease. Crenezumab was selected for a landmark study aiming to prevent the onset of Alzheimer's disease in a group of people whose genetic heritage causes them to develop the disease early in life.

In the area of metabolic diseases, Roche is investigating **aleglitazar** for cardiovascular risk reduction in patients with type 2 diabetes who have experienced acute coronary syndrome further cardiovascular events. The cardiovascular outcomes study AleCardio completed enrollment in May 2012. Data read-out is expected in 2015.

Xeloda generated sales of SFr1.35 billion ($1.53 billion) in 2011.

Anti-PCSK9, or RG7652, is a monoclonal antibody directed against PCSK9, a secreted protein that increases levels of low-density lipoprotein cholesterol in the blood by promoting the degradation of LDL receptors in the liver. Inhibition of PCSK9 decreases circulating low-density lipoprotein cholesterol, thereby potentially improving cardiovascular outcomes. As its mode of action differs from that of statins, anti-PCSK9 may provide benefit to people who do not achieve desirable low-density lipoprotein cholesterol levels with statins or cannot tolerate them. A Phase I study in healthy people with elevated low-density lipoprotein cholesterol demonstrated significant decreases in LDL-C levels both with and without statin combination. A Phase II study is ongoing to investigate different dosing schedules. Results are expected in 2013.

In the area of immunology, **rontalizumab** is a humanized anti-interferon-alpha antibody in development for moderately to severely active systemic lupus erythematosus. A proof-of-concept Phase II study with rontalizumab in systemic lupus erythematosus patients was designed with a biomarker program in place to identify the subpopulation of patients most likely to respond to anti-interferon-alpha treatment.This study has been completed and the data from it was slated to be presented at an upcoming medical conference later in 2012.

The company received good news for one of its top-selling drugs, Lucentis, in August 2012, when FDA approved the product for the treatment of diabetic macular edema. Lucentis is the first and only FDA-approved medicine for diabetic macular edema, a condition for which the standard of care has not changed significantly in more than 25 years. Lucentis 0.5 milligrams once monthly was first approved by FDA for treatment of wet age-related macular degeneration in 2006 and for macular edema following retinal vein occlusion in 2010. Lucentis 0.3 milligrams once monthly was approved for diabetic macular edema. ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

Conquering the cliff

With Plavix and other medicines going off patent in 2012, Sanofi executives believe the company will be able to overcome these challenges and move forward.

by Christiane Truelove chris.truelove@ubm.com

"Looking forward to 2015 and I think as I look at the business today, I'm completely confident in our ability to continue to grow back the business and really, I think, present one of the best growth pictures in our industry," says Christopher Viehbacher, chief executive.

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BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Lantus	$5,455	$4,890
Lovenox/ Clexane	$2,941	$3,909
Plavix/ Iscover	$2,842	$2,902
Aprovel, CoAprovel	$1,798	$1,849
Eloxatin/ Eloxatine	$1,492	$595
Taxotere	$1,284	$2,956
Allegra/Telfast	$808	$846
Ambien/ Stilnox/ Myslee	$683	$1,141
Cerezyme	$614	N/A
Amaryl	$607	$666
Copaxone	$607	$715
Depakine	$541	$518
Tritace and Delix	$522	$571

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Revenue	$46,514	$45,090
Net income	$7,913	$7,616
EPS	$5.98	$5.61
R&D	$6,702	$6,347
	1H12	**1H11**
Revenue	$24,213	$22,468
Net income	$4,320	$3,288
EPS	$3.15	$2.35
R&D	$3,364	$3,200

All figures are in millions of dollars except EPS.

Executives say 2011 was an important year for Sanofi, with the acquisition and integration of the biotech company Genzyme and the integration of the animal health business Merial. "We took the opportunity with these acquisitions really to think about the productivity of the company, so we completely restructured our support functions in the United States," says Christopher Viehbacher, chief executive of Sanofi. "We've engaged upon an ambitious plan to restructure our research operations, we've restructured our European commercial operations, and in all of that we've still managed to find time to file five dossiers for new medicines, which is pretty much without precedent in our industry. So, it was an enormous year in terms of how we have transformed again towards our growth platforms, but also were disciplined on costs and made sure we advanced on R&D."

Mr. Viehbacher says 2012 is going to be another challenging year for Sanofi, with the patent losses for the blood thinner **Plavix**, the blood pressure drug **Avapro**, and the chemotherapy drug **Eloxatin**, and a full year of generic exposure for the chemotherapy drug **Taxotere** in the United States. But even with these challenges, he anticipates a strong performance of the company's growth platforms, including Genzyme. "We'll have a full year of Genzyme and we continue to be very disciplined on costs and we've already launched another cost reduction programme of a further €2 billion [$2.79 billion]," he says.

Because of these patent losses, Sanofi expects a decline in earnings of 12 percent to 15 percent in 2012, but this is consistent with the guidance the company gave in September 2011. "Looking forward to 2015 and I think as I look at the business today, I'm completely confident in our ability to continue to grow back the business and really, I think, present one of the best growth pictures in our industry," Mr. Viehbacher says. "We'll have one of the lowest exposures to patent expiry coming from that. So it'll be a challenging 2012, but most of us in management are now focused on growth post the patent cliff period."

According to Mr. Viehbacher, in looking at the patent exposure for small-molecule drugs in Europe, the United States, and Japan, only 6 percent of Sanofi's 2012 sales will be affected, making it one of the lowest exposures in the pharmaceutical industry. Meanwhile, Sanofi's growth platforms are performing strongly and are expected to continue to do so in the future.

"So we feel very confident in our medium-term guidance – which we gave in September of 2011 – and that was really to come out of the patent cliff with compound average sales growth of about 5 percent between 2012 and 2015," Mr. Viehbacher says. "We would expect to have a leveraged P&L and of course we're going to continue to think about returns to shareholders in that period."

Sanofi is the fifth largest pharmaceutical company in the world and the third largest pharmaceutical group in Europe, according to IMS Health. The company is present in 100 countries on five continents with 113,719 employees by the end of 2011.

In 2011, the company's sales amounted to €33.39 billion ($46.51 billion), 3.2 percent more than in 2010. Net income was €5.69 billion ($7.93 billion), 4.1 percent more than in 2010. Diluted earnings per share were €4.29 ($5.98), 2.6 percent more than in 2010.

First-half 2012 results all showed increases in sales, net income, and earnings per share. The company generated €17.38 billion ($24.21 billion) in revenue, 7.8 percent more than in the first half of 2011. Net income was €3.10 billion ($4.32 billion), 31.4 percent more than the same period last year. Diluted earnings per share were €2.26 ($3.15), 33.7 percent more than in the first half of 2011.

Sanofi's business primarily comprises three division: Pharmaceuticals; Human Vaccines through Sanofi Pasteur; and Animal Health products through Merial. The company also has a Consumer Health Care business.

Pharmaceuticals generated net sales of €27.89 billion ($38.85 billion) in 2011, 4.9 percent more than in 2010. In the first half of 2012, Pharmaceuticals sales were €13.73 billion, 8 percent more than in the first half of 2011.

Sanofi's major project categories in Pharmaceuticals are Diabetes, Rare Diseases, and Oncology.

Sales of products in the Diabetes area came to €4.30 billion ($5.99 billion), a 9.2 percent increase from 2010 at a constant exchange rate, driven by growth in sales of **Lantus**, **Apidra**, and **Amaryl**. Lantus was Sanofi's leading drug in 2011 sales, generating €3.92 billion ($5.46 billion), 11.6 percent more than in 2010. First-half 2012 sales were €2.35 billion ($3.27 billion), 23.9 percent more than the same period last year.

"Diabetes is an extremely important growth platform for us, so I was extremely happy to see that we had double-digit growth in all four quarters [of 2011]," Mr. Viehbacher says. "When I look around the world, I think we've seen success everywhere. In the United States we actually saw growth in excess of 16 percent that was principally driven by a switch to SoloSTAR and in the fourth quarter of 2011, we actually achieved 50 percent of our sales with SoloSTAR. That's up 9.8 percent versus the fourth quarter of 2010. Emerging markets – growth of over 30 percent."

Other flagship products include Plavix; **Lovenox**, a low molecular weight heparin indicated for the prevention and treatment of deep-vein thrombosis and for unstable angina and myocardial infarction; **Multaq**, an anti-arrhythmic agent launched in 2009; the hypertension drugs **Aprovel/CoAprovel**; the renal drugs **Renagel/Renvela**; and the viscosupplements **Synvisc** and **Synvisc-One**.

Lovenox was Sanofi's second best-selling drug in 2011, with sales of €2.11 billion ($2.94 billion), 24.8 percent less than in 2010. The drug has faced generic competition in the United States since 2010. In the first half of 2012, Lovenox sales were €1.02 billion ($1.41 billion), 9.3 percent less than in first-half 2011.

Plavix, which is jointly marketed by Sanofi and **Bristol-Myers Squibb**, is known outside the United States as **Iscover**. The product was Sanofi's third best-selling drug in 2011, generating €2.04 billion ($2.94 billion), 2.1 percent less than in 2010. First-half 2012 sales were €2.86 billion ($1.47 billion), 23.1 percent less than in first-half 2011, reflecting competition from generics in the United States.

Sanofi's fourth best-selling product in 2011 was **Aprovel/CoAprovel**, also marketed as **Avalide** by Bristol-Myers Squibb. In 2011, worldwide sales were €1.29 billion ($1.8 billion), 2.7 percent less than in 2010. Sales of the drug were down 20.1 percent in the first half of 2012 compared with the same period last year, to €786 million ($1.09 billion), largely due to the loss of exclusivity in March 2012.

Lantus generated sales of $5.46 billion in 2011.

In October 2012, Sanofi and Bristol-Myers Squibb announced they have restructured their long-term alliance following the loss of exclusivity of Plavix and the hypertension drug Avapro/Avalide in many major markets. Under the terms of the revised agreement, which will go into effect Jan. 1, 2013, Bristol-Myers Squibb will return to Sanofi its rights to Plavix and Avapro/Avalide in all markets worldwide with the exception of Plavix in the United States and Puerto Rico, giving Sanofi sole control and freedom to operate commercially. In exchange, Bristol-Myers Squibb will receive royalty payments on Sanofi's sales of branded and unbranded Plavix worldwide, excluding the United States and Puerto Rico, and on sales of branded and unbranded Avapro/Avalide worldwide, in each case through 2018, and will receive a terminal payment of $200 million from Sanofi in December 2018. Plavix rights in the United States and Puerto Rico will continue unchanged under the terms of the existing agreement through December 2019.

"Our alliance with Bristol-Myers Squibb has been extremely successful and value-generating for both partners," says Hanspeter Spek, president, Global Operations, Sanofi. "The revised agreement further supports Sanofi's strategic priorities while continuing to offer the clinical benefits of these well-established products to millions of patients around the world."

In the Oncology area, Sanofi's main products are Taxotere; Eloxatin/Eloxatine, a key treatment for colorectal cancer; and **Jevtana**, a new taxane derivative, indicated for patients with prostate cancer, which was launched in 2010 in the United States and in the second quarter of 2011 in Europe.

Eloxatin/Eloxatine was Sanofi's fifth best-selling drug in 2011, posting sales of €1.07 billion ($1.49 billion), compared with €427 million ($594.9 million) in 2010. Eloxatin/Eloxatine in the United States was subject to generic competition for part of 2010 until a court ruling prevented further sales of unauthorized generics from June 2010 till Aug. 9, 2012. Wholesalers worked down their inventories of generic products in the second half of 2010 and in the first half of 2011. First-half 2012 sales were €759 million ($1.06 billion), 74 percent more than in the same period last year.

Sanofi is working on replacing its oncology blockbusters as they experience generic erosion. In August 2012, the company received FDA approval for **Zaltrap**, in combination with 5-fluorouracil, leucovorin, and irinotecan, for the treatment of metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen. Zaltrap is a recombinant fusion protein that acts as a soluble receptor that binds to VEGF-A, VEGF-B, and placental growth factor. Sanofi was expected to make Zaltrap available in the United States in the third quarter of 2012.

Sanofi's seventh best-selling drug in 2011 was the allergy drug **Allegra/Telfast**, which generated sales of €580 million ($808 million), 4.5 percent less than in 2010. In the first half of 2012, sales were €308 million ($429.1 million), 8.1 percent less than in first-half 2011. Sanofi launched an over-the-counter version of Allegra in the United States in March 2011, and Allegra products have become the company's No. 1 OTC brand globally.

The insomnia drug **Ambien/Stilnox/Myslee** was the company's eighth best-selling drug in 2011. Ambien generated sales of €490 million ($683 million) compared with €819 million ($1.14 billion) in 2010. In first-half 2012, sales were €254 million ($353.8 million), 9.5 percent more than in the same period last year.

The tenth best-selling drug for Sanofi in 2011 was the diabetes drug Amaryl, generating €436 million ($607 million), 8.8 percent less than in 2010. Sales in first-half 2012 were €213 million ($296.7 million), 1.8 percent less than in the first half of 2011.

Sanofi's eleventh best-selling drug in 2011 was the multiple sclerosis drug **Copaxone** at €436 million ($607 million), 15 percent less than in 2010. Sales in the first half of 2012 were €24 million ($33.4 million) compared with €233 million ($324.6 million) in the same period last year. The drop reflects the ending of the Copaxone joint-promotion agreement with **Teva** in all territories during the first quarter of 2012.

The twelfth best-selling drug for Sanofi in 2011 was the epilepsy drug **Depakine**, which generated €388 million ($541 million), 3.2 percent more than in 2010. First-half 2012 sales were €202 million ($281.4 million), 3.1 percent more than in first-half 2011.

Tritace/Delix was Sanofi's thirteenth best-selling drug in 2011, posting sales of €375 million ($522 million), 8.5 percent less than in 2010. Sales in the first half of 2012 for the cardiac drug were €180 million ($250.8 million), a drop of 7.2 percent compared with the first half of last year.

Plavix sales were $2.84 billion in 2011, but will take a steep dive in 2012 now that the product has lost its patent protection.

In the rare diseases area, Sanofi markets **Cerezyme** to treat Gaucher disease; **Fabrazyme** to treat Fabry disease, and **Myozyme/Lumizyme** to treat Pompe disease. Cerezyme was Sanofi's ninth best-selling drug in 2011, with sales of €441 million ($614 million). In the first half of 2012, Cerezyme sales were €299 million ($416.5 million) compared with €166 million ($231.3 million) in first-half 2011. Sanofi, however, only consolidated net sales from the acquisition of Genzyme in the April 2011. Because of this, the sales do not include the first quarter of 2011, and taking this into account, Cerezyme sales actually fell 4.6 percent.

Sanofi was preparing to launch two new multiple sclerosis medicines through Genzyme in 2012: **Aubagio**, a new once-daily, oral treatment indicated for patients with relapsing forms of the disease; and **Lemtrada**, a monoclonal antibody that selectively targets CD52, a protein abundant on T and B cells. Treatment with Lemtrada results in the depletion of circulating T and B cells thought to be responsible for the damaging inflammatory process in multiple sclerosis.

Aubagio was approved in September 2012, but Lemtrada has run into some difficulties. In August 2012, Sanofi and Genzyme received a refusal to file letter from FDA in response to the supplemental biologics license application for the drug's approval. Genzyme executives say the company will work with FDA to resubmit the application. The marketing authorization application submitted to the European Medicines Agency for Lemtrada has been accepted and the review process is under way.

Sanofi is a world leader in the vaccines industry through its Sanofi Pasteur subsidiary, with net sales coming to €3.47 billion ($4.83 billion) in 2011, 8.9 percent less than in 2010. The company has leading vaccines in five areas: pediatric combination vaccines, influenza vaccines, adult and adolescent booster vaccines, meningitis vaccines, and travel and endemics vaccines.

The influenza vaccines, which include seasonal vaccines such as **Fluzone** and pandemic vaccines, generated €826 million ($1.15 billion) in 2011, a 36.3 percent drop from 2010. The business suffered in 2011 from the absence of sales of A/H1N1 pandemic influenza vaccines, which amounted to €452 million ($629.7 million) in 2010. Excluding these sales, growth for the Vaccines business reached 7.2 percent at constant exchange rates, driven primarily by Emerging Markets, which were up 10.7 percent.

In the first half of 2012, influenza vaccine sales were €169 million ($235.4 million), 7 percent more than in first-half 2011.

The pediatric combination vaccines, including **Pentacel** and **Pentaxim**, posted sales of €1.08 billion in 2011, 12 percent more than in 2010. First-half 2012 sales of these vaccines was €518 million ($721.6 million), an increase of 4.9 percent compared with the same period last year.

Sales of meningitis vaccines, including **Menactra**, in 2011 were €520 million ($724.4 million), a decline of 3.2 percent compared with 2010. In the first half of 2012, sales were €202 million ($281.4 million), 10.4 percent more than first-half 2011.

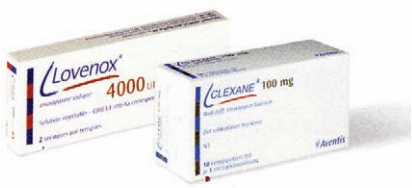
Adult booster vaccine sales, including **Adacel**, in 2011 were €465 million ($647.8 million), 3.6 percent more than in 2011. Sales in the first half of 2012 were €233 million ($324.6 million), 13.1 percent more than in the same period last year.

2011 sales of travel vaccines were €370 million ($515.4 million), 3.1 percent less than in 2010. Sales of these vaccines in the first half of 2012 were €177 million ($246.6 million), 3.5 percent more than in first-half 2011.

Sales of the animal health division, Merial, were €2.03 billion ($2.83 billion) in 2011, up 2.4 percent from 2010. In the first half of 2012, sales were €1.15 billion ($1.61 billion), 6 percent more than in the same period last year.

Consumer Health Care sales were €2.67 billion ($3.71 billion) in 2011. Sales in the first half of 2012 were €1.54 billion ($2.15 billion), a 13.8 percent improvement over first-half 2012.

Generics sales in 2011 were €1.75 billion ($2.43 billion), 16.2 percent more than in 2010. First-half 2012 generics sales were €907 million ($1.26 billion), 7 percent more than in first-half 2011.



Sales of Lovenox/Clexane were $2.94 billion in 2011, slipping downward from generic erosion.

In 2011, Sanofi generated 30.3 percent of its sales in emerging markets, and sales grew 10.1 percent at constant exchange rates. Emerging markets accounted for 25 percent of Merial's sales, and almost half of the company's consumer healthcare sales were in emerging markets.

Mr. Viehbacher says Sanofi is focused on growing its presence in emerging markets. In February 2011, the company acquired BMP Sunstone, a traditional Chinese medicine company. In acquiring a brand called "Good Baby," which was one of the few national brands in China, Sanofi was able to open new distribution channels.

"This [emerging markets] is where I think the greatest opportunity for growth is in the pharmaceutical sector," Mr. Viehbacher says. "There are 7 billion people in the world; our industry has traditionally focused on 1 billion of those people. Sanofi has local production. We have a product portfolio that's adapted to those markets. In most cases we've been there for decades, so we have depth of management and a true understanding of the culture and needs of customers and patients in those countries. So this is, I think, a truly fabulous strength of the company and I think a very strong result."

In October 2012, Sanofi announced an agreement to acquire Genfar SA, a pharmaceuticals manufacturer headquartered in Bogota, Colombia. The acquisition is expected to close in the first quarter of 2013.

Executives say with this acquisition, Sanofi will become a market leader in Colombia and expand its portfolio of affordable pharmaceuticals in Latin America. Genfar is the second largest generic company in sales and leader in units in Colombia and has a commercial presence in Venezuela, Peru, Ecuador, and 10 other countries in Latin America. In 2011, Genfar's total sales were $133 million, with 30 percent of sales generated outside of Colombia.

"With the acquisition of Genfar, Sanofi has a unique opportunity to strengthen its presence in Latin America through a large portfolio of affordable pharmaceuticals in a broad range of markets in the Andean countries and Central America," says Heraldo Marchezini, senior VP, Latin America, Sanofi. "This acquisition will allow Sanofi to better serve the 200 million people in the region."

Personnel changes, partnerships, and in the pipeline

Like many companies, Sanofi has conducted a review of its R&D operations, but unlike their peers elsewhere, the company's leaders have not decided to slash its budget. In 2011, the company spent €4.81 billion ($6.7 billion), 5.6 percent more than in 2010. In first-half 2012, R&D spending was €2.42 billion ($3.36 billion), 5.1 percent more than in the same period last year.

The company in October announced a new global medical director. Dr. Paul Chew will become senior VP, chief medical officer, and head of Global Medical Affairs in January 2013.

Dr. Chew, who is senior VP, chief science officer, and chief medical officer at Sanofi U.S., is succeeding Jean-Pierre Lehner, who will retire on Dec. 31, 2012, after more than 20 years with the company. Dr. Chew will report to Dr. Elias Zerhouni, president, Global Research & Development, and will be based in Bridgewater, N.J., and Paris, France.

"The knowledge and experience Paul has gained through his previous roles, including his work as a cardiologist, his expertise in diabetes, and work within R&D, make him ideally suited for this important role and continue the medical excellence which Jean-Pierre instilled within our organization," Dr. Zerhouni says.

Dr. Chew will be overseeing a potentially growing portfolio. Sanofi executives say the company has 18 potential new medicines targeted to launch by 2015. Among the promising late-stage drugs identified by Sanofi include the cholesterol compound SAR236553; Lyxumia, a once-daily drug for diabetes; and a dengue vaccine.

SAR236553, which is being jointly developed with **Regeneron**, is being developed for the treatment of high cholesterol. The drug is an investigational, high-affinity, subcutaneously administered, fully human monoclonal antibody that targets the PCSK9 proprotein to lower low-density lipoprotein cholesterol. In July 2012, Sanofi and Regeneron announced that they had launched a comprehensive Phase III clinical program for the drug. The ODYSSEY program will comprise more than 10 clinical trials and include more than 22,000 patients.

In addition, Sanofi announced the creation of a dedicated PCSK9 Development & Launch Unit. Jay Edelberg, M.D., Ph.D., was appointed head of the Development & Launch Unit, reporting to Dr. Zerhouni and Mr. Spek. "The creation of a dedicated unit for this new PCSK9 inhibitor underscores Sanofi's commitment to develop this poten-

tial first-in-class therapeutic agent," executives say.

In October 2012, Sanofi reported results from a study that demonstrated that the mechanism of action of once-daily **Lyxumia** significantly delayed gastric emptying, a process accompanied by significant post-prandial glucose lowering. These data were presented at the 48th Annual Meeting of the European Association for the Study of Diabetes in Berlin, alongside Phase III trial results that support the clinical rationale for Lyxumia as a potential once-daily GLP-1 receptor agonist in combination with basal insulin. Lyxumia was submitted for approval in Japan in June 2012. Also in June, Sanofi announced data that demonstrated the drug, in combination with basal insulin plus oral diabetic agents, significantly reduced HbA1c in people with type 2 diabetes who were either new to insulin therapy or already treated with insulin.

Mr. Viehbacher says he is "particularly excited" about the potential of the dengue vaccine in development. "Wherever you go, in particular emerging markets, people are very keen to see the launch of the dengue vaccine," he says. "This is the second biggest disease in terms of epidemiology after malaria. There's currently no treatment for dengue, so this offers extremely high hopes and I think meets a real public health need. I think it could be an extremely strong commercial opportunity for the company as well."

In July 2012, Sanofi Pasteur announced that the tetravalent vaccine demonstrated proof of efficacy against dengue. "Results of this first efficacy trial with Sanofi Pasteur's dengue vaccine candidate represent a key milestone in the quest to develop a safe and efficacious human vaccine against dengue," says Michel De Wilde, Ph.D., executive VP, Research & Development, Sanofi Pasteur. "This is also an important development for global public health, since there is currently no specific treatment or prevention for dengue. We are fully committed to making dengue a vaccine preventable disease by bringing a safe and effective vaccine to people living in endemic regions of the world."

Aprovel sales were $1.79 billion in 2011.

Large-scale Phase III dengue vaccine clinical studies with 31,000 participants are under way in 10 countries of Asia and Latin America. Executives say these studies will generate important additional data in a broader population and in a variety of epidemiological settings to demonstrate vaccine efficacy against the four circulating dengue virus serotypes.

In October 2012, Genzyme reported that ENGAGE, the first Phase III trial for **eliglustat tartrate**, met its primary endpoint. Patients who took the oral drug, which is being developed for the treatment of Gaucher disease type 1, showed a statistically significant improvement in spleen size at nine months compared with placebo. The current standard of care, Cerezyme, is administered through intravenous infusions, and executives believe that an oral capsule would provide a convenient treatment alternative for patients and provide a broader range of treatment options to achieve individual therapeutic goals.

"The efficacy and safety data from our ENGAGE trial are consistent with what were observed in our Phase II study, continuing to suggest that eliglustat tartrate is a potent, well-tolerated oral compound that may become a meaningful option for patients and physicians," says David Meeker, M.D., president and CEO of Genzyme. "The development of eliglustat tartrate has been underway for more than a decade and is the largest clinical program ever focused on Gaucher disease, demonstrating our ongoing commitment to innovation on behalf of this community."

To advance its pipeline in 2012, Sanofi has engaged in academic and nonprofit research partnerships ands collaborations. In June the company announced a partnership with the Joslin Diabetes Center, a teaching and research affiliate of Harvard Medical School, to promote the development of new medicines for the treatment of diabetes and related disorders. Under the terms of the agreement, Sanofi has options to commercialize the results of the research. Both parties will have access to intellectual property for internal research use. Financial terms of the collaboration were not disclosed.

In April, Sanofi entered into a collaboration with the Michael J. Fox Foundation to conduct a clinical trials to assess the safety and tolerability of **AVE 8112**, a PDE4 inhibitor, in patients with Parkinson's disease. The Michael J. Fox Foundation will sponsor a Phase Ib clinical trial of the drug. All data and results generated by the clinical trial will be owned by Michael J. Fox Foundation and shared with Sanofi. Further development plans will be based upon the results of the study. The clinical trial will be conducted at clinical sites in the United States in Baltimore, Md., and Los Angeles. Patient enrollment in the study is expected to begin later this year. ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

A new Takeda

The acquisition of a top 50 pharmaceutical company, expansion into emerging markets, and a promising late-stage product pipeline are propelling the next growth phase for Japan's leading drug manufacturer.

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BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Pioglitazone (including Actos)	$3,592	$4,704
Candesartan (including Blopress)	$2,623	$2,644
Lansoprazole (including Takepron)	$1,481	$1,620
Leuprorelin (including Leuplin)	$1,464	$1,411
Velcade	$705	$616
Enbrel	$502	$466

All sales are in millions of dollars.
2011 = fiscal year ended March 31, 2012
2010 = fiscal year ended March 31, 2011

FINANCIAL PERFORMANCE

	2011	2010
Sales	$18,298	$17,212
Net income	$1,506	$3,006
EPS	$1.91	$3.81
R&D	$3,418	$3,503

	1Q12	1Q11
Sales	$4,830	$4,332
Net income	$1,062	$917
EPS	$1.34	$1.16
R&D	$956	$700

All figures are in millions of dollars except EPS, and were translated using the Federal Reserve Board's March 2012 average rate of ¥82.4659.

2011 = fiscal year ended March 31, 2012
2010 = fiscal year ended March 31, 2011
1Q12 = fiscal first quarter ended June 30, 2012
1Q11 = fiscal first quarter ended June 30, 2011

Since fiscal 2010, this Osaka, Japan-based entity has been striving to attain sustainable growth via innovation and fostering an empowered corporate culture to realize the goal of "transformation into a New Takeda." During the company's fiscal 2011 (which ended March 31, 2012), Takeda acquired and consolidated **Nycomed** A/S, which had strong business foundations in Europe and emerging markets. Takeda's late-stage R&D portfolio made strong progress in various therapeutic areas during fiscal 2011. Based on these accomplishments and other factors, Takeda has formed and launched its 2012-2014 Mid-Range Plan to ensure sustainable medium-term and long-term growth beginning in fiscal 2012.

Through the new Mid-Range Plan, Takeda intends to generate top-line synergy by introducing its products in countries where the company obtained a strong base through the Nycomed acquisition. Takeda additionally plans to bolster the company's presence by providing products suitable to the market needs of developed as well as emerging countries. Takeda is seeking to gain marketing clearance for its late-stage pipeline products. The company will also continue investment that is required for future sustainable growth to improve R&D productivity by creating new compounds by intensively allocating resources to Takeda's core therapeutic fields and maximizing the value of existing products via life-cycle management.

For the three-year Mid-Range Plan, Takeda has been developing a strategy to generate stable growth from fiscal 2012 – ending March 31, 2013 – when its best-selling drug **Actos** (pioglitazone) faces U.S. generic competition. Particularly, in addition to the growth from sales of legacy Nycomed products in emerging markets, Takeda is concentrating on using the Nycomed sales platform to expand sales of the Japanese company's products. Takeda is also looking to launch new products and attain their rapid market penetration in Japan, Europe and the United States. Takeda is therefore approaching developed and emerging markets with different strategies tailored to their respective characteristics.

Takeda is concentrating R&D investments on the most promising areas of the company's pipeline. Takeda is striving to strengthen the pipeline and improve R&D productivity. The company also continues to hone its abilities to work with different regulatory authorities across various countries and regions.

Takeda's financial strategy for maximizing its operating cash flow is based on upgrading the company's cash-management capabilities. By steadily repaying debt, Takeda intends to maintain a sound financial base and to reinforce it over time.

The implementation of the Mid-Range Plan's three strategies are anticipated to generate sustainable growth for the entire corporation. Takeda is targeting compound annual growth in sales of about 5 percent and in operating income of about 25 percent from fiscal 2012 through fiscal 2016.

Takeda is geared toward areas in which there are high unmet medical needs and the company's R&D experience and platform can be fully employed. Takeda is concentrating its resources on these core therapeutic fields: Cardiovascular & Metabolic, Oncology, Central Nervous System, Respiratory & Immunology, General Medicine (Gastrointestinal & Genitourinary), and Vaccine. In each of those areas, Takeda intends to create highly innovative new medicines that can prevent or cure diseases. In particular, the company will leverage its worldwide in-house R&D network structured around Drug Discovery Units (DDUs) that are concentrated on the core therapeutic fields. At the same time, Takeda will bolster its drug-discovery research based on collaborative links with external research and academic institutions.

Additionally, Takeda will strengthen the company's competitive portfolio via aggressive in-licensing and R&D alliance activity as well as the promotion of life-cycle management. Takeda will build upon its regulatory affairs function worldwide, and concentrate on obtaining approvals for late-stage pipeline compounds. In the vaccines area, the company is developing its worldwide business to serve the pressing needs of emerging markets, in particular.

The corporation's overall aim is to increase R&D productivity by accurately determining the efficacy, safety and market potential of compounds at early stages. By doing so, Takeda can then best prioritize for allocation of R&D resources.

Takeda continues to create an empowering international corporate culture and working environment throughout the entire organization, based on recruiting and developing a worldwide talent base and promoting greater employee diversity. Takeda is actively promoting the exchange of personnel between Japan and overseas sites to develop a worldwide framework for the diversity-oriented development of human resources within the Group. Takeda continues to promote a strict compliance regimen in all aspects of its worldwide operations, while seeking to promote an active role as a corporate citizen in environmental and CSR activities. These activities include supporting continuing post-disaster reconstruction and relief effort in Japan as well as healthcare initiatives in emerging markets.


Takeda CEO and President Yasuchika Hasegawa

The company is pursuing strategies where management is targeting developed and emerging markets, based on their varying characteristics. Takeda believes that the major growth potential in these markets is in new drugs for treating diseases with high, unmet medical needs. In emerging markets, the compound annual growth through to 2016 is projected to remain in double digits despite the relatively high business risks in these economies. These markets have been predicted to generate about 70 percent of the total growth in the global pharma market during fiscal 2012-2016. Though branded generics for off-patent products will spur this growth in the short-to-medium term, in the longer term there will be growing opportunities for patented products.

Based on this outlook for the worldwide pharma arena, Takeda intends to shift its product portfolio for developed markets in Japan, the United States, and Europe from a product mix focused on mature, high-selling medicines to a more diverse portfolio targeting disease areas with unmet medical needs. Takeda managers say this approach will depend on the early and rapid market penetration of new products. At the same time, the company is working to reduce its costs and restructure Takeda's business model to generate sustainable growth.

In the United States, Takeda already has acted to boost its product lineup by completing the acquisition of **URL** Pharma Inc. in June 2012. URL's lead product is **Colcrys**, for treating gout flares.

In emerging economies – which are the growth drivers in the industry – market growth through to fiscal 2016 is forecasted at around 11 percent. Takeda intends to outpace this rate by steadily expanding sales of products of the legacy Nycomed to generate growth of about 17 percent during that time frame. In China, Russia/CIS (Commonwealth of Independent States) and Latin America, Takeda will actively invest in acquiring talented human resources and preparations for the market introduction of new products.

As a result, Takeda expects to bolster its business base to ensure that these markets serve as medium-term to long-term growth drivers. A example of this initiative was a deal struck during May 2012 to acquire **Multilab** Indústria e Comércio de Produtos Farmacêuticos Ltda., which is involved with products that are in high demand in Brazil. Additionally, Takeda plans to maximize synergies with legacy Nycomed by launching a steady stream of its own products via the new business base acquired through that acquisition, while also steadily realizing cost synergies.

For fiscal 2012, Takeda projected net sales of ¥1,550 billion (which would be a 2.7 percent year-over-year increase), operating income of ¥160 billion (dropping 39.6 percent year over year), and net income of ¥155 billion (rising 24.8 percent). Company executives expect a loss of U.S. sales revenue due to the arrival of generic competition versus Actos to be more than offset by varying factors. These factors include full-year contributions from Nycomed and URL Pharma; growth in Japan generated by the type 2 diabetes treatment **Nesina** and the anti-cancer agent **Vectibix**; and U.S. growth from the multiple myeloma and mantle cell lymphoma drug **Velcade**, the gastroesophageal reflux disease treatment **Dexilant**, and **Uloric** for treating hyperuricemia in gout patients.

The projected decrease in operating income for fiscal-year 2012 reflects the effect on profits of decreased sales revenue from Actos, increased amortization of intangibles and goodwill, increasing R&D expenses, and Takeda's aggressive investment program primarily concentrated on emerging markets. The expected increase in net income accounts for anticipated extraordinary gains from the receipt of a government subsidy related to the construction of a new manufacturing site for influenza vaccines and a separate tax refund associated with the re-investigation of a corrective notice on transfer pricing.

From fiscal 2012, management expect sales and profits to recover due to the expansion of the company's business in emerging markets and contributions from the growth of new products. Nets sales are expected to grow from ¥1,508.9 billion in fiscal 2011 to ¥1,700 billion for fiscal-year 2014. Operating income is projected to come in at ¥240 billion in fiscal-year 2014 compared with ¥265 billion in fiscal 2011, with net income amounting to ¥120 billion, compared with ¥124.2 billion in fiscal 2011. The R&D budget is projected to increase from ¥281.9 billion during fiscal-year 2011 to ¥310 billion in fiscal 2014.

The acquisition of URL Pharma is factored into these projected positive impacts, including ¥44 billion in sales and ¥5 billion in operating income for fiscal-year 2012.

The basic policy of Takeda's financial strategy during the fiscal 2012-2014 period is to maintain and enhance a sound financial position, while executing growth strategies to increase corporate value. The company will tighten its capital management, including the streamlining of Takeda's assets by disposing of marketable securities and idle real estate. As a result, Takeda will be able to steadily repay debt, invest roughly ¥300 billion in R&D for sustainable growth as well as perform strategic investments.

Company performance

Fiscal 2011 accelerated the company's "Transformation into a New Takeda" based on the 2011–2013 Mid-Range Plan. One of the major accomplishments was the Nycomed purchase for €9.6 billion during September 2011. The integration of the Swiss company as a wholly owned subsidiary of Takeda is on course to be fully completed by fiscal 2014. Takeda is reinforcing Group operations using legacy Nycomed's infrastructure throughout Europe and to establish a sales base in fast-growing emerging markets.

During fiscal 2011, Takeda produced net sales of ¥1,508.9 billion, compared to ¥1,419.4 billion during the previous 12-month term, marking a 6.3 percent improvement. The company's globally developing prescription drug business accounted for 90.1 percent of total net sales at ¥1.358.8 billion during fiscal 2011, representing a 7.2 percent increase versus fiscal 2010. Consumer Healthcare business sales accounted for ¥61.7 billion, and Other businesses contributed sales of ¥93.1 billion.

Takeda's Rx drug revenue growth during fiscal 2011 reflected a six-month sales contribution from Nycomed and the successful market introduction of new products in Japan. These new products included Nesina and Vectibix. U.S. sales growth was aided by major products, including Velcade. These factors helped to offset the impact of a strong yen and a decrease in sales revenue from the type 2 diabetes treatment Actos.

Operating income for fiscal 2011 dropped 27.8 percent to ¥265 billion, reflecting the amortization of intangibles and goodwill associated with the Nycomed acquisition as well as other factors. Net income fell 49.9 percent to ¥124.2 billion. This result was due to posting extraordinary losses due to the restructuring and rationalization costs at overseas operations and other one-off factors, including an upward revision of income taxes following a change in Japanese corporate tax rates.

The company's R&D successes during fiscal 2011 included gaining regulatory approval in Japan for the antihypertensive agent **Azilva** (azilsartan) during January 2012. FDA granted clearance of a new subcutaneous route of administration for Velcade in all approved indications during January 2012. U.S. health regulators additionally approved for marketing **Omontys**, a treatment for anemia due to chronic kidney disease, in March 2012. Also, significant products in Takeda's pipeline moved into the final stages of clinical development.

On the sales front, in the United States Takeda introduced the antihypertensive agent **Edarbi** (azilsartan) during February 2012 followed by **Edarbyclor**, which combines azilsartan with the diuretic chlorthalidone. Elsewhere, sales of Edarbi commenced in Europe during January 2012. In Japan, Takeda generated steady sales growth of products launched during fiscal 2010 including Nesina and Vectibix. The company concentrated on rapid early market penetration with the type 2 diabetes treatment **Liovel**, a fixed-dose combination of Nesina and Actos that was introduced during September 2011.

Takeda in November 2011 established the new position of chief medical and scientific officer to lead the company's drive to promote innovation and spur R&D productivity. Also created was the new position of chief commercial officer to preside over Takeda's international sales and marketing organizations (excluding domestic sales and **Millennium**). During January 2012, Takeda established the Vaccine Business Division to bolster worldwide vaccine operations. Each of these moves has reinforced Takeda's global operating structure and governance.

Takeda's fiscal 2012 got off to a positive start with first-quarter net sales of ¥398.3 billion, up 11.5 percent compared to the comparable period ended June 30, 2011. The performance was bolstered by the addition of product sales from Nycomed. Domestic sales were aided by the availability of Nesina, which has been projected by industry analysts to be a $2+ billion sales generator in 2018. Overseas sales growth during first-quarter fiscal 2012 came from Velcade, Dexilant and Uloric. The sales increase absorbed the yen's appreciation against the U.S. dollar and Euro (negative effects: ¥4.8 billion), and the decline in sales of Actos and the hypertension treatment **Candesartan** in the United States, Europe and Japan. Candesartan is marketed in Japan, Asia and certain European countries as **Blopress**, as well as under other trade names depending on the market.

First-quarter fiscal 2012 net sales in the Ethical Drug Business rose by ¥40.7 billion (up 12.7 percent) to ¥360.6 billion year over year. Operating income fell by ¥53.9 billion (down 49.5 percent) to ¥55.0 billion.

Net sales in Japan for first-quarter fiscal-year 2012 dropped off ¥2.7 billion (down 1.8 percent) versus April-June 2011, to ¥145.5 billion. Despite an increase in sales of products introduced in 2010 such as Nesina, a decrease in Actos and Blopress sales could not be completely offset.

Sales in the overseas markets improved by ¥43.4 billion (up 25.3 percent) to ¥215.0 billion compared to first-period fiscal-year 2011. The improvement was mainly due to the addition of Nycomed's sales, which absorbed the decrease in sales of Actos and **Prevacid** in the United States and Europe. This included negative effects of the Yen's appreciation.

Net sales in the Consumer Healthcare business elevated by ¥0.9 billion (up 6.1 percent) to ¥15.9 billion versus April-June 2011, primarily because of sales growth of **Alinamin** health tonics and tablets (vitamin-containing products) and **Benza** (a combination cold remedy). Operating income improved by ¥0.5 billion (up 12 percent) to ¥4.5 billion because of the increase in gross profit.

First-quarter fiscal 2012 sales in the Other business declined by ¥0.6 billion (down 2.4 percent) to ¥23 billion year over year. Operating income fell by ¥0.2 billion (4.8 percent) to ¥3.6 billion during first-quarter fiscal 2012.

Takeda's R&D expenditure for the fiscal 2012 first quarter rose by ¥21.2 billion (up 36.7 percent) to ¥78.9 billion.

Acquisition activity

Takeda's acquisition of Nycomed ranked as the No. 2 healthcare deal of 2011 at $13.1 billion, trailing only **Sanofi**'s purchase of **Genzyme** Corp. for a transaction value of $20.1 billion. Takeda purchased the Zurich-headquartered company for 9.6 billion euros on a cash-free, debt-free basis. The acquisition excluded Nycomed's U.S. dermatology business.

According to Takeda, this transformational transaction is a strategic fit with the company's sustainable growth strategy as outlined in its 2011–2013 Mid-Range Plan. Already strongly established in Japan and the United States, this move firmly positions Takeda with an important business infrastructure in Europe and high-growth emerging markets. Access to these markets enhances Takeda's regulatory development expertise and commercialization capability.

Assets coming from Nycomed to Takeda include the **roflumilast** franchise (branded as **Daxas** in Europe). The first-in-class treatment for chronic obstructive pulmonary disease is anticipated to be a major source of revenue growth for Takeda. The transaction also gives Takeda an immediate and stable increase in cash flow. Nycomed generated more than 2.8 billion euros in yearly revenue, excluding its U.S. dermatology business.

Nycomed's diversified product portfolio includes established prescription pharma products as a primary revenue driver, as well as OTC products. The company has a strong European commercial network and is aggressively growing in emerging markets, which represent more than half of its worldwide pharma growth. Nycomed's key success factors include the use of its expansive product range, and the application of commercialization and development strategies that fit with the market environment and medical needs in each individual country and region.

The privately owned pharma company Nycomed was acquired by Nordic Capital along with co-investors during 2005. Nycomed has followed an aggressive growth strategy that has transformed the company into an international player with an expansive and strong market presence.

"Takeda is committed to transforming our organization through the acquisition of Nycomed," commented Yasuchika Hasegawa, president and CEO of Takeda. "Nycomed enables Takeda to maximize the value of our portfolio and gives us an immediate strong presence in the high-growth emerging markets while doubling Takeda's European sales. Nycomed's strength in a geographically wide range of markets and its diverse talent base will be a strong driver to helping us realize our important mission of striving toward better health for patients worldwide through leading innovation in medicine."

To help reinforce Takeda's oncology franchise, the company completed its acquisition of **Intellikine** Inc. during January 2012. The La Jolla, Calif.-based privately held company has concentrated on the discovery and development of innovative small-molecule drugs. Intellikine was purchased for $190 million up front, with potentially another $120 million in clinical-development milestone payments.

Intellikine's product arsenal consists of proprietary small-molecule kinase inhibitors. These drug compounds selectively target isoforms of the phosphoinositide-3 kinase/mammalian target of rapamycin (PI3K1/mTOR2) pathway. Intellikine assets include continuing Phase 1 clinical programs involving selective inhibition of mTOR kinase and isoform-specific inhibition of PI3K alpha; a partnered program involving the R&D of isoform-specific inhibitors of PI3K gamma/delta; and a robust discovery research platform in small-molecule kinase inhibitors.

The company's most advanced drug candidate is **INK128**, a novel mTORC1/2 inhibitor. INK128 has generated encouraging data in multiple Phase I studies, with Phase II trials launching in 2012. **INK1117**, a novel and selective inhibitor of the PI3K alpha isoform, entered human clinical testing during September 2011.

Takeda's Millennium business unit is responsible for global oncology strategy and development. Millennium holds worldwide development responsibility for INK128 and INK1117.

"INK128 and INK1117 are potential best-in-class inhibitors of critical pathways driving cancer cell growth," noted Deborah Dunsire, M.D., president and CEO of Millennium. "As single agents or in different combinations with novel molecules within our robust pipeline, we anticipate that these assets will be able to deliver transforming therapies to cancer patients."

The Multilab acquisition was finalized during July 2012. Multilab significantly bolsters Takeda's existing presence in Brazil, positioning it as a top 10 pharma entity in that country. Multilab brings a diverse line-up of complementary branded generics and OTC products. The portfolio includes **Multigrip**, Brazil's top-selling over-the-counter product for cold and flu treatment in units. OTC products represent 30 percent of the entire Brazilian pharma market. The addition of Multigrip strengthens Takeda's existing OTC portfolio: **Neosalodina** for anti-pain, **Eparema** for digestive support, and **Nebacetin** dermatological treatments.

The mid-sized pharma company Multilab generated net revenue of BRL 140 million during 2011. Retail sales for Multilab exceeded 20 percent p.a. during 2009-2011. This transaction is expected to add ¥5 billion to Takeda's consolidated revenue for fiscal 2012.

URL Pharma's acquisition by Takeda was finalized in early June 2012 for an up-front payment of $800 million. The deal includes future performance-based contingent earn-out payments. **Takeda Pharmaceuticals U.S.A.** Inc. is integrating URL and immediately assumed responsibility for the marketing and promotion of Colcrys. As URL's lead product, Colcrys is available for the treatment and prevention of flares associated with gout.

The URL acquisition is expected to add more than $550 million to Takeda's FY 2012 net sales. The addition of Colcrys bolsters Takeda's U.S. presence by increasing the company's gout treatment portfolio to provide patients with more management options for acute and chronic aspects of the disease. Colcrys complements Takeda's presence in the gout marketplace with Uloric, which is used to lower blood uric acid levels in adult patients with gout.

Takeda during early August 2012 landed exclusive distribution rights in Japan for seven OTC brands marketed by **Johnson & Johnson**. The two companies already had an existing deal through which Takeda holds the exclusive distribution rights in Japan of **Nicorette**, a non-prescription smoking-cessation aid. Takeda intended to begin its sales and promotional activities of the seven OTC products by year-end 2012. The seven brands are the antitussive/expectorant and treatment rhinitis **Aneton**; the antipyretic/analgesic **Tylenol**; the rhinitis treatment **Cor-Tyzine**; **Visine** eye drops; and the dermatological preparations **Terres Hi**, **Terra-Cortril** and **Terramycin**.

Through this pact, Takeda has bolstered its existing categories of cold remedies and eye drops, and added a new category in dermatological treatments. The improved product line-ups enable the company to enhance its presence in the growing OTC drug market.

Pipeline updates and recent product approvals

Fiscal 2011 was successful for Takeda in terms of the company's research and development activities. Takeda obtained regulatory clearance for the antihypertensive agent Azilva in Japan and for the renal anemia treatment Omontys in the United States. Several late-stage pipeline assets positioned as major products to Takeda for the next generation advanced to another phase of clinical development. The most notable of these products were the type 2 diabetes treatment **TAK-875** and the prostate cancer treatment **orteronel/TAK-700**. These moves are helping Takeda to lay a foundation for sustainable future growth.

Azilva was approved by Japanese health authorities in January 2012 and launched in that country four months later. The angiotensin II receptor blocker reduces blood pressure by blocking the action of angiotensin II, which is a vasopressor hormone. Azilva is a once-a-day, orally administered single tablet available in dosages of 20 milligrams and 40 milligrams.

The Azilva approval submission was based on four Phase III studies carried out in Japan. One of the studies was a multi-centre, double-blind trial with 636 patients of grade I and II hypertension to evaluate the efficacy and safety of Azilva versus Blopress. The ARB blockbuster Blopress was discovered and is marketed by Takeda in Japan as the most popular Rx drug in that country. The study demonstrated that Azilva was superior to Blopress with statistical significance in reducing the change from baseline in sitting diastolic blood pressure. Azilva additionally was superior to Blopress with sta-

tistical significance in lowering the mean diastolic blood pressure and systolic blood pressure throughout 24 hours, measured by Ambulatory Blood Pressure Monitoring (ABPM). The product was safe and well tolerated, with a safety profile comparable to Blopress.

Takeda has projected fiscal-year 2012 sales of ¥3.5 billion for Azilva.

Omontys gained FDA regulatory clearance right before the end of Takeda's fiscal 2011 and was introduced to the U.S. marketplace in April 2012. The product is the first once-monthly erythropoiesis-stimulating agent (ESA) for anemia to be made available to the U.S. dialysis patient population.This is the only ESA that is peptide-based, with its building blocks (amino acids) arranged in different fashion than erythropoietin (i.e., it has no sequence homology to endogenous erythropoietin).

FDA's decision was based on a new drug application, which included results from two randomized, controlled, open-label, Phase III trials (EMERALD 1 and 2). The studies showed the safety and efficacy of the product dosed once per month compared to epoetin administered between one to three times per week (according to product labels), in maintaining hemoglobin (Hb) levels in anemic chronic kidney disease patients on dialysis. The most commonly reported adverse reactions were shortness of breath, diarrhea, nausea, cough and arteriovenous fistula site complication.

The EMERALD studies were part of the largest clinical program to support the new drug application of an ESA in treating anemia in chronic kidney disease. Enrolling 2,606 patients, including 1,600 dialysis patients, the Phase III program was the first to prospectively compare in a head-to-head manner the cardiovascular safety of different ESAs. Cardiovascular safety was reviewed based on a composite cardiovascular safety endpoint adjudicated by a blinded and independent committee.

Anemia is a condition in which blood has a lower than normal amount of red blood cells. Anemia is a common complication in dialysis patients because their kidneys no longer create enough erythropoietin, the hormone that stimulates the body's red blood cell production.

TAK-875 is the first GPR40 (G-protein-coupled receptors agonist) to reach Phase III studies. TAK-875 is an investigational type 2 diabetes therapy undergoing Phase III programs in Japan, the United States, Latin America, and Europe. In Phase II trials, the drug – at doses ranging from 6.25 to 200 milligrams a day – met its primary endpoint of statistically significantly lowering HbA1c (blood glucose) levels throughout a 12-week period versus placebo. Agonists of GPR40, one of the GPCRs expressed in pancreatic islet cells, have a mechanism of stimulating insulin in a glucose-dependent manner that differs from other diabetes drug classes such as sulfonylureas.

Orteronel is an orally active, selective nonsteroidal inhibitor of the 17, 20 lyase, which is a key enzyme in producing male steroidal hormones. The drug candidate is undergoing Phase III studies for treating prostate cancer in Japan, the United States, and Europe. Phase II trials tested orteronel dosed without prednisone in patients with non-metastatic castration resistant prostate cancer and rising prostate-specific antigen. Non-metastatic castration resistant prostate cancer is a field of unmet need, and therapies that reduce prostate-specific antigen without requiring concomitant corticosteroids are of significant interest in earlier lines of prostate cancer treatment.

Alogliptin is awaiting marketing approval in Europe and the United States. The drug submission was filed with U.S. health authorities in July 2012 and with EU regulators during April 2012. Alogliptin already is branded in Japan as Nesina and in a fixed-does combo with pioglitazone as Liovel. The combination product is additionally awaiting FDA and EU marketing approval.

The U.S. filings in July 2012 for alogliptin and alogliptin/pioglitazone were resubmitted as a result of a complete response letter Takeda received from FDA on April 25, 2012. The resubmission includes additional data from three Phase III studies involving 3,275-plus patients carried out at 1,384 centers globally. When combined with previously filed Phase III clinical data, which included over 8,000 patients conducted in more than 1,000 centers, almost 10,000 patients have been treated with alogliptin in the clinical-development programs as of July 2012.

The selective dipeptidyl peptidase-4 inhibitor (DPP-4i) alogliptin is undergoing review for treating type 2 diabetes as an adjunct to diet and exercise. The drug is designed to slow the inactivation of incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide), which help regulate blood glucose levels. The FDC alogliptin and pioglitazone unite two complementary agents with distinct mechanisms of action. If cleared for marketing, this would be the first type 2 diabetes treatment option in the United States to include both a DPP-4i and the thiazolidinedione pioglitazone in one tablet. Pioglitazone-containing medicines have been available in the United States since 1999 for treating type 2 diabetes as an adjunct to diet and exercise, including Takeda's blockbuster medicine Actos.

Rienso (ferumoxytol) gained approval from the European Commission during June 2012. The new intravenous drug treats iron-deficiency anemia in adult patients with chronic kidney disease. Ferumoxytol significantly raises Hb levels in chronic kidney disease patients with iron-deficiency anemia, both on dialysis and in patients not on dialysis compared with oral iron. Clinical studies showed that the iron therapy ferumoxytol is well tolerated.

The product was developed by **AMAG** Pharmaceuticals Inc. and is marketed outside the United States by Takeda based on a joint-marketing deal reached in March 2010. Ferumoxytol is approved for use in Canada and the United States as **Feraheme**.

Takeda reported excellent results for a Phase III study of **vedolizumab/MLN0002** during May 2012. In the top-line results, the product met primary endpoints of improvement in clinical remission in induction and maintenance phase from the GEMINI II Phase III study. This clinical trial is evaluating vedolizumab in patients with moderately to severely active Crohn's disease who have failed at least one conventional therapy, including TNF alpha antagonists.

Developed by Millennium, the drug candidate is an inhibitor of alpha(4)beta(7) integrin. MLN0002 is undergoing Phase III studies in the United States and Europe for two major inflammatory bowel diseases: ulcerative colitis and Crohn's disease. The product has met the primary endpoints in each set of studies.

Ixazomib/MLN9708 during June 2012 became the first oral proteasome inhibitor to enter Phase III development. The international multicenter study is evaluating MLN9708 in patients with relapsed and/or refractory multiple myeloma. The Phase III trials are being conducted in Europe, North America, Latin America and the Asia-Pacific region.

The drug compound is being studied in multiple myeloma, various hematologic malignancies and solid tumors. This is the first oral proteasome inhibitor to enter clinical studies in patients.

The European Commission during September 2012 granted marketing clearance to **Revestive** (teduglutide) as a once-per-day treatment for adult patients with short bowel syndrome. SBS is a rare and highly disabling condition that affects patients' quality of life and can result in serious life-threatening complications. Teduglutide is the first approved treatment in Europe for the debilitating disease. The drug was given orphan-drug designation for treating SBS from EMA and FDA authorities. Teduglutide is awaiting U.S. marketing clearance under the trade name **Gattex**.

The novel, recombinant analogue of human glucagon-like peptide 2 (GLP-2) is a naturally occurring protein involved in the rehabilitation of the intestinal lining. Teduglutide has been developed to reduce dependence on parenteral nutrition in adult patients with short bowel syndrome. Two Phase III trials showed a favorable safety profile and significant reductions in mean parenteral nutrition volume from baseline to end of treatment. Some patients were able to be weaned off parenteral nutrition and continue their life without parenteral support.

During 2007, **NPS** Pharmaceuticals Inc. granted Nycomed the rights to develop and commercialize teduglutide outside the United States, Canada, Mexico and Israel. NPS is a specialty pharma company developing innovative therapeutics for rare gastrointestinal and endocrine disorders. NPS retains North American rights to teduglutide. The company filed a new drug application for teduglutide to FDA during November 2011.

Takeda launched a Phase III study for **motesanib/AMG 706** in Japan, Hong Kong, South Korea and Taiwan during July 2012. The drug is an investigational, orally administered small-molecule antagonist of vascular endothelial growth factor receptors 1, 2, and 3, platelet-derived growth factor receptors, and stem cell factor receptor. Motesanib is being evaluated in the Phase III trial in combination with chemotherapy in patients with advanced non-squamous non-small cell lung cancer.

Takeda and U.S. biotech giant **Amgen** Inc. entered into a new deal during July 2012 providing the Japanese company with the exclusive global rights to independently develop, manufacture and commercialize motesanib. During 2008, the two companies agreed on a worldwide joint-development and profit-share arrangement for motesanib through which Takeda had exclusive development and commercialization rights to motesanib in Japan and both entities were to share profits outside of Japan. Amgen was given an up-front payment and is eligible to receive milestones and net sales royalties.

EU health authorities during July 2012 granted a positive CHMP opinion for **Adcetris** for two indications. One indication is for the treatment of adult patients with relapsed or refractory CD30 positive Hodgkin lymphoma following autologous stem cell transplant or following at least two prior therapies when autologous stem cell transplant or multi-agent chemotherapy is not a treatment option. The other indication is for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma.

Brentuximab is an antibody-drug conjugate directed to CD30, which is a defining marker of classical Hodgkin lymphoma and systemic anaplastic large cell lymphoma. The anti-CD30 monoclonal antibody is attached by a protease-cleavable linker to the microtubule disrupting agent monomethyl auristatin E (MMAE). The ADC uses a linker system designed to be stable in the bloodstream that releases MMAE upon internalization into CD30-expressing tumor cells.

Millennium and **Seattle Genetics** Inc. are jointly developing brentuximab. Seattle Genetics holds U.S. and Canadian commercialization rights. Takeda maintains rights to market brentuximab in the rest of the world. Seattle Genetics and Takeda are funding co-development costs for brentuximab on a 50/50 basis except in Japan. Takeda is solely responsible for development costs in Japan.

In early October 2012, Takeda and **H. Lundbeck** A/S announced the filing of a new drug application to FDA for the investigational agent **vortioxetine/Lu AA21004**. The NDA is for treating major depressive disorder in adult patients. Vortioxetine has been studied as an antidepressant with multimodal activity that is believed to work via a combination of two complementary mechanisms of actions: receptor activity modulation and reuptake inhibition.

The NDA includes data from six short-term placebo controlled clinical trials – including one dedicated study in the elderly – that have been carried out in regions around the globe and support statistically significant efficacy of vortioxetine in a dose range of 5 to 20 milligrams daily. Efficacy of vortioxetine was additionally shown in a long-term relapse-prevention study in major depressive disorder. The vortioxetine worldwide clinical-development program included 7,500-plus individuals exposed to the product. *In vivo* non-clinical studies have demonstrated that the drug enhances levels of the neurotransmitters serotonin, noradrenaline, dopamine, acetylcholine and histamine in particular areas of the brain.

A new drug application for **Lotriga** granular capsule 2g as a treatment for hyperlipidemia was approved in Japan during September 2012. Discovered by **Pronova** BioPharma ASA of Norway, the omega 3-derived prescription drug contains highly concentrated and purified EPA-E (eicosapentaenoic acid ethyl ester) and DHA-E (docosahexaenoic acid ethyl ester). The product is available in at least 60 countries, including the United States and Europe. Takeda and Pronova entered into a license and supply deal during 2005. Takeda was granted exclusive development and marketing right to Lotriga in Japan. This is the first prescription product in Japan that consists of both EPA-E and DHA-E.

Takeda and fellow Japanese companies **AstraZeneca** K.K., **Mitsubishi Tanabe** Pharma Corp. and **Eisai** Co. announced during August 2012 the filing of a joint application to the Ministry of Health, Labour and Welfare. The application seeks approval in Japan of *Helicobacter pylori* gastritis as another indication for *H. pylori* eradication by concomitant therapy with four proton-pump inhibitors: **lansoprazole**, **omeprazole**, **rabeprazole** sodium and **esomeprazole** magnesium hydrate. Those drugs are manufactured and marketed by the four aforementioned companies in Japan under five trade names. This concomitant therapy consists of the proton-pump inhibitor **amoxicillin** hydrate with either **clarithromycin** or **metronidazole**.

The four companies anticipate that the new indication will significantly contribute to the prevention and treatment of diseases related to *H. pylori*. The joint applicants of the new indication also consist of five other companies marketing amoxicillin hydrate, clarithromycin and metronidazole: **Kyowa Hakko Kirin** Co., **Astellas** Pharma Inc., **Abbott Japan** Co., **Shionogi** & Co. and **Taisho** Pharmaceutical Co.

In other Takeda news occurring in August 2012, the company established a research collaboration with the BC Cancer Agency to explore new drug targets based on gene analysis. The research is being performed at Takeda's new Shonan Research Center. The BC Cancer Agency's chair of breast cancer research, Dr. Sam Aparicio, was invited to the center to head this research.

This is the first project initiated as part of Takeda's new Shonan Incubation Laboratories. Distinguished researchers from external institutions will work with Takeda scientists in the state-of-the-art Shonan Research Center, bringing new insights to drug discovery via intensely collaborative research. The three-year new drug target exploration project brings together Dr. Aparicio's leading-edge insights with gene analysis and the BC Cancer Agency's next-generation DNA sequencing technique with Takeda's drug-discovery technologies, expertise and world-class facilities. ■ MEDADNEWS

TOP 50 PHARMA COMPANIES

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TEVA

BEST-SELLING RX PRODUCTS

PRODUCT	2011 SALES	2010 SALES
Generics	$10,196	$9,907
Copaxone	$3,570	$2,958
Provigil	$1,179*	$1,124
OTC	$765	$496
Treanda	$502*	$394
Women's Health	$438	$374
ProAir	$436	$396
Qvar	$305	$250
Azilect	$290	$244

** Estimated. Provigil and Treanda joined Teva's portfolio with the acquisition of Cephalon in October 2011.*

All sales are in millions of dollars.

FINANCIAL PERFORMANCE

	2011	2010
Sales	$18,312	$16,121
Net income	$2,768	$3,339
EPS	$3.09	$3.67
R&D	$1,095	$951

	1H12	1H11
Sales	$10,096	$8,292
Net income	$1,714	$1,345
EPS	$1.96	$1.49
R&D	$590	$482

All figures are in millions of dollars except EPS.

PHARMACEUTICAL COMPANY OF THE YEAR

All grown up

While the rest of the industry plays defense, no pharmaceutical company in the world has grown quite like Teva in the past decade.

By Joshua Slatko joshua.slatko@ubm.com

Teva Pharmaceutical Industries Inc. doesn't look much like any other company profiled in this issue. It is the only company on *Med Ad News*' Top 50 Pharma list to be founded and headquartered in Israel. It leads the world in total prescriptions filled, thanks to its gigantic portfolio of generic products, which also leads the world – but it also boasts two blockbuster branded products, with others possibly on the way. And through a strategy of aggressive acquisition and global growth, it has developed a habit of jumping its top line at a furious pace, from $3.28 billion in 2003 to $9.41 billion in 2007 to $18.3 billion in 2011 and likely more than $20 billion this year. In an industry filled with "me-too" business strategies, this unique company has followed its own path to unprecedented success, which is why the editors of *Med Ad News* have chosen Teva as our Company of the Year.

Teva's mission, simply put, is to provide a broad range of affordable and effective medicines to patients around the world. The company seeks to capitalize on the dynamics of a growing generic market, including aging populations, economic pressures on governments to provide less expensive healthcare options, legislative reform and the movement of decision-making power to payors, unmet needs in the market for pharmaceuticals, and the growing importance of OTC medications.

Teva is the leading generic drug company in the world and has held the leading position in the United States for almost a decade. Teva is also the leading generic drug company in Europe, where the company boasts a balanced presence throughout the region. In addition, the company has increased its presence in its "rest of the world" markets. Teva is now the third leading generics company in Japan and has experienced significant growth in Russia and Latin America.

But generics aren't the end of Teva's story. With the recent addition of Cephalon's branded business, the company has significantly broadened its specialty pharmaceutical business with an extensive late-stage pipeline. As of the end of 2011, Teva had more 40 products in various stages of clinical development, more than half of which were in Phase III or beyond. The company's focus is two-fold: strengthening existing therapeutic areas, such as its central nervous system, oncology, respiratory, and women's health products, while exploring opportunities to expand into other niche therapeutic areas. The company is also making a push into over-the-counter products. Teva significantly strengthened its OTC business in November 2011 through the creation of a joint venture with Procter & Gamble, whose marketing expertise and expansive global platform, company leaders believe, will provide a competitive advantage.

Teva's revenue grew by 14 percent to $18.3 billion in 2011. The company's growth was primarily driven by the inclusion of a full year of Ratiopharm's revenue, the consolidation of Cephalon's revenue beginning in October 2011, and its Japanese acquisitions, including the consolidation of Taiyo in July 2011. In addition, sales of Copaxone, the company's leading product, grew by more than 20 percent. Net income for the year was down 17.1 percent to $2.77 billion and EPS dropped 58 cents to $3.09. According to company leaders, this drop came due to increases in operating expenses as a result of the Ratiopharm, Cephalon, Taiyo, and Theramex acquisitions, an increase in legal settlements, higher charges related to the amortization of Ratiopharm's and Cephalon's intangible assets, as well as higher impairment charges mainly related to the company's animal health plant in the United States and a divestiture in connection with the Cephalon acquisition. Adjusting for all this, Teva's accountants estimate the company would have enjoyed 7.4 percent income growth for the year.

In 2011, about 56 percent of Teva's revenue was generated from generic pharmaceuticals, including active pharmaceutical ingredients sold to third parties, and about 35 percent from branded products, which include Copaxone for multiple sclerosis, Azilect for Parkinson's disease, the company's respiratory and women's health products, and products from the newly acquired Cephalon portfolio. With the acquisition of Cephalon in late 2011, Teva's branded portfolio was expanded to include, most significantly, Provigil for excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work disorder, and Treanda for chronic lymphocytic leukemia and indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. The company's remaining revenue was generated from its joint venture with P&G and other activities such as its Hungarian and Israeli distribution services to third parties. Company leaders expect the branded share of Teva's revenue to increase markedly in 2012 due to the effects of the Cephalon acquisition.

Teva generated about 48 percent of its revenue in the United States in 2011, about 31 percent in Europe, and about 21 percent in its rest of the world markets (primarily Canada, Latin America, Israel, Russia, and other Eastern European countries that are not members of the European Union). The company's European and rest of the world markets grew by 43 percent and 39 percent respectively. Revenue in the United States declined by $594 million, due to lower generic sales, partially offset by increased sales of branded products.

"I have known and admired Teva for many years, not just as a global leader in generic drugs, but as an outstanding innovator in pharmaceutical development and new strategic approaches to serve patients worldwide," says Jeremy Levin, the company's new CEO. "Demographic trends and economic pressures in developed and emerging markets are intensifying the challenge to provide good medicines at affordable prices. Teva, with its multiple platforms in generics, branded, and OTC drugs, is in an especially good position to meet this challenge."

The new year has brought more impressive growth for Teva. In the first half of 2012, the company's revenue rose another 21.8 percent, with net income up 27.4 percent to $1.71 billion and earnings rising 47 cents to $1.96.

New leadership

On the first day of 2012, Teva announced that Shlomo Yanai, president and CEO of the company for the past five years, was planning to retire effective May 2012, and that the board of directors had named Dr. Jeremy Levin, a former senior executive at Bristol-Myers Squibb, to succeed him at that time.

Dr. Levin brought more than 25 years of experience in the global pharmaceuticals industry, leading companies and people in the creation, development, and delivery of medicines. He joined Bristol-Myers Squibb in 2007, and had direct responsibility for strategy, alliances, and transactions while managing Bristol-Myers Squibb's portfolio of alliances. Before joining Bristol-Myers Squibb, Dr. Levin served from 2003 to 2007 as global head of business development and strategic alliances at Novartis. Earlier, he was CEO of Cadus Pharmaceuticals, a company he took public.

"Dr. Levin is an exceptionally talented business leader with a deep understanding of the opportunities and challenges of the pharmaceutical industry," says Phillip Frost, M.D., Teva's board chairman. "He brings to Teva a wealth of experience and the hands-on skills required to foster the growth of a global pharmaceutical business. As a business leader and as a physician, he is passionately committed to bringing effective treatments to patients, worldwide. His combination of vision, creative energy and an effective team-building management style make him an ideal choice to lead Teva into its next growth phase."

Dr. Levin was born in South Africa and has lived in the United States since 1986. In addition, he has lived in Zimbabwe, Great Britain, Switzerland, and Israel. He received an undergraduate degree from Oxford University in Zoology, masters and doctoral degrees from Oxford University in Molecular Biology, and a medical degree from Cambridge University. Among numerous honors, he was the 2005 recipient of the Albert Einstein Award for Leadership in Life Sciences, awarded by Shimon Peres. Dr. Levin has served as a practicing physician at University hospitals in South Africa, the United Kingdom, and Continental Europe. He and his wife, Margery Feldberg, have been married for 25 years and have two college-age daughters.

"I have known and admired Teva for many years, not just as a global leader in generic drugs, but as an outstanding innovator in pharmaceutical development and new strategic approaches to serve patients worldwide," Dr. Levin says. "Demographic trends and economic pressures in developed and emerging markets are intensifying the challenge to provide good medicines at affordable prices. Teva, with its multiple platforms in generics, branded, and OTC drugs, is in an especially good position to meet this challenge. It will be a privilege to work

with the talented and dedicated people of Teva to fulfill this mission."

Acquisitions and partnerships

Teva's largest M&A transaction in its history began last May, when the company's board approved a definitive agreement to acquire all of the outstanding shares of Cephalon for $81.50 per share in cash, or a total of about $6.8 billion. After passing through regulatory review, the deal was completed in October. The transaction, company leaders say, will reinforce Teva's long-term strategy of building out its branded and specialty pharmaceuticals business through diversification and expansion of its product portfolio and pipeline. The combined company will utilize its complementary commercial, R&D, and operational capabilities, and capture value by providing customers with a broad spectrum of specialty branded products. The combined company's branded portfolio represents about $7 billion in sales, with a pipeline of than 30 late-stage compounds. Teva leaders expect the deal to create immediate and sustainable value in niche therapeutic areas including CNS, oncology, respiratory, and pain management.

"We are embarking today on a new and exciting future for Teva's branded business, and we are delighted that we will be working together with the Cephalon team," said Shlomo Yanai, the outgoing president and CEO of Teva, on the announcement of the acquisition. "This is transforming for Teva's branded business, as it will help us to deliver on our strategic goal of creating a diversified, multi-faceted company. Our significantly broader portfolio will permit marketing and sales synergies and enhance profitability. We look forward to welcoming our colleagues at Cephalon to the Teva family."

Teva took two major steps to solidify its presence in Japan in mid-2011. In May, the company signed a definitive agreement to acquire 57 percent of the shares in privately held Taiyo Pharmaceutical Industry Co. for $460 million in cash paid to private shareholders. Teva also extended an offer to purchase all remaining outstanding shares of Taiyo. The deal duly closed in July, with Teva succeeding in acquiring 100 percent of Taiyo's outstanding shares for a total of $934 million.

Taiyo is the third largest generic pharmaceutical company in Japan with sales of $530 million in 2010. The company has one of the most comprehensive generic product portfolios in the Japanese market, with more than 550 generic drugs in a variety of therapeutic areas and dosage forms. The company has strong presence in all major distribution channels in Japan, particularly in hospitals due to its wide range of injectable product offerings. Taiyo's marketing efforts are supported by a strong back-end with top tier production capabilities in a wide range of technologies (including sterile manufacturing) in two manufacturing facilities, as well as a strong R&D team and local regulatory expertise.

"This acquisition will enable Teva to deliver on our strategic objective of becoming a leading player in the fast-growing Japanese generics market," Mr. Yanai says. "In fact, we now expect to reach our 2015 target of $1 billion in sales in Japan ahead of schedule. Taiyo's strong market reach, cutting-edge production facilities, and impressively large product portfolio, combined with Teva's scale and capabilities as the world's largest generics company, will enable us to offer a much wider range of high quality, affordable generics to a much larger segment of the Japanese market."

Then, in September, Teva acquired the 50 percent interest formerly held by **Kowa** Company Ltd. in Teva's Japanese joint venture for a total purchase price of $150 million. With this, Teva took over 100 percent of the venture, which immediately began to do business as a wholly owned member of the Teva Group.

Teva and Kowa announced the establishment of Teva-Kowa Pharma Co. in September 2008, and have since grown the joint venture into one of the top five generic players in Japan. The joint venture generated sales of about $200 million in 2010.

"We are happy to have reached this agreement to bring all our Japanese operations under Teva's full control and ownership," Mr. Yanai says. "Full ownership of all our activities including Taiyo will allow us to better grow our business in Japan. With this stronger platform, Teva will be in a better position to further drive penetration of high quality generic pharmaceuticals in Japan and make better healthcare accessible to the Japanese people."

In November, Teva and **Procter & Gamble** announced the creation of a new partnership and joint venture in consumer healthcare. The new venture, named PGT Healthcare, is headquartered in Geneva, Switzerland and will operate in essentially all markets outside of North America. The partnership between P&G and Teva will also develop new brands for the North American market.

PGT Healthcare, company leaders say, will focus on best-in-class development and state-of-the-art commercialization of branded OTC medicines. The venture will bring together each company's complementary capabilities and existing over-the-counter medicines. As a result, PGT Healthcare expects to accelerate growth for its parent companies and compete for leadership in the fast-growing $200 billion consumer healthcare industry. The partnership will start from a base of about $1.3 billion in annual sales, with the potential to grow to $4 billion in annual sales towards the end of the decade.

"This unique and transformational partnership creates one of the broadest and deepest OTC product portfolios and geographic footprints in the industry," Mr. Yanai says. "Each company's leading brands will experience tremendous growth by combining our strengths. We will be better together."

PGT Healthcare will be led by a management team comprising experienced senior leaders from both companies, including CEO Briain de Buitleir from P&G, and chief operating officer Eli Shani from Teva. A supervisory board representing both parent companies will govern the venture. Tom Finn, P&G's president of Global Health Care, will be chairman of the supervisory board. In connection with the formation of the new venture, P&G has sold its OTC plants in Greensboro, N.C. (Vicks production) and Phoenix, Ariz. (Metamucil production) and transferred the employees of both plants to Teva. As part of the partnership, Teva will be the manufacturer and supplier for the PGT Healthcare business and P&G's North American OTC business.

In March, Teva and **OncoGenex** Pharmaceuticals Inc. announced an update on their development program for **custirsen**, a product candidate being evaluated in Phase III studies for castrate-resistant prostate cancer. In a revised agreement between the two companies, the clinical trial program will now include the initiation of a Phase III study to evaluate if custirsen has the potential to improve survival rates for prostate cancer patients when combined with the recently approved, second-line chemotherapy drug Jevtana. The new trial, which aims to enroll about 630 men and is expected to begin later this year, will be conducted in lieu of the Prostate Cancer Saturn Study, a trial designed with a primary endpoint of measuring a durable pain palliation benefit for custirsen in second-line treatment of CRPC. The shift in focus to evaluate overall survival in second-line prostate cancer is a result of numerous, recently approved agents that are redefining the standard of care in this patient setting.

"The amendments made to the Phase III program reflect the rapidly evolving CRPC

Sales of the multiple sclerosis drug Copaxone grew by just over 20 percent in 2011, to $3.57 billion.

landscape and our commitment to ensure custirsen data are aligned with requirements to demonstrate improvements in survival across the treatment continuum," says Lesley Russell, senior VP, head of R&D for global branded products at Teva. "Developing custirsen for patients suffering from advanced prostate cancer remains a top priority within the Teva Oncology product-line and we believe this new trial is a reflection of that commitment."

This September was a particularly busy month for Teva's dealmakers, with four significant M&A transactions. First up, Teva and **Bayer** HealthCare LLC signed an agreement through which Bayer will acquire the U.S. based animal health business of Teva for up to $145 million. The purchase price includes an upfront payment of $60 million plus a total of $85 million in milestone payments, which are linked to the successful and timely achievement of manufacturing and sales targets. The deal, company leaders say, reflects Teva's commitment to focus its efforts on human health and its core expertise of providing generic and branded medicines to patients around the world. The transaction, encompassing a manufacturing site in St. Joseph, Mo. and about 300 employees, is expected to close in 2013, subject to antitrust clearance and satisfaction of other conditions.

"We are pleased with the sale of our animal healthcare business to Bayer HealthCare, a leader in animal healthcare," says Itzhak Krinsky, group executive VP and head of business development for Teva. "[This] transaction represents a successful outcome for both parties and is a part of our global strategic planning. We are committed to making disciplined decisions that focus on our core businesses and strategically position the company as setting a new standard in both generic and branded medicines. As part of our overall strategy to refine our global footprint, we will continue to leverage our product portfolio and R&D efforts while selling or outlicensing assets that no longer fit within the scope of our business."

Also in September, Teva signed a collaboration option to license and share purchase agreements to invest in **Cocrystal** Discovery Inc., a biopharmaceutical company focused on the discovery and development of novel antiviral therapeutics for the treatment of serious and chronic viral diseases. The investment will be utilized by Cocrystal to continue its development program of novel antiviral drugs that target viral replication enzymes. Currently, Cocrystal is using its technologies to develop oral, once-a-day, broad-spectrum antivirals for the treatment of hepatitis C, influenza, and rhinovirus (common cold).

Under the terms of the agreement, Teva will initially invest $7.5 million in Cocrystal, and the company will develop for Teva an antiviral drug targeting the polymerase enzyme of the hepatitis C virus. Upon completion of the initial development plan, Teva will have the option to make additional investments under certain milestones. Teva will have the right to exclusively license the drug for further development and commercialization, under agreed-upon commercial terms. Teva also has the option to further invest in Cocrystal for the development of two additional antiviral or antibacterial drugs. For all such investments, Teva will receive up to about 23 percent holdings in Cocrystal.

"This new partnership further illustrates Teva's commitment to develop innovative therapies," says Dr. Aharon Schwartz, head of Teva's Innovative Ventures. "If successful, these novel technologies could revolutionize the drug discovery process for antivirals, an area of a high unmet need. We believe this technology offers significant promise for pharmaceutical discovery in areas of strategic importance for Teva."

Also in September, Teva announced its decision to exercise an option to make an additional $19 million investment in **CureTech** Ltd., and to finance up to $50 million of the company's R&D program. Teva's decision follows the positive final results from a Phase II trial in diffuse large B-Cell lymphoma using CT-011, an investigational anti-PD-1 monoclonal antibody. The study met its primary end point and results showed significant improvement in both the overall survival and the progression-free-survival of the patients. Based on the Phase II results in DLBCL, CureTech intends to initiate a Phase III trial in this indication. A Phase II trial for colorectal cancer is on going, and CureTech intends to start a third Phase II trial in metastatic melanoma in the near future. Additional potential indications are also being explored. Under the terms of the recently amended agreements between Teva, CureTech, and its shareholders, Teva's investment will bring its holdings in CureTech to 75 percent. Teva holds the option to reach full ownership of CureTech.

"We are excited at this opportunity to continue working with CureTech on the development of CT-011," Dr. Schwartz says. "We believe CT-011 has great potential to help many currently unserved cancer patients. This investment is part of Teva's strategy to expand our branded activities into specialty therapeutic areas, such as oncology."

Closing out the month, Teva concluded an asset transfer agreement with **NeuroSearch** A/S to purchase all rights, assets, and obligations relating to **Huntexil**, a drug candidate being developed for the symptomatic treatment of hand movement, balance, and gait disturbances in Huntington disease. Under the agreement, Teva will pay NeuroSearch about $26 million over a period of at least six months. Regulatory and commercialization milestone payments may result in additional funding for NeuroSearch.

Previous trials in the United States, EU, and Canada demonstrated significant symptomatic relief for patients with Huntington disease, including improved hand movements and improved gait and balance. These results were observed without any side effects such as sedation and depression seen with other therapies such as neuroleptics and tetrabenazine.

"Based on the clinical trial evidence to date, we believe Huntexil holds promise for symptomatic relief for HD and merits additional study in late-stage clinical development," says Michael R. Hayden, M.D., Ph.D., president of global R&D and chief scientific officer of Teva. "Teva has a broad commitment to find new approaches to managing devastating CNS diseases, such as Huntington disease. This promising development for Teva is just one example of our covenant with patients to develop medicines to improve their quality of life all around the world."

Product performance

Although branded product revenue is now more than a third of Teva's top line, the company's generic portfolio still accounts for more than half of its sales, rolling up $10.2 billion in 2011, a 2.9 percent improvement over the previous year. In the first half of 2012, generic revenue

Q&A with Jeremy Levin

In an exclusive interview with *Med Ad News*, the recently-appointed Teva CEO discusses his new job, his company's strengths, and his vision of the industry's future.

Med Ad News: In taking stock of your first few months of leadership at Teva, what would you say your major accomplishments have been? What have you learned? What were the biggest surprises? What do you think still needs to be addressed?

Jeremy Levin: As I entered Teva, it was important to understand the core competitive advantages and culture of the company; core strengths of the leadership team; items that needed immediate attention; and most important, that I meet as many different employees as possible, ask them questions, let them ask me questions and understand the "soul" of the organization – what makes Teva truly unique. I wanted to clearly understand where I should most effectively spend my time. I also wanted to convey the fact that I came in with an open mind and would develop ideas about our future based on our interactions. With the help of the team, this was accomplished and allowed me to map out the critical actions and steps we needed to take for the immediate future.

I worked to develop relationships with all of Teva's key stakeholders – internally – our board of directors, senior management and employees at all levels of the organization. Externally, I spent time meeting with and listening to patients, customers, and shareholders to learn more about their interests and better understand their expectations of our company.

I believe it's important to listen, understand and communicate with our stakeholders – patients, employees, and shareholders. Each has perspectives and ideas that can help us to be more successful.

I was both pleasantly surprised and inspired to experience the determination and resolution our employees have to make Teva a truly special company. At every layer of this organization I found deeply committed employees dedicated to making quality medicines for patients and building a truly extraordinary company. Their belief in this company and our ability to do something both different and unique in our industry is unparalleled and a constant source of inspiration for me. They were waiting to take the next step and looking to the leaders of the company to show them the direction.

In other words, the fundamental aspects of the company – its people and culture – were waiting to drive it forward. The organization believes in and sees a company with an exciting future where much needs to be done to build on the successes of our past.

To encourage these values and to optimize the performance of the company, we created an internal strategic initiative, known as Project Spring. This initiative identifies areas for improvement, creates opportunities, solicits new ideas, and implements practical steps and recommendations across all parts of the organization. These initiatives were identified and generated based on my discussions with employees and are championed by leaders from all levels within Teva. Project Spring is a catalyst for how we enhance our organization and drive necessary change within Teva. Employees at all levels of the organization are encouraged to suggest how we can make improvements in our company and our systems, and our leadership takes ownership and accountability for solving major problems.

Some of the steps central to our strategy have already been taken, including globalizing certain functions, consolidating research and development, and recruiting or promoting new management. I fully expect that other core changes will occur throughout the remainder of 2012, and over the next several years.

Med Ad News: Before joining Teva you were a leader at Bristol-Myers Squibb, one of the "traditional" pharma giants. How would you compare the two companies? Any particularly striking differences?

Jeremy Levin: The global industry continuously evolves driven by, amongst other things, political, economic, social, and technological changes. Each company develops its own path. The true differentiator is how well companies adapt to change. BMS and Teva are two very different but both excellent companies. Teva's focus is to develop and manufacture medicines at reasonable prices for large populations across the globe. Each day, we serve over 116,000 patients in the United States alone! In addition, over the last five years Teva has faced significant changes in the differences in the markets it serves. These changes necessitate changes in the way we operate. Other large companies focus on developing and marketing medicines at higher prices with higher margins for smaller subsets of patients with significant diseases. Teva has a nearly unique circumstance in that our patients are in 120 countries, our portfolio consists of more than 1300 medicines, and our cultural diversity is unparalleled. This sets the stage for us to develop solutions to take advantage of the market evolution adapted to our particular circumstances.

In general however, there is one significant difference between Teva and all "traditional" pharma giants, to use your words. At Teva, we focus on "medicines," and not in terms of brand or generic drugs. Our focus is more attuned to access, distribution, manufacturing, and regional portfolio differentiation to meet the needs of different patient populations. We must be able to serve the needs of patients, customers, and other stakeholders in North America, Europe, South America, Asia, and Africa.

As part of this focus on medicines we recently established, for the first time in the industry, one R&D division for the entire company, combining Generic with Branded R&D, led by Dr. Michael Hayden. We deploy common technologies and remove an artificial barrier in the industry that implies there is "innovation" only on one side of the business. We believe that through our focus on the patient and unmet medical need, in R&D we can achieve greater success for our patients.

Med Ad News: Tell us a little more about Jeremy Levin the person. What are the decisions, principles, experiences, and inspirations that enabled you to reach the top echelon of corporate management? How do you maintain a good work-family balance with such a high-profile, high-stress job?

Jeremy Levin: I am driven by a philosophy based on a covenant I have adopted that underlies my thinking as it pertains to development and commercialization of medicines for patients. The covenant is one where I believe that a company takes deep responsibility for and is committed to excellence and quality in all aspects of our actions, products, and interactions with third parties, particularly patients and customers that provide access to medicines for them. Effective medicines, and the industry that develops them, are important to the wellbeing of patients, their families, societies, and nations. This philosophy began when I treated patients as a medical doctor in specialty and rural hospitals in developed and developing nations, and continues to drive me today. I am deeply honored to be able to work in and contribute to this industry. When we develop, manufacture, and distribute our products, it must be done with the needs of our patients as the top priority. Our focus on research and development, quality, service, and pricing all must come together in a way that supports that philosophy.

Our intent is to build a company that is differentiated from other companies, built on the philosophy of that covenant with our patients. With that basic principle as our foundation, coupled with excellence in execution, we will help drive sustainable growth and shareholder return.

Work-life balance is very important for me personally, as a father, husband, and as a leader of a company, I try to emphasize this to our employees as well. I believe that one's mind is refreshed when you've created the right balance between work and how you enjoy yourself outside of work. That balance is critical to being successful in anything you do.

I am deeply impressed and humbled by the support given to me by my wife, daughters, family, and friends around the world who know that my intent is to create something that is philosophically sound, sustainable, and helps solve truly important needs in society. The support of my family is vital. We try to spend as much time together as possible, even as my children establish their own exciting and independent lives. What's really important is to share experience as often as possible. The Internet and Skype allows me to spend time with my family no matter where I am in a way that was not possible years ago. They are probably a little fed up with the photographs of foreign countries I am visiting!

Med Ad News: Describe a typical day for you. When does it start and end? Are you checking your Blackberry or iPhone as soon as you wake up for the most recent headlines or emails? What are your favorite sources of information? How many meetings a day are you involved in? Where are you spending your time?

Jeremy Levin: In Israel, my typical day starts at 5 am. If I am able to, I'll go for a run or a bike ride. The mornings in Tel Aviv are beautiful. I then check my Blackberry, chat with my wife, and by 7 am, I am on my way into the office. I spend the vast majority of my day in meetings and discussions with both internal and external colleagues. I balance my internal meetings between senior management and people in different parts of the business so I can learn about their interests and expertise, which enables me to understand how we can make Teva even more special together. I have lunch most days in the employee cafeteria at one of our facilities in Israel or elsewhere, where I'll sit with different employees and spend time getting to know them. In the evening, I usually have a business dinner to attend. In Israel, the work week is Sunday to Thursday; however, around the world, Friday is still a work day. I try to find balance with that schedule to support the business as needed, but still spend time with my family and friends on the weekend.

Med Ad News: Teva's big splash in the M&A world of late was its acquisition of Cephalon last October. How is the integration coming along, and what are next steps?

Jeremy Levin: The integration has progressed very well. The next steps are to define the portions of the pipeline that fit with our strategic vision. Dr. Michael Hayden was brought on this year as our Global Head of R&D. He continues to work through this process and we look forward to sharing the results later this year.

We also recently announced an Asset Transfer Agreement with NeuroSearch A/S of Denmark to purchase all rights, assets, and obligations relating to Huntexil (pridopidine / ACR16), a drug candidate being developed for the symptomatic treatment of hand movement, balance, and gait disturbances in Huntington disease. Teva has a deep expertise in neurodegenerative disorders, and we plan to pursue this area as one of a few select areas of R&D. We will seek to complement our internal pipeline and find complementary medicines or programs based on mechanisms that we believe we can impact a disease.

Med Ad News: We've noticed a number of high-level appointments at Teva over the past few months, including a new president of global operations and chief scientific officer. What goes into your choice of the company's new leaders? Are there particular characteristics or backgrounds you are seeking? A particular overarching strategy of leader selection?

Jeremy Levin: We are revitalizing and increasing the capabilities of the company on many levels to meet the needs of our evolving environment. We have moved employees to different roles and brought in new talent. This dynamic will continue. Whether we appoint from within or recruit externally it is essential that our senior leaders have an extensive professional expertise for the roles they take, have broad global experience, a desire to help build managerial capability second to none, and have the goal to aggressively build a unique company. These individuals must be willing and able to develop their employees both through training and development as well as encouragement to go the extra mile and put forth the extra effort. I believe that nurturing employees is vital to the success of the company – it helps bring forth new ideas and better ways of doing things. Ultimately, however, it's most important to me that each of these individuals be responsible, accountable, and team players – that they work together to take Teva to the next level.

Med Ad News: Not as many CEOs of big pharma companies come from clinical backgrounds as used to be the case. How do you think your clinical/academic background plays into your decision-making at Teva today?

Jeremy Levin: I believe that a focus on helping people is fundamental to anyone who works in our industry. We make medicines for patients – and each and every employee in our industry should take that responsibility seriously. If an individual leader of a company sees the patient only as a revenue source, they can't truly understand the value of the business they run. My background provides me with great insight into this important aspect of our industry, and helps me build the fundamentals of a sustainable, long-term business. Being a doctor has allowed me to see different strengths and capabilities that I can bring to patients around the world.

I also believe that companies need to give back to the communities in which they operate and where their employees live and work. There must be an ongoing dialog between the company and the community, including patients, customers, and other stakeholders. For Teva, that community is truly global. As a doctor I worked with patients on several continents. This provides me with a very helpful insight into how we as a company need to think and operate in different cultures.

Being a physician also allows me to think about medicines as distinct from other products. As I meet with leaders around the world, pricing is often at the top of the list of topics they wish to discuss. It is incumbent upon us to find the right balance between access and making high-quality medicines for our patients. I often use the analogy of shopping for shoes to describe this. When you buy an inexpensive shoe, you have an expectation that it will last for a short period of time; conversely, if you buy an expensive shoe, you expect

it will last for much longer. A different profile but the same product. With medicine, an inexpensive medicine must have the same impact as an expensive one – they must all work equally well and have high quality and safety built into the production of each and every part of that medicine. There is no margin for error, no place to "cut corners" in this process, no place for a lesser product. It must be the same product with the same profile. As a socially responsible company, it is incumbent upon us to find the delicate balance between pricing, access, innovation, and production. This is a task we take very seriously.

Med Ad News: What do you believe is the future of innovative research at Teva? What areas of the pipeline do you think are particularly promising?
Jeremy Levin: I am extremely excited about several areas of our research. In one, neurology and the neurodegenerative arena, we have great historical strengths. As you know, we currently have a great product for CNS in our portfolio, Copaxone. This product is considered by many patients to help them manage their RRMS. The product has a demonstrated safety profile and I couldn't be more proud to meet patients every day who thank Teva for this great product. Copaxone continues to be the most-prescribed RRMS treatment worldwide. Copaxone continues to be developed.

The recent results from the GALA trial showed that three times a week dosing with an investigational 40 milligram formulation of Copaxone met the primary endpoint of significant relapse rate reduction. This is yet another step forward in our ability to provide patients with medicines that meet their needs. We will continue to build on our CNS franchise. As we move forward, we will carefully use our R&D funds to invest in medicines that can make a true difference in a patients' life. We intend to be highly focused in our approach to R&D, and I look forward to sharing more information on this approach in the future.

I'm also extremely excited about laquinimod – I believe this is a very special asset in our pipeline. What is remarkable about this asset is that many of its modes of action and its ability to prevent inflammatory changes are potentially extrapolatable to some of the more common and serious disorders for which there are few or no therapies, including some of the neurodegenerative disorders.

Med Ad News: What are some of the harder decisions you've had to make so far, and what do you believe will be the hard choices you and other industry leaders will have to make in the future?
Jeremy Levin: As a leader, I believe the hardest decisions you make are related to your people; however, this is where you have the greatest impact and responsibility. The most difficult tasks in the near term were to find the right fit for really good, loyal employees who'd been placed in the wrong positions within the company. These were great employees who had been given positions that didn't showcase their talent and allow them to fully contribute to the organization. I have made several moves in this regard and will continue to make these moves until we have a management team across the entire organization that can enhance and drive our strategic goals while fulfilling their life's ambitions.

As an industry, I believe the greatest challenge we have is to address the image of the pharmaceutical industry and its interactions with society. We must recognize the extensive changes occurring in societies and economies across the world, make structural changes, invest in differentiated medical needs, and communicate clear commitment to link value to effectiveness. We need to address how our patients, policy makers, and society view us.

In addition, to be truly effective as an industry and serving the needs of patients and societies we need to find the synergy between both the brand and generic portions of the industry. We've seen this synergy between biotech and brand companies, and we need to see more of it throughout our industry. Both brand and generic companies need to look for opportunities to collaborate if they want to serve the burgeoning populations who face both economic and social change.

Med Ad News: What will the Teva of the future look like?
Jeremy Levin: I firmly believe Teva's future is very bright and the changes we have embarked on require very hard work. We will be global, include many of the elements which made us strong in the past and many more which will make us stronger in the future. We will deliver medicines to all portions of the globe. I am privileged to lead this company and help drive change in what I believe is a unique entity with unique opportunity. Patients across the globe will benefit, our shareholders will benefit. It is my hope that we as employees will look back in pride at the impact we have had, not just on the company but on the industry and the societies we live in.

rose another 10.4 percent to $5.23 billion. Teva has launched a long list of new generics over the past year, including the former multi-billion-dollar sellers Zyprexa (October 2011), Lipitor (December 2011), Lexapro (March 2012), Seroquel (March 2012), Avapro (August 2012), and Actos (August 2012).

Dollar for dollar, though, Teva's most impressive growth engine in 2011 was its leading branded product, **Copaxone**. The company's multiple sclerosis drug generated $3.57 billion in sales for the year, an improvement of 20.1 percent. In October, results from a five-year study of treatment-naïve patients with relapsing-remitting multiple sclerosis demonstrated that patients treated with Copaxone showed significant reduced loss of brain volume compared to patients treated with other disease modifying therapies. Though all DMT treatment arms resulted in a reduction in brain volume loss compared to the control group of non-treated patients, Copaxone had a significantly better effect than both low and high dose interferons, in reducing loss of brain volume.

"These data represent the importance of ongoing research in a practical clinical setting to better understand multiple sclerosis and the impact of therapy on the course of the disease," says Jon Congleton, senior VP and general manager, Teva Neuroscience. "Not only does this study highlight the benefit of Copaxone in reducing brain volume loss, it underscores the value of early treatment in influencing long-term outcomes."

The positive news for Copaxone has continued into the new year. In February, Teva completed the assumption of marketing responsibility for Copaxone from **Sanofi** in Europe, and in March the company assumed marketing responsibility in Australia and New Zealand, both of which are expected to increase net sales of the drug for Teva. In April, interim data from a prospective, open label survey study evaluating spasticity in patients with relapsing-remitting multiple sclerosis who transitioned to Copaxone from interferon-beta treatment revealed a significant reduction in muscle stiffness, pain, and discomfort, as well as the effect of spasticity on the ability to walk, body movements, and activities of daily living. Improvement was also found in reduction of total spasticity scores during the six month period. Then, in June, top-line results from the GALA Phase III clinical trial assessing the efficacy, safety, and tolerability of 40 mg/1 ml Copaxone injection administered subcutaneously three times a week compared to placebo in relapsing-remitting multiple sclerosis patients showed that Copaxone 40 mg/1 ml significantly reduced disease activity, while maintaining a favorable safety and tolerability profile. The 40 mg/1 ml dose is higher than the currently marketed 20 mg/1 ml daily Copaxone dosage. Perhaps helped by this positive news, Copaxone sales rose another 10.3 percent in the first six months of 2012 to $1.89 billion.

The sleep disorder drug **Provigil** joined Teva's portfolio in October with the acquisition of Cephalon. Provigil generated an estimated $1.08 billion in sales in 2011, mostly for Cephalon, but the product won't be performing so well in 2012; Teva itself launched an authorized generic in March. Provigil sales in the first half of 2012 totalled $339 million, while sales of the the follow-on to Provigil, **Nuvigil**, were $175 million. Nuvigil is expected to maintain its patent protection until June 2016.

Treanda, a cancer drug also acquired in the Cephalon deal, generated an estimated $502 million in sales in 2011. The compound is approved in the United States for the treatment of patients with chronic lymphocytic leukemia and patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. Teva is conducting a Phase III clinical trial of Treanda in combination with Rituxan as a frontline treatment for NHL. In December, the company submitted results of another Phase III study to FDA as an sNDA for Treanda for the treatment of frontline indolent B-cell NHL. Also in December, Teva submitted a request to FDA for pediatric extension for Treanda. If the pediatric extension is granted, the exclusivity for Treanda will be extended until September 2013. For the first half of 2012, Treanda sales totalled $287 million, an improvement of about 18 percent.

Several of Teva's other branded products have also enjoyed strong growth of late. **ProAir**, the company's short-acting beta-agonist for asthma, COPD, and exercise-induced bronchospasm, grew its sales by 10.1 percent to $436 million in 2011, maintaining a market share of just over 50 percent in the short-acting beta-agonist market; the product generated another $177 million in sales in the first half of 2012, about the same as the first half of the previous year. The inhaled corticosteroid **Qvar**, indicated for long-term control of bronchial asthma, brought in $305 million in sales in 2011, good for growth of 22 percent and a market share of 23.6 percent in its category; Qvar sales in the first half of 2012 also remained steady at $143 million. Finally, the Parkinson's disease drug **Azilect** generated $290 million in sales for full-year 2011, an improvement of 18.9 percent; the product's sales in the first half of 2012 rose another 22.8 percent to $167 million.

In the pipeline

Teva spent $1.1 billion on R&D in 2011, 15.1 percent more than the previous year. In the first half of 2012, R&D expenses rose another 22.4 percent to $590 million.

In September 2011, Teva and **Alcobra** Ltd. announced top-line results from a six week, randomized, placebo-controlled, Phase II multicenter study designed to assess the safety and efficacy of **MG01CI** in adults with attention deficit hyperactivity disorder. Results showed MG01CI met the primary efficacy outcome, demonstrating a significant improvement on the Conners' Adult ADHD Rating Scale-Investigator Rated Total ADHD Symptoms Score (CAARS-INV) compared to placebo.

In the study, 56 percent of subjects treated with MG01CI experienced an improvement in their CAARS-INV score of at least 25 percent, compared to 36 percent of patients in the placebo group. Additionally, 44 percent of the subjects treated with MG01CI demonstrated an improvement of more than 40 percent in their CAARS-INV score, versus only 25 percent in the placebo group. MG01CI was well tolerated, with no drug-related serious adverse events reported and no clinically or statistically significant differences in adverse event profiles between the MG01CI and placebo treatment arms. Importantly, no increase in blood pressure or appetite suppression was recorded in the treatment group.

"Our collaboration with Alcobra on the development of MG01CI for ADHD complements Teva's focus on developing a portfolio of products within our core specialty area of expertise - neurological disorders," Dr. Schwartz says.

In March, Teva and partner developer **Active** Biotech announced the publication of results from the laquinimod Phase III ALLEGRO study in the New England Journal of Medicine. Data from the two-year study showed that oral once-daily **laquinimod** reduced inflammatory disease activity as measured by clinical relapses and MRI, slowed disability progression, and decreased brain tissue loss, while maintaining a favorable safety and tolerability profile in patients with relapsing-remitting multiple sclerosis.

"The publication of the ALLEGRO results in a prestigious peer-reviewed journal is an important landmark as we continue to research and develop laquinimod," Ms. Russell says. "We look forward to continuing to work with regulatory authorities in both the EU and the United States to bring this novel therapy to the MS community."

Five months later, Teva and Active Biotech provided an update on the clinical development program of once-daily oral laquinimod for the treatment of relapsing-remitting multiple sclerosis. The companies plan to initiate a third Phase III study of laquinimod, following the written agreement reached with FDA on the Special Protocol Assessment. The third Phase III laquinimod trial, CONCERTO, will evaluate two doses of the investigational product (0.6 milligram and 1.2 milligrams) in about 1,800 patients for up to 24 months. The primary outcome measure will be confirmed disability progression as measured by the Expanded Disability Status Scale.

"The results achieved in the previous Phase III trials of laquinimod support the clinical utility of this compound as a unique treatment option for multiple sclerosis," Dr. Hayden says. "We are encouraged by FDA's agreement on the trial design and planned analysis, and look forward to further developing laquinimod as a potential treatment option for RRMS patients."

In July, Teva presented clinical results for two of its biologic oncology candidates, **lipegfilgrastim** and **balugrastim**. Both compounds are long-acting granulocyte colony-stimulating factors (G-CSF) being evaluated for their ability to reduce the duration of severe neutropenia in breast cancer patients undergoing chemotherapy. Neutropenia is a condition in which the number of white blood cells is decreased, leaving patients more susceptible to potentially life-threatening bacterial infections. Both product candidates have completed Phase III clinical trials. In both Phase III breast cancer studies the primary endpoint was achieved, demonstrating reduction in the duration of severe neutropenia in cycle 1, comparable to pegfilgrastim results in both efficacy and safety measures.

"Teva is committed to advancing these investigational biologic drugs, which are the most advanced of several biologic products that we have in development," Dr. Hayden says. "Biologics constitute one of the fastest growing segments of the global pharmaceutical market, aimed at offering safe and effective approaches for patients with few therapeutic options." ■ MEDADNEWS

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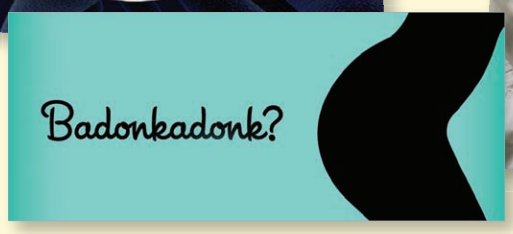

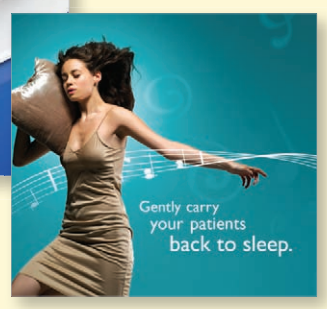

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