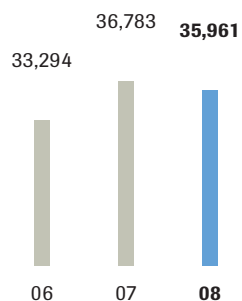


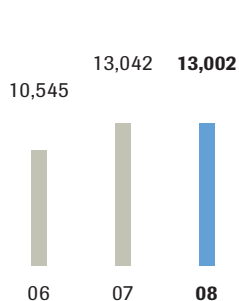
Pharmaceuticals | *In 2008 the division again delivered strong underlying sales and operating profit growth while advancing key projects in its promising R&D portfolio. Roche will continue to develop clinically differentiated solutions that address significant unmet needs in the treatment of cancer and other complex diseases. The Roche Group's Pharmaceuticals Division is made up of Roche Pharmaceuticals, represented in over 150 countries, and majority shareholdings in Genentech in the United States and Chugai in Japan.*

Pharmaceuticals Division in brief

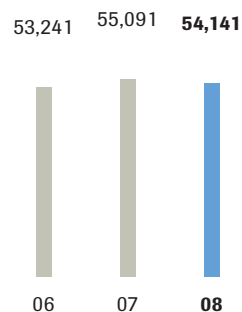
Sales | in millions of CHF



Operating profit | in millions of CHF



Number of employees



Key figures

	In millions of CHF	% change in CHF	% change in local currencies	% of sales
Sales	35,961	-2	5	100
– Roche Pharmaceuticals	22,164	-4	3	62
– Genentech	10,461	0	11	29
– Chugai	3,336	-2	-4	9
Operating profit	13,002	0	8	36.2
Operating free cash flow	12,053	20	31	33.5
Research and development	7,904	4	11	22.0

Pharma Executive Committee | 31 December 2008

William M. Burns	CEO Division Roche Pharmaceuticals
George B. Abercrombie	North America
Jennifer M. Allerton	Informatics
Silvia Ayyoubi	Human Resources
Lee E. Babiss	Pharma Research
Henry-Vincent Charbonné	Strategic Marketing
Jean-Jacques Garaud	Development
Peter Hug	Western Europe
Jonathan K.C. Knowles ¹	Group Research
Dominic P. Moorhead	Finance and Controlling
Christopher Murray ¹	Commercial Operations, Chugai
Pascal Soriot	Commercial Operations
Jan van Koeveringe	Global Technical Operations
Daniel Zabrowski	Pharma Partnering

¹ Extended team.

The Pharmaceuticals Division again delivered strong performance in 2008. Excluding pandemic sales of Tamiflu, pharmaceutical sales grew around twice the global market growth rate. The division's operating profit also increased strongly.

Pharmaceuticals Division

In 2008 the Pharmaceuticals Division translated strong underlying sales growth into a strong increase in operating profit. In addition, the division passed key regulatory and development milestones in projects expected to support the Roche Group's future growth. The most important of these are the marketing approvals gained by Chugai and Roche for their novel rheumatoid arthritis medicine Actemra/RoActemra in Japan, Switzerland and the European Union. Ongoing development of key marketed products resulted in regulatory filings and approvals in important new indications for MabThera/Rituxan and Avastin in the United States and the European Union. The division initiated twelve major new phase III projects in 2008, including clinical trials of the novel compounds pertuzumab, for breast cancer, taspoglutide, for type 2 diabetes, and dalcetrapib, for cardiovascular risk reduction. With a diversified pipeline of major line extensions and innovative new molecular entities in late-stage development, the division has unique opportunities for sustained growth in the years to come.

Results

The Pharmaceuticals Division maintained its strong performance throughout 2008, with solid growth of the underlying business more than compensating for the expected sharp decline in pandemic sales of Tamiflu to governments and corporations. Divisional sales increased 5% in local currencies (-2% in Swiss francs; 8% in US dollars) to 36.0 billion Swiss francs.¹ Excluding pandemic sales of Tamiflu, pharmaceutical sales grew 10% in local currencies, or around twice the global market growth rate – the sixth double-digit increase in as many years. Growth was driven primarily by key products in the division's oncology, inflammation and transplant, virology and metabolism/bone portfolios (for full-year sales and growth rates of individual products, see below and table, 'Top-selling pharmaceutical products – Roche Group', p. 39). On the same basis, the division recorded above-market growth in all key

Sales by region

North America	41%	(+5%)
Asia-Pacific	5%	(+6%)
Latin America	6%	(+15%)
Others	1%	(-1%)
CEMAI	9%	(+5%)
Western Europe	29%	(+5%)
Japan	9%	(-4%)

Italics = growth rates

CEMAI: Central and Eastern Europe, Middle East, Africa, Central Asia, Indian Subcontinent.

regions. The division's sales performance is broadly based: in 2008 nine products generated annual turnover of more than 1 billion Swiss francs each, three of which achieved sales of over 5 billion francs each.

In 2008 the Pharmaceuticals Division's operating profit advanced even faster than sales, rising 8% in local currencies (0% in Swiss francs) to 13.0 billion Swiss francs. The corresponding margin increased 0.7 percentage points to 36.2% compared with 2007 despite significantly lower Tamiflu pandemic sales and increased investments in research and development. For more information on the division's operating results, see p. 5 of the Finance Report (Part 2 of this Annual Report).

Therapeutic areas

Oncology – key products post sustained double-digit growth

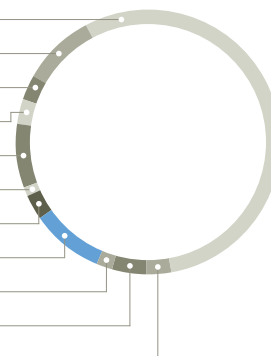
Cancer | According to the latest International Agency for Research on Cancer estimate, in 2008 over 12 million people worldwide were diagnosed with cancer, and some 7.6 million died of the disease. The IARC anticipates that cancer will

¹ Unless otherwise stated, all growth rates are in local currencies.

In 2008 Roche continued to strengthen its position as the world's leading supplier of medicines to treat cancer.

Sales by therapeutic area

Oncology	55% (+15%)
Inflammatory and autoimmune diseases, transplantation	9% (+19%)
Central nervous system	3% (-3%)
Respiratory	3% (+10%)
Metabolic diseases, bone diseases	8% (+7%)
Infectious diseases	1% (-12%)
Cardiovascular diseases	3% (-19%)
Virology	9% (-27%)
Others	2% (-14%)
Renal anemia	4% (-11%)
Ophthalmology	3% (+7%)



Italics = growth rates

surpass heart disease as the leading cause of death worldwide in 2010 and also forecasts that by 2030 there will be over 26 million new cases and 17 million deaths per year from cancer. In Europe alone, one in three people can expect to develop cancer in their lifetime. Cancer is not one disease but a group of more than 100 distinct disorders, each with its own medical challenges.

In 2008 Roche continued to strengthen its position as the world's leading supplier of medicines to treat cancer. Sales of the Pharmaceuticals Division's oncology portfolio² rose 15% to 19.7 billion Swiss francs for the year, or 55% of total pharmaceutical sales, with all key brands contributing double-digit growth. Just as importantly, the Group advanced key development programmes and filed marketing applications aimed at making more effective treatment options available to doctors and cancer patients or expanding the range of conditions for which innovative medicines such as MabThera/Rituxan, Avastin, Herceptin, Tarceva and Xeloda can be prescribed.

Non-Hodgkin's lymphoma | A group of over 30 cancers that affect the lymphatic system. This class of cancer has grown in incidence by

80% since the early 1970s and currently affects over 1.5 million people worldwide.

Chronic lymphocytic leukemia | The most common type of leukemia in adults, accounting for approximately 25–30% of all forms of leukemia. The incidence of CLL in Western countries is around 2–4 per 100,000, and it is twice as common in men as in women.

MabThera/Rituxan (rituximab) is the leading treatment for patients with non-Hodgkin's lymphoma (NHL) and the first and only selective B cell therapy approved for the treatment of rheumatoid arthritis (see p. 44). In 2008 combined sales of the product in the oncology and inflammation/autoimmune segments grew 16% versus the prior-year period to 5.9 billion Swiss francs. Strong to solid growth was recorded in Europe/Rest of World (RoW)³ (19%), the US (14%) and Japan (10%). Growth in oncology is being driven by sustained expansion in the use of MabThera/Rituxan for induction and maintenance

² Oncology portfolio (main products): MabThera/Rituxan, Herceptin, Avastin, Tarceva, Xeloda, NeoRecormon, Kytril, Neutrogen, Neupogen, Bondronat, Roferon-A, Furtulon, Vesanoid.

³ Roche defines Europe/Rest of World as covering Europe and all other countries except Japan and the United States.

All of the division's key cancer medicines contributed double-digit sales growth. In addition, Roche and its partners achieved important milestones in the development of MabThera/Rituxan, Avastin, Herceptin, Tarceva and Xeloda in new treatment indications.

therapy of NHL and improved access in emerging markets for all approved indications.

During the year Roche and its partners, Genentech and Biogen Idec, achieved important milestones in the ongoing development of MabThera/Rituxan. In January Roche announced results of a major phase III trial (CLL8) of MabThera as first-line treatment for chronic lymphocytic leukemia (CLL). The study showed that combined treatment with MabThera and the current standard chemotherapy achieved significantly better outcomes than chemotherapy alone. Roche used these data to support an application, filed in July, to add this new indication to the medicine's EU marketing authorisation. In January 2009 the EU's Committee for Medicinal Products for Human Use (CHMP) recommended approval of MabThera in this indication. In December Roche received approval in Switzerland for MabThera as initial (first-line) treatment in certain patients with CLL.

In October a study of MabThera/Rituxan in patients with relapsed or refractory CLL (REACH) met its primary endpoint, demonstrating that patients treated with MabThera combined with the current standard chemotherapy showed a significant improvement in progression-free survival (the time patients live without their cancer getting worse) compared with those who received chemotherapy alone. These data formed the basis for a regulatory filing in the EU for this indication, submitted by Roche in January 2009. The results of CLL8 and REACH were presented at the American Society of Hematology annual meeting in December. Genentech and Biogen Idec are evaluating the data from both trials and expect to submit supplementary Biologic License Applications for these indications in the US by the third quarter of 2009.

Colorectal cancer | Cancer of the large intestine or rectum, which accounts for over 1 million new cases (around 10% of all newly diagnosed cancers) worldwide each year. It is the second most common cause of cancer deaths in Europe and the third most common worldwide.

Kidney cancer | This type of cancer is newly diagnosed in around 200,000 people and causes 100,000 deaths worldwide every year, rates that are expected to increase. Renal cell carcinoma accounts for 90% of all kidney cancers.

Global sales of Avastin (bevacizumab), the world's leading antiangiogenesis treatment for advanced colorectal, breast, lung and kidney cancer, rose strongly throughout 2008, advancing 37% to 5.2 billion Swiss francs, with all key regions contributing. Dynamic sales growth in Europe/RoW (67%) was driven primarily by increased use of the medicine for metastatic colorectal and breast cancer. Sales in Europe also benefited from the rollout of new indications and increasing uptake for non-small cell lung cancer and renal cell carcinoma. In the United States solid double-digit growth continued (17%), driven primarily by increased use in metastatic non-small cell lung and in metastatic breast cancer following accelerated approval by the US Food and Drug Administration (FDA). In Japan, where Avastin is approved for metastatic colorectal cancer, sales continue to grow strongly.

Avastin received additional regulatory approvals in key markets during the year. In January the EU authorities approved an extension of the product's metastatic colorectal cancer indication, permitting the combination of Avastin with the most commonly used chemotherapy regimens in all lines of treatment. As a result, virtually all patients with metastatic colorectal cancer can now have access to the proven survival benefits of Avastin. In February Genentech received accelerated approval from the FDA for Avastin, in combination with paclitaxel chemotherapy, for the first-line treatment of patients with HER2-negative metastatic breast cancer.

In July Roche filed an application to expand and update the current EU approval for Avastin in metastatic breast cancer with final data from the AVADO study, which were also presented at the 2008 meeting of the American Society of Clinical Oncology (ASCO) in June. This phase III clinical study confirmed the

In 2008 nine pharmaceutical products generated sales of more than 1 billion Swiss francs each, including three with sales of over 5 billion francs each.

Top-selling pharmaceutical products – Roche Group

Product	Active substance	Indication	Sales in millions of CHF	% change in local currencies
MabThera/Rituxan	rituximab	non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis	5,923	16
Avastin	bevacizumab	colorectal cancer, breast cancer, non-small cell lung cancer, kidney cancer	5,207	37
Herceptin	trastuzumab	HER2-positive breast cancer	5,092	12
CellCept	mycophenolate mofetil	transplantation	2,099	13
NeoRecormon, Epogin	epoetin beta	anemia	1,774	-13
Pegasys	peginterferon alfa-2a	hepatitis B and C	1,635	6
Tarceva	erlotinib	advanced non-small cell lung cancer, advanced pancreatic cancer	1,215	23
Xeloda	capecitabine	colorectal cancer, breast cancer, stomach cancer	1,211	13
Bonviva/Boniva	ibandronic acid	osteoporosis	1,108	35
Lucentis ¹	ranibizumab	wet age-related macular degeneration	960	7
Tamiflu	oseltamivir	treatment and prevention of influenza A and B	609	-68
Xolair ¹	omalizumab	asthma	560	10
Valcyte, Cymevene	valganciclovir, ganciclovir	cytomegalovirus infection	553	10
Xenical	orlistat	weight loss, weight control	502	-13
Pulmozyme	dornase alfa/DNase	cystic fibrosis	496	12
Nutropin	somatropin	growth hormone deficiency	413	-2
Neutrogin	lenograstim	neutropenia associated with chemotherapy	404	-3
Rocephin	ceftriaxone	bacterial infections	344	-10
Activase, TNKase	alteplase, tenecteplase	acute myocardial infarction (heart attack)	342	-1
Madopar	levodopa + benserazide	Parkinson's disease	311	4

¹ Jointly marketed by Genentech and Novartis.

results of an earlier trial (E2100), showing that Avastin combined with taxane chemotherapy significantly improves progression-free survival in this setting. In September Genentech filed a supplementary application with the FDA for approval of Avastin in combination with interferon alfa to treat advanced renal cell carcinoma. In November Genentech also applied for US approval of the medicine as monotherapy for people with previously treated (relapsed) glioblastoma, the most aggressive form of brain tumour, based on positive results from a phase II clinical trial (BRAIN). Roche applied for EU approval of Avastin alone and combined with chemotherapy for the same indication in December. In November Chugai filed a supplementary application in Japan

for expansion of the product's marketing approval to include non-small cell lung cancer.

Other important clinical data on the benefits of Avastin in breast and lung cancer were published during the year. In November Roche announced that a phase III trial (RIBBON-1) investigating Avastin in first-line metastatic HER2-negative breast cancer in combination with commonly used chemotherapies met its primary endpoint of increasing the time women with breast cancer lived without their disease advancing (progression-free survival) compared with chemotherapy alone. After AVADO and E2100, RIBBON-1 is the third study to confirm the benefit of Avastin combined with chemotherapy for women

with metastatic breast cancer. In October Roche announced the first results from a phase III study (BeTa Lung) investigating the use of Avastin plus Tarceva for the second-line treatment of patients with advanced non-small cell lung cancer. While the combination did not meet the primary endpoint of overall survival, there was clear evidence of clinical activity, with improvements in the secondary endpoints of progression-free survival and response rate when Tarceva was added to Avastin.

Breast cancer | The most common cancer among women worldwide. Over 1 million women are newly diagnosed and over 500,000 die from the disease each year. As there are several different types of breast cancer, knowledge of tumour characteristics is important for treatment decisions. Some 20–30% of women with breast cancer have tumours with abnormally high levels of a protein known as HER2. HER2-positive tumours are particularly aggressive, fast-growing and likely to relapse.

Herceptin (trastuzumab), for early and advanced HER2-positive breast cancer, posted solid double-digit sales growth (12%) throughout 2008, for a total of 5.1 billion Swiss francs. Growth was especially strong in Japan (47%) due to continuing uptake after approval of Herceptin for early breast cancer in February. Solid single-digit growth was recorded in the United States (7%), while double-digit gains were achieved in Europe/RoW (13%). The main contributions to growth in the latter region came from the CEMA⁴ countries and key emerging markets. More modest growth in the US and Western Europe reflects the product's high market penetration in these regions, particularly in the early breast cancer setting. Adoption of Herceptin for metastatic breast cancer remained stable. In January the FDA approved the use of Herceptin as a single agent for the adjuvant treatment of HER2-positive breast cancer following multimodality anthracycline-based therapy. In May Genentech received FDA approval for a supplemental regimen for adjuvant HER2-positive breast cancer combining Herceptin with docetaxel and carboplatin chemotherapy. This

combination has been shown to reduce the rate of heart problems observed when Herceptin is given with anthracycline-containing regimens, thereby potentially allowing more patients to benefit from Herceptin.

The final analysis of a phase III trial (GBG-26), presented at ASCO 2008 in June, confirmed that Herceptin helps women with metastatic HER2-positive breast cancer live longer without their cancer progressing (progression-free survival). The results also showed that Herceptin continued to be effective in women who needed additional treatment after their cancer progressed during previous Herceptin treatment. Results of the Gepar-Quattro and NOAH trials presented at medical conferences in April and December, respectively, showed that Herceptin, given in combination with standard chemotherapy before surgery (known as neoadjuvant therapy), helps shrink locally advanced tumours, enabling breast-conserving surgery and improving long-term outcomes. Final analysis of the NOAH data showed that adding Herceptin to chemotherapy eradicated the tumour in nearly twice as many patients as treatment with chemotherapy alone.

Lung cancer | The most common form of cancer worldwide and the leading cause of cancer deaths. There are an estimated 1.4 million new cases annually. Non-small cell lung cancer is the most common form, accounting for approximately 80% of all cases.

Pancreatic cancer | A particularly aggressive disease that is extremely difficult to treat. It kills a higher proportion of patients in the first year after diagnosis than any other cancer. The fifth leading cause of cancer deaths in the developed world, pancreatic cancer claims nearly 80,000 lives every year.

⁴ Central and Eastern Europe, Middle East, Africa, Central Asia, Indian Subcontinent.

Tarceva (erlotinib) is the only oral medicine targeting the epidermal growth factor receptor with proven and significant survival and symptom benefits in a broad range of patients with non-small cell lung cancer (NSCLC). Since its initial launch four years ago, Tarceva has been approved in over 90 countries and used to treat more than a quarter of a million patients. In addition, in combination with chemotherapy, Tarceva is the first treatment in over a decade to have shown a significant survival benefit in treating patients with pancreatic cancer. Sales of Tarceva continued to increase strongly in 2008, growing 23% to 1.2 billion Swiss francs overall, with the main contributions coming from Western Europe and the Asia–Pacific region. Market uptake is particularly strong in Japan and China. Market penetration in Western Europe also continued to expand strongly, while double-digit sales growth was maintained in the United States. Expanding uptake in all regions reflects doctors' growing experience with and confidence in the product. In November the UK's National Institute for Health and Clinical Excellence (NICE) issued final guidance for Tarceva as an alternative to docetaxel chemotherapy for the second-line treatment of NSCLC, opening the way for reimbursement by the National Health Service.

New data from the phase II FAST-ACT trial, presented at the 2008 ASCO and European Society for Medical Oncology meetings, showed that first-line treatment with Tarceva alternating with chemotherapy and followed by Tarceva maintenance therapy significantly improved progression-free survival in Asian patients with advanced NSCLC compared with chemotherapy alone, irrespective of tumour type or mutation status. In November Roche announced that the phase III SATURN study had met its primary endpoint, demonstrating that first-line maintenance treatment with Tarceva (given immediately following initial treatment with platinum-based chemotherapy) significantly extended progression-free survival for patients with advanced NSCLC. The results show for the first time that earlier treatment with Tarceva delays lung cancer progression. Roche will discuss the data with regulatory agencies and plans to submit

a marketing application for this new indication. OSI Pharmaceuticals, in collaboration with Genentech and Roche, expects to submit a supplemental New Drug Application to the US FDA in the first half of 2009 based on the SATURN data.

Gastric (stomach) cancer | Accounts for close to 1 million new cases and well over 800,000 deaths each year, making it the second-largest cause of cancer deaths worldwide. The vast majority of cases occur in Asia, where, with lung cancer, it is the leading malignancy.

Xeloda (capecitabine), an oral chemotherapy medicine for colorectal, stomach and breast cancer, recorded sustained double-digit sales growth throughout 2008, with sales increasing 13% to 1.2 billion Swiss francs. Growth in Japan was particularly strong (74%), and solid increases were also achieved in the United States (9%) and Europe/RoW (14%). Sales were driven by expanded indications approved in 2007 and 2008, notably stomach cancer and advanced colorectal cancer, along with continued uptake in breast cancer. Growth is also being helped by new clinical data and reimbursement approvals, as combination regimens with Xeloda gain acceptance as standard therapy in these indications. Xeloda is generating strong double-digit sales growth in China following approval there in September for advanced stomach cancer. In February the EU authorities approved Xeloda for the treatment of metastatic colorectal cancer in combination with any chemotherapy in all lines of treatment, with or without Avastin. This approval provides new treatment options for the large number of patients with metastatic disease. Also in February, Chugai filed an application in Japan to expand the product's approval to allow its combination with oxaliplatin chemotherapy, with or without Avastin, for the treatment of metastatic colorectal cancer.

Transplantation – CellCept continues to expand market share

CellCept (mycophenolate mofetil), a leading component of immunosuppressant combination therapy

A broad commitment to fighting cancer

Cancer type	Marketed products	Products in clinical development phases II or III (including additional indications for marketed products)
Gastrointestinal tract ¹	Avastin, Furtulon, Tarceva, Xeloda	Avastin, Herceptin, Xeloda
Breast	Avastin, Furtulon, Herceptin, Xeloda	Avastin, pertuzumab, trastuzumab-DM1, Xeloda, R1507 (anti-IGF-1R)
Lung	Avastin, Tarceva	Avastin, Apomab, Apo2L/TRAIL, Tarceva, R1507
Blood and immune system ²	MabThera/Rituxan, Vesanoïd	Avastin, MabThera/Rituxan, R7159 (3rd-generation anti-CD 20), dacetuzumab, Apomab, Apo2L/TRAIL
Genitourinary system ³	Avastin, Furtulon, Roferon-A	Avastin, pertuzumab, R3484
Skin and soft tissue		R1507, Apomab, R3616 (hedgehog pathway inhibitor)
Brain		Avastin
Childhood cancers		R1507, Xeloda, Avastin
Supportive care	Bondronat, Kytril, NeoRecormon, Neulastim, Neupogen, Neutrogen	Epogin

¹ Includes colon, rectum, stomach, pancreas, liver.

² Includes non-Hodgkin's lymphoma, chronic lymphocytic leukemia, acute promyelocytic leukemia.

³ Includes kidney, prostate, ovary, cervix.

For more information on development projects see 'Major development activities', p. 47, and 'Pharmaceuticals pipeline', inside back cover.

to prevent rejection of solid organ transplants, again recorded a double-digit increase in sales in 2008, advancing 13% to 2.1 billion Swiss francs. Growth was driven primarily by strong demand in the US and Japan. (See below, p. 44, for a review of Valcyte and Cymevene.)

Anemia – Overall sales decline in a competitive, cost-sensitive market

Anemia | Occurs when the level of red blood cells and/or the hemoglobin they contain falls below normal, starving organs and tissues of oxygen. It is seen in over 80% of patients with chronic kidney (renal) disease, which affects more than 500 million people worldwide. In addition, anemia affects three out of four cancer patients undergoing chemotherapy. Patients with untreated anemia may need blood transfusions. The potential long-term effects of anemia include cardiovascular disease in renal patients, while in patients with cancer it is associated with diminished quality of life.

The Roche Group's anemia franchise includes three erythropoietin-stimulating agents (ESAs): Roche's **Mircera** (methoxy polyethylene glycol-epoetin beta), the first continuous erythropoietin receptor activator, and the established shorter-acting ESAs **NeoRecormon** and **Epogin** (epoetin beta), from Roche and Chugai, respectively. All three medicines are used to treat symptomatic anemia in patients with chronic kidney disease. In addition, **NeoRecormon** is approved to treat chemotherapy-induced anemia in cancer patients.

Combined sales of NeoRecormon and Epogin declined 13% to 1.8 billion Swiss francs in 2008, in an increasingly competitive, highly cost-sensitive market, characterised by heavily discounted contract tenders and group purchasing. New guidelines on the use of ESAs in cancer and renal patients issued during the year by the European Medicines Agency (EMA) and other regulators also contributed to the overall contraction of the global anemia market. In Europe/RoW erosion of NeoRecormon sales has

Roche Diagnostics' highly sensitive cobas PCR tests are helping to personalise treatment with Pegasys for people with chronic HCV infection.

been moderate (-10%) despite the entry of several biosimilar versions of epoetin alfa since late 2007. In Japan, where Epogin remains the market leader, an 18% decline in sales of the medicine was due primarily to sustained pricing pressure and government-mandated price cuts that came into effect in April. As of January 2009 Mircera has been approved in 72 countries worldwide and launched in 56, including the major EU markets. Physician feedback in the early launch markets is positive. Sales are modest but are progressing as the product's global rollout continues.

Virology – Pegasys maintains clear market leadership, expands market share

Hepatitis B and C | The hepatitis B and C viruses (HBV, HCV), which are commonly transmitted through blood-to-blood contact, cause acute and chronic liver disease, potentially leading to liver failure, cirrhosis and liver cancer. Worldwide, 350 million people are thought to be chronically infected with HBV, a highly infectious virus that is responsible for an estimated 1 million deaths annually. More than 170 million people around the world are infected with HCV, and 3 to 4 million new cases occur each year. Hepatitis C is the main reason for liver transplantation. A recent study on the HCV-related burden of disease in 22 European countries estimated that between seven and nine million people, or over 1% of the population, are infected with HCV.

Pegasys (peginterferon alfa-2a) is indicated for the treatment of chronic hepatitis B and C. It is used alone in the treatment of hepatitis B, and in combination with Copegus (ribavirin) in the treatment of hepatitis C. In addition, Pegasys is the pegylated interferon of choice for use in clinical trials with the new generation of direct antiviral agents (see below, p. 50), which are expected to increase cure rates and/or shorten treatment duration. In 2008 Pegasys maintained its clear leadership of the global pegylated interferon market and continued to gain market share worldwide. Global sales advanced 6% to 1.6 billion Swiss francs, driven by strong growth in Japan and

key emerging markets, combined with solid market-share growth in the United States, where Pegasys now accounts for 70% of new prescriptions for hepatitis C. In June the EU authorities approved a shortened course of treatment with Pegasys plus Copegus for patients with genotype 2 or 3 HCV infection who have very low virus levels and show a rapid virological response. The approval personalises therapy for these patients, offering a chance for cure with only four months' treatment. This new approach is made possible by Roche Diagnostics' highly sensitive, real-time cobas PCR diagnostic tests. In November Roche also received EU approval for the retreatment of patients whose chronic HCV infection did not respond to previous treatment with interferon alfa (pegylated or non-pegylated), alone or in combination with ribavirin. Pegasys is the first and only pegylated interferon to be indicated for retreatment of up to 72 weeks, allowing therapy to be personalised and optimised. The recommended retreatment period depends on the HCV genotype, the type of previous treatment and the patient's virological response during retreatment.

Influenza, or flu | A highly contagious, debilitating viral illness that occurs mainly in the autumn and winter months in temperate climates and year-round in tropical areas. It is particularly dangerous for young children, the elderly and people with chronic health problems. Each year, 100 million people fall ill with the flu in Europe, Japan and the US alone. It is estimated that more than 500,000 people globally die each year from the disease or its complications. Pandemics, or global epidemics, are caused by novel strains of influenza to which people have no immunity. Pandemics are associated with significant levels of illness and death and occur every 10 to 40 years. The World Health Organization (WHO) and medical experts continue to warn that the next influenza pandemic may be imminent.

As forecast, total sales of the anti-influenza medicine Tamiflu (oseltamivir) continued to decline in 2008, with the fall of 68% to 609 million Swiss francs due

Pegasys maintained its clear leadership of the global pegylated interferon market and continued to gain market share worldwide. As expected, sales of Tamiflu continued to decline due to substantially reduced pandemic stockpiling orders from governments and corporations.

Worldwide uptake of MabThera/Rituxan for rheumatoid arthritis is strong. It is now the market leader outside the US for the treatment of RA that has not responded adequately to TNF inhibitor therapy. Actemra/RoActemra was approved for RA in Japan and Switzerland in 2008 and in the EU in January 2009.

to substantially reduced pandemic stockpiling orders from governments and corporations. The expected sharp fall-off in pandemic sales, down 1.6 billion Swiss francs compared with 2007, more than outweighed a significant increase in seasonal sales, which rose 76% to 372 million Swiss francs. The main contributions to seasonal sales came from the United States, where the 2007/2008 flu season was particularly severe. As part of its policy to help ensure pandemic readiness, Roche continued to work with governments worldwide on appropriate Tamiflu stockpiles, in line with WHO recommendations. Based on data provided by Roche and Chugai, the authorities in the United States, Japan, Canada, Australia and elsewhere have increased the shelf-life of government stockpiles of Tamiflu to seven years. Roche has filed data to support similar shelf-life extensions in other countries.

Combined sales of **Valcyte** (valgancyclovir) and **Cymevene** (ganciclovir), the standard of care for the treatment of cytomegalovirus (CMV) retinitis in patients with HIV/AIDS and for the prevention of CMV disease in at-risk transplant patients, rose 10% to 553 million Swiss francs in 2008. Robust growth throughout the year was driven mainly by demand in Europe/RoW, with very strong gains recorded in Germany and Spain. In July the FDA granted pediatric exclusivity for Valcyte in the United States. This extends the medicine's patent protection for six months, to September 2015.

In the third quarter of 2008, following extensive toxicology studies by Roche, both the EU and the Swiss authorities confirmed that the presence of a chemical impurity in some batches of the HIV medicine **Viracept** (nelfinavir) last year did not present a risk to patients. The authorities have determined that there is now no need to follow patients in registries. The discovery of the impurity led to a global recall of Viracept in June 2007. Since then, Viracept has been reintroduced in the EU, Switzerland and other markets where Roche supplies the product.

Inflammation and autoimmune disorders – Actemra/RoActemra approved for rheumatoid arthritis in Japan, Switzerland and EU

Autoimmune disorders | Occur as a result of a mistaken immune response to the body's own tissues. The causes are unknown. Rheumatoid arthritis, multiple sclerosis and lupus erythematosus are among the most common autoimmune disorders, which affect millions of people worldwide.

Rheumatoid arthritis (RA) | A chronic, progressive inflammatory disease of the joints and surrounding tissues that is associated with intense pain, irreversible joint destruction and systemic complications. B cells (a type of immune cell) are known to play a key role in the inflammation associated with RA. Several key cytokines, or proteins, are also involved, including TNF alfa, interleukin-1 (IL-1) and interleukin-6 (IL-6). IL-6 has been identified as having a pivotal role in the inflammation process. Around 21 million people worldwide are thought to be affected by RA.

Estimated sales⁵ of MabThera/Rituxan (rituximab) in the inflammation/autoimmune segment amounted to approximately 800 million Swiss francs in 2008, driven by strong worldwide uptake of the product for the treatment of severe rheumatoid arthritis. The first and only selective B cell therapy approved in this indication, MabThera/Rituxan has rapidly established itself as a proven choice for RA patients with inadequate response to tumour necrosis factor (TNF) inhibitor therapy and is now the market leader in this indication outside the US. Observational data showing the superiority of MabThera/Rituxan over sequential use of TNF inhibitors and the product's increasingly positive long-term efficacy and safety profile are convincing more and more rheumatologists to move patients to MabThera/Rituxan following inadequate response to their first TNF inhibitor. The use of MabThera/Rituxan in this setting is supported by a growing body of evidence, including new clinical trial data presented at medical conferences in 2008

⁵ Based on data from Genentech and from Roche territories.

Eleven major new marketing applications filed and 13 major regulatory approvals gained.

Major regulatory filings in 2008¹

Product	Active substance	Indication and/or dosage form	Country
Avastin	bevacizumab	metastatic breast cancer, combination with docetaxel	EU, Switzerland
		metastatic colorectal cancer, combination with Xeloda and oxaliplatin	Japan
		first-line metastatic renal cell carcinoma, combination with interferon alfa-2a	USA
		relapsed glioblastoma multiforme	USA, EU
		non-small cell lung cancer	Japan
Rituxan	rituximab	rheumatoid arthritis, patients with an inadequate response to a disease-modifying antirheumatic drug	USA
MabThera	rituximab	first-line chronic lymphocytic leukemia	EU, Switzerland
		relapsed or refractory chronic lymphocytic leukemia	EU ²
Xeloda	capecitabine	metastatic colorectal cancer, monotherapy and combination with Avastin and oxaliplatin	Japan

Major regulatory approvals in 2008¹

Product	Active substance	Indication and/or dosage form	Country
Actemra	tocilizumab	rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis	Japan
RoActemra	tocilizumab	rheumatoid arthritis	Switzerland, EU ²
Avastin	bevacizumab	renal cell carcinoma	Switzerland
		first- and second-line metastatic colorectal cancer, combination with oxaliplatin	EU, Switzerland
		HER2-negative metastatic breast cancer, first-line, combination with paclitaxel	USA ³ , Switzerland
Herceptin	trastuzumab	adjuvant HER2-positive breast cancer, as a single agent following multimodality anthracycline-based therapy	USA
		adjuvant HER2-positive breast cancer, combined with a non-anthracycline regimen containing docetaxel and carboplatin; or with docetaxel following a regimen containing doxorubicin and cyclophosphamide	USA
		adjuvant HER2-positive breast cancer	Japan
MabThera	rituximab	first-line chronic lymphocytic leukemia	Switzerland
Xeloda	capecitabine	metastatic colorectal cancer, first- and second-line, combination treatment	EU, Switzerland

¹ Includes supplemental indications; updated to 23 January 2009.

² January 2009.

³ Accelerated approval (FDA).

The Group's R&D activities are focused on creating clinically differentiated medicines based on small molecules, therapeutic proteins and next-generation biologics. In addition, Roche R&D is exploring RNA interference, a promising new approach that uses targeted gene silencing.

showing sustained or improved reduction of disease activity with repeated treatment courses and sustained inhibition of the progression of joint damage.

Roche, Genentech and Biogen Idec continued development programmes evaluating additional RA settings in which MabThera/Rituxan may provide benefit to patients. Two major trials in a phase III programme investigating the medicine for use in RA patients with less advanced disease met their primary endpoints in 2008. In January results from the SERENE study in patients with an inadequate response to previous therapy with disease-modifying antirheumatic drugs (DMARDs) showed that significantly more patients treated with MabThera/Rituxan plus methotrexate (MTX) achieved an improvement in disease signs and symptoms compared with those who received MTX alone. In December Roche announced that IMAGE, a radiographic study assessing the ability of MabThera/Rituxan to inhibit structural joint damage in patients not previously treated with MTX, had also met its primary endpoint. Roche plans to use the signs and symptoms data in conjunction with the radiographic data to support a combined EU regulatory filing for additional RA indications in 2009. In September, based on the SERENE data, Genentech filed a supplementary marketing application in the US seeking approval for Rituxan in RA patients with inadequate response to DMARD therapy.

Actemra/RoActemra (tocilizumab) is a first-in-class therapy based on IL-6 inhibition, representing a novel approach to the treatment of patients with moderate to severe RA. Following approval in April of Actemra for RA in adults and for related pediatric disorders and the subsequent rollout by Chugai, sales uptake in Japan has been very encouraging. In December the Swiss authorities approved RoActemra for the treatment of moderately severe to severe, active rheumatoid arthritis in adult patients who have not responded adequately to treatment with DMARDs or TNF inhibitors. Roche received EU marketing approval for RoActemra in the same indication in January 2009. In September, in a complete response

letter to Roche's US marketing application for Actemra, the FDA requested additional documentation. Following further discussions and as a result of the FDA's evolving Risk Evaluation and Mitigation Strategy (REMS) requirements for medications, in December the agency asked Roche to prepare a REMS plan for Actemra. In addition, based on the evolving requirements for approval of new biologics, the FDA has asked Roche for non-clinical animal model data, beyond that which was included in the original marketing application. Roche is performing the requested preclinical studies and expects to submit the complete response for Actemra to the FDA in the third quarter of 2009. The FDA has not requested additional clinical studies prior to approval.

Metabolic disorders – Bonviva/Boniva maintains robust growth in a competitive market

Osteoporosis | A systemic skeletal disease characterised by a loss of bone mass, leading to bone weakness and a susceptibility to fracture. Millions of people worldwide are affected – one in three postmenopausal women and one in five men over the age of 50.

Bonviva/Boniva (ibandronic acid) is a highly effective and well tolerated medicine for women with postmenopausal osteoporosis. It is available as a once-monthly tablet and a three-monthly injection. In an increasingly competitive market environment Bonviva/Boniva recorded solid overall sales performance in 2008, with sales increasing 35% to 1.1 billion Swiss francs. Further market-share gains supported robust growth in Europe/RoW and the United States despite the entry of generic versions of competitor products in the US and Europe. New data from a retrospective observational study in over 64,000 postmenopausal women (VIBE) presented at a major European rheumatology congress in June provided additional evidence for the effectiveness of once-monthly Bonviva compared with weekly bisphosphonates in preventing vertebral, non-vertebral and hip fractures. In November, the FDA expanded the existing marketing approval for once-monthly Boniva to include prevention of postmenopausal osteoporosis.

Roche is uniquely positioned to help realise the promise of personalised healthcare.

Research and development

In 2008 the Pharmaceuticals Division continued to build the value of its research and development portfolio, advancing twelve projects in the areas of oncology, metabolic and inflammatory–autoimmune diseases into phase III clinical testing (see ‘Pharmaceuticals pipeline’, fold-out at the end of this Business Report).

Over the last 18 months Roche Pharmaceuticals has decentralised the management of its R&D projects by creating five Disease Biology Areas (DBAs). The Oncology, Viral Diseases, Inflammation, Metabolic Diseases and Central Nervous System DBAs set priorities and make portfolio decisions for their specific diseases. This is already helping to streamline the research portfolio and is expected to increase the number and quality of programmes being advanced into clinical development.

The Group’s R&D activities are focused on creating clinically differentiated medicines based on small molecules (chemical compounds) and therapeutic proteins (mainly monoclonal antibodies and peptides), including glycoengineering and next-generation biologics. In addition, Roche R&D is now exploring small interfering ribonucleic acid molecules (also known as RNA interference, or RNAi), a promising approach based on the concept of targeted gene silencing that it is hoped will eventually yield powerful new therapeutic options.

In addition, Roche is uniquely positioned to help realise the promise of personalised healthcare, an approach that seeks to tailor treatments to specific patient subpopulations based on knowledge of the biological differences between patients and the characteristics of their disease (see ‘Personalised healthcare’, p. 30). The Roche Group’s combined pharmaceuticals and diagnostics expertise gives us a clear competitive advantage in this area. Roche has already achieved notable successes with this approach in oncology and virology, and we expect our focus on personalised healthcare to contribute

greater value in the future, thus meeting growing stakeholder expectations for safer, more effective and more cost-efficient treatments.

Major development activities

Oncology | The global development programme for Avastin currently includes more than 450 clinical trials with around 40,000 patients in over 30 different tumour types. Phase III studies in diseases such as ovarian, prostate and gastric (stomach) cancer are scheduled to report over the next two years. Final results from a key clinical trial of Avastin in the early colon cancer setting (NSABP C08) are expected in 2009, with the results of another trial in the same setting (AVANT) due in 2010. Important milestones were passed in several Avastin programmes in 2008: BETH, a global phase III trial of Avastin combined with Herceptin in adjuvant HER2-positive breast cancer, started in May; patient recruitment for the phase III AVAGAST trial in first-line advanced gastric cancer was completed in December; and BERNIE, a phase II trial to assess Avastin in combination with standard chemotherapy in children and adolescents with sarcoma, commenced in July. In October the EU authorities approved a pediatric investigation plan for Avastin; the studies included will eventually provide physicians with new data on dosing and safety that can improve clinical outcomes specifically for children.

In collaboration with OSI Pharmaceuticals and Genentech, Roche is conducting an extensive development programme of more than 130 clinical studies with Tarceva at earlier stages of lung cancer and in combination with other treatments, including Avastin, to further evaluate the life-extending benefits of Tarceva for patients with NSCLC. Ongoing and planned phase III studies in the Tarceva development programme include a randomised phase III trial (ATLAS) evaluating the addition of Tarceva to Avastin for maintenance therapy following first-line treatment with Avastin and chemotherapy in patients with advanced NSCLC. Initial results from this trial are expected in the first half of 2009.

The global development programme for Avastin includes more than 450 clinical trials with around 40,000 patients in over 30 different tumour types. Phase III studies with Avastin in colon, ovarian, prostate and stomach cancer are scheduled to report over the next two years.

The first phase III trial with pertuzumab in HER2-positive breast cancer began in 2008. Progress was also made with oncology projects in earlier stages of development, including the novel antibody-drug conjugate T-DM1, which will soon enter the last phase of development.

Several studies are currently evaluating Herceptin in combination with Avastin or pertuzumab in patients with HER2-positive breast cancer. In addition to BETH (see above, Avastin), CLEOPATRA and NEOSPHERE (see below, pertuzumab), Herceptin is also being studied in a global phase III study (AVEREL) in combination with Avastin in the first-line treatment of advanced breast cancer. Herceptin is also being investigated in HER2-positive advanced gastric cancer in the phase III ToGA study. Around 20% of patients with gastric cancer have HER2-positive disease.

Interim results from a phase III trial with 1,500 patients by the Finnish Breast Cancer Group, presented at the San Antonio Breast Cancer Symposium in December, suggest that **Xeloda**, which is already approved for advanced breast cancer, may also reduce cancer recurrence and extend survival in patients with early breast cancer. A similar Roche-sponsored study with Xeloda in early breast cancer (NO17629) is ongoing. Roche plans to seek regulatory approval for Xeloda in this indication. A phase III trial of the medicine in early colon cancer (NO16968) is due to report in 2009, and data from a phase IV adjuvant study in patients with gastric cancer are expected in 2010.

Pertuzumab (R1273), currently being studied in combination with Herceptin and standard chemotherapy in HER2-positive breast cancer, entered phase III development in 2008. Pertuzumab inhibits the pairing of HER2 with other HER receptors, a key mechanism of tumour growth. CLEOPATRA, a phase III study evaluating the addition of pertuzumab to Herceptin and chemotherapy in first-line treatment of patients with advanced disease, commenced in the first quarter of 2008. In addition, NEOSPHERE, a phase II trial investigating neoadjuvant (presurgical) treatment with pertuzumab, started in the first half of the year. Data from a phase II trial (17929) presented at ASCO 2008 showed that half of the patients with advanced HER2-positive breast cancer whose disease had progressed during previous treatment with a regimen including Herceptin benefited from a combination of Herceptin and pertuzumab.

In 2008 progress was also made with a range of oncology projects in earlier stages of development, including one that will soon move into phase III, the last stage of clinical testing before a marketing application is filed. **Trastuzumab-DM1** (T-DM1, R3502) is a novel antibody-drug conjugate linking trastuzumab (the active ingredient of Herceptin) and the cytotoxic agent DM1. By targeting the HER2 proteins expressed by tumours, the conjugate delivers chemotherapy to the cancer cells in a precise manner. T-DM1 has shown promising clinical efficacy and good tolerability in phase II clinical trials in women with HER2-positive metastatic breast cancer. Roche and Genentech have decided to move T-DM1 into phase III development for second-line HER2-positive metastatic breast cancer; the first trial in this programme is scheduled to start in the first half of 2009.

R1507 is a monoclonal antibody targeting the IGF-1R receptor. The IGF pathway is important for the growth and survival of a variety of cancers. R1507 is well tolerated and is currently in phase II development for sarcoma, non-small cell lung cancer, and breast cancer.

R7159 (GA101), a fully humanised, type II, glyco-engineered third-generation anti-CD20 monoclonal antibody developed by GlycArt and Roche, is being co-developed with Chugai, Genentech and Biogen Idec for the treatment of CD20-positive haematological malignancies, including CLL and NHL. R7159 targets the same B cell protein (CD20) as MabThera/Rituxan and has been engineered to increase both direct and indirect tumour cell death, thereby enhancing efficacy. In phase I studies R7159 has shown good tolerability and very encouraging clinical activity in patients with no other treatment options who have previously received MabThera/Rituxan. Phase II development in NHL commenced in December.

R7204 is a novel inhibitor of B-Raf kinase being co-developed by Plexikon and Roche. Currently in phase I testing, R7204 selectively targets the product

Roche currently has compounds targeting several mechanisms of action in development for type 2 diabetes.

of the mutant B-Raf^{V600E} gene, an abnormality that has been shown to drive certain cancers. The mutation occurs only in tumour cells. It is found in many thyroid cancers and malignant melanomas and in a small proportion of colorectal cancers. A diagnostic test is being developed in collaboration with Roche Molecular Diagnostics to select patients who carry the B-Raf^{V600E} mutation and are therefore most likely to respond to treatment with R7204.

R7334 (TB-403), a human monoclonal antibody targeting placental growth factor (PlGF), entered the Roche portfolio in June 2008 via a licensing agreement with ThromboGenics and BioInvent. Malignancy of solid tumours is dependent on new blood vessel formation, a process known as angiogenesis, and PlGF is an important growth factor in this process. It is anticipated that R7334 will be used in combination with other antiangiogenic treatments such as Avastin. R7334 is currently being tested in a phase I study in patients with solid tumours.

Inflammation and autoimmune diseases | In the second quarter of 2008 Roche and Genentech decided to discontinue development of **MabThera/Rituxan** in systemic lupus erythematosus after a phase II/III study failed to reach its primary endpoint. Phase III development of the drug for lupus nephritis is continuing as planned, and the results of a clinical trial (LUNAR) investigating the benefits of adding MabThera/Rituxan to CellCept are expected in the first half of 2009.

Ocrelizumab (R1594) is a humanised anti-CD20 monoclonal antibody being developed by Roche, Genentech and Chugai for the treatment of autoimmune diseases. Like MabThera/Rituxan, ocrelizumab also targets B cells. As a humanised antibody, it has the potential to be less immunogenic, better tolerated and more convenient to administer. An extensive phase III programme involving more than 2,700 patients with rheumatoid arthritis is ongoing, and recruitment for a phase III trial in lupus nephritis is continuing as planned. In May a phase III trial of ocrelizumab in systemic lupus erythematosus

was discontinued due to the negative results of a trial with MabThera/Rituxan in a similar patient population.

Promising early-stage projects in the inflammation/autoimmune area are proceeding on track, including **R667**, currently in phase II clinical testing for emphysema, and **R4930** (huMAb anti-OX40L), a novel biologic being jointly developed by Roche and Genentech as a treatment for asthma (currently in phase I). In November Actelion and Roche agreed to progress **R3477**, a selective S1P1 receptor agonist, into phase II clinical development for autoimmune diseases.

Metabolic and cardiovascular diseases | Many people with elevated levels of certain blood fats remain at risk of heart attack or stroke despite treatment with currently available medications. This risk may be reduced by new treatments that increase high-density lipoprotein cholesterol (HDL), sometimes called 'good' cholesterol. **Dalcetrapib** (R1658, JTT-705, licensed from Japan Tobacco) increases levels of HDL by blocking the action of the cholesteryl ester transfer protein (CETP), thereby potentially reducing the risk of cardiovascular disease and death in high-risk patients. A phase III morbidity and mortality study of dalcetrapib (dal-OUTCOMES) started in April, and patient recruitment is proceeding well. Phase II data presented at the American Congress of Cardiology in March show that dalcetrapib is well tolerated and has a good general and cardiovascular safety profile when given alone or in combination with statins. Additional data presented at the American Heart Association meeting in November showed that dalcetrapib has a unique chemical structure and, unlike certain other CETP inhibitors, does not activate enzymes or genes involved in blood-pressure regulation.

Diabetes | Recognised as a global epidemic by the World Health Organization. The International Diabetes Federation estimates that some 380 million people worldwide will have diabetes

by 2025. According to the WHO, type 2 (adult onset) diabetes accounts for around 90% of all cases.

Taspoglutide (R1583, BIM 51077, licensed from Ipsen), the first once-weekly human glucagon-like peptide-1 (GLP-1) hormone analogue, is being developed by Roche for type 2 diabetes. The structure of the molecule is similar to that of the natural human hormone. In clinical trials to date, taspoglutide was generally well tolerated and significantly improved glucose control and weight loss after only eight weeks of treatment. Roche initiated an extensive phase III clinical development programme with taspoglutide in July. In late 2008 the FDA issued new guidance on the clinical testing of new treatments for type 2 diabetes. Roche is reviewing the taspoglutide programme to comply with these recommendations.

Roche currently has compounds targeting several mechanisms of action in development for use in patients with type 2 diabetes. One of these, **aleglitazar** (R1439), is a dual PPAR agonist that has demonstrated effects on blood fats, blood pressure and blood glucose. Phase II clinical testing is nearing completion, and Roche expects to make a decision in the first half of 2009 on phase III development of the compound. Phase II development of **R1579**, a dipeptidyl peptidase IV (DPP-IV) inhibitor, was completed in the second half of the year. While demonstrating adequate glucose reduction and excellent tolerability, the compound did not satisfy Roche's internal clinical differentiation criteria for transition into phase III testing, and Roche has therefore decided to outlicense it.

Virology | Development of **R1626**, a polymerase inhibitor being investigated as a treatment for hepatitis C infection, was terminated during the year due to new and unexpected safety findings from a phase IIb study. Roche's pipeline of direct antiviral agents for HCV remains robust, with the polymerase inhibitor **R7128** (collaboration with Pharmasset) and the protease inhibitor **R7227** (collaboration

with InterMune) in phase I clinical development. Both of these oral agents are being investigated in combination with Pegasys and Copegus. In addition, Roche has started a clinical trial with combined R7128 and R7227, an important first step in evaluating the therapeutic potential of an all-oral, interferon-free combination treatment for hepatitis C.

Central nervous system | Evidence is evolving on the role of B cells in the multiple sclerosis disease process. Based on promising phase II data with **MabThera/Rituxan** in relapsing-remitting multiple sclerosis (RRMS), Roche and its partners are conducting a phase II dose-finding study with the next-generation anti-CD20 antibody **ocrelizumab** in this disease. In April a phase II/III study (OLYMPUS) of MabThera/Rituxan in primary progressive MS (PPMS), led by Genentech, did not meet its primary endpoint. However, as secondary analysis suggests that the medicine may benefit certain patient subgroups, Genentech and Roche are evaluating possibilities for further development of anti-CD20 therapy in progressive MS.

R1678, an inhibitor of glycine transporter type 1 (GlyT1), is in phase II development for the treatment of schizophrenia. Preclinical and clinical evidence suggests that this novel mechanism of action may improve negative symptoms of schizophrenia, an area of high unmet medical need not adequately addressed by current treatments. **R3487**, a nicotinic alpha7 receptor agonist, is being developed to treat cognitive impairment in schizophrenia and Alzheimer's disease. R3487 is expected to provide significant improvement in memory and ability to perform activities of daily living compared with current treatments. First results from a phase II trial investigating the benefit of R3487 in cognitive impairment associated with schizophrenia are expected towards the middle of 2009. A phase IIb study in Alzheimer's disease is scheduled to start in the first part of 2009.

The division currently operates six major biotech manufacturing facilities worldwide.

Manufacturing infrastructure

Biotech manufacturing | Uses cell-culture technology to produce bulk quantities of genetically engineered active pharmaceutical ingredients such as monoclonal antibodies and other therapeutic proteins while meeting strict quality requirements. The manufacturing process – comprising cell growth, fermentation, purification and filling operations – takes place under highly controlled conditions. The facilities are subject to rigorous regulatory inspection and approval procedures. The Roche Group's Pharmaceuticals Division currently operates six major biotech manufacturing facilities worldwide, including those at Roche Pharmaceuticals' Basel and Penzberg sites, Genentech's plants in South San Francisco, Vacaville and Oceanside, and Chugai's Utsunomiya facility.

Roche's new biotech production facilities in Penzberg (Germany) and Basel (Switzerland) are now fully operational. Roche received European Medicines Agency (EMA) approval in May for the production of trastuzumab (the active ingredient of Herceptin) at the Penzberg facility for European markets, just under four years after the start of construction work. Roche filed for approval of production of bevacizumab (the active ingredient of Avastin) in the new Basel facility with the EMA in December.

In 2008 the Group made further progress with important infrastructure projects. Construction of a new technical research and development building at Roche's Basel site commenced in October. In addition, new sterile vial filling capacity is being installed at Roche's Kaiseraugst (Switzerland), Genentech's Hillsboro (Oregon, USA) and Chugai's Utsunomiya (Japan) sites.

In 2008 Roche Pharmaceuticals continued to optimise its global manufacturing network. During the year the decision was taken to close manufacturing in Nutley (New Jersey, USA) by 2010 and to phase out chemical manufacturing in Mannheim (Germany) over three years. Products currently manufactured

in Mannheim and Nutley will be transferred to other sites. In addition, the Cenexi galenical manufacturing site in Fontenay sous Bois (France) was sold.

In addition to these and other steps to strengthen and focus its manufacturing network, Roche further improved its supply chain management systems to ensure continuous worldwide supply of its innovative medicines.

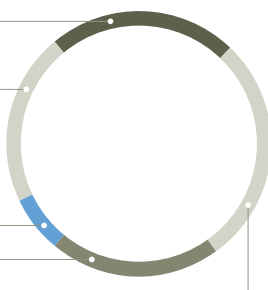
Pharmaceuticals pipeline | *The Pharmaceuticals Division's R&D activities are focused on creating clinically differentiated medicines. In 2008 the division continued to build the value of its research and development portfolio. Twelve major phase III projects were initiated, including clinical trials of the novel compounds pertuzumab, taspoglutide and dalcetrapib.*

R&D pipeline

In 2008 the Pharmaceuticals Division filed 11 major new marketing applications and gained 13 major regulatory approvals. At the beginning of 2009 the division's R&D pipeline comprised 120 clinical projects, including 62 new molecular entities (NMEs) and 58 additional indications. Forty NMEs are currently in phase I, 16 in phase II and six in phase III or filed for regulatory review.

Roche Pharmaceuticals – 100 research projects in major therapeutic areas | January 2009

Central nervous system diseases	23
Cardiovascular and metabolic diseases	21
Viral diseases	7
Oncology	21
Inflammatory and autoimmune diseases	28



Roche Pharmaceuticals currently has 100 projects in preclinical research across five therapeutic areas and 84 development projects in five therapeutic areas, including five in phase 0 (transition from preclinical to clinical development).

In 2008 twelve Roche-managed projects were terminated: six in phase I, four in phase II and two in phase III. Two of these projects reverted to our R&D partners, and decisions were taken to outlicense another two.

Quarterly Pharmaceuticals pipeline updates are posted at www.roche.com/pipeline

Pharma Partnering

Licensing and targeted acquisitions play an important role in strengthening Roche's R&D portfolio and expanding the company's technology capabilities. In 2008 Roche Pharmaceuticals signed a total of 57 new agreements, including seven product transactions and 43 research and technology collaborations.

In May Roche acquired Piramed Limited, a UK company with therapeutic research programmes targeting the PI3-kinase pathway in oncology and inflammatory disease. In June Roche consolidated its leading position in the antiangiogenesis field through a licensing agreement with ThromboGenics and BioInvent for their jointly developed anticancer agent TB-403 (R7334). The acquisition of Mirus Bio Corporation (now Roche Madison Inc.) in September enables Roche to further advance its research in the field of ribonucleic acid interference (RNAi) delivery.

In September Roche completed the acquisition of ARIUS Research Inc., which has a proprietary antibody platform that rapidly identifies and selects antibodies based on their functional ability to affect disease. Following a merger agreement and successful tender offer, in January 2009 Roche acquired US-based Memory Pharmaceuticals, which develops innovative drug candidates for the treatment of debilitating central nervous system disorders such as Alzheimer's disease and schizophrenia. Memory's nicotinic alpha-7 agonist drug candidates in these disease areas were already in partnered programmes with Roche.

Pharmaceuticals pipeline

Building value and opportunities for growth

Project ID	Project/product (generic name)	Pharmacological class	Indication	Phase	Partner
Oncology					
R105	MabThera/Rituxan (rituximab)	anti-CD20 monoclonal antibody	chronic lymphocytic leukemia (1st line)	filed EU	Genentech and Biogen Idec
R105	MabThera/Rituxan (rituximab)	anti-CD20 monoclonal antibody	chronic lymphocytic leukemia, relapsed	filed EU	Genentech and Biogen Idec
R340	Xeloda (capecitabine)	fluoropyrimidine	metastatic colorectal cancer (1st line) – combo	approved EU, filed US	
R340	Xeloda (capecitabine)	fluoropyrimidine	metastatic colorectal cancer (2nd line) – combo	approved EU, filed US	
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	renal cell carcinoma	approved EU, filed US	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	metastatic breast cancer (1st line) – combo docetaxel	filed EU	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	glioblastoma multiforme (relapsed)	filed US, EU	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	non-small cell lung cancer (NSCLC) with previously treated CNS metastases	II, filed EU	Genentech
R435 + R597	Avastin+Herceptin (bevacizumab+trastuzumab)	anti-VEGF monoclonal antibody + anti-HER2 monoclonal antibody	metastatic breast cancer (1st line) – HER2-positive	III	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	ovarian cancer (1st line)	III	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	prostate cancer, hormone-refractory	III	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	metastatic breast cancer (1st line) – combo standard chemotherapies	III	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	metastatic gastric cancer	III	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	adjuvant colon cancer	III	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	adjuvant NSCLC	III	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	adjuvant breast cancer, HER2-negative	III	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	adjuvant breast cancer, HER2-positive	III	Genentech
R435 + R105	Avastin+MabThera/Rituxan (bevacizumab+rituximab)	anti-VEGF monoclonal antibody + anti-CD20 monoclonal antibody	aggressive non-Hodgkin's lymphoma	III	Genentech
R597	Herceptin (trastuzumab)	anti-HER2 monoclonal antibody	gastric cancer, HER2-positive	III	
R105	MabThera/Rituxan (rituximab)	anti-CD20 monoclonal antibody	indolent non-Hodgkin's lymphoma – maintenance (1st line)	III	Genentech and Biogen Idec
R1415	Tarceva (erlotinib)	EGFR inhibitor	NSCLC (1st line) – maintenance	III	Genentech and OSI Pharmaceuticals
R1415	Tarceva (erlotinib)	EGFR inhibitor	adjuvant NSCLC	III	Genentech and OSI Pharmaceuticals
R435 + R1415	Avastin+Tarceva (bevacizumab+erlotinib)	Anti-VEGF monoclonal antibody + EGFR inhibitor	NSCLC (1st line) – maintenance	III	Genentech and OSI Pharmaceuticals
R340	Xeloda (capecitabine)	fluoropyrimidine	adjuvant breast cancer	III	
R340	Xeloda (capecitabine)	fluoropyrimidine	adjuvant colon cancer – combo oxaliplatin	III	
R340	Xeloda (capecitabine)	fluoropyrimidine	adjuvant colon cancer – combo Avastin	III	
R1273	(pertuzumab)	HER2 dimerisation inhibitor	metastatic breast cancer, HER2-positive (1st line)	III	Genentech
R1273	(pertuzumab)	HER2 dimerisation inhibitor	neoadjuvant breast cancer, HER2-positive	II	Genentech
R1273	(pertuzumab)	HER2 dimerisation inhibitor	ovarian cancer	II	Genentech
R3502	Trastuzumab-DM1	anti-HER2 monoclonal antibody-cytotoxic conjugate	metastatic breast cancer, HER2-positive	II	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	NSCLC, squamous	II	Genentech
R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	glioblastoma multiforme (1st line)	II	Genentech
R1415 + R435	Tarceva+Avastin (erlotinib+bevacizumab)	EGFR inhibitor + anti-VEGF monoclonal antibody	NSCLC (1st line)	II	Genentech
R1507		anti-IGF1R monoclonal antibody	Ewing's sarcoma	II	Genmab
R1507		anti-IGF1R monoclonal antibody	metastatic breast cancer	II	Genmab
R1507		anti-IGF1R monoclonal antibody	NSCLC	II	Genmab
R7159		3rd-generation anti-CD20 antibody	non-Hodgkin's lymphoma	II	GlycArt ¹ (GA101)
R3616		hedgehog pathway inhibitor	cancer	II	Genentech
R4733			solid tumours	I	
R7204		B-Raf kinase inhibitor	malignant melanoma	I	Plexixikon
R7112		MDM2 antagonist	cancer	I	
R7160			solid tumours	I	GlycArt ¹ (GA201)
R7167			solid tumours	I	Chugai
R7304			solid tumours	I	Chugai
R7347			solid tumours	I	Genentech
R7334		anti-PIGF huMAB	solid tumors	I	ThromboGenics/ BiolInvent (TB403)

¹ GlycArt is a wholly-owned subsidiary of Roche.

Project ID	Project/product (generic name)	Pharmacological class	Indication	Phase	Partner
Inflammatory and autoimmune diseases					
■ R1569	Actemra (tocilizumab)	humanised anti-IL-6 receptor monoclonal antibody	rheumatoid arthritis	filed US, approved Jpn, EU	Chugai
■ R1569	Actemra (tocilizumab)	humanised anti-IL-6 receptor monoclonal antibody	systemic onset juvenile idiopathic arthritis	III, approved Jpn, EU	Chugai
■ R105	MabThera/Rituxan (rituximab)	anti-CD20 monoclonal antibody	rheumatoid arthritis, DMARD inadequate responders	III, filed US	Genentech and Biogen Idec
■ R1594	(ocrelizumab)	humanised anti-CD20 monoclonal antibody	rheumatoid arthritis	III	Genentech
■ R1594	(ocrelizumab)	humanised anti-CD20 monoclonal antibody	lupus nephritis	III	Genentech
■ R99	CellCept (mycophenolate mofetil)	IMPDH inhibitor	pemphigus vulgaris	III	Aspreva
■ R667		nuclear receptor agonist	emphysema	II	
■ R3477		S1P1 receptor agonist	autoimmune diseases	I	Actelion
■ R7103			chronic obstructive pulmonary disease	I	
■ R1671			asthma	I	
■ R4930		OX40L huMAb	asthma	I	Genentech
Cardiovascular and metabolic diseases					
■ R1583	(taspeglutide)	GLP-1 analogue	type 2 diabetes	III	Ipsen (BIM51077)
■ R1658	(dalcatrapib)	CETP inhibitor	dyslipidemia	III	Japan Tobacco (JTT-705)
■ R1439	(aleglitazar)	dual PPAR agonist	cardiovascular risk reduction	II	
■ R7201			type 2 diabetes	I	Chugai
■ R1511		glucokinase activator	type 2 diabetes	I	
■ R7089			type 2 diabetes	I	
■ R4929			type 2 diabetes	I	
■ R7234			type 2 diabetes	I	
■ R1512			peripheral vascular disease	I	Genmab
■ R7232			dyslipidemia	I	
■ R7376			polycystic kidney disease	I	Plexxikon (PLX5568)
Viral and other infectious diseases					
■ R127	Valcyte (valganciclovir)	inhibitor of CMV replication	cytomegalovirus, extension of treatment	III	
□ R3484		HPV16 vaccine	cervical neoplasia	II	Transgene (TG4001)
■ R7128		polymerase inhibitor	hepatitis C	I	Pharmasset
■ R7227		protease inhibitor	hepatitis C	I	InterMune (ITMN-191)
Central nervous system					
■ R1594	(ocrelizumab)	humanised anti-CD20 monoclonal antibody	relapsing remitting multiple sclerosis	II	Genentech
■ R1678		GlyT1 inhibitor	schizophrenia	II	
■ R3487		nicotinic alpha7 receptor agonist	Alzheimer's disease, schizophrenia	II	Memory ² (MEM3454)
■ R1450		anti-amyloid β-peptide antibody	Alzheimer's disease	I	Morphosys
■ R1646			pain	I	
■ R4996		nicotinic alpha7 receptor agonist	Alzheimer's disease	I	Memory ² (MEM63908)
■ R1578			Alzheimer's disease	I	
Opt-in opportunities					
■ R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	gastrointestinal stromal tumour	III	Genentech
■ R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	adjuvant rectal cancer	III	Genentech
■ R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	metastatic breast cancer (2nd line)	III	Genentech
■ R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	metastatic HER2-negative breast cancer, combo hormonal therapy	III	Genentech
■ R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	high risk carcinoid	III	Genentech
■ R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	metastatic head and neck cancer	III	Genentech
■ R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	ovarian cancer (2nd line)	III	Genentech
■ R105	MabThera/Rituxan (rituximab)	anti-CD20 monoclonal antibody	lupus nephritis	III	Genentech
■ R105	MabThera/Rituxan (rituximab)	anti-CD20 monoclonal antibody	ANCA-associated vasculitis	III	Genentech

Project ID	Project/product (generic name)	Pharmacological class	Indication	Phase	Partner
■ R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	relapsed or refractory multiple myeloma	II	Genentech
■ R435	Avastin (bevacizumab)	anti-VEGF monoclonal antibody	extensive small-cell lung cancer	II	Genentech
■ Anti-CD40	(dacetuzumab)	anti-CD40 monoclonal antibody	diffuse large B cell lymphoma	II	Genentech and Seattle Genetics
■	APO2L/TRAIL		cancer	II	Genentech
■	Apomab		non-small cell lung cancer, non-Hodgkin's lymphoma	II	Genentech
■	ARQ501		cancer	II	ArQule
■ Anti-CD40	(dacetuzumab)	anti-CD40 monoclonal antibody	diffuse large B cell lymphoma, non-Hodgkin's lymphoma, multiple myeloma	I	Genentech and Seattle Genetics
■	Apomab		colorectal cancer	I	Genentech
■		MEK inhibitor	cancer	I	Genentech
■		IAP antagonist	cancer	I	Genentech
■		3rd-generation anti-CD20 antibody	hematologic malignancies	I	Genentech
■		anti-cMet	cancer	I	Genentech
■	PI3K alpha	PI3 kinase inhibitor	cancer	I	Genentech
■	TP300		colorectal cancer	I	Chugai
■	Anti-IL13	Anti-IL13	asthma	II	Genentech
■		anti-IFN alfa	systemic lupus erythematosus	I	Genentech
■	VAP-1		inflammatory diseases	I	BioTie
■	Anti-oxLDL	Anti-oxLDL	secondary prevention of cardiovascular events	I	Genentech
■	NA808		hepatitis C	I	Chugai
■	rhuMab Beta7	rhuMab Beta7	ulcerative colitis	I	Genentech
■	Anti-CD4	Anti-CD4	rheumatoid arthritis	I	Genentech
■	Anti-Abeta	Anti-Abeta	Alzheimer's disease	I	Genentech

Participation through Chugai

■	EPOCH	Epogin (epoetin beta)	chemotherapy-induced anemia	III	
■	ED-71	activated vitamin D derivative	osteoporosis	III	
■	GM-611	(mitemincinal fumarate)	motilin agonist	II	

Participation through Genentech

■	Lucentis (ranibizumab)	antibody fragment to VEGF	diabetic macular edema	III	
■	Lucentis (ranibizumab)	antibody fragment to VEGF	retinal vein occlusion	III	
■	TNkase (tenecteplase)	thrombolytic agent	catheter clearance	III	
■	Xolair (omalizumab)	anti-IgE antibody	pediatric asthma	Filed US	Novartis
■	Raptiva (efalizumab)	humanised anti-CD11a monoclonal antibody	renal transplant	II	Merck Serono
■	ABT-869		solid tumours	II	Abbott
■	ABT-263		solid tumours and hematologic malignancies	I	Abbott

At the beginning of 2009 the division's R&D pipeline comprised 120 clinical projects, including 62 new molecular entities (NMEs) and 58 additional indications. Forty NMEs are currently in phase I, 16 in phase II and six in phase III or filed for regulatory review.

■	Therapeutic protein	First indication	Blue type	Phase I	Initial studies in healthy volunteers and possibly in patients
■	Small molecule	Additional indications	Black type	Phase II	Efficacy, tolerability and dose-finding studies in patients
■	Peptide	Current as of	January 2009	Phase III	Large-scale studies in patients for statistical confirmation of safety and efficacy
□	Therapeutic vaccine				
■	Antibody fragment				