

2000

*collaborations
between Pharmaceuticals
and Diagnostics*



RESEARCH AND DEVELOPMENT

Committed. 8,073 million Swiss francs invested in research and development.

Innovative. Our Pharmaceuticals pipeline is one of the strongest in the industry. As of January 2012 it included 122 projects: 79 involving new molecular entities and 43 additional indications or line extensions for existing medicines.

Successful. The Pharmaceuticals Division filed 21 major marketing applications – including three for new molecular entities – gained 24 major approvals and announced positive results from 17 out of 20 late-stage clinical trials.

Impactful. The Diagnostics Division launched 50 tests delivering enhanced information for medical decision-making and 13 new or upgraded instruments in key markets.

Integrated. Our Pharmaceuticals and Diagnostics Divisions are collaborating on more than 200 projects across all therapeutic areas of interest at Roche.

Key figures

Core R&D expenditures in 2011

Roche Group¹	8,073 millions of CHF	-1% (CER ²)	19.0% of sales
Pharmaceuticals	7,173 millions of CHF	-2% (CER)	21.9% of sales
Diagnostics	900 millions of CHF	+12% (CER)	9.2% of sales

- 1 Decrease by 1% due to resource prioritisation and savings from the Operational Excellence programme.
 2 Constant exchange rates (average full-year 2010).

Employees in R&D	18,449 Roche Group	15,502 Pharmaceuticals	2,947 Diagnostics
Patients in clinical trials	332,183		

Pharmaceuticals clinical development projects

	Phase I	Phase II	Phase III, registration
New molecular entities (investigational new medicines)	47	21	11
Line extensions (additional indications, new dosage forms for marketed or investigational medicines)	2	7	34

Our R&D strategy

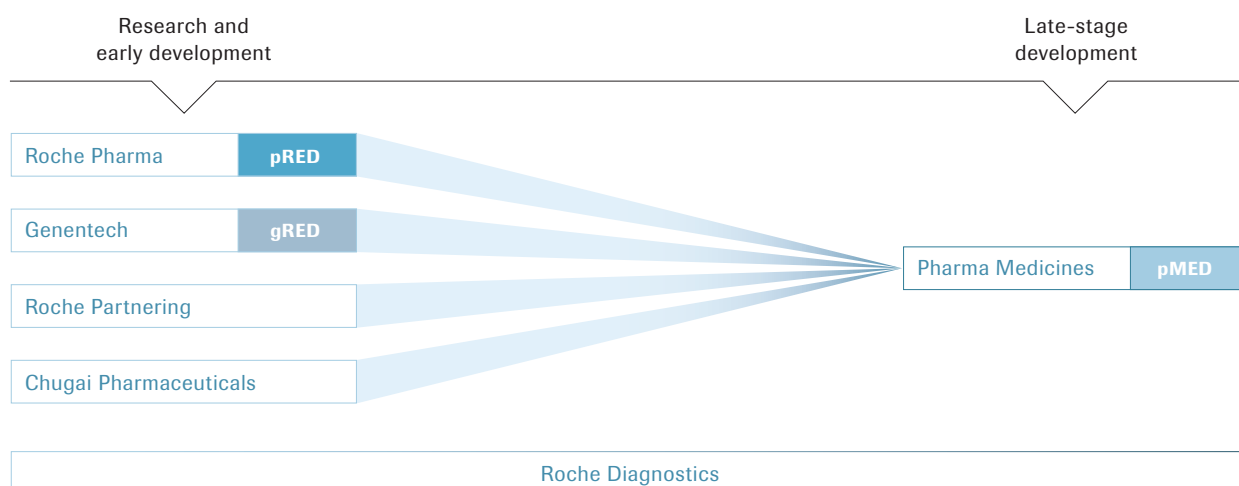
No company in the world invests more than we do in the quest for innovative healthcare solutions. In 2011 Roche invested 8.1 billion Swiss francs in R&D (core basis¹), a decline of 1%, on a currency-adjusted basis, versus 2010. More than 330,000 patients are currently enrolled in over 2,100 clinical trials involving investigational or currently marketed Roche Group medicines. We plan to maintain high levels of R&D investment so that we can continue to move the most advanced projects towards market launch while ensuring a steady flow of promising new compounds into late-stage development. We will also

continue to develop newer and better diagnostic systems and expand the range of tests they can perform, which is already one of the broadest in the *in vitro* diagnostics industry.

People react differently to medications due to variations in their genetic makeup. Identifying specific gene variants that determine how well a certain treatment works and is tolerated is a key element of our research and development efforts. This is what drives our personalised healthcare approach – fitting treatments to defined groups of patients. And its success depends on systematically leveraging the combined capabilities of our Pharmaceuticals and Diagnostics Divisions. Over the last few years Roche has shown how the interweaving of diagnostic and pharmaceutical expertise is increasingly paving

¹ For a full explanation of the core results concept, see page 146 of the Finance Report (part 2 of this Annual Report).

Unique structure fosters innovation



the way for personalised healthcare, especially in oncology, but now also in immunology and neuroscience. Our aim is to provide healthcare professionals and patients with more powerful diagnostic tools and targeted treatments based on new insights into how diseases arise at the molecular level.

Diversity of approaches

Scientific breakthroughs are most likely to occur when scientists are free to tackle problems from different angles and in different ways. Roche scientists have this freedom. We believe that a diversity of views, cultures and approaches promotes creativity, especially in research and early development: Pharma Research and Early Development (pRED), Genentech Research and Early Development (gRED), Roche Diagnostics and Chugai operate independently within the Group, forming the hubs of an innovation network that includes alliances with more than 150 outside partners, such as universities, research institutes and biotech companies. In 2011 Roche was again recognised as one of our industry's top partnering organisations. Together with our partners we turn the multiplicity of ideas into medical innovation; about one third of the current projects in Roche's pipeline have come from these alliances. You will find details of the Group's partnering activities in 2011 under *Accessing external innovation* (page 47, below).

Collaborate from discovery to commercialisation

Over the past few years we have continuously improved the organisational and technological framework for cooperation

between our Pharmaceuticals and Diagnostics Divisions. Although they have different R&D processes, the two divisions can share research facilities, technologies and discoveries when working together on internal projects. This is a unique advantage that sets Roche apart from other companies.

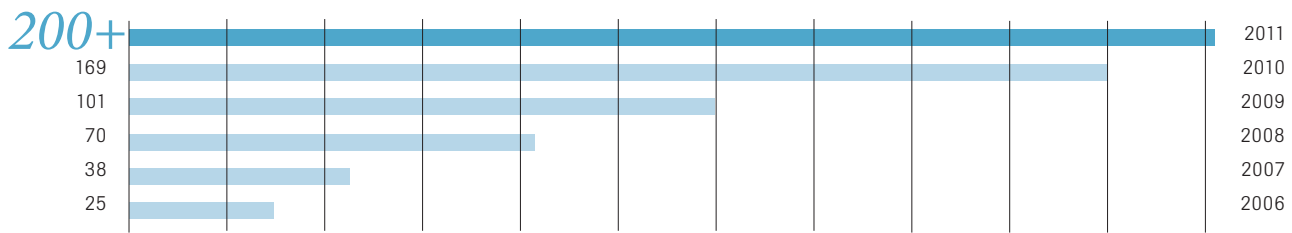
Diagnostic tools are finding increasing use in pharmaceutical research. Most importantly, close cooperation is the basis for the successful implementation of our personalised healthcare strategy. Roche has identified a multitude of potential biomarkers² that can be used to evaluate disease processes, understand disease diversity, identify drug targets and recognise differences between patients. Once a biomarker is found, a standardised diagnostic test can be developed before or during clinical trials and prepared for regulatory approval alongside the drug.

Today, Roche has biomarker programmes and dedicated biomarker teams for every drug in development. Our Pharmaceuticals and Diagnostics Divisions are currently collaborating on more than 200 projects across all therapeutic areas of interest at Roche. More than half of these projects are in oncology, followed by inflammation/immunology, neuroscience, virology and metabolic diseases.

Our collaborative efforts improve not only the prospects for more effective healthcare and better use of healthcare resources but also the efficiency of bringing new therapies and diagnostic tests to market.

² Biomarker: a characteristic that can be measured and evaluated as an indicator of a normal biological process, a disease process, or a response to treatment.

Number of collaborations between Roche Pharmaceuticals and Roche Diagnostics



Improving development with Personalised Healthcare

We continue to intensify our efforts to improve R&D productivity and innovate drug development through our Personalised Healthcare approach. Here and in other areas the Roche Group's expertise in molecular biology gives us a clear competitive advantage.

Understanding the heterogeneity of diseases and using diagnostic tools to improve drug discovery and clinical development, we can identify better drug targets and select patient subgroups that are most likely to benefit from our treatments. This is the core of Roche Personalised Healthcare, and this targeted approach has already proven effective in reducing the attrition rate of drug candidates by:

- better profiling of drug candidates at early stages in development
- improving clinical trials results through better selection of endpoints and stronger data
- increasing the efficacy of drug candidates in clinical studies by recruiting suitable patient subgroups

This allows us to pursue projects that might otherwise be stopped because of side effects or lack of significant efficacy in the patient sample as a whole, despite promising results in some patients.

R&D pipeline

Growing number of new drug candidates and diagnostic tests

Roche has produced a steady flow of new drug candidates and diagnostic tests in key therapeutic areas over the past few years by leveraging its strengths in biotechnology and in vitro diagnostics. By the end of 2011, our late-stage pipeline included 13 investigational new medicines (new molecular entities, NMEs), compared with two in 2007. Seven of these are being developed as personalised therapies.

Our goal in each case is to produce new medicines that are first in class or best in class. Our commitment to following the science translated into positive results in 17 out of 20 late-stage clinical trials in 2011, seven of which have already formed the basis for regulatory approvals or filings. The results suggest that many of our investigational medicines have the potential to offer significant advances in areas where new treatment options are needed, including breast, lung and skin cancer, asthma, and adult and childhood forms of rheumatoid arthritis.

At the end of 2011 the Pharmaceuticals Division's clinical development portfolio (phases I to III and registration) included 79 new molecular entities (NMEs), up from 62 a year earlier, and 43 additional indications. In 2011 we filed marketing applications for no fewer than three NMEs. Roche's pharmaceuticals development pipeline is shown on pages 38–39 of this report. Further details are available at www.roche.com.

The Diagnostics Division's R&D efforts resulted in the launch of 50 tests and 13 new or upgraded instruments in key mar-

Roche companion diagnostics on the market or in late development*

Disease area	Disease	Drug	Diagnostic test**	Technology	Application	
Virology	CMV	Valcyte	CMV viral load	PCR	monitoring	
	HBV	Pegasys and other antivirals	HBV viral load	PCR	monitoring	
	HBV	Pegasys, peginterferon alfa-2b (Merck/SP)	HBsAg levels	immunoassay	monitoring	
	HCV	Pegasys, peginterferon alfa-2b (Merck/SP)	HCV viral load	PCR	monitoring	
	HCV	merictabine (R7128)	HCV viral load	PCR	monitoring	
	HCV	danoprevir (RG7227)	HCV viral load	PCR	monitoring	
	HIV	antivirals	HIV viral load	PCR	monitoring	
	HIV	abacavir (GlaxoSmithKline)	HLA-B genotype	PCR	screening	
	Oncology	breast cancer	Herceptin, lapatinib (GlaxoSmithKline)	HER2 expression/ gene amplification	IHC, ISH	selection
breast cancer		tamoxifen and other hormonal therapies	ER/PR expression	IHC	selection	
breast cancer		pertuzumab (RG1273)	HER2 expression/ gene amplification	IHC, ISH	selection	
breast cancer		trastuzumab emtansine (T-DM1, RG3502)	HER2 expression/ gene amplification	IHC, ISH	selection	
cancer		compound (Merck)	p53 mutations	microarray	selection	
colon cancer		cetuximab (Merck)	KRAS mutations	PCR	selection	
colon cancer		panitumumab (Amgen)	KRAS mutations	PCR	selection	
gastric cancer		Herceptin	HER2 expression/ gene amplification	IHC, ISH	selection	
melanoma		Zelboraf	BRAF mutation	PCR	selection	
NSCLC		Tarceva***, gefitinib (AstraZeneca)	EGFR mutations	PCR	selection	
NSCLC		onartuzumab (MetMAb, RG3638)	Met expression	IHC	selection	
NSCLC		TG4010 (Transgene)	MUC1 expression	IHC	selection	
NSCLC		crizotinib (Pfizer)	ALK	IHC	selection	
pancreatic cancer		CP-4126 (Clovis Oncology)	hENT1 expression	IHC	selection	
sarcoma		MDM2 antagonist (RG7112)	p53 mutations	PCR	selection	
Inflammation		asthma	lebrikizumab (RG3637)	serum periostin levels	immunoassay	selection
		rheumatoid arthritis	MabThera/Rituxan	RF, anti-CCP Ab	immunoassay	selection
Others	osteoporosis	Bonviva/Boniva and other bisphosphonates	B-Crosslaps; P1NP levels	immunoassay	monitoring	
	transplantation	CellCept	MPA levels	immunoassay	monitoring	

* We have further projects with other pharmaceutical companies which are not disclosed for confidentiality reasons.

** not available in all markets;

*** selection of patients eligible for first-line treatment.

black type = on the market, grey type = in development. monitoring = monitoring of a patient's response to a particular treatment; screening = screening of patients for a particular genetic variation of HLA associated with hypersensitivity to abacavir; selection = selection of patients eligible for a particular treatment. ALK= anaplastic lymphoma receptor tyrosine kinase; anti-CCP = antibodies against cyclic citrullinated peptide; BRAF = B-isoform of the rapidly growing fibrosarcoma oncogene; CMV = cytomegalovirus; EGFR = epidermal growth factor receptor; ER/PR = estrogen receptor/progesterone receptor; HBV = hepatitis B virus; HBsAg = HBV surface antigen; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; hENT1 = human equilibrative nucleoside transporter; HLA = human leucocyte antigen; IHC = immunohistochemistry; ISH = *in situ* hybridisation; KRAS = member of the Ras family of oncogenes; MPA = mycophenolic acid; NSCLC = non-small cell lung cancer; PCR = polymerase chain reaction; P1NP = procollagen type 1 N-terminal propeptide; RF = rheumatoid factor; SP = Schering Plough.

kets. These product launches enhance the information available to guide treatment decisions and drive efficiency in clinical laboratories and research centres.

Pharmaceuticals for unmet medical needs

In addition to progress with key investigational compounds, in 2011 Roche also passed significant regulatory and development milestones with several currently marketed medicines. An overview can be found in the tables of clinical trials, approvals and filings on pages 36, 42 and 43. The main regulatory and clinical highlights from programmes in the fields of oncology, immunology and ophthalmology are summarised below, together with status updates on promising investigational medicines being developed to address viral diseases and disorders of the central nervous system.

Oncology

We currently have 42 new compounds in development in oncology. In addition to obtaining positive results from ten key clinical trials in 2011, we filed marketing applications for the most advanced of our investigational new medicines in the US and the European Union: Zelboraf, for metastatic melanoma (now approved in the US, Switzerland and Brazil); vismodegib, for basal cell carcinoma (a form of skin cancer); and pertuzumab, for HER2-positive metastatic breast cancer. In addition, we made significant progress in the development of other investigational compounds and with projects aimed at extending approved indications or introducing new dosage forms of marketed products such as Avastin, Herceptin and Tarceva.

Zelboraf approved in US for metastatic melanoma

In August the US Food and Drug Administration (FDA) approved Zelboraf for the treatment of BRAF V600E mutation-positive inoperable or metastatic melanoma, as determined by an FDA-approved test. The FDA simultaneously approved Roche Diagnostics' cobas BRAF test, a companion diagnostic used to identify patients for whom treatment with Zelboraf is appropriate. The approvals enabled Genentech to launch this new oral, targeted cancer medicine in the US less than four months after the marketing application was filed, and only five years after the start of clinical trials. Marketing approval was also obtained in Switzerland and Brazil in the fourth quarter. In December the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) unanimously recommended that Zelboraf be granted full EU marketing approval. The approvals and recommendation are based on

results from two clinical studies (BRIM3 and BRIM2), which demonstrated a significant clinical benefit with Zelboraf in patients with BRAF V600-mutated unresectable or metastatic melanoma. We have filed marketing applications in a number of other countries worldwide, including Australia and New Zealand, where rates of malignant melanoma are high. Roche Diagnostics' BRAF test received CE Mark³ certification in August.

Zelboraf (vemurafenib; RG7204, PLX4032) is being co-developed under a 2006 licence and collaboration agreement between Roche and Plexikon, a member of the Daiichi Sankyo Group. Zelboraf is designed to target and inhibit some mutated forms of the BRAF protein found in about half of all cases of melanoma, the deadliest and most aggressive form of skin cancer. The BRAF protein is a key component of the RAS-RAF pathway involved in normal cell growth and survival. Certain mutations at position V600 keep the BRAF protein in an active state and may cause excessive signalling in the pathway, leading to uncontrolled cell growth and survival. Roche is conducting a broad development programme with Zelboraf that includes testing combinations with other medicines (both approved and investigational, from Roche, Genentech and other companies), as well as studies in other tumour types. In December 2011, in collaboration with Bristol Myers Squibb, we initiated a phase I/II study with combined Zelboraf and Yervoy (ipilimumab) in BRAF-mutated metastatic melanoma.

Vismodegib filed in US and EU for BCC skin cancer

In November the FDA accepted and filed Genentech's new drug application for vismodegib for the treatment of adults with advanced basal cell carcinoma (BCC) for whom surgery is considered inappropriate. The application was granted Priority Review status, and the FDA has assigned an action date in March 2012. In December Roche submitted a marketing application for the same indication in the EU. Both applications are based on results from the pivotal phase II ERIVANCE BCC study, which showed that vismodegib substantially shrank tumours or healed visible lesions in 43% of patients with locally advanced BCC and 30% of patients with metastatic BCC. Vismodegib (RG3616) is an investigational, oral, targeted medicine designed to selectively inhibit abnormal signalling in the Hedgehog pathway, an underlying molecular driver of BCC that is implicated in more than 90% of cases. Roche is developing vismodegib under a collaboration agreement with Curis. BCC is the most common type of skin cancer and is generally considered curable by surgery. However, when advanced,

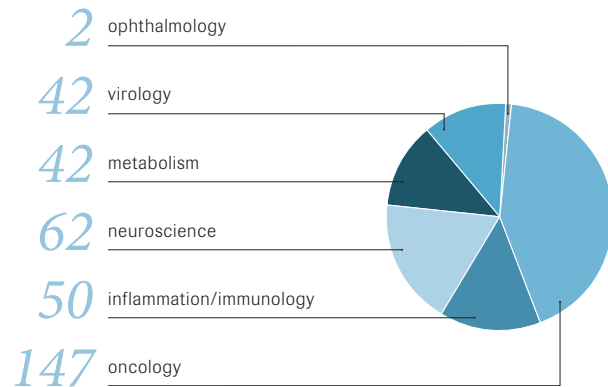
³ Certification that an *in vitro* diagnostic product complies with all requirements for use in the EU.

R&D projects by therapeutic area (Roche and Genentech)

Research and early development

Discovery programmes + phase 0, I and II projects

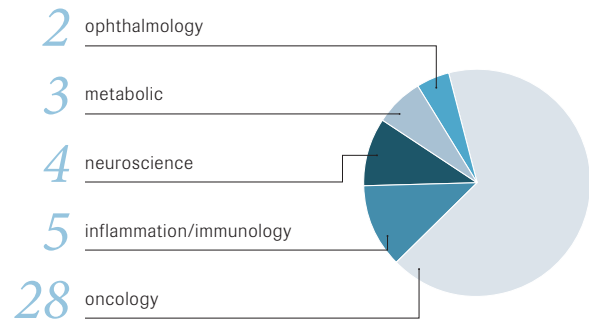
345 projects



Late development

Phase III and registration

42 projects



BCC can cause disfiguring and debilitating effects and in some patients can ultimately be life-threatening.

Pertuzumab filed for HER2-positive breast cancer

In December we submitted marketing applications in the US and EU for pertuzumab as a treatment for previously untreated HER2-positive metastatic breast cancer. The filings are based on results from CLEOPATRA, the first randomised phase III study with pertuzumab, which compared combined pertuzumab, Herceptin (trastuzumab) and docetaxel chemotherapy with Herceptin and chemotherapy alone in people with previously untreated HER2-positive metastatic breast cancer. People who received pertuzumab in combination with Herceptin and chemotherapy experienced a 38% reduction in the risk of their disease worsening or death (progression-free survival, PFS). Median PFS improved by 6.1 months from 12.4 months for Herceptin and chemotherapy to 18.5 months for pertuzumab, Herceptin and chemotherapy.

Pertuzumab (RG1273) is the first in a new class of targeted anticancer agents known as HER2 dimerisation inhibitors. It is designed to block the dimerisation (pairing) of HER2 with other members of the HER family of receptors. HER dimerisation is believed to play an important role in the growth and formation of several different cancer types. The mechanisms of action of pertuzumab and Herceptin are believed to complement each other, as both bind to the HER2 receptor but on different regions. This is thought to provide a more compre-

hensive blockade of HER signalling pathways. Pertuzumab is being studied with the current standard of care, Herceptin plus chemotherapy, in HER2-positive breast and stomach cancer.

Avastin regulatory update

Breast cancer. In July the European Commission approved an extension to the Avastin EU breast cancer label. Avastin may now be used in combination with Xeloda (capecitabine) for the first-line treatment of women with metastatic breast cancer in whom other chemotherapy options are not considered appropriate. In September the Japanese authorities approved Avastin for the treatment of inoperable or recurrent breast cancer. In November the FDA issued a final decision revoking US approval of Avastin for the treatment of metastatic breast cancer. This followed a recommendation in July 2010 by an FDA expert panel, the agency's initial notice of revocation in December 2010, and an appeal in 2011 by Roche against removal of the indication. The FDA decision does not affect the medicine's other approved indications in the US and elsewhere.

Ovarian cancer. Avastin received EU approval in December for the treatment of women with newly diagnosed advanced ovarian cancer. Based on the results of the phase III ICON-7 and GOG 218 trials, the new approval allows the use of Avastin in combination with standard chemotherapy (carboplatin and paclitaxel) for the front-line treatment (first-line treatment following surgery) of advanced epithelial ovarian, primary peritoneal or fallopian tube carcinoma. Roche filed an additional EU

Pharmaceuticals Division – major clinical trials in 2011

Product	Indication	Trial (phase)	Outcome	Aim
Actemra	moderate to severe rheumatoid arthritis, Actemra monotherapy vs combined Actemra + methotrexate	ACT-RAY (IIIb)	efficacy (remission) and safety	additional data
Actemra (subcutaneous formulation)	rheumatoid arthritis	double-blind, randomised, parallel group study (III)	non-inferiority of efficacy of subcutaneous formulation versus intravenous formulation	registration (new dosage form)
Actemra	ankylosing spondylitis	Builder 1 + 2 (III)	Builder 1 did not meet protocol-specified primary endpoint; programme terminated	registration (potential new indication)
Avastin	recurrent platinum-sensitive ovarian cancer, versus chemotherapy	OCEANS (III)	significantly improved PFS	registration (potential new indication)
Avastin	previously untreated, advanced non-squamous NSCLC, maintenance treatment in combination with pemetrexed chemotherapy	AVAPERL (III)	significantly improved PFS	additional data
Avastin + Herceptin	HER2-positive metastatic breast cancer	AVEREL (III)	study did not meet protocol-specified primary endpoint	registration (potential new indication)
dalcetrapib	patients with CHD, or CHD risk equivalents	dal-PLAQUE (IIb)	data suggest possible beneficial vascular effects, generally well tolerated	exploratory (safety, efficacy)
dalcetrapib	patients with CHD, or CHD risk equivalents	dal-VESSEL (IIb)	endothelial function preserved, no change in blood pressure, generally well tolerated	exploratory (safety, efficacy)
Herceptin (subcutaneous formulation)	HER2-positive early breast cancer	HannaH (III)	comparable efficacy of subcutaneous formulation versus intravenous formulation	registration (new dosage form), personalised medicine
lebrikizumab	adult asthma not adequately controlled by inhaled corticosteroids	MILLY (II)	significantly improved pre-bronchodilator FEV1	proof of concept, personalised medicine
Lucentis	diabetic macular edema, compared with sham injection	RIDE, RISE (III), 2-year data	rapid and sustained improvement in vision (significantly improved eye chart scores versus baseline)	registration (potential new indication)
Lucentis	wet age-related macular degeneration, comparing alternative dosing regimens with monthly Lucentis	HARBOR (III)	efficacy data do not support initiation of further high-dose studies, 0.5 mg PRN dosing to be discussed with FDA	registration (new dosing regimen)
obinituzumab (GA101)	relapsed indolent NHL, head-to-head comparison with MabThera/Rituxan	GAUSS (II)	higher response rates with GA101 versus MabThera, phase III testing initiated	proof of concept
ocrelizumab	relapsing-remitting multiple sclerosis	randomised, multi-centre, placebo-controlled study (II)	significant reduction in disease activity, maintained through 96 weeks	dose-finding with open-label extension
onartuzumab (MetMab)	2 nd -/3 rd -line NSCLC, combination with Tarceva	OAM4558g (II), final data (including OS)	significantly improved PFS and OS	proof of concept, personalised medicine
pertuzumab	HER2-positive metastatic breast cancer, combination with Herceptin and docetaxel	CLEOPATRA (III)	significantly improved progression-free survival	registration, personalised medicine
Tarceva	metastatic non-small cell lung cancer with epidermal growth factor receptor-activating mutations, first-line treatment, versus chemotherapy	EURTAC (III)	significantly improved PFS	potential new indication, personalised medicine
trastuzumab emtansine (T-DM1)	HER2-positive metastatic breast cancer, previously untreated HER2-positive, versus Herceptin plus chemotherapy	TDM4450g (II)	significantly improved PFS	proof of concept, personalised medicine
vismodegib	advanced basal cell carcinoma, (single-arm trial)	ERIVANCE BCC/SHH4476G (II)	objective response rate (tumour shrinkage, lesion healing)	registration
Zelboraf	previously untreated BRAFV600 mutation-positive metastatic melanoma, versus chemotherapy	BRIM3 (III)	significantly improved OS and PFS	registration, personalised medicine

BRAF = B-isoform of the rapidly growing fibrosarcoma oncogene; CHD = coronary heart disease; FEV1 = forced expiratory volume 1 (the volume of air that can be forced out in one second after taking a deep breath; a measure of lung function); HER2 = human epidermal growth factor receptor 2; NHL = non-Hodgkin's lymphoma; NSCLC = non-small cell lung cancer; OS = overall survival (time between the start of treatment and death); PFS = progression-free survival (time between the start of treatment and disease progression); PRN = pro re nata (as needed).

marketing application in August, seeking approval of Avastin for use in relapsed ovarian cancer. The EU filing is based on the results of the phase III OCEANS study. The results, which were also presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in June, show that an Avastin-based regimen halved the risk of the disease getting worse in women with recurrent ovarian cancer. These data add to the growing body of evidence supporting the potential role of Avastin in this disease, which includes the ICON-7 and GOG 218 trials of Avastin in newly diagnosed ovarian cancer. Roche plans to make a decision on whether to seek US marketing approval for Avastin in ovarian cancer when final overall survival results from all phase III trials are available (expected 2013). Ovarian cancer is the sixth type of cancer for which Avastin has been approved.

Upon its initial approval in the US in 2004 for metastatic colorectal cancer, Avastin (bevacizumab) became the first anti-angiogenic therapy made widely available for the treatment of patients with an advanced cancer. Today, Avastin continues to transform cancer care through its proven survival benefit across several types of cancer. It is approved in the US and Europe for the treatment of advanced stages of colorectal, non-small cell lung and kidney cancer, and is also available in the US and over 32 other countries for the treatment of patients with glioblastoma, a type of brain tumour. Avastin is approved in more than 80 countries, including the EU and Japan, for breast cancer.

Herceptin SC achieves positive phase III results

In October Roche announced that a phase III study (HannaH) had achieved its primary objectives, demonstrating comparable efficacy of a new investigational subcutaneous (SC) formulation of Herceptin to the current intravenous (IV) infusion formulation in women with HER2-positive early breast cancer. Herceptin SC uses Halozyme Therapeutics' Enhance technology, which enables the injection of large volumes of a medication under the skin. The SC formulation takes around five minutes to administer, compared with around 30 minutes for the IV infusion. Subcutaneous administration may allow patients to spend less time in hospital receiving their treatment than is the case with intravenous delivery.

Herceptin (trastuzumab) is a humanised antibody, designed to target and block the function of HER2, a protein produced by a specific gene with cancer-causing potential. Herceptin activates the body's immune system and suppresses HER2 to target and destroy the tumour. Herceptin has demonstrated unprecedented efficacy in treating both early and advanced (metastatic) HER2-positive breast cancer as well as HER2-positive advanced (metastatic) stomach cancer. Since 1998

Herceptin has been used to treat almost one million patients with HER2-positive breast and stomach cancer worldwide. It is approved in more than 150 countries.

Tarceva approved for genetically distinct type of NSCLC

In August the EU authorities approved Tarceva for use in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR-activating mutations. Based on the results of the phase III EURTAC study and additional data, this approval enables the use of Tarceva as first-line monotherapy in people with this genetically distinct type of NSCLC. Treatment with Tarceva in this setting has been shown to more than triple the number of patients whose tumours shrink (response rate) and to nearly double progression-free survival (the time patients live without their disease progressing) compared with chemotherapy. Roche filed a marketing application for this indication with the Swiss health authorities in August, and a regulatory submission in the US is planned for 2012.

Tarceva (erlotinib) is a once-daily, oral non-chemotherapy treatment for advanced or metastatic NSCLC and advanced pancreatic cancer. It has been shown to potently inhibit the epidermal growth factor receptor (EGFR), a protein involved in the growth and development of cancers. Tarceva is developed in partnership with OSI Pharmaceuticals, a member of the Astellas global group of companies.

Onartuzumab extends overall survival in Met-positive NSCLC

Final data from a key phase II trial presented at the ASCO annual meeting in June showed that people with metastatic NSCLC whose tumours had high levels of Met, as determined by Roche's tissue-based companion diagnostic, lived twice as long without their disease getting worse and lived three times longer overall when they received onartuzumab plus Tarceva compared with Tarceva alone. A phase III trial of combined onartuzumab and Tarceva as second- and third-line treatment in patients with metastatic Met-positive NSCLC (MetLung) started in January 2012.

Onartuzumab (MetMAb, RG3638) is a unique monovalent (one-armed) monoclonal antibody designed to target Met, a protein associated with poor outcome in many cancers. The compound blocks Met signalling in cancer cells by binding specifically to the cell-surface Met receptor. Onartuzumab is being investigated as a potential treatment for metastatic NSCLC, breast and colorectal cancer.

Pharmaceuticals pipeline

Oncology

- 1 approved in the EU
 - 2 submitted in the EU
 - 3 approved in US, CHMP positive opinion in EU
 - 4 submitted in the US
 - ⊙ Personalised Healthcare project
- RG-No Roche- and/or Genentech-managed
 CHU Chugai-managed
 RG105 MabThera is branded as Rituxan in the US and Japan
 RG1569 Actemra is branded as RoActemra in the EU

- AMD age-related macular degeneration
 BC breast cancer
 CRC colorectal cancer
 DMARD-IR disease-modifying antirheumatic drug, inadequate response
 DME diabetic macular edema
 RVO retinal vein occlusion
- MAB monoclonal antibody
 NSCLC non-small cell lung cancer
 rhu recombinant, humanised
 s.c. subcutaneous

Project ID	Project/Product	Indication
RG7112	⊙ MDM2 antagonist (2)	solid and hematologic tumours
RG7116	anti-HER3 MAb	solid tumours
RG7155	CSF1R MAb	solid tumours
RG7167	⊙ CIF/MEK inhibitor	solid tumours
RG7204	Zelboraf+ ipilimumab	metastatic melanoma
RG7212	⊙ Tweak MAb	cancer
RG7256	⊙ BRAF inhibitor (2)	BRAF-mutated melanoma
RG7304	⊙ RAF + MEK dual inhibitor	solid tumours
RG7334	⊙ anti-PLGF MAb	solid tumours
RG7356	⊙ anti-CD44 MAb	solid tumours
RG7420	⊙ MEK inhibitor	solid tumours
RG7421	⊙ MEK inhibitor	solid tumours
RG7388	MDM2 (4)	cancer
RG7440	⊙ AKT inhibitor	solid tumours
RG7444	⊙ anti-FGFR3 MAb	cancer
RG7446	tumour immunotherapy	cancer
RG7450	antibody-drug conjugate	prostate cancer
RG7458	antibody-drug conjugate	ovarian cancer
RG7459	IAP antagonist (2)	solid tumours and lymphoma
RG7593	anti-D22 antibody-drug conjugate	hematologic malignancies
RG7594	anti-angiogenic	solid tumours
RG7596	antibody-drug conjugate	hematologic tumours
RG7597	anti-HER3/EGFR MAb	metastatic epithelial tumours
RG7598	antibody-drug conjugate	multiple myeloma
RG7599	antibody-drug conjugate	cancer
RG7600	antibody-drug conjugate	cancer
RG7601	Bcl-2 inhibitor	chronic lymphocytic leukemia
RG7602	Chk-1 inhibitor	tumours or lymphoma
RG7603	(not disclosed)	solid tumours or non-Hodgkin's lymphoma
RG7604	⊙ PI3K inhibitor	cancer
RG7686	⊙ anti-glypican-3 MAb	liver cancer
CHU	ALK inhibitor	non-small cell lung cancer
CHU	PI3 kinase inhibitor	solid tumours
CHU	WT-1 peptide cancer vaccine	cancer
RG1273	⊙ pertuzumab	HER2-positive metastatic breast cancer, 2nd-line
RG1273	⊙ pertuzumab	HER2-positive metastatic gastric cancer
RG3502	⊙ T-DM1	HER2-positive early breast cancer
RG3616	vismodegib	operable basal cell carcinoma
RG3638	onartuzumab (MetMAB)	metastatic breast cancer
RG3638	onartuzumab (MetMAB)	metastatic colorectal cancer, 1st-line
RG7160	⊙ anti-EGFR MAb (GA201)	solid tumours
RG7204	⊙ Zelboraf	papillary thyroid cancer
RG7321	⊙ PI3 kinase inhibitor	solid tumours
RG7422	⊙ PI3 K/mTOR inhibitor	solid and hematologic tumours
RG7414	⊙ anti-EGFL7 MAb	metastatic colorectal cancer, 1st-line
RG105	MabThera/Rituxan	non-Hodgkin's lymphoma, s.c. dosage form
RG435	Avastin	HER2-positive breast cancer, adjuvant treatment
RG435	Avastin	HER2-negative breast cancer, adjuvant treatment
RG435	Avastin	triple-negative breast cancer, adjuvant treatment
RG435	Avastin	metastatic breast cancer, 2nd-line
RG435	Avastin	non-small cell lung cancer, adjuvant treatment
RG435	Avastin	high-risk carcinoma
RG435	Avastin	glioblastoma, 1st-line
RG435	Avastin	metastatic CRC, treatment through multiple lines
RG435 ¹	Avastin	ovarian cancer, 1st-line
RG597	Herceptin	HER2-positive breast cancer, s.c. dosage form
RG597	Herceptin	HER2-positive BC, adjuvant treatment (2 years)
RG1273	⊙ pertuzumab	HER2-positive early breast cancer
RG1415 ¹	⊙ Tarceva	NSCLC, EGFR-activating mutations, 1st-line
RG1415	Tarceva	NSCLC, adjuvant treatment
RG3502	T-DM1 (antibody-drug conjugate)	HER2-positive advanced metastatic breast cancer
RG3502	T-DM1 (antibody-drug conjugate)	HER2-positive metastatic breast cancer, 3rd-line

RG3502	T-DM1 (antibody-drug conjugate)	HER2-positive metastatic breast cancer, 1st-line	Inflammation Immunology	Phase I	Phase II	Phase III	Registration
RG3638	onartuzumab (MetMAB)	metastatic non-small cell lung cancer					
RG7159	obinituzumab (GA101)	chronic lymphocytic leukemia					
RG7159	obinituzumab (GA101)	indolent non-Hodgkin's lymphoma, relapsed					
RG7159	obinituzumab (GA101)	diffuse large B cell lymphoma					
RG7159	obinituzumab (GA101)	indolent non-Hodgkin's lymphoma, front-line					
RG105	MabThera/Rituxan	non-Hodgkin's lymphoma, fast infusion					
RG435 ²	Avastin	relapsed ovarian cancer					
RG1273	pertuzumab	HER2-positive metastatic breast cancer, 1st-line					
RG3616	vismodegib	advanced basal cell carcinoma					
RG7204 ³	Zelboraf	metastatic melanoma					
RG4934	anti-IL-17 MAb	autoimmune diseases					
RG7185	CRTH2 antagonist	asthma					
RG7258	anti-TSLPR MAb	asthma					
RG7624	anti-IL 17 MAb	autoimmune diseases					
CHU	anti-IL 6 MAb	rheumatoid arthritis					
RG3637	lebrikizumab	severe asthma					
RG7413	rhu MAb Beta7	ulcerative colitis					
RG7415	rontalizumab	systemic lupus erythematosus					
RG7416	anti-LT alpha MAb	rheumatoid arthritis					
RG7449	anti-M1 prime MAb	asthma					
RG105	MabThera/Rituxan	ANCA-associated vasculitis					
RG1569	Actemra/RoActemra	rheumatoid arthritis, s.c. dosage form					
RG1569	Actemra/RoActemra	early rheumatoid arthritis					
RG1569	Actemra/RoActemra	rheumatoid arthritis, DMARD-IR, vs adalimumab					
RG3648	Xelair	chronic idiopathic urticaria					
CHU	Suvenyl	enthesopathy					
RG7795	TLRH7 agonist	hepatitis C					
RG7667	(not disclosed)	infectious disease					
RG7128	mericitabine	hepatitis C					
RG7227	danoprevir	hepatitis C					
RG7790	setrobuvir	hepatitis C					
RG7236	Cat S antagonist	cardiovascular risk in chronic kidney disease					
RG7273	ABCA1 inducer	dyslipidemia					
RG7652	(not disclosed)	metabolic diseases					
RG7685	GIP/GLP-1 dual agonist	type 2 diabetes					
RG4929	11 beta HSD inhibitor	metabolic diseases					
RG1512	anti-P selectin MAb	acute coronary syndrome/cardiovascular disease					
RG7418	anti-oxLDL MAb	secondary prevention cardiovascular events					
RG1439	alegitazar	cardiovascular risk reduction in type 2 diabetes					
RG1658	dalcetrapib	atherosclerosis, cardiovascular risk reduction					
CHU	tofogliflozin (SGLT2)	type 2 diabetes					
RG3626 ⁴	Acthase	extended time window, acute ischemic stroke					
RG1662	GABA-A $\alpha 5$ inverse agonist	cognitive disorders					
RG7314	V1 receptor antagonist (2)	autism					
RG7129	BACE inhibitor	Alzheimer's disease					
RG1450	gantenerumab	Alzheimer's disease					
RG1577	MAO-B inhibitor	Alzheimer's disease					
RG1578	mGluR2 antagonist (2)	depression					
RG7090	mGluR5 antagonist (2)	treatment-resistant depression					
RG7412	anti- β -beta MAb	Alzheimer's disease					
RG1594	ocrelizumab	relapsing-remitting multiple sclerosis					
RG1594	ocrelizumab	primary-progressive multiple sclerosis					
RG1678	bitopertin (glycine reuptake inhibitor)	schizophrenia, negative symptoms					
RG1678	bitopertin (glycine reuptake inhibitor)	schizophrenia, suboptimally controlled					
RG3645	Lucentis	AMD/RVO/DME, sustained-delivery dosage form					
RG7417	anti-factor D MAb	geographic atrophy					
RG3645	Lucentis	AMD, 0.5mg, pro re nata (as needed)					
RG3645 ⁴	Lucentis	diabetic macular edema					
CHU	EPOCH	chemotherapy-induced anemia					
			Others				

Trastuzumab emtansine (T-DM1) extends PFS in HER2-positive breast cancer

In September promising phase II proof-of-concept data were presented at the annual meeting of the European Society of Medical Oncology (ESMO). The results of the TDM4450g study showed that patients with previously untreated HER2-positive metastatic breast cancer who received T-DM1 lived significantly longer with their disease under control (progression-free survival, PFS) and experienced fewer side effects typical of chemotherapy than patients who received standard treatment with Herceptin (trastuzumab) plus docetaxel chemotherapy. Recruitment has been completed for a phase III trial (EMILIA) comparing T-DM1 treatment versus combined Xeloda and lapatinib in patients whose HER2-positive metastatic breast cancer had progressed on previous therapy. Results are expected in the second quarter of 2012. We plan to use the data as the basis for marketing applications in Europe and the US in the second half of 2012.

Trastuzumab emtansine (T-DM1, RG3502) is a novel antibody-drug conjugate that combines the therapeutic effect of trastuzumab (the active substance of Herceptin) with intracellular delivery of DM1, a highly potent chemotherapy agent, to specifically target HER2-positive tumours. The trastuzumab antibody component blocks the signals that make HER2-positive cancer cells more aggressive and sends a message to the patient's immune system to destroy the cancer cells. It also delivers the DM1 chemotherapy agent directly to tumour cells to induce cell death.

Obinituzumab increases overall response rate in relapsed NHL

Final results from a phase II study (GAUSS) comparing single-agent obinituzumab with single-agent MabThera/Rituxan (rituximab) in patients with relapsed indolent non-Hodgkin's lymphoma (NHL) were announced in the first half of 2011 and presented at the annual meeting of the American Society of Hematology in December. The study showed that obinituzumab increased the overall response rate (ORR) of patients with CD20+ indolent NHL, a common type of blood cancer, compared with MabThera/Rituxan. Two phase III registration trials in first-line diffuse large B-cell lymphoma (DLBCL) and first-line indolent NHL were initiated in 2011. The phase III programme also includes ongoing studies which are assessing obinituzumab in chronic lymphocytic leukemia (CLL) and relapsed/refractory indolent NHL.

Obinituzumab (RG7159, GA101) is a type II, glycoengineered, anti-CD20 monoclonal antibody being developed as a potential treatment for NHL and CLL. It has been specifically designed to enhance the destruction of cancerous B cells by

activating other immune cells to attack the cancer cells and by inducing direct cell death.

Immunology, ophthalmology

Further regulatory approvals and filings, along with new data from phase III clinical trials again confirmed the benefits of Actemra/RoActemra in rheumatoid arthritis (RA) and of Lucentis for people with common types of eye disease. In addition, we currently have ten investigational new medicines in development for chronic and progressive inflammatory and autoimmune disorders such as rheumatoid arthritis, ulcerative colitis, systemic lupus erythematosus and asthma.

Lebrikizumab improves lung function in adult asthma

Positive results announced in August from MILLY, a phase II proof-of-concept study with the investigational medicine lebrikizumab showed that treatment with lebrikizumab resulted in a significant increase in FEV1 (a measure of lung function) in adults with asthma whose symptoms were inadequately controlled with inhaled corticosteroids.

Lebrikizumab is a humanised monoclonal antibody being developed for the treatment of moderate to severe persistent asthma. It is designed to bind specifically to interleukin-13 (IL-13), which is thought to play a key role in the airway inflammation, hyperresponsiveness and obstruction experienced by asthma patients. In addition to contributing to the features of asthma, IL-13 increases levels of periostin, a protein which can be measured with a blood test. In MILLY patients with high pretreatment periostin levels experienced a greater improvement in lung function with lebrikizumab than patients with low periostin levels. The results support further investigation of lebrikizumab as a potential personalised medicine for patients who suffer from moderate to severe uncontrolled asthma. Roche is developing a periostin immunoassay as a companion diagnostic test. It will be used to support phase III studies with lebrikizumab, which are planned to start in early 2012.

Actemra/RoActemra approved for childhood arthritis

In April the FDA approved Actemra for the treatment of active systemic juvenile idiopathic arthritis (sJIA, also known as juvenile rheumatoid arthritis), a rare, debilitating form of arthritis, in children aged two years and older. The European Commission approved RoActemra for this indication in August. Both approvals are based on positive data from the phase III TENDER study, which showed that treatment with Actemra/RoActemra can significantly improve the signs and symptoms of sJIA. Actemra/RoActemra can be given alone or in combination with methotrexate in patients with sJIA.

Effective in RA when used alone. In May a two-year phase IIIb study (ACT-RAY) showed that Actemra/RoActemra is effective when used on its own in people with RA who do not respond to methotrexate (MTX). The results demonstrated that Actemra/RoActemra alone had comparable clinical efficacy to Actemra/RoActemra plus MTX, a disease-modifying antirheumatic drug widely prescribed for people with RA. Up to 40% of people given MTX do not adequately respond to treatment or experience adverse events and require other drugs to help control their inflammation.

Non-inferiority of new subcutaneous formulation. In July Chugai announced positive results from a phase III trial with a new subcutaneous formulation of Actemra in RA patients, showing non-inferiority of efficacy of the new formulation compared with the current intravenous formulation. Subcutaneous injection is more convenient for patients and healthcare providers, as it does not require intravenous access and takes less time to administer than the intravenous infusion. The subcutaneous formulation is being developed by Chugai in Japan and jointly by Chugai and Roche outside Japan, with filings planned for 2012 and 2013.

Actemra (tocilizumab), known as RoActemra in Europe, is the result of research collaboration by Chugai and Osaka University. It is being co-developed globally by Roche, Chugai and Genentech. Actemra/RoActemra is the first interleukin-6 (IL-6) receptor-inhibiting monoclonal antibody approved to treat RA. IL-6 is an immune system protein that plays a pivotal role in the inflammation process associated with RA and certain other autoimmune conditions. Actemra/RoActemra is available in the US, EU, Japan and over 90 other countries for the treatment of RA, alone or in combination with methotrexate or other disease modifying antirheumatic drugs. It is also approved in the US and EU for the treatment of systemic juvenile idiopathic arthritis and in Japan for the treatment of Castleman's disease and polyarticular and systemic juvenile idiopathic arthritis.

Lucentis filed for DME in US

In December the FDA accepted and filed Genentech's supplemental biologics licence application (sBLA) for approval of Lucentis for the treatment of diabetic macular edema (DME), assigning an action date in August 2012. The sBLA is based on the results of two phase III studies, RISE and RIDE, which showed that patients who received Lucentis experienced significant, rapid and sustained improvement in vision compared with those who received placebo (sham) injections.

Lucentis (ranibizumab) is a vascular endothelial growth factor (VEGF) inhibitor approved by the FDA for the treatment of neovascular (wet) age-related macular degeneration (AMD)

and for macular edema following retinal vein occlusion (RVO). Lucentis is designed to bind to and inhibit VEGF, a protein that is believed to play a critical role in the formation of new blood vessels (angiogenesis) and the hyperpermeability (leakiness) of the vessels. In wet AMD these blood vessels grow under the retina and leak blood and fluid, causing rapid damage to the macula (the central portion of the retina). In RVO, angiogenesis and hyperpermeability can lead to macular edema (swelling and thickening of the macula). Macular degeneration and macular edema may lead to impairment or loss of vision. Lucentis was discovered by Genentech, which retains commercial rights in the US. Novartis has exclusive commercial rights for the rest of the world.

Virology

Expanded portfolio of investigational medicines for hepatitis C

The hepatitis market is evolving and, to meet the different needs of people infected with the hepatitis C virus (HCV), future treatment options are likely to include interferon-free, as well as interferon-containing triple- and quadruple-combination therapy regimens. Roche has several oral, direct-acting antiviral agents in late-stage development for hepatitis C: the nucleoside polymerase inhibitor mericitabine (RG7128; partnered with Pharmasset), the protease inhibitor danoprevir (RG7227) and, following the acquisition in late 2011 of Anadys Pharmaceuticals, the non-nucleoside polymerase inhibitor setrobuvir. **Danoprevir** (in phase II development, LIP⁴ decision made in 2011) and **mericitabine** (in phase II, LIP decision made in 2010) are being investigated in combinations in interferon-free and interferon-containing regimens. Results from phase II trials (INFORM SVR, DAUPHINE, MATTERHORN, PROPEL and JUMP-C) are expected in 2012. **Setrobuvir** is currently being evaluated in a phase II study in combination with the current standard of care, Roche's pegylated interferon Pegasys and ribavirin (Copegus). Under a strategic agreement, Roche and Merck have initiated the first of a series of clinical trials to examine novel combinations of marketed and investigational medicines for chronic hepatitis C. DYNAMO 1, a phase II study evaluating the combination of mericitabine, Merck's Victrelis, Pegasys and Copegus in patients who have not responded to prior therapy, began in late 2011.

⁴ Lifecycle Investment Point: decision to commence late-stage development leading to submission of marketing applications.

Pharmaceuticals Division – major regulatory approvals in 2011

Product	Clinical data supporting filing	Indication or dosage form	Country
Avastin	RIBBON 1	metastatic breast cancer, combination with Xeloda	EU
Avastin	international phase III data, Japanese phase II data	inoperable or recurrent breast cancer, first-line treatment	Japan
Avastin	ICON-7, GOG 218	metastatic ovarian cancer, following surgery	EU
Actemra/ RoActemra	LITHE (2-year data)	rheumatoid arthritis, reduction or inhibition of progression of joint damage and improvement of physical function	USA
	TENDER	systemic onset juvenile idiopathic arthritis	USA, EU, Switzerland
Herceptin	ToGA	advanced HER2-positive stomach cancer in patients who are not candidates for curative surgery	Japan
Herceptin	NOAH (Japan: NOAH and data in the public domain)	HER2-positive breast cancer, neoadjuvant and/or adjuvant treatment	Japan, EU
MabThera/ Rituxan	PRIMA	advanced follicular lymphoma, first-line maintenance following induction treatment with Rituxan/MabThera plus chemotherapy	USA
	RAVE	Wegener's granulomatosis, microscopic polyangiitis (severe forms of ANCA-associated vasculitis)	USA
Pegasys	Japanese phase II/III data	chronic hepatitis B	Japan
	4 clinical studies	Pegasys pre-filled pen, Pegasys ProClick Auto-Injector	EU, USA, Switzerland
Tarceva	SATURN	non-small cell lung cancer, first-line maintenance after chemotherapy	China
	EURTAC, published clinical experience	metastatic non-small cell lung cancer with epidermal growth factor receptor-activating mutations, first-line treatment	EU
	PA 3, Japanese phase II data	pancreatic cancer not amenable to curative resection, combination with gemcitabine	Japan
Xeloda	data in the public domain	advanced or recurrent stomach cancer in patients who are not candidates for curative surgery	Japan
	XELOXA	adjuvant colon cancer, combination with oxaliplatin	Switzerland
Zelboraf	BRIM2, BRIM3	BRAF-mutated inoperable or metastatic melanoma	USA, Switzer- land, Brazil

Metabolism, cardiovascular diseases

Roche has ten compounds in development for metabolic and cardiovascular diseases. Two promising compounds with novel modes of action are dalcetrapib for the treatment of coronary heart disease, atherosclerosis and dyslipidemia, and aleglitazar for reduction of the risk of heart attack and stroke in patients with type 2 diabetes.

Dalcetrapib development update

In August Roche announced the results of two exploratory phase IIb studies investigating the effects of dalcetrapib on atherosclerotic disease progression (dal-PLAQUE) and vascular function (dal-VESSEL) in patients with or at risk of

coronary heart disease. The studies, which were presented at a major European medical conference, further support the compound's safety profile and potential for slowing atherosclerotic plaque progression.

Dalcetrapib (RG1658, JTT-705; licensed from Japan Tobacco) is a novel cholesteryl ester transfer protein (CETP) modulator that has been shown to raise levels of 'good' functional high-density lipoprotein cholesterol (HDL-C), potentially promoting removal of cholesterol from the blood vessels. The ongoing phase III dal-OUTCOMES study, involving over 15,800 patients, is investigating whether dalcetrapib reduces the risk of heart attack and stroke in patients who have experienced a recent acute coronary syndrome.

Pharmaceuticals Division – major regulatory filings in 2011

Product	Clinical data supporting filing	Indication or dosage form	Country
Avastin	ICON-7, GOG 218	metastatic ovarian cancer	Switzerland
	OCEANS (AVF4095)	ovarian cancer, relapsed	EU
Herceptin	NOAH (Japan: NOAH and data in the public domain)	HER2-positive breast cancer, neoadjuvant and/or adjuvant treatment	EU, Switzerland, Japan
Lucentis	RISE, RIDE	diabetic macular edema	US
MabThera/ Rituxan	RAVE	anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis	Switzerland
	RATE	faster (90 minute) infusion schedule of Rituxan in combination with chemotherapy for treatment of NHL	USA
RoActemra	TENDER	systemic onset juvenile idiopathic arthritis	Switzerland
Tarceva	EURTAC	metastatic non-small cell lung cancer with epidermal growth factor receptor-activating mutations, first-line treatment	Switzerland
Pegasys	Japanese phase II/III data	chronic hepatitis B	Japan
pertuzumab	CLEOPATRA	HER2-positive metastatic breast cancer	EU, USA
vismodegib	ERIVANCE BCC (SHH4476G)	adult patients with advanced basal cell carcinoma for whom surgery is considered inappropriate	USA, EU
Zelboraf	BRIM2, BRIM3	BRAF-mutated inoperable or metastatic melanoma	EU, USA, Switzerland, Australia, NZ, Brazil

Aleglitazar development update

More than 60% of patients with type 2 diabetes (T2D) die from heart disease and stroke, not from an inability to control blood glucose. Aleglitazar (RG1439) is an oral medicine with the potential to be the first therapy to specifically reduce cardiovascular risk in people with T2D. A global phase III programme (ALECARDIO), which started in 2010, is investigating whether aleglitazar can reduce cardiovascular morbidity and mortality in patients with T2D who have suffered a recent acute coronary syndrome event. In addition, in 2011 enrolment was completed for a phase II study (AleNEPHRO) which is evaluating the benefits of aleglitazar in people with T2D and mild to moderate renal (kidney) impairment.

Aleglitazar represents a new approach to reducing cardiovascular risk in people with T2D, as it activates two key proteins that regulate metabolic signalling in pathways that are compromised in T2D: peroxisome proliferator-activated receptors alfa and gamma (PPAR α and PPAR γ). PPAR α activation is thought to increase fat combustion, lower triglycerides and increase HDL-C ('good' cholesterol), potentially slowing the advance of atherosclerosis. Activation of PPAR γ improves glucose metabolism and combats insulin resistance.

Neuroscience

Roche's pharmaceuticals pipeline includes ten novel compounds in development for central nervous system disorders representing high unmet medical need. The most advanced of these are investigational medicines in phase III clinical testing for schizophrenia and multiple sclerosis. In addition, we have several compounds in earlier stages of development as potential treatments for Alzheimer's disease.

Bitopertin development update

Bitopertin (RG1678, formerly known as GlyT-1) is a glycine reuptake inhibitor that is being co-developed globally with Chugai. A phase III programme was initiated in late 2010, with three trials investigating bitopertin in combination with anti-psychotics in the treatment of negative symptoms of schizophrenia and another three trials in patients with suboptimally controlled positive symptoms of schizophrenia. A phase II proof-of-concept study with bitopertin as monotherapy in patients with acute exacerbations of schizophrenia began in the first quarter of 2011. As the first in a new class of medicines, bitopertin has the potential to become the first compound of its type for the treatment of negative symptoms of schizophrenia. In addition, bitopertin in combination with current treatments has the potential to treat suboptimally controlled posi-

tive symptoms, with little or no increase in side effects. Its novel mode of action could also have valuable therapeutic applications in other psychiatric disorders.

Ocrelizumab maintains reduction of MS activity up to 96 weeks

Ocrelizumab (RG1594) is an investigational, humanised monoclonal antibody designed to selectively target CD20-positive B cells, which are believed to play a critical role in multiple sclerosis (MS). The ocrelizumab phase III clinical programme consists of two studies (Opera I and II) in patients with relapsing-remitting multiple sclerosis (RRMS) and one (Oratorio) in patients with primary-progressive multiple sclerosis (PPMS). The programme was initiated in 2011 and is now enrolling patients into all three trials. Results from a phase II study of ocrelizumab in patients with RRMS, the most common clinical form of the disease, were presented at a major medical conference in October. The study showed that the significant reduction in disease activity previously reported for 24 weeks was maintained through 96 weeks of treatment. RRMS is characterised by infrequent, acute exacerbations, with full or partial recovery between attacks. There is no approved therapy to treat PPMS, a much rarer form of the disease, which affects about 10% of those with MS.

Differential targeting of amyloid in Alzheimer's disease

Current research into Alzheimer's disease (AD) suggests that accumulation of amyloid beta (A-beta) peptides in the brain is a hallmark of the disease and the main cause of loss of memory in AD patients. We are currently developing two monoclonal antibodies that are designed to bind to A-beta. Both are in phase II clinical testing and represent two different approaches to reducing amyloid burden in the brain.

Gantenerumab (RG1450), a fully human antibody originating from a research collaboration with MorphoSys, binds and neutralises disease-relevant aggregated forms of A-beta: those that accumulate as plaques in the brain and those which interfere with brain-cell functioning. A phase I study using positron emission tomography (PET) imaging demonstrated that treatment with gantenerumab resulted in reduction of brain amyloid, possibly through an immunological clearance mechanism involving glial cells. An ongoing phase II trial, SCarlet RoAD, is designed to identify patients with early (prodromal) AD and treat them before more substantial damage to the brain has occurred.

RG7412, a humanised antibody licensed from AC Immune, binds to all forms of A-beta, including plaques, in the brain. Two phase II studies began in 2011, evaluating treatment with RG7412 in patients with mild to moderate AD: ABBY, a cogni-

tion study designed to detect a reduction in cognitive decline to provide proof of clinical activity; and BLAZE, a biomarker imaging study designed to measure changes in brain amyloid plaque load using PET.

Diagnostics for better treatment decisions

In 2011 Roche invested 900 million Swiss francs in developing novel diagnostic tests and platforms designed to provide better information for treatment decisions and drive efficiency in clinical laboratories and research centres.

Product launches in 2011

Our R&D efforts resulted in 50 tests and 13 new or upgraded instruments and devices being introduced in key markets (see table on page 45). The most important approvals and launches, helping to broaden and differentiate our offering, are summarised below.

Screening for cervical cancer

In April the US Food and Drug Administration approved the cobas HPV test for identifying women at the highest risk for cervical cancer. This is the only FDA-approved test that identifies 14 human papillomavirus (HPV) genotypes, twelve as a pooled result, and genotypes 16 and 18 individually, which are responsible for more than 70% of cervical cancers. It thereby helps detect disease missed by current screening methods, as shown by the ATHENA study, one of the largest-ever diagnostics registration trials. The cobas HPV test is currently being piloted in Sweden for primary cervical cancer screening.

Personalising cancer treatment

In the second half of 2011 CE Marks⁵ were obtained for three automated molecular tests that assist in tailoring treatment for melanoma, colorectal and lung cancer patients:

- The cobas BRAF test is a companion diagnostic for our melanoma medicine Zelboraf; it was also approved by the FDA in August (see page 34).
- The cobas EGFR test identifies patients with non-small cell lung cancer who might be eligible for first-line treatment with epidermal growth factor receptor (EGFR) inhibitors such as Tarceva.

⁵ Certification that an *in vitro* diagnostic product complies with all requirements for use in the European Union.

Diagnostics Division – major product launches in 2011

Area	Product name	Description	Market	Timeline
Instruments/devices				
Laboratories	cobas c 702	clinical chemistry module for high-volume laboratories	EU, US	Q1, 3
	OptiView	detection system for BenchMark tissue staining instruments	EU, US	Q2
	Ultimate Reagent Access	upgrade to BenchMark ULTRA tissue stainer for expedited slide processing	WW	Q2, 3
	iScan Coreo	scanner that enables digital viewing of tissue slides	EU	Q2
Diabetes Care	Accu-Chek Mobile	next-generation strip-free blood glucose meter	EU, AP	Q4
	Accu-Chek FastClix	one-click lancing device supporting blood glucose monitoring	EU	Q1
Life sciences	LightCycler Nano	desktop unit for real-time PCR analysis	WW	Q2
	GS FLX+ System	upgraded sequencing instrument and kit	WW	Q2
	SeqCap EZ Choice, SeqCap EZ Exome v3	microarrays for sequence capture	WW	Q1, 4
	4.2M CGH, 2.1M CGH/SNP	microarrays for high-resolution analysis of genomic variations	WW	Q4
	Cedex Bio	bioprocess analyser for biotherapeutics manufacturing	WW	Q3
Tests/assays				
Oncology	HE4	immunoassay for early ovarian cancer detection	EU	Q1
	HPV	PCR test for cervical cancer screening	US	Q2
	BRAF	PCR test, identifies patients eligible for treatment with Zelboraf	EU, US	Q3
	KRAS	PCR test, supports therapy selection for colorectal cancer	EU	Q3
	EGFR	PCR test, supports therapy selection for lung cancer	EU	Q4
	HER2 Dual ISH	tissue test, supports diagnosis of HER2-positive breast cancer	US	Q2
	29 IHC Primary Antibodies	for IHC tissue testing including BCL2 (lymphomas), ERG (prostate cancer), H. pylori (precursor of gastritis and ulcers), MLH1 (colorectal cancer) and PR (breast cancer)	WW	Q1-4
	HER2 (4B5) Algorithm	analytical imaging software, supports HER2 diagnostics	US	Q4
Virology/ Infectious diseases	HBsAg quant	immunoassay for hepatitis B therapy monitoring	EU	Q1
	CMV Avidity, Toxo IgG Avidity	immunoassays, help distinguish primary and non-primary cytomegalovirus infections in pregnancy	EU	Q1, 4
	MPX 2.0	PCR blood screening test, detects HIV, HCV and HBV	EU	Q2
	DPX	PCR test, detects parvovirus B19 and HAV in human plasma	US	Q1
	CMV	PCR test to monitor cytomegalovirus infections	EU	Q1
	HIV-1 2.0	PCR dual test, detects two HIV subtypes	EU	Q2
	HCV 2.0	PCR test to measure hepatitis C viral load	US	Q1
	HCV 2.0 (qual. and quant.)	PCR tests to detect active HCV infections and measure viral load	EU	Q4
	HLA-B 5701	PCR test to screen HIV patients for hypersensitivity to abacavir	EU	Q4
	Metabolism	Vitamin D total	immunoassay, measures vitamins D2 and D3	EU
hGH		immunoassay, supports diagnosis of human growth hormone disorders	EU, US	Q1, 2
PTH (1-84)		immunoassay to monitor patients with chronic kidney disease	EU	Q3
Maltose-independent test strip chemistries		for the Accu-Chek Aviva blood glucose meter	US, Japan	Q3
GS GType HLA Primer Sets		gene sequencing primer sets for research on the immune system	WW	Q1

black type = new product/first market launch, grey type = new product/launch in additional markets.
AP = Asia-Pacific; EU = European Union; US = United States; WW = worldwide.

BCL2 = B-cell lymphoma 2 gene; BRAF = B-isoform of the rapidly growing fibrosarcoma oncogene; CGH = comparative genomic hybridisation; EGFR = epidermal growth factor receptor; ERG = ETS (E-twenty-six)-related gene; GS = Genome Sequencer; HAV = hepatitis A virus; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HE4 = human epididymis secretory protein E4; HER2 = human epidermal growth receptor 2; HIV = human immunodeficiency virus; HLA = human leucocyte antigen; HPV = human papillomavirus; IHC = immunohistochemistry; ISH = in situ hybridisation; KRAS = member of the Ras family of oncogenes; MLH1 = MutL Homolog 1 gene; PCR = polymerase chain reaction; PR = progesterone receptor; PTH = parathyroid hormone; SNP = single nucleotide polymorphism; Toxo IgG = toxoplasma-specific immunoglobulin G antibodies.

- The cobas KRAS test identifies mutations in the KRAS gene that occur in 35% to 45% of colorectal cancers and are predictive of non-response to anti-EGFR antibody therapies such as cetuximab and panitumumab.

All three assays run on the cobas 4800 platform and offer unmatched levels of sensitivity.

In June the FDA approved our Inform HER2 Dual ISH test, which helps to verify whether a patient with breast cancer is likely to respond to therapy with Herceptin. As the first fully automated tissue-based assay able to detect both the HER2 gene and a central part of chromosome 17 on a single tissue slide, the test allows pathologists to easily identify variations in gene expression throughout the tumour, increasing the accuracy of diagnosis. The test can be combined with our HER2 (4B5) IHC test and Companion Algorithm HER2 (4B5) analytical imaging software, making Roche the only company offering a complete HER2 diagnostic workflow solution for laboratories.

Improved monitoring of hepatitis B therapy

In February our quantitative HBsAg immunoassay for hepatitis B monitoring received CE Mark certification. The test uses our Elecsys technology to measure levels of hepatitis B virus surface antigen in serum or plasma. This enables doctors to assess sustained treatment success with Pegasys or other interferon-based medicines, helping them to tailor therapy to individual needs.

Making blood glucose monitoring safer and easier

In September our maltose-independent test strips for the Accu-Chek Aviva blood glucose meter received clearance by the US FDA. The new strips do not cross-react with maltose and hence offer increased safety; maltose interference can on rare occasions result in falsely elevated blood sugar readings. Their clearance paves the way for the launch of our new Accu-Chek portfolio in the US. In November we started the roll-out of our next-generation Accu-Chek Mobile with launches in Australia and the Netherlands. Smaller than its predecessor, the blood glucose meter provides 50 tests on a continuous tape, eliminating the handling of single test strips.

Broadening laboratory offering

We expanded our cobas series of fully automated modular analysers for central laboratories with the launch of the cobas c 702 clinical chemistry module in the US and the EU. Capable of performing up to 2,000 tests per hour, the module's innovative reagent manager provides uninterrupted workflow for high-volume testing. Following the launch of seven immunoassays, including a Vitamin D total test, the Elecsys test menu

for cobas analysers now stands at 95, making it the broadest immunoassay menu available on a single platform.

Bringing PCR analysis to more researchers

In June Roche launched LightCycler Nano, a compact and affordable desktop unit for real-time polymerase chain reaction (PCR) analysis for genotyping, gene expression studies and other applications. The Nano complements the larger instruments in our LightCycler series, putting real-time PCR capabilities within reach of many more researchers around the world.

Ongoing R&D priorities

Roche Diagnostics maintained its significant R&D investments in 2011, developing technologies and products for launch in the coming years. Efforts are focused on the five areas highlighted below:

Novel biomarkers

In 2011 we continued to engage in biomarker research with our pharmaceutical partners, drawing on our breadth of technologies for protein, genetic and tissue-based testing. The primary focus was on oncology, virology, inflammatory, cardiovascular and metabolic diseases. Roche Diagnostics collaborated with Roche Pharmaceuticals on more than 200 projects, including those addressing Met expression and periostin levels (see pages 37, 40), and with more than 20 other pharmaceutical partners on companion diagnostics.

Laboratory coagulation testing

We made significant investments in novel solutions for testing of patients' blood coagulation and hemostatic factors. In 2012 we plan to introduce a new instrument for mid- and high-throughput testing in laboratories together with a comprehensive assay menu, complementing our leading portable coagulation testing systems for use at home and in doctors' offices. Our acquisition of Verum Diagnostica, a leader in platelet function testing, will further strengthen Roche's coagulation portfolio.

All-in-one diabetes care systems

Our development pipeline emphasises integrated solutions that facilitate personalised diabetes management and reduce the number of devices and steps needed to monitor blood glucose and deliver insulin. The SOLO micropump, for instance, features a semi-disposable insulin pump patch and remote control that allow the micropump to continuously deliver insulin based on the patient's needs. It is scheduled for launch in the EU in 2012. In addition, a development and distribution

Diagnostics Division – key product launches planned for 2012

Area	Product name	Description	Market
Instruments/devices			
Laboratories	cobas t 611	coagulation analyser for mid- and high-throughput testing	EU
	BenchMark Special Stains	fully automated tissue stainer	WW
	VENTANA iScan HT	high-throughput scanner that enables digital viewing of tissue slides	WW
Point-of-care	cobas b 101	multi-blood lipid and glucose point-of-care analyser	EU
	cobas b 123*	blood gas analyser for critical care	US
Diabetes Care	Accu-Chek Nano	small blood glucose meter requiring no coding of test strips	US
	SmartView*		
	Accu-Chek Mobile	next-generation strip-free blood glucose meter	EU
	Accu-Chek Combo*	insulin pump with remote control and blood glucose meter	US
	SOLO Micropump	insulin micropump with remote control and blood glucose meter	EU
Tests/assays			
Oncology	HE4	immunoassay for early ovarian cancer detection	US
	p16 Histology	IHC tissue test for cervical cancer early detection	EU, US
	ER*	IHC tissue test for diagnosis of breast cancer	US
	GS GType TET2/CBL/ KRAS & RUNX1 Primer Sets	gene sequencing primer sets for leukemia research	WW
Virology/ Infectious diseases	CMV	PCR test to monitor cytomegalovirus infections	US
	CT/NG	PCR test to detect chlamydia and gonorrhoea infections	US
Metabolism	Vitamin D total	immunoassay, measures vitamins D2 and D3	US

black type = new product/first market launch, grey type = new product/launch in additional markets.
EU = European Union; US = United States; WW = worldwide.

* These products were initially scheduled for launch in 2011; they have been filed with the FDA and will be launched as soon as they are approved.

CBL = Casitas B-cell lymphoma gene; CT/NG = *Chlamydia trachomatis/Neisseria gonorrhoeae*; ER = estrogen receptor; GS = Genome Sequencer; HE4 = human epididymis secretory protein E4; IHC = immunohistochemistry; KRAS = member of the Ras family of oncogenes; p16 = protein p16INK4a; PCR = polymerase chain reaction; RUNX1 = Runt-related transcription factor 1; TET2 = member of the TET family of oncogenes.

agreement reached with DexCom in November 2011 will enable Roche to integrate DexCom's leading continuous glucose sensing technologies into future insulin delivery systems.

High-volume DNA testing

We are developing platforms that we expect will be the first to combine molecular tests for women's health, virology and blood screening. The platforms will bring greater automation, throughput and cost efficiency to molecular diagnostics and blood-screening laboratories, simplifying workflows and reducing equipment and complexity. Development is scheduled to continue through 2012.

Next-generation sequencing

In 2011 we remained focused on developing faster, more efficient sequencing systems to enable even broader study of the human genome and genetic causes of disease. We maintained

an exclusive partnership with DNA Electronics for the development of an electrochemical DNA sequencer and a collaboration with IBM to develop a nanopore-based single molecule sequencer. In October Roche licensed several technologies from Arizona State University and Columbia University, to directly read the sequence of nucleic acids in a single DNA molecule as it passes through a nanopore. These technologies will help advance the development project with IBM.

Accessing external innovation

Access to external innovation through targeted acquisitions, licensing agreements to exchange intellectual property and academic alliances are a significant means of strengthening and expanding our global innovation network. Through collaboration agreements Roche explores ideas with some of the

world's leading scientists for translating science into clinically differentiated medications and novel diagnostics. In a recent survey by The Boston Consulting Group that measured the partnering functions of the major pharmaceutical companies, biotech companies ranked Roche as one of the best companies with which to partner. We had the highest average score across all attributes, with particular strengths in deal structure flexibility, executive leadership, alliance management and manufacturing expertise. We also had the most nominations as 'top partner' by survey respondents.

Acquisitions and licensing agreements

Roche Partnering signed 67 new agreements in 2011, including three product transactions covering four products in total and 53 research and technology collaborations. In addition, 11 product outlicensing agreements were signed. A special team was created to source 'open innovation' by collaborating at the earliest stages with academic institutions and other external partners to establish product development partnerships. Among the team's main transactions in 2011 was the collaboration between PTC Therapeutics and the SMA Foundation, giving Roche access to a first-in-class treatment for spinal muscular atrophy, a devastating disease effecting children and adolescents and the leading genetic cause of mortality in infants and toddlers. The acquisition of Anadys Pharmaceuticals brought setrobuvir into the Roche virology pipeline. The US-based company is also developing ANA773, an oral, small-molecule inducer of innate immunity, currently in phase I clinical trials, that may prove useful for treating HCV and other chronic infections and cancer. In addition, Roche entered into an agreement with Evotec AG of Germany to co-develop and commercialise EVT-302, a compound that may slow the progression of Alzheimer's disease.

Genentech Partnering completed three product transactions and signed six new research and technology collaborations in 2011. These agreements support the work of gRED and include an in-licensing agreement, with an option to purchase, with US-based Forma Therapeutics covering a new cancer target. The agreement was nominated for Alliance of the Year by IN VIVO, a leading healthcare industry information provider. An in-licensing agreement with US-based Array Biopharma adds a second compound for an important cancer target, a ChK1 inhibitor, to gRED's development portfolio.

Roche Diagnostics signed more than 40 licensing agreements in 2011, as well as acquiring PVT Probenverteiltechnik (Germany)/PVT Lab Systems (US), mtm laboratories (Germany) and, in early 2012, Verum Diagnostica (Germany). PVT

is a global market leader in providing customised automation and workflow solutions for *in vitro* diagnostic (IVD) testing in large commercial and hospital laboratories. mtm is a tissue diagnostics company with a leading portfolio of IVDs for early detection and diagnosis of cervical cancer. Verum Diagnostica is specialised in laboratory coagulation testing. The division also entered into a number of new research and technology collaborations, including the development of PCR biomarker tests (Merck and Clovis), tissue-based companion diagnostics (Bayer and Pfizer), and automated target enrichment for biomedical research (Caliper).

Academic alliances

Roche's innovation network expanded further during the year thanks to new collaborations with academic institutions around the world. pRED has developed an academic network with 130 partners in 76 academic institutions and 15 nations in the Americas, Asia and Europe. In 2011 we added several leading academic institutions to our Expanding the Innovation Network programme, which has now 11 umbrella agreements, including with the Hebrew University in Jerusalem and the Harvard University. Four new agreements are pending in Europe, the US and China. The collaborations have already produced tangible results, with two projects brought in-house and joint intellectual property created. In 2011 Roche formed a strategic partnership with the Cancer Prevention and Research Institute of Texas, a cooperation with the Swedish life science initiative Uppsala BIO, and a three-way research agreement with Harvard University and the Chinese biotechnology organisation Biobay.

Since its inception in 2010, pRED has established translational R&D hubs with academic institutions through its academic alliances group. Operating in France, the US, Canada, Switzerland, the Netherlands and Singapore, these hubs had more than 80 programmes and projects under way at year-end. In 2011 pRED opened an R&D institute in France that serves as a single entry point for academic collaborations across multiple disease areas and scientific disciplines. Similarly, a translational research hub opened in Zurich will foster collaborations between Roche Pharmaceuticals and Roche Diagnostics and academic researchers from the Swiss Federal Institute of Technology (ETH), the University of Zurich and University Hospital Zurich.

Conducting responsible R&D

Safe and transparent clinical trials

Clinical trials determine the safety and efficacy of new medicines and the clinical value of diagnostic tests. They also provide critical information on the cost-effectiveness of a treatment or diagnostic test and how a treatment improves quality of life. This information is shared with regulatory authorities and payers in order to gain marketing approval and, ultimately, reimbursement. In 2011 more than 330,000 patients received state-of-the-art care and free treatment as participants in Roche-sponsored clinical trials. In addition, more than 35,000 participating medical centres received educational, financial and medical support.

Clinical trials

	2011	2010	2009
Number of clinical trials	2,174	2,173	2,182
Number of healthcare centres involved	35,849	34,636	34,508
Number of patients in phase I-IV clinical trials*	332,183	277,079	268,614

* Numbers do not include patients in Genentech studies initiated prior to the merger.

Roche follows strict policies and processes to ensure the safety, well-being and legal rights of people participating in clinical trials, including the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines. To ensure compliance with these standards, we train, monitor and audit those involved in our clinical trials, including contract research organisations (CROs) that conduct or manage trials on our behalf. We do not perform trials in countries where we do not plan to market the medicine being tested.

We maintain a searchable database of clinical trials at www.clinicaltrials.gov and www.roche-trials.com. Details of Roche clinical trials are also available through the International Federation of Pharmaceutical Manufacturers and Associations clinical trials portal and the US National Institutes of Health global registry.

Roche further ensures sharing of clinical data by encouraging its scientists to publish results of their work in medical journals and to present them at scientific and medical congresses. In 2011 Roche scientist contributed 1025 scientific publications, including articles that appeared in high-impact journals such as *Nature*, *Cell*, *Science* or *the New England Journal of Medicine*.

Ethical practices

We have clear policies and procedures in place to maintain high ethical standards in our R&D activities, including providing regular ethics training for employees.

Employees who encounter an ethical dilemma in their work, and cannot resolve it with their colleagues, can contact our Global Ethics Liaison Office, which then consults both internal and external experts to seek a solution. In 2011 this office received and resolved no enquiries.

The company has established the Roche Scientific and Ethics Advisory Group (SEAG) to offer advice and counsel on a broad range of ethical matters. The panel meets annually and is made up of independent external experts appointed by Roche from the fields of genetics, bioethics, law and sociology, as well as lay members, such as representatives from patient advocacy groups. In 2011 SEAG provided valuable input into Roche's new pre-approval access policy. The policy provides a global approach to enabling access to medicines, prior to commercial approval, for patients who have life-threatening diseases but are unable to participate in clinical trials. SEAG also advised on the development of principles for conducting stem cell research at Roche.

Bioethics

Roche integrates ethical practices into its scientific research through responsible, accountable and transparent approaches to the development of diagnostics and therapeutics. The company has published several position papers on its R&D activities in areas such as genetics, stem cells and animal research. We routinely review and update these positions and our policies for research involving either humans or animals, taking into account scientific developments and public concerns.

The Roche Charter on [Genetics](#) ensures excellence and social responsibility in our genetic research. We believe in the right of every individual to self-determination, privacy and confidentiality regarding the collection and use of genetic information. Roche will not pursue the creation of genetically identical human beings.

[Stem cells](#) and their application in drug research offer tremendous potential to establish disease models to help identify potential novel targets and screen compounds. Roche conducts stem cell research in-house and through external collaborations as a means of improving drug development while reducing animal testing and potential serious adverse events in

How Personalised Healthcare works

On average, only about five out of ten patients who receive a given therapy actually benefit from it, while some may experience side effects.

Thanks to advances in new research disciplines, scientists now have a better understanding of disease at the molecular level. As a result, they are able to distinguish patient subgroups in which different causes drive what has traditionally been regarded as a single disease. In oncology, this has led to efforts to identify genetic characteristics affecting patients' responses to particular therapies.



Identifying clinically significant patient subgroups is a key element of our Personalised Healthcare strategy, which marries new diagnostic techniques with advances in biotechnology in an effort to develop more targeted, more efficient therapies.

This strategy is being systematically implemented at every stage of new product development at Roche and is aimed at helping us

- better understand disease diversity
- identify differences between patients
- identify the best drug targets
- improve the quality and efficiency of our R&D efforts
- develop biomarkers and diagnostic tests

clinical trials. Our goal is to establish treatment strategies for incurable or inadequately treated severe diseases, such as central nervous system, cardiovascular and metabolic disorders, and viral diseases. Roche is also exploring the potential therapeutic use of stem cells for incurable or inadequately treated severe diseases.

Animal welfare

Roche has a long-standing commitment to maintaining high standards of animal welfare, and we take public concern about animal research seriously. Wherever possible, we seek alternatives to the use of animals, such as computer simulation or *in vitro* testing using differentiated cells or stem cells rather than animals.

Even so, animal research remains indispensable to biomedical research for scientific and legal reasons. Regulatory authorities require all healthcare companies to test the safety and efficacy of new drugs in animals before they can be used in humans. Roche is committed to acting ethically and to applying the highest standards of care to animals used in scientific procedures, including conforming to all laws, regulations and industry standards.

In 2011 we used 469,004 animals in our research, an 6.6% decrease from 2010. The number of animals used by CROs performing research on our behalf increased to 68,606 compared with 55,913 in 2010. Approximately 98% of the animals used were mice and rats.

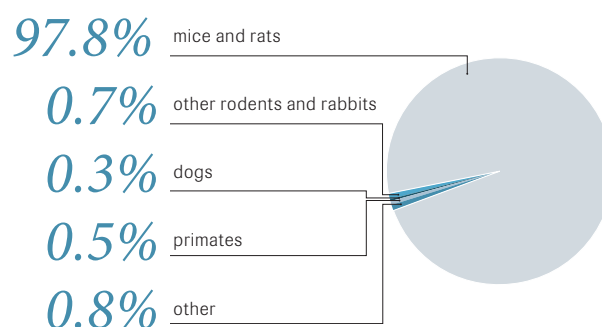
Animals used in research

We aspire to use as few animals as possible without putting at risk the reliability and validity of research and test results by following a 3Rs approach:

- Reduce: the number of animals needed
- Refine: by tailoring procedures to minimise pain and discomfort
- Replace: with other methods that do not involve animals or use only cells or tissues of animals

In 2011, the Roche Ethics Committee on Animal Welfare sponsored the third Roche 3Rs Award, which recognises employees and contractors for their commitment to the 3Rs approach and for improving animal welfare in three categories: laboratory animal care and management; scientific progress; and surgery, methodology, training and techniques. Award-winning projects included the development of a computer-aided prediction tool that can be used to avoid toxicological effects and reduce the number of animal experiments, and a project

Animals used in research (Roche and contract research organisations) in 2011



that enables researchers to produce human antibodies without first having to immunise laboratory animals.

Roche is a signatory to the Swiss Charter on Animal Welfare that was adopted in 2010 by Interpharma, the association of research-based pharmaceutical companies in Switzerland. The charter commits us to consistently high standards of animal welfare through a programme of auditing, employee training, stakeholder dialogue, promotion of the 3Rs approach and management of external contractors.

More on the web

- Roche's Pharmaceuticals and Diagnostics Pipelines: www.roche.com/pipeline
- Personalised healthcare: www.roche.com/personalised_healthcare
- Group policies, positions and guidelines: www.roche.com/policies_guidelines_and_positions
- Clinical trials and patient safety: www.roche.com/clinical_trials; www.roche.com/managing_medication_safety
- New products and technologies: www.roche.com/innovation_and_technologies
- Ethical standards: www.roche.com/ethical_standards
- Genetics and bioethics: www.roche.com/genetics_and_bioethics
- Animal welfare: www.roche.com/animal_welfare