

Report of the Management Board

Overview of the year

The year 2008 was truly unique for Crucell as we achieved net profit for the first time in the history of the Company. In addition we exceeded our revenue targets, considerably improved our gross margin and were cash flow positive. It is Crucell's ambition to deliver on promises and we clearly exceeded the targets set at the beginning of the year. Our 2008 financial highlights include:

- Growth of 33% in revenues and other operating income in 2008;
- Net profit of € 14,586 in 2008 compared to a net loss of € 42,910 in 2007;
- Gross margin for the year improved to 45% in 2008 compared to 34% in 2007; and
- Positive cash flow of € 7,721 increasing the 2008 year-end cash position to €170,969.

Our mission is to develop, produce and market vaccines and antibodies that prevent or treat infectious diseases. We have a fully-integrated infrastructure for in-house development, production and marketing of vaccines, and we are now leveraging our knowledge in this area to enter the antibodies market for infectious diseases. Our business strategy is based on the following business drivers:

- Leveraging presence of our marketed vaccines in public and private markets;
- Building a product pipeline with sustainable competitive advantage; and
- Building upon ongoing technology licensing programs.

The weakness of the global economy in 2008 is a challenge for many companies worldwide.

The ongoing financial crisis became prominent in September 2008 with the failure or near-failure of several United States and European based financial institutions. The resulting deterioration in financial and market conditions spread around the globe. In recent months, the financial crisis has adversely affected businesses in many industries and geographical areas all over the world at an unexpected pace.

Despite the weak global economic climate we achieved all targets we set ourselves for the financial year 2008. Our success depends in part on our solid customer-base, which is relatively unaffected by deterioration in the global economy, since many of our customers are governmental agencies or supranational organizations. We do not expect our business will be significantly affected by the weak global economy in 2009.

Leveraging presence of our marketed vaccines

For the full year 2008, product sales were € 226,055, representing sales of paediatric vaccines (49%), travel and endemic vaccines (25%), respiratory vaccines (14%) and other products (12%). Our product sales grew by € 48,486 or 27.3%. The increase is primarily attributable to increased sales of our paediatric vaccines, specifically Quinvaxem, of € 33,668 and travel and endemic vaccines of € 8,290.

Quinvaxem is our fully liquid pentavalent vaccine against five important childhood diseases that is approved by the WHO. In 2008 we more than doubled the production and we were able to continue the success of Quinvaxem as sales grew from 21.3 million units in 2007 to 39.6 million units in 2008. In anticipation of the expected further growth of Quinvaxem in 2009, we continued to build up stock of Quinvaxem in the fourth quarter of 2008.

In 2008, the Chinese authorities approved Hepavax-Gene, our recombinant Hepatitis B vaccine, which is a significant advancement in the expansion of Crucell's business in the highly strategic Chinese vaccine market. This will accelerate the growth of our Chinese operations.

Operations

In February 2008, our Chief Operating Officer, Cees de Jong, was nominated to join the Management Board. This nomination was approved by our shareholders at the Company's annual general meeting on May 30, 2008. Cees joined Crucell in September 2007 and he was already part of Crucell's Management Committee, prior to his nomination to the Management Board.

In 2008, we also attracted several new senior managers to further improve the quality of our operations. During 2008 we strengthened the manufacturing organization and we were able to improve our performance significantly as yields of important production processes increased and scrap rates decreased. Expenses on operations were more or less stable compared to 2007 despite a significant increase in production volumes.

All our facilities were audited multiple times during the year by customers and/or regulatory authorities. All audits were successful, confirming our compliance with relevant rules and regulations. In Bern, Switzerland, we successfully refurbished our MoRu-Viraten (MR) filling line and obtained approval from Swissmedic to recommence production. In Madrid, Spain, we installed a new filling line for syringes, bringing the total capacity of our dedicated fill/finish center in Spain to approximately 100 million syringes per annum. The Spanish authorities audited and approved the new line in December 2008.

In October 2008, we announced that an agreement was reached to relocate our Korean production facility, that manufactures Quinvaxem and Hepavax-Gene, from the Shingal site in Yongin City to the Incheon, Free Economic Zone. We agreed on the time-line and conditions of this relocation with all parties involved, facilitating a smooth transition to the new production facility. The new facility will enable the further growth and efficient production of Quinvaxem and Hepavax-Gene. All litigation surrounding our production facility has been settled.

In August 2008, we announced the intention to move Dukoral and rCTB bulk production, formulation and fill/finish activities from Sweden to other sites within the Crucell organization. The Group is currently conducting a feasibility study to determine the scope and timing of a potential move. The research activities conducted at our Swedish site were discontinued in 2008 and are now concentrated in Leiden, the Netherlands.

We entered into an exclusive vaccine development agreement with Wyeth Pharmaceuticals in which we will be responsible for the development and manufacturing of certain components of a vaccine for use by Wyeth in clinical studies. Wyeth will be responsible for the clinical development of the

vaccine. The development activities will take place in Crucell's dedicated vaccine manufacturing facilities in Bern, Switzerland, which had been fully impaired in 2006, enabling a partial reversal of that impairment in 2008.

Product pipeline with sustainable competitive advantage

Our rabies candidate product achieved positive preliminary results in the phase II study that was carried out in the US. No adverse events were reported and the study confirmed the neutralizing activity of the monoclonal antibody product against the rabies virus. A second phase II clinical study evaluating the monoclonal antibody cocktail in combination with a vaccine in healthy children and adolescents was conducted in the Philippines from May to October 2008. Final data from this study is expected to become available in the first half of 2009. An additional phase II study in healthy adults evaluating Crucell's monoclonal antibody in combination with another rabies vaccine is scheduled to start in India in the second quarter of 2009.

For our Ebola and Marburg vaccine research we secured a contract with the US National Institute of Allergy and Infectious Diseases (NIAID), which is part of the National Institutes of Health (NIH) aimed at advancing the development of Ebola and Marburg vaccines, the ultimate goal being a multivalent filovirus vaccine. The contract provides us with funding of up to US Dollar (\$) 30 million, with additional options that may be triggered at the discretion of the NIH worth a further \$ 40 million. The phase I study of an adenovirus 5 (Ad5)-based Ebola vaccine, being developed in partnership with the Vaccine Research Center (VRC) of the NIAID/NIH, showed safety and immunogenicity. Based on these results, a second phase I study of an Ebola and/or Marburg vaccine is anticipated. The study will use alternative adenovirus vectors, which are able to bypass pre-existing immunity against Ad5.

Our research on a tuberculosis vaccine in collaboration with Aeras is ongoing. In October 2008, Crucell and the Aeras Global TB Vaccine Foundation announced the start of a phase I clinical trial in Kenya. The main parameters of the study are to test the safety of the vaccine candidate in healthy adults. We also started the enrollment of the first phase II study of the vaccine candidate, which will be conducted in South Africa by the University of

Cape Town Lung Institute in conjunction with the South African Tuberculosis Vaccine Institute.

Our malaria research in collaboration with the NIAID/ NIH is progressing as we are carrying out a phase I trial in the US. The study is being carried out at two sites: Vanderbilt University in Nashville, Tennessee, US, and Stanford University in Palo Alto, California, US. The first three groups have been enrolled and ongoing safety monitoring has revealed no significant safety concerns to date, but formal analysis awaits. Enrollment for the fourth and final group of volunteers is ongoing.

In our influenza research, Crucell's scientists discovered a set of human monoclonal antibodies that provides immediate protection and neutralizes the broadest range of H5N1. When tested in pre-clinical models for prevention or treatment of a potentially lethal H5N1 infection, these antibodies were shown to prevent death and cure the disease.

In another pre-clinical study, Crucell's mAb CR6261 was compared with the anti-influenza drug oseltamivir in terms of their value for flu prevention and treatment. In December 2008, we announced that our monoclonal antibody strongly outperformed oseltamivir in the tests that were conducted. The flu strains tested included the 'bird flu' strain H5N1, which, experts fear, has the potential to cause a pandemic, and H1N1, which is similar to the flu strain responsible for the devastating pandemic in 1918. Importantly, the study showed that CR6261 provides immediate protection against the influenza virus, suggesting that it will be able to prevent the spread of disease. In contrast, oseltamivir was less efficacious and in some cases not effective at all.

Registration submission of Flavimun, our yellow fever vaccine in Switzerland was completed in the first quarter of 2009. Registration submission in Germany is expected in 2009.

Unique technologies for licensing business

In 2008, our license revenues grew by € 17,991 or 147.3%. The increase is mainly due to revenues generated by our collaboration with sanofi pasteur.

In 2008, Crucell signed licensing agreements with Abraxis Bioscience, Inc., Affitech AS, Arana Therapeutics Ltd, Bioceros, Biochrom, Cangene Corp., Celltrion, Inc., Gedeon Richter, GlaxoSmithKline, CSL Ltd., Lonza, Medarex Inc., MorphoSys AG, Profibrix B.V., Synthon B.V., Talecris Biotherapeutics and Toyobo Gene Analysis Co. Ltd.

We signed two exclusive, commercial license agreements with Talecris Biotherapeutics for two undisclosed and specific proteins and the exclusive rights to produce those proteins using the PER.C6 cell line. In total, we received upfront payments of \$ 4 million upon the execution of the agreement and will be eligible for milestone payments of approximately \$ 50 million more.

There were also positive developments for our intellectual property. We were successful in opposing European patents of our competitors as we managed to obtain complete revocations of European patents owned or controlled by GenVec, Genentech, Baxter, Novartis Vaccines & Diagnostics, Wellcome Foundation (GlaxoSmithKline (GSK)), and others. In addition, we obtained a favorable decision from the South-Korean Supreme Court in the longstanding invalidity law suit in South Korea against GSK's multivalent Hepatitis B virus vaccine patent. These developments further paved the way for Crucell's pipeline development activities and marketed products. Conversely, we were successful in defending our own PER.C6 and AdVac patents against attacks by its competitors. Except for one PER.C6 patent that has been maintained in amended form and is now pending before the board of appeal, all PER.C6 patents have survived opposition before the European Patent Office essentially intact.

The following technological progress was achieved during 2008:

- We achieved important advances in antibody production using our PER.C6 technology platform together with our partner DSM Biologics. By employing the PER.C6 human cell line and proprietary XD™ technology, we achieved a record yield of over 27 grams per liter of IgG antibodies. In addition the high-titer fed-batch process was scaled up to 250 liters by DSM Biologics scientists at their GMP facility in Groningen, The Netherlands;

- Our PER.C6 technology licensee Ark Therapeutics has entered a phase III study with its product Trinam. Ark Therapeutics is the first of our licensees to enter into a phase III study with a product produced on Crucell's PER.C6 human cell line; and
- We announced that the novel recombinant adenovirus serotype 26 (rAd26) vector, which is jointly developed by Crucell and the Beth Israel Deaconess Medical Center (BIDMC) in the US, will be used in a phase I clinical study to test a new HIV vaccine. The rAd26 vector is specifically designed to avoid pre-existing immunity to the more commonly used adenovirus serotype 5 (Ad5), which has recently shown limitations as an HIV vaccine vector. This clinical trial is the first 'in man' study of this newly developed vector, which could provide a solution to problems seen in previous HIV vaccine trials. The rAd26 vaccine is the first HIV vaccine candidate to emerge from the Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) program.

In November 2008, the leading scientific journal 'Nature' published a study that demonstrated the value of our alternative adenovirus serotype technologies. Using Crucell's AdVac vaccine technology and PER.C6 manufacturing technology, scientists engineered the rare adenovirus serotypes Ad26 and Ad35 to express a protein of SIV, the primate equivalent of HIV. We have developed rare serotype adenoviral vectors, such as rAd26 and rAd35, to provide more potent prime-boost vaccine regimens. The study, which investigated the immunogenicity and protective efficacy of different vaccination regimes using rAd26, rAd35 or rAd5 as a primer, followed by a boost with rAd5, showed that in particular the rAd26/rAd5 combination elicits a strong T-cell immune response and provides protection against the HIV-like virus in primate subjects. We have several vaccines in development using alternative rAd26 and rAd35 vectors, including vaccines against malaria and tuberculosis.

For further details on licenses and licensees please see 'Information on the Company – Overview of Licensees and Partners' in this Annual Report.

Subsequent events

On January 7, 2009, we announced that we were in friendly discussions with Wyeth regarding a potential combination of the two companies. On January 26, 2009, we announced that Wyeth withdrew from these discussions.

Outlook 2009

The key to our strategy is continued growth. The outlook for 2009 is promising as we expect revenue and other operating income to grow, operating profits to increase significantly and to achieve a solid cash flow despite significant investments. Our Healthy Ambition program has a clear focus on achieving operational excellence and is on track to realize cost savings of € 30 million by the end of 2009. We do not expect our business to be adversely affected in 2009 by the weak global economy resulting from the continuing international financial crisis.

In 2009, we will focus on continued growth.

- We expect our combined full-year 2009 total revenue and other operating income to grow by 20% in constant currencies that are set at a guidance rate of Euro/US Dollar of 1.35;
- Operating profit for 2009 is expected to improve significantly compared to 2008;
- Furthermore, the Company expects solid cash flow despite significant investments in the new facility being built in Korea. These investments are expected to total approximately € 50 million, with the majority of the spending in 2009;
- We do not expect our business to be significantly affected by the weak global economy in 2009; and
- We will pursue key partnerships, focus on progress in clinical development and continue with broadly licensing our technologies.

In the course of 2009, we expect to make further decisions that may impact our income statement. Consequently we cannot comment on expected 2009 results in more detail than described above.

Our Healthy Ambition program has a clear focus on achieving operational excellence. The program works towards exploiting synergies, reducing costs and funding growth. Important elements of the program include: product portfolio optimization, process and infrastructure optimization, network rationalization and further integration and streamlining of various functions. Healthy Ambition is targeting savings of € 30 million by the end of 2009. For 2009, the focus will be on reducing complexity and further streamlining the organization.

We expect continued investments in our manufacturing facilities to ensure that they remain state-of-the-art and continue to meet the highest applicable regulatory standards. In October 2008, we announced that we will relocate our Korean production facility. The investments in the new facility are expected to total approximately € 50 million, with the majority of spending occurring in 2009. We entered into a mortgage loan facility in Korea for an amount of KRW 50 billion to partly finance the investments in the new Korean facility in 2009.

Our continued growth strategy also includes continued investments in R&D to ensure solid progress in clinical development. Both vaccine and antibody research is being focused on combating infectious diseases, with an emphasis on the existing categories of paediatric, travel and endemic, and respiratory illnesses. In addition, we will continue to invest in discovery programs and progress these into the clinical trial phase. Lifecycle investments are required to ensure that we continue to meet the highest regulatory standards and to further improve the lifecycle of our products.

We expect the deal flow from our PER.C6 licensing business to continue. We believe that the number of licenses and the revenue flow from the PERCIVIA joint venture will continue to be significant.

We expect revenues throughout 2009 to be phased similarly to those in 2008. Our cash flow position is expected to deteriorate significantly in the first half of 2009, which is normal due to the seasonality of our business. We build-up inventory in the first half of the year and sell our respiratory and travel vaccine products principally in the second half of the year.

Information on the Company

History and development of Crucell

We are a public limited liability company under Dutch company law, incorporated in Leiden, the Netherlands with the legal and commercial name Crucell N.V., ('Crucell' or the 'Company') registered under number 28087740. We were incorporated on October 9, 2000, as the holding company for Crucell Holland B.V., formerly called IntroGene B.V., following the combination of IntroGene B.V. and U-BiSys B.V. Our principal executive office is located at Archimedesweg 4-6, 2333 CN Leiden, the Netherlands. Our telephone number is +31 (0)71 519 9100. Our registered agent in the US is CT Corporation, 111 Eighth Avenue, New York, New York 10011. Crucell and its subsidiaries together constitute the Crucell Group, or the 'Group'. The Company has subsidiaries in the Netherlands, Switzerland, Spain, Italy, Sweden, Korea and the US.

In February 2006, we acquired a controlling interest in the Swiss biotech company Berna Biotech AG in a share exchange. In September 2006, we acquired the remaining 1.6% minority interest. Berna Biotech AG was founded in 1898. Prior to the acquisition, Berna was a fully integrated biotechnology company that marketed numerous vaccines on a global scale.

In October 2006, the Company purchased, via its subsidiary Crucell Vaccines Inc., the assets and liabilities of the Florida-based Berna Products Corp. from Acambis plc. Berna Products Corp. was originally established in 1990 by Berna Biotech AG to market Vivotif, Berna's oral typhoid fever vaccine, in the US and Canada and was acquired by Acambis plc in 2003.

In November 2006, we acquired the shares of Stockholm-based SBL Vaccin Holding AB (SBL) from 3i and SEB. SBL was a fully integrated independent Swedish biotechnology company. SBL's main product was Dukoral. In addition, SBL had a sales and distribution organization for vaccines in Scandinavia.

In November 2006, we and our technology partner DSM Biologics opened the PERCIVIA PER.C6 Development Center in Cambridge, Massachusetts, US. The joint venture was conceived and designed to further develop the PER.C6 cell line and provide turnkey solutions for the production of monoclonal antibodies and recombinant proteins.

On January 7, 2009, we announced that we were in friendly discussions with Wyeth regarding a potential

combination of the two companies. On January 26, 2009, we announced that Wyeth withdrew from these discussions.

Business drivers

Our business strategy is based on the following business drivers:

Products

Leveraging presence of our marketed vaccines in public and private markets.

We produce and sell established paediatric, respiratory and travel vaccines. We intend to enhance our position in these markets by highlighting the unique features of these products and by providing outstanding customer service in terms of delivery, reliability and quality and by leveraging our worldwide presence in both public and private markets.

Our core portfolio consists of the following products:

- Quinvaxem, a fully-liquid vaccine for protection against five important childhood diseases;
- Hepavax-Gene, a recombinant vaccine against hepatitis B;
- MoRu-Viraten, a vaccine against measles and rubella (all age groups);
- Epaxal and Epaxal Junior, the only aluminum-free and biodegradable vaccine against hepatitis A;
- Vivotif, the only oral vaccine against typhoid fever;
- Dukoral, the only oral vaccine against diarrhea caused by cholera and ETEC (Enterotoxigenic E. Coli); and
- Inflexal V, the only virosomal adjuvanted influenza vaccine for all age groups.

Research and Development (R&D) product pipeline with competitive advantage

We believe that each of our selected products targets unmet medical needs, improves current medications or is otherwise believed to be marketable due to predictive study models and/or perceived favorable regulatory conditions. These products are predominantly based on our PER.C6 technology. In addition, we have various discovery programs to find new vaccine and antibody products.

Besides our portfolio of well known vaccines, we have a pipeline of new potential vaccines and antibodies. Product pipeline programs include

vaccines against yellow fever, influenza, tuberculosis, Ebola and Marburg, malaria, HIV, rabies and H5N1 antibodies. Our R&D activities are concentrated in our headquarters in the Netherlands, but we also have R&D facilities in Switzerland and Korea. Product development is concentrated at our Swiss operations in Bern.

Technologies – ongoing technology licensing program

We have a broad base of excellent technologies with applicability to vaccines, antibodies, other recombinant proteins and gene therapy. Our licensing program provides a source of revenue as well as the potential for future, additional revenue in the form of royalties from products developed by our licensees. In areas where we are not developing our own products, we offer our technologies to the biopharmaceutical industry for the development and production of diverse biopharmaceutical products.

We have developed various proprietary technologies such as PER.C6, AdVac, MAbstract, STAR, our virosomal technology, rCTB as well as our *Hansenula polymorpha* expression system. We believe our proprietary PER.C6 technology is well suited for the development and large-scale manufacturing of a wide range of biopharmaceuticals including vaccines, monoclonal antibodies, therapeutic proteins and gene therapy products. AdVac is used to develop novel adenoviral-based products. MAbstract can be used to develop human antibodies. Our STAR technology is useful for increasing production output of recombinant antibodies and therapeutic proteins on mammalian cell lines and there are indications that the technology is complementary to our PER.C6 technology.

Products

Overview

Our products are marketed by our own sales force as well as by our distribution partners. Our sales are subject to seasonal variations with the majority of our sales coming in the second half of the financial year. This is specifically the case for our influenza vaccines as vaccination programs mainly take place in the second half of the year. In addition, our travel vaccines are also subject to seasonal travel patterns. See 'Partners, agreements, investments and other collaborations – Marketing and sales partners' in this section for more details on our partners.

Vaccine markets

Our core product portfolio currently consists of seven marketed vaccines in three areas of the vaccine market: paediatric vaccines, travel and endemic vaccines and respiratory vaccines.

Paediatric vaccines

Our core paediatric vaccines are Quinvaxem, Hepavax-Gene and MoRu-Viraten.

Quinvaxem

Quinvaxem combines antigens for protection against five important childhood diseases: diphtheria, tetanus, pertussis (whooping cough), hepatitis B and *Haemophilus influenzae* type b, one of the leading causes of bacterial meningitis in children. It is the first internationally available fully-liquid vaccine containing all five of the above antigens, offering a major advantage in terms of convenience of use. Quinvaxem was co-developed with Novartis, which provides four of the five components in bulk. The fifth component is our vaccine Hepavax-Gene.

We produce Quinvaxem together with our hepatitis B vaccine Hepavax-Gene in Korea. In October 2008, we announced that we will relocate the Korean production facility from Yongin City to the Incheon, Free Economic Zone. The new facility will enable the further growth and more efficient production of Quinvaxem and Hepavax-Gene.

As Quinvaxem has been pre-qualified by the World Health Organization (WHO), it is available for purchase by supranational organizations. Supranational organizations are major customers for combination vaccines, which are used in large vaccination programs around the world. In September 2008, we were awarded with new contracts totaling over \$ 140 million for our Quinvaxem and Hepavax-Gene paediatric vaccines by supranational organizations. The contracts provide for the supply of these vaccines for the period 2008 – 2009, bringing the total value of the contracts for the period 2007 – 2009 to \$ 500 million.

Hepavax-Gene

Hepavax-Gene is a recombinant hepatitis B (HBV) vaccine made using Crucell's proprietary *Hansenula polymorpha* expression system. It is one of the WHO's pre-qualified vaccines for active immunization against HBV. A key competitive advantage for Hepavax-Gene is our stable and efficient production system.

In 2008, the Chinese authorities released Hepavax-Gene for registration and quality control in China. Market researcher Decision Resources estimates that the Chinese HBV drug market will more than double between 2007 and 2012 (from \$340 million in 2007 to \$800 million in 2012).

About hepatitis B

HBV is a viral infection of the liver that causes various complications if left untreated and may even ultimately cause death. Transmission of HBV occurs as a result of the exchange of blood, the exchange of fluids during sexual intercourse or the exchange of bodily fluids between an infected mother and a newborn baby at birth.

MoRu-Viraten

MoRu-Viraten is a safe, well-tolerated and effective vaccine for protection against measles and rubella in children, adolescents and adults. The immunogenicity and safety of MoRu-Viraten have been confirmed in clinical trials and extensive post-marketing surveillance. MoRu-Viraten is free of avian proteins and antibiotics, posing no risk to children with allergies to these substances. The vaccine has been marketed since 1986 and is on the WHO list of vaccines for purchase by UN agencies.

About measles and rubella

Measles is a highly contagious disease caused by the measles virus. It is spread by droplets or direct contact with nasal or throat secretions of infected persons and less commonly through the air or indirect contact. Measles continues to remain a serious public health concern worldwide with 30-40 million cases occurring annually. It may be ultimately responsible for more child deaths than any other single agent and is a major cause of preventable blindness in the world. Rubella is a moderately contagious disease caused by the rubella virus. Transmission of the virus is via airborne droplets. It has been estimated that over 100,000 cases of congenital rubella syndrome (CRS) occur in developing countries each year.

Travel and endemic vaccines

Our core travel vaccines are Epaxal, Vivotif and Dukoral.

Travel vaccines include all vaccine products that protect against diseases that are not native to the region travelers are from, but are present in the regions to which they travel. Generally, the target

population groups for these vaccine products are individuals travelling to endemic and epidemic regions. Our vaccines for hepatitis A, typhoid and cholera are classified as travel vaccines.

Our travel vaccines are also increasingly used in expanded immunization programs. Vaccines used in countries with medium to high endemicity could also be characterized as routine or paediatric vaccination. Furthermore, even in some European countries where endemicity is low, childhood vaccination against Hepatitis A virus (HAV) is recommended. This vaccine represents a large potential upside for vaccine manufacturers as they can be targeted at multiple markets.

Epaxal

Epaxal is the only aluminum-free and biodegradable HAV vaccine on the market, offering significant advantages in terms of tolerability. It was the first product to be based on the virosome technology developed and patented by the Crucell company, Berna Biotech AG. It induces protective antibody levels within 10 days of primary vaccination, and provides seroprotection for at least 20 years following the second (booster) dose. In most countries, the vaccine is licensed for adults and children over the age of one. It is currently licensed in more than 40 countries under the brands Epaxal, HAVpur and VIROHEP-A.

About hepatitis A

Hepatitis A (HAV) is a highly contagious infection that causes temporary acute inflammation of the liver. It can range in severity from a mild illness lasting a few weeks to a severe illness lasting several months. HAV infection produces a self-limited disease that does not result in chronic infection or chronic liver disease. HAV is generally contracted orally and commonly spreads through improper handling of food, contact with household members, sharing toys at day-care centers or eating raw shellfish taken from polluted waters.

Vivotif

Vivotif is a live attenuated typhoid fever vaccine for oral administration. The vaccine is indicated for adults and children over the age of five and has an excellent track record for safety, having been on the market for more than 20 years. Protective efficacy is proven in several large-scale field trials including more than 500,000 subjects. It is currently licensed in over 30 countries, including the United States. Data suggests that Vivotif may be unique in also protecting against paratyphoid A and B fever

which is caused by Salmonella strains similar to Salmonella Typhi.

About typhoid fever

Typhoid fever is a debilitating and life-threatening illness caused by the bacteria Salmonella Typhi. Symptoms of the disease include fever, stomach pain, weight loss, loss of appetite, delirium, severe diarrhea (in children), constipation (in adults), cerebral dysfunction and intestinal perforation. The disease is transmitted by faecal contamination of food or water, or by person to person contact.

Typhoid fever is endemic in many parts of Africa, Asia and Latin America. 21 million people are estimated to develop typhoid fever each year. 1-4% of persons with typhoid fever die. At least 5 million people are believed to develop paratyphoid fever annually.

Dukoral

Dukoral is an oral vaccine that protects against cholera and the enterotoxigenic Escherichia coli (ETEC) and is registered in more than 60 countries. The vaccine has demonstrated a protective efficacy against cholera of approximately 85% and 60% against ETEC. Dukoral acts by inducing antibodies against both the bacterial components and cholera toxin (CTB). The vaccine is suitable for travelers and is indicated for use in adults and children over two years of age. Pregnant and lactating women may use it. Other than Dukoral there is no cholera and ETEC combination vaccine available in the world.

About Cholera

Cholera is an acute, diarrheal illness caused by infection of the intestine with the bacterium vibrio cholerae. Over 90% of all cholera cases are mild to moderate and present themselves as ordinary traveller's diarrhea. Approximately 10% of infected persons have a severe case, characterized by profuse watery diarrhea, leg cramps and vomiting, resulting in rapid loss of body fluids leading to shock and dehydration. Without treatment, death can occur within hours. According to the US Center for Disease Control and Prevention, cholera has been very rare in industrialized nations for the last 100 years; however, the disease is still common in other parts of the world and the cholera bacteria can be found in many travel destinations, for example in most part of Asia, Africa and South America. It spreads via contaminated food and water.

Respiratory vaccines

Our core respiratory vaccine is Inflexal V.

Inflexal V

Inflexal V is a virosomal adjuvanted Influenza vaccine (subunit), based upon the virosome technology developed and patented by the Crucell company, Berna Biotech AG. It is the only adjuvanted flu vaccine licensed for all age groups (from 6 months and up). The vaccine's antigen composition follows yearly WHO recommendations. Inflexal V was originally introduced in 1997, is registered in 38 countries and has extensive market experience, with more than 41 million doses confirming its safety profile. The tolerability of Inflexal V is excellent due to its biocompatibility and purity.

About influenza

Influenza, commonly known as 'flu', affects large sections of the world's population each year. The disease is characterized by annual winter outbreaks, which often reach epidemic proportions due to the fact that the virus can mutate quickly, often producing new strains against which human beings do not have immunity. Typical symptoms of flu are usually relatively mild but can become life threatening in vulnerable patient groups, such as the elderly and immunodeficient individuals. In a growing number of countries, small children have been added to the list of preferred protection groups. Transmission of the flu virus occurs through airborne particles and upon infection, the incubation period ranges from one to three days.

Each year approximately 5%-15% of the world's population contracts influenza and an estimated 250,000 to 500,000 people die annually from influenza-associated complications according to the World Health Organization. As well as these annual epidemics, a major genetic shift in the influenza virus can occasionally lead to a deadly new virus strain to which the human population does not have immunity, resulting in a global pandemic. Concerns currently exist that a new avian influenza strain (H5N1) endemic among birds in Asia, and showing high pathogenicity for humans, could present a genuine pandemic threat.

Several factors contribute to the rapid growth of the influenza vaccine market. We expect that the threat of a pandemic of avian flu, the ageing of the population in numerous developed countries,

national government-sponsored vaccination programs in many countries, higher awareness of the value of a flu vaccination among the public at large, as well as specific production contracts for vaccines that combat strains of pandemic flu and ongoing activities to increase the preparedness for a flu pandemic will lead to further growth in the seasonal flu markets.

Research and Development pipeline

Overview

Our product development programs comprise vaccines against yellow fever, influenza, tuberculosis, Ebola and Marburg, malaria, HIV, human monoclonal antibodies against rabies and human monoclonal antibodies against a broad range of influenza.

Overview of our pipeline based on proprietary technologies

Our PER.C6 technology, complemented by our AdVac and MAbstract technologies, drives the development of our product pipeline. We continue to develop our technologies while selecting product leads for further development based on careful product selection criteria that support our long-term business objectives. We have in the past and may again in the future, enter into collaborative and/or strategic alliance arrangements with third parties to co-develop and market products.

Our primary focus is the development of a range of novel vaccine and antibody products in the area of infectious diseases. We currently have a number of core potential products we are developing using our core technologies:

- An influenza vaccine, in collaboration with sanofi pasteur is being developed using our PER.C6 technology;
- Our Ebola and Marburg, malaria and TB vaccine candidates are recombinant vaccines based on PER.C6 technology that also employ AdVac technologies; and
- Our candidate rabies and influenza antibodies are generated and produced using our PER.C6 and MAbstract technologies.

Of the potential products we have under development, only our yellow fever vaccine does not use our core technologies.

Overview of our late-stage pipeline

Yellow fever vaccine

CruCell has developed the yellow fever vaccine, Flavimun, based on a well-established vaccine formerly produced by the Robert Koch institute in Germany. We acquired the rights and know-how for this vaccine against yellow fever from the Robert Koch Institute, which has produced the vaccine since 1963. Over 2.5 million doses of the vaccine have been distributed. The vaccine is safe, highly immunogenic and well tolerated. Protection starts ten days after a single dose and persists for ten years. The product was submitted for registration with the Swiss authorities in the first quarter of 2009. Registration submission in Germany is expected in 2009.

Overview of our early-stage pipeline

The following is a short description of our main potential products in the early-stage pipeline as well as the diseases those products target.

Influenza

Influenza vaccines were classically produced on embryonated chicken eggs. Currently, cell culture systems are being developed for more efficient influenza vaccine production based on Madin Darby Canine Kidney (MDCK) cells and VERO cells. In contrast to MDCK and VERO cells, PER.C6 cells grow well in suspension and are thus easily scalable, permitting the production of cost-efficient vaccines in large quantities. PER.C6 cells possess the different receptors required for the production of vaccines against both human and avian strains of influenza that may present a pandemic threat.

Sanofi pasteur

In December 2003, we entered into a strategic agreement with sanofi pasteur to further develop and commercialize novel influenza vaccines using our PER.C6 technology. Since the inception of the collaboration, production processes have been under development, with the production of a Good Manufacturing Practice (GMP) master cell bank already completed. Currently, we are working to develop a pandemic flu vaccine as well as an inter-pandemic, or seasonal, flu vaccine under this contract. A phase II testing of the cell culture-based seasonal influenza vaccine was initiated in the US and started in the fourth quarter of 2007. In the third quarter 2008, we received a milestone payment for the progress of the phase II trials involving healthy adult volunteers in the US.

The trials focus on the safety profile and immunogenicity of the cell-based vaccine.

Tuberculosis

Crucell is developing a recombinant tuberculosis (TB) vaccine based on our AdVac and PER.C6 technology. The development of this vaccine is being carried out in collaboration with the Aeras Global TB Vaccine Foundation (AERAS). The Crucell-Aeras TB vaccine program is focusing on an AdVac based vaccine that can boost the immune response against TB, initially induced by Bacille Calmette-Guérin (BCG) vaccine, using our PER.C6 and AdVac technologies.

A first phase I clinical trial, launched in October 2006 in Kansas, US, indicated that the vaccine candidate, AERAS-402/Crucell Ad35, is safe in healthy adults in the US. The preliminary results of a second study, launched in May 2007, showed that both critical arms of the cellular immune system, CD4 and CD8 immune T-cells, were induced and that in those participants who responded, CD8 immune responses were considerably higher than had ever previously been seen in a TB vaccine study. A third phase I study in St. Louis, Missouri, US was launched in December 2007 and focuses on the immunogenicity and safety of two AERAS-402/Crucell Ad35 boost doses administered at three to six month intervals after BCG priming in healthy adults.

An ongoing study in St. Louis, MO, US is evaluating a longer prime-boost interval. The study has been fully enrolled and has discovered no safety issues. Immunological data is expected to be available in the first half of 2009.

In October 2008, Crucell and AERAS announced the start of a phase I clinical trial in Kenya. The main parameters of the study will be to test the safety of the vaccine candidate in healthy adults, all of whom have been previously vaccinated with the BCG vaccine and a subset of whom have evidence of having been exposed to TB. This study is fully enrolled and now in its follow-up segment, with no safety issues identified. The companies also started the enrollment of the first phase II study of the vaccine candidate. The study is being conducted in Cape Town, South Africa by the University of Cape Town Lung Institute in conjunction with the South African Tuberculosis Vaccine Institute. No evidence of an unacceptable safety issue has been found in its dose escalation design.

About tuberculosis

TB is a major cause of illness and death worldwide, especially in Asia and Africa, with over 9 million new cases diagnosed in 2006. According to the World Health Organization (WHO), an estimated 1.7 million people died from TB in 2006. One third of the world's population has been infected with the TB bacillus and current treatment takes 6-9 months. The current TB vaccine BCG, developed over 85 years ago, reduces the risk of severe forms of TB in early childhood but is not very effective in preventing pulmonary TB in adolescents and in adults, the populations with the highest TB rates. As the disease is changing and evolving, new vaccines are even more crucial to control any pandemic. TB is the leading cause of death for people living with HIV/AIDS, particularly in Africa. Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are hampering treatment and control efforts. A need for an alternative vaccination approach has emerged in the last two decades.

Ebola and Marburg

Crucell is developing an Ebola vaccine in collaboration with the Vaccine Research Center (VRC) of the NIAID.

In May 2002, we entered into a Collaborative Research and Development Agreement (CRADA) with the VRC to jointly develop, test and manufacture an adenovirus-based Ebola vaccine. Under the terms of the agreement, we have an option for exclusive worldwide commercialization rights to the Ebola vaccine resulting from this collaboration. In August 2002, the CRADA was extended to cover vaccines against Marburg and lassa infections.

In experiments conducted by the VRC together with the US Army Medical Research Institute of Infectious Diseases (US.AMRIID) during the first half of 2004, our vaccine candidate confirmed single-dose protection in pre-clinical testing against Ebola. What set the results of this trial apart from the earlier successful trial, which established a proof-of-concept, was that the vaccine in this instance was produced on PER.C6 technology.

In March 2005, we extended the CRADA with the US NIH and continue to develop this vaccine and will use the Ebola vaccine results in the development of Marburg and lassa vaccines. In addition, we obtained an exclusive license to certain NIH patents to develop and commercialize recombinant vaccines against Ebola.

In October 2008, we secured a NIAID/ NIH contract aimed at advancing the development of Ebola and Marburg vaccines, ultimately leading to a multivalent filovirus vaccine. The contract provides funding of up to \$ 30 million, with additional options that may be triggered at the discretion of the NIAID for an additional \$40 million. The phase I study of an Ad5 based Ebola vaccine, being developed in partnership with VRC, showed safety and immunogenicity at the doses evaluated. Based on these results a second phase I study of an Ebola and/or Marburg vaccine is anticipated.

About Ebola and Marburg

The Ebola and Marburg viruses are capable of causing hemorrhagic fever, a severe, often-fatal disease in humans characterized by high fever and massive internal bleeding, causing death in 50% to 80% of all cases. Ebola and Marburg outbreaks occur regularly in tropical Africa, affecting both human and great ape populations. Since the Ebola virus was first recognized, approximately 2,200 cases, including over 1,500 deaths, have been reported. To date, over 440 cases of Marburg have been reported with approximately 360 fatalities. Ebola and Marburg usually appear in sporadic outbreaks, and spread within a health-care setting. Because of the high disease-related mortality rates and lack of any vaccine or therapy, the Ebola and Marburg viruses are on the US Centers for Disease Control and Prevention Category 'A' list of bio terror agents, together with smallpox and anthrax.

Malaria

We are developing a recombinant malaria vaccine based on our AdVac technology and produced on our PER.C6 production technology. The vaccine is made by inserting the gene for the circumsporozoite protein (CSP) from a malaria parasite into an adenoviral vector, which acts as a 'vehicle' for vaccination delivery.

The efficacy of our malaria vaccine candidate was tested in pre-clinical models. The study showed that a single administration of a prototype AdVac vaccine, provided protection against the specific parasite. Since March 2004, we have collaborated with the NIAID for the support of the development of our candidate malaria vaccine. In September 2006, we extended our collaboration with the NIAID by signing a clinical trial agreement.

In partnership with the NIAID, Crucell's malaria vaccine entered a phase I trial in the US in January 2007. The study is being carried out on two sites,

Vanderbilt University in Tennessee and Stanford University in California. The first three groups have been enrolled and ongoing safety monitoring has revealed no significant safety concerns to date, but formal analysis awaits unblinding of the data. Further updates on this program are expected in the second quarter of 2009.

About malaria

Malaria is a life-threatening infectious disease caused by the plasmodium parasite and transmitted from person-to-person through the bite of a female Anopheles mosquito. It is currently one of the most lethal communicable diseases. The disease currently represents one of the most prevalent infections in tropical and subtropical areas causing severe illness in 300 to 500 million individuals worldwide according to the World Health Organization and causing 1 to 3 million deaths every year. Most of these deaths occur among children and pregnant women in the developing world, especially in sub-Saharan Africa. Unfortunately, mortality associated with severe or complicated malaria still exceeds 10-30%. The widespread occurrence and elevated incidence of malaria are a consequence of discontinued malaria control programs and increasing numbers of drug-resistant parasites and insecticide-resistant parasite vectors. Other factors include environmental and climatic changes, civil disturbances and increased mobility of populations. Although the overwhelming majority of morbidity and mortality associated with malaria occur in the developing world, this disease also affects travelers.

HIV

In August 2005, Crucell, along with Harvard Medical School, was awarded a \$ 19.2 million grant by the US NIH to develop new adenovirus vector-based vaccines against HIV/AIDS. The Investigational New Drug Application (IND) for phase I of the trial with Harvard Medical School (supported by the NIH) was approved by the FDA in January 2008. In April 2008, the Company announced the start of a Phase I clinical study of the novel recombinant HIV vaccine that Crucell is jointly developing with the Beth Israel Deaconess Medical Center, using adenovirus serotype 26 (rAd26) as vector. The rAd26 vector is specifically designed to avoid the pre-existing immunity to the more commonly used adenovirus serotype 5 (Ad5). The phase I clinical study is being conducted at the Brigham and Women's Hospital in Boston, MA, US and is focused on assessing the safety and immunogenicity of the vaccine. Enrollment is currently ongoing.

About HIV

Human immunodeficiency virus or HIV is a retrovirus that causes acquired immune deficiency syndrome (AIDS), a condition in humans in which the immune system begins to fail, leading to life-threatening infections. HIV infection occurs on a global scale. A joint United Nations Program on HIV/ AIDS and the WHO estimate that AIDS has killed more than 25 million people since it was first recognized on December 1, 1981, making it one of the most destructive pandemics in human history.

There currently is no treatment for HIV or AIDS. The only known methods of prevention are based on avoiding exposure to the virus or, failing that, an antiretroviral treatment directly after a highly significant exposure, called post-exposure prophylaxis (PEP). Protective sex is another form of prevention of the deadly disease. Antiretroviral drugs (ARVs) which significantly delay the progression of HIV to AIDS and allow people living with HIV to live relatively normal, healthy lives, have been available in wealthier parts of the world since around 1996.

Antibodies

Rabies monoclonal antibody combination

We are developing a human monoclonal antibody combination for the post-exposure treatment of rabies. The use of Crucell's MAbstract technology resulted in a combination of two human anti-rabies antibodies. The monoclonal antibodies are produced on Crucell's PER.C6 technology.

Post-exposure treatment for rabies, when given timely, is 100% effective and involves the use of a vaccine plus antibodies. Neither vaccine nor antibodies are effective independent of one another. Current supply and quality of rabies vaccine is sufficient, but anti-rabies antibodies (Human Rabies Immune Globulin (HRIG) and Equine Rabies Immune Globulin (ERIG)) are widely recognized as being insufficient in quality and supply, and pose safety concerns because they originate from human or equine serum. Market opportunities for rabies treatments are projected to grow significantly as the customer base grows in affected countries such as India and China.

We have developed the human monoclonal antibody combination in collaboration with the Thomas Jefferson University (TJU) based in Pennsylvania, US and the Center for Disease Control (CDC) in Georgia, US using MAbstract and

PER.C6 technology. Our rabies monoclonal antibody combination demonstrated protection at least equivalent to HRIG in pre-clinical trials.

In December 2007, we signed an exclusive collaboration and commercialization agreement with sanofi pasteur for our rabies monoclonal antibody combination to be used in association with rabies vaccine for post-exposure prophylaxis against this disease. We will continue to perform the development activities and will be responsible for the manufacturing of the final product and will retain exclusive distribution rights in Europe, the rights to sell to supranational organizations such as UNICEF and co-exclusive distribution rights in China.

The program has been granted a Fast Track designation by the US Food and Drug Administration (FDA).

Phase I clinical trials demonstrated that the antibody product is well tolerated, provides the expected immediate passive neutralizing activity and that it can be safely administered in combination with a rabies vaccine without interfering with the vaccine's ability to induce an active immunity.

Phase II clinical trials began in the US in March 2008. In October 2008, the positive preliminary results of the US study were presented. No serious adverse events were reported and the study confirmed the neutralizing activity of the antibody product against the rabies virus. In May 2008, a second phase II clinical study began in the Philippines and was completed before year-end 2008. Final data from this study are expected to become available in the first half of 2009.

An additional phase II study in healthy adults evaluating Crucell's monoclonal antibody in combination with a rabies vaccine started in February 2009.

About rabies

Rabies is a viral disease of mammals most often transmitted through the bite of an infected animal. The virus infects the central nervous system, causing encephalopathy and ultimately death if medical treatment is not sought before symptoms become more severe. Rabies is prevalent in all the continental regions of Europe, Asia, America and Africa. Globally, approximately 10 million people a year are treated after exposure to rabies. Some

40,000 to 70,000 people are thought to die of the disease each year, mainly in China and India, according to various medical publications.

Human monoclonal antibodies against a broad range of influenza

Crucell's scientists discovered a set of human monoclonal antibodies that provides immediate protection and neutralizes the broadest range of H5N1 strains. When tested in pre-clinical models for prevention or treatment of a potentially lethal H5N1 infection, this antibody was shown to prevent death and cure the disease.

In another pre-clinical study, Crucell's mAb CR6261 was compared with the anti-influenza drug oseltamivir in terms of its value for flu prevention and treatment. In December 2008, Crucell announced that its monoclonal antibody had strongly outperformed the most current anti-influenza drug in these tests.

The flu strains tested included the 'bird flu' strain H5N1, which, experts fear, has the potential to cause a pandemic, and H1N1, which is similar to the strain responsible for the devastating pandemic in 1918. Importantly, the study showed that CR6261 provides immediate protection against the influenza virus, suggesting that it will be able to prevent disease spread. In contrast, oseltamivir was less efficacious and in some cases not effective at all.

Technologies

Licensing our technologies to the market

We generate a portion of our revenues and other operating income from licensing our proprietary technologies to pharmaceutical and biotechnology companies, from grants and government subsidies obtained to support the development of our technologies and potential products and from service fees earned under development contracts with our partners. We intend to increase our revenues in the future from initial license fees, license maintenance fees and milestone and royalty payments from products that our licensees develop using our technologies.

Our business development strategy historically involved contacting prospective licensees and partners and assessing their interest in our technologies and products. If the prospective licensee or partner indicates interest we negotiate a license and/or collaboration agreement pursuant to which we deliver the applicable technology to, or

collaborate with, the licensee or partner. For some of the contracts we provide services, for which we are paid at different rates.

Core proprietary technologies

Our product portfolio is supported through five core proprietary technology platforms.

PER.C6 technology

Overview

Our PER.C6 technology provides a manufacturing system that can be used to produce a variety of biopharmaceutical products. Crucell's PER.C6 cell line is derived from a single, human retina-derived cell, which was purposely immortalized using recombinant DNA technology. As a result, PER.C6 cells can replicate indefinitely, allowing them to be cultured in single cell suspension under serum-free conditions in quantities appropriate for large-scale manufacturing.

The technology has been successfully adapted to grow without the need for serum components or materials that allow cell attachment (micro carriers) and demonstrates excellent cell densities in bioreactors. These features are important because they allow us to produce safe biopharmaceutical products in sufficient quantities.

In September 2008, DSM Biologics and Crucell announced that the high-titer-fed batch process developed at the PERCIVIA PER.C6 Development Center, their joint venture in Massachusetts, US (PERCIVIA) was scaled up to 250 liters by DSM Biologics scientists at their GMP facility in Groningen, the Netherlands. They successfully achieved 8 grams per liter for an IgG antibody expressed by PER.C6 cells using chemically defined cell culture medium in a single-use bioreactor. In June 2008, the Company reported record-breaking protein yields of 27 grams per liter using DSM's innovative XD™ technology.

There are four areas in which our PER.C6 technology is currently being applied:

Vaccine production

PER.C6 technology can be used as a production system for developing and manufacturing both classical and recombinant vaccines.

- For classical vaccine production, PER.C6 cells are infected with the virus against which the vaccine is meant to protect. The virus is subsequently

multiplied on PER.C6 cells to high virus titer, yielding a potent starting material that can be processed and purified to produce a final formulation of a whole-killed, split or sub-unit vaccine; and

- For recombinant vaccine production, the PER.C6 technology produces delivery agents called adenoviral vectors. These vectors have been made replication incompetent and thus are only capable of delivering into the human body a portion of DNA encoding for a protein from the pathogen against which the vaccine is meant to protect. The DNA inserted into the vector can be derived from a virus, a parasite or even bacteria, providing a versatile vaccine vector platform.

Protein production

PER.C6 technology can be used as a production system for developing and manufacturing both antibodies and other proteins. DNA encoding for a particular protein of interest is inserted into PER.C6 cells. These modified PER.C6 cells will secrete the desired antibody or other protein. We are further developing the application of PER.C6 for protein production at PERCIVIA.

Gene therapy

The primary function of PER.C6 technology in the field of gene therapy is the production of adenoviral vectors a gene delivery mechanism based on a common cold virus that carries therapeutic genes and facilitates the delivery of the gene into the cells. Since the PER.C6 technology is the only available cell line that does not allow any formation of classical replication competent adenoviruses during the production of replication deficient vectors, the cell line may be applied across the entire adenovirus gene therapy field.

Functional genomics

Our PER.C6 technology can be used to produce libraries of adenoviruses into which individual human genes are inserted to study gene function. The adenovirus libraries carry many genes with unknown functions, which can be used to determine the role of individual genes in a disease process. We believe that our PER.C6 technology, therefore, represents a key analytical tool in the discovery of new genes and their role in biological pathways and human disease.

Key features and advantages

We believe that our PER.C6 technology has the following key advantages over alternative manufacturing systems:

- PER.C6 technology potentially offers a system for high yield, large-scale biopharmaceutical product production. PER.C6 technology can be cultured at high densities and engineered to produce large quantities of biopharmaceuticals and may reduce production expense.
- PER.C6 cells can be cultured in a serum-free medium, without micro-carriers, using a variety of scaling systems, including bioreactors. This simplifies the expansion from laboratory- to industrial-scale production, which may lead to the production of cost-efficient biopharmaceuticals in large quantities. The use of a serum-free medium also offers the potential to significantly improve the purification of biopharmaceuticals produced using the PER.C6 technology and may facilitate regulatory approval.
- We have filed a Cell Substrate Biologics Master File (BMF) with the US Food and Drug Administration (FDA) describing the PER.C6 technology, including its establishment, development and potential use in production processes. The FDA will only evaluate the PER.C6 technology in the context of Investigational New Drug (IND) applications. We believe that the information in the BMF will facilitate the FDA's approval of any biopharmaceutical product that we or our licensees produce using the PER.C6 technology.
- The PER.C6 technology can now claim to have achieved a broad endorsement within the industry. For an overview of our most important licensees and partners subsidiaries please see the 'Appendix Overview licensees and partners'.
- We believe that antibody and other protein products based on the human based PER.C6 technology may demonstrate enhanced biological properties, rendering them potentially more efficacious. In addition, PER.C6 technology efficiently supports the growth of certain human viruses for vaccine development.

AdVac technology

Overview

Crucell has been a key player in the development of adenoviral-based vaccines for more than five years, resulting in the availability of proprietary AdVac vectors. Crucell has generated a wide variety of research and GMP clinical batches based on AdVac technology for diverse infectious diseases.

AdVac technology is based on vectors constructed from adeno viruses that do not regularly occur in the human population, such as Ad35. The technology supports the practice of inserting DNA coding of pathogen-derived proteins into a vector. AdVac technology may also be used to develop gene therapy products. AdVac vectors are used in combination with our PER.C6 technology. Currently AdVac technology is used by Crucell and its licensees to develop vaccines against hemorrhagic fevers (Ebola, lassa, Marburg), malaria, TB, HIV/AIDS and hepatitis C (HCV). While no adenovirus-based recombinant vaccines are currently licensed for human use, AdVac-based vaccines for malaria, HIV/AIDS, HCV, hemorrhagic fevers, and TB have been successfully constructed and are currently in clinical trials.

Crucell has generated a series of adenoviruses including Ad35 and derivatives thereof as well as manufacturing platforms for these vectors. The AdVac vectors can be produced to carry genetic information derived from viruses, parasites and bacteria, and thereby have the potential to allow immunization against life-threatening diseases.

Crucell has laboratories to develop purification methods closely resembling an end-stage manufacturing process. With this facility we can manufacture Ad35 vaccine vectors for comprehensive pre-clinical programs. These products can be manufactured using PER.C6 technology under serum-free conditions.

Key features and advantages

We believe our AdVac technology has the following key advantages over other commonly used vector systems:

- Vectors used with AdVac technology share the advantages of the commonly used adenoviral vectors such as: scalable production, high yields and the ability to mediate a strong T-cell immune response;
- The AdVac technology can circumvent pre-existing immunity offering accurate dose control of the vaccines; and

- AdVac vectors can be engineered to contain small genetic fragments of different viruses, parasites and bacteria. This makes possible the development of a wide variety of novel vaccines against a broad range of dangerous human pathogens.

MAbstract technology

Overview

Our MAbstract technology can be applied to the discovery of novel drug targets and the identification of human antibodies against those drug targets. MAbstract technology employs a bacteria-infecting virus called a bacteriophage, or phage, which expresses part of a human antibody on its surface. The technology employs a library of phages that carry many different human antibodies. To identify and subsequently isolate relevant antibodies, the library is put in contact with pathogens, or cells suspected of carrying the drug target, or if the target is already known in advance, the library may be put in contact with the target directly. Subsequently, phage antibodies binding to the diseased cells or the known target are separated from phage antibodies that do not bind at all, or bind to healthy cells added to eliminate irrelevant phage antibodies present in the library. Since irrelevant phage antibodies for the target in question are often present in great abundance, the elimination step aids in enriching the phage-antibody population for potentially relevant, selectively binding phage antibodies.

Once such phage antibodies have been isolated, they can either be used to subsequently identify the target or a specific binding place on the target (referred to as epitope), or be used to subsequently isolate the DNA coding for the binding part of the antibody. This part may genetically be combined with other parts of the antibody that have no binding function but have accessory functions in the human immune system. Thus, different formats of antibodies with different modes of action or functions can be made, but with the same specificity for the target.

We use our MAbstract technology to identify antibodies reactive with whole pathogens, antibodies against protein elements from pathogens or antibodies directed against targets already known to be associated with disease. In addition MAbstract can be used to identify targets or epitopes on disease-causing agents that were previously unknown and may make suitable candidates for antibody-based diagnosis, prevention or therapy of the associated disease.

Key features and advantages

MAbstract employs a human-based antibody-display technology. We believe that MAbstract allows for the discovery of therapeutic antibodies with several potential advantages over current technologies. These advantages include the following:

- MAbstract technology selects antibodies for possible therapeutic use and discovers novel drug targets using whole cells, tissues or infectious agents.
- MAbstract technology does not have inherent limitations on antibody specificity.
- MAbstract technology has been used to isolate antibodies for numerous disease applications. Selected antibody specificities can be directly reformatted into antibodies for production using PER.C6 technology.

STAR technology

Overview

STAR technology is useful for increasing production of recombinant antibodies and therapeutic proteins on mammalian cell lines. It is a two component system consisting of (a) STAR elements that counteract gene silencing, resulting in increased levels of production and improved stability of recombinant proteins, and (b) STAR-select, a very stringent selection system that is directly coupled to the expression of the gene of interest, resulting in only a few cell lines that all produce the recombinant protein at high levels.

Multiple companies and licensees are investigating whether the STAR technology can increase production yields of biological substances. We acquired STAR technology in 2004 through the purchase of ChromaGenics B.V., a privately held biotechnology company based in Amsterdam. In connection with the purchase, we also entered into a contingent payment agreement with the former shareholders of ChromaGenics that could result in us making additional payments of up to € 7.0 million, based upon our receipt of revenues generated from the STAR technology. In 2007, we paid € 2.0 million to the former shareholders under this agreement.

Key features and advantages

We believe our STAR technology has the following key advantages over other gene expression technologies:

- Established mammalian cell banks for antibody and protein production are the starting point for STAR technology, thus specially engineered mammalian cells are not needed;
- The STAR technology allows for very rapid stable mammalian cell clone generation; and
- The STAR technology typically yields stable mammalian cell clones that produce five- to ten-fold more antibody or other therapeutic proteins compared to cell clones generated without STAR.

Virosomal technology

Overview

One of the challenges in vaccine development is the creation of products that contain defined antigens of high purity that efficiently induce a protective immune response. Many antigen preparations are therefore supplemented with adjuvants to enhance the body's immune response to the specific antigens. The most commonly used and approved adjuvants for human use are aluminum salt derivatives, which are known to cause adverse reactions such as irritation and inflammation at the injection site. Virosomes are a broadly applicable adjuvant and carrier system with prospective applications in areas beyond conventional antigen-based vaccines. Our virosome technology offers a tool for developing novel, predominantly synthetic vaccines applicable to infectious and chronic diseases. These vaccines offer additional benefits because they are effective even in immune-suppressed patients and infants.

Key features and advantages

We believe our Virosome technology has the following key advantages over other antigen delivery technologies:

- Virosome technology provides a broadly applicable delivery system for antigens or DNA/RNA encoding specific immune stimulatory proteins;
- Virosome technology enables target-specific delivery of antigens and amplification of the immune response;

- Virosomes stimulate both arms of the immune system, eliciting both antibody and cellular immune responses, against inserted immune stimulatory proteins derived from human pathogens;
- Virosomes are completely biodegradable and can exert an immune response via different routes of administration; and
- Virosome technology is used in the manufacture of several of Crucell's registered products where it has an excellent safety record.

Other proprietary technologies

In addition to our core proprietary technology platforms the company employs numerous other technologies. Of these other proprietary technologies we would like to highlight the following two.

Hansenula polymorpha

Overview

The yeast expression technology Hansenula polymorpha provides us with a highly efficient production technology for proteins, which can be used as a basis for developing and manufacturing new vaccines. The yeast Hansenula polymorpha production system provides superior characteristics for a wide range of industrial applications. In particular its lack of pyrogens, pathogens or viral inclusions, its ease of genetic manipulation and its robustness in industrial scale fermentations add to its attractiveness for the synthesis of pharmaceutical compounds. Our registered HBV vaccine Hepavax-Gene is based on recombinant production in this yeast.

Key features and advantages

We believe our Hansenula polymorpha technology has the following key advantages over other yeast expression technologies:

- Hansenula polymorpha provides an expression system with superior characteristics for the synthesis of pharmaceutical compounds, including vaccines;
- Hansenula polymorpha provides a safe production platform lacking pyrogens, pathogens or viral inclusions; and
- Hansenula polymorpha is easy to manipulate genetically and is robust in industrial scale fermentations.

Recombinant Cholera Toxin B sub-unit technology

Cholera Toxin B (CTB) sub-unit is a powerful inducer of immunity both systemically and mucosally. Numerous applications have shown that coupling of antigen to CTB increases the immunogenicity of the antigen. In some applications simple co-administration of CTB with the antigen has been shown to be effective. This has been shown both for parenteral as well as mucosal (intranasal) applications.

CTB is an efficient mucosal carrier for induction of peripheral immunological tolerance. Oral ingestion of antigen coupled with CTB suppresses peripheral T-cell reactivity to the coupled antigen. The Group has a state-of-the-art GMP manufacturing facility for recombinant CTB. The production system is designed so that CTB is produced completely devoid of the toxins.

Partners, agreements, investments and other collaborations

Strategic partners

In addition to our own research and development activities, Crucell collaborates with several leading companies. Through these agreements, our technologies are playing a vital role in the development of a number of vaccine and antibody products.

Merck

Since 2000, Crucell and Merck have developed a close working partnership, entering into a number of agreements. In June 2003, Merck and Crucell expanded an existing cooperation agreement and agreed to work closely on matters related to maintenance of the PER.C6 Cell Substrate BMF. We further expanded the relationship in December 2006, when we signed a cross-licensing agreement for vaccine production technology. The agreement allows Merck to use our technology on an exclusive basis in additional undisclosed vaccine fields. In return, we received access to Merck's large scale manufacturing technology for our AdVac-based vaccines under development. In September 2007, Merck exercised an option for the exclusive use of our PER.C6 technology and access to our AdVac vaccine technology in two infectious disease areas.

DSM Biologics

In December 2002, we formed an alliance with DSM Biologics to license our PER.C6 technology as a production platform for monoclonal antibodies

and recombinant proteins. The combination of the PER.C6 technology and DSM's manufacturing services provides companies with a turn-key biologic manufacturing solution reducing cost, risk and time to market. Furthering this commitment to the PER.C6 technology, Crucell and DSM established PERCIVIA in August 2006. The innovations resulting from this partnership will be available to PER.C6 licensees to further enhance their development capabilities.

Sanofi pasteur

We have a strategic agreement with sanofi pasteur since 2003 to further develop and commercialize novel influenza vaccine products based on our PER.C6 technology. The agreement covers both seasonal and pandemic influenza vaccines. Sanofi pasteur has the worldwide rights to develop, manufacture and commercialize PER.C6-based influenza vaccines. Crucell has the commercial rights for Japan.

In December 2007, we signed an exclusive collaboration and commercialization agreement with sanofi pasteur for our rabies monoclonal antibodies to be used in association with rabies vaccine for post-exposure prophylaxis.

Novartis

Our largest selling vaccine is Quinvaxem. The vaccine is produced by Crucell in Korea and was co-developed with Novartis (formerly Chiron), which provides four of the five vaccine components in bulk. We have a profit sharing agreement with Novartis for this product.

MedImmune

In October 2007, we entered into an exclusive license and research collaboration with MedImmune to further develop and commercialize bacterial antibodies primarily for the treatment and prevention of hospital-acquired bacterial infection. Crucell discovered these antibodies with use of the MAbstract-technology.

Wyeth

In March 2008, we entered into an exclusive agreement with Wyeth pursuant to which we perform contract manufacturing for Wyeth at our Swiss facilities. We will develop and manufacture certain vaccine components that Wyeth will use in clinical studies. The development activities will take place in our facilities in Bern, Switzerland. Wyeth will be responsible for the overall clinical development of the vaccine.

Other collaborations and agreements

Manufacturing service arrangements

We have signed manufacturing service agreements with a number of our licensees and partners. Under these agreements, we have produced and may produce in the future clinical batches of adenoviral materials, antibodies, or other materials using our PER.C6 technology for the applicable licensee. We have received and may receive in the future initial fees upon signing and subsequent payments upon delivery of the batches we produce in accordance with the terms of the agreement.

University collaborations

We collaborate with a number of universities worldwide in the areas of vaccines, antibodies, cell lines, gene therapy, cancer and cardiovascular disease. Some of our collaborations provide for royalty payments to be made to the universities in the event product sales arise out of the collaborations. Generally, these collaboration agreements specify that Crucell provides the applicable university with a specific amount of funding and the Group receives certain intellectual property rights and access to the results of the university research.

Overview licensees and partners

For an overview of our most important licensees and partners subsidiaries please see the 'Appendix Overview licensees and partners'.

Our equity investments

Subsidiaries

The following transactions changed the scope of consolidation in 2008:

- In December 2008 SBL Vaccin Holding AB and Vitec AB Rhein Vaccines B.V. legally merged into SBL Vaccin AB; and
- In November 2008 we sold our fully-owned subsidiary Etna Biotech Srl (Catania, Italy) to Zydus Cadila (Ahmedabad, India).

For a complete overview of our most significant subsidiaries please see '1.1 Corporate information – List of consolidated companies' in the financial statements.

We are not aware of any legal or economic restrictions on the ability of our subsidiaries to transfer funds to the Company in the form of cash dividends, loans or advances other than withholding taxes due in certain countries in which we operate.

Associates and joint ventures

On July 3, 2008 the Group sold all of the 2,625,000 shares it owned in Kenta Biotech AG to Ingro Finanz AG. Prior to this sale, our ownership interest had already been diluted from 37% in 2006 to 22% by the end of 2007. We realized an accounting gain of € 1.6 million on the sale in 2008.

For a complete overview of our associates and joint ventures please see '5.9 Investments in associates and joint ventures' in the financial statements.

Other equity investments

Galapagos N.V. ('Galapagos') is a discovery company focused on the rapid identification of disease modifying drug targets through the functional screening of human disease models, and the subsequent progression of these targets into drug discovery. The company is listed on the NYSE Euronext Brussels and NYSE Euronext Amsterdam stock exchanges (ticker symbol: GLPG).

Galapagos holds a royalty free exclusive license to use our PER.C6 technology for conducting activities in the field of functional genomics research. Under the license, Galapagos uses PER.C6 technology in conjunction with Tibotec's bioinformatics technology to generate adenoviral gene libraries. We have agreed with Tibotec to not compete with the activities of Galapagos, which holds the rights to the products and technologies that it develops. The Group owns 5.8% of Galapagos as of December 31, 2008 (2007: 5.8%).

Marketing and sales partners

We have our own sales and marketing infrastructure in our markets in the Benelux, Switzerland, Italy, Spain, Scandinavia, US and Canada, Argentina, China, Korea, Indonesia and Vietnam. This sales and marketing infrastructure includes a dedicated sales force for supranational organizations. We have also established a strong network of partnerships to ensure broader market access for our products. Through these measures, we have established a global marketing and sales organization with strong presence in the US, US, South-East Asia and supranational organizations.

We also distribute and market other companies' products, to strengthen our presence in vaccine or therapeutic protein markets. The most significant collaborations in terms of current sales value are:

Our partners:	Marketing, sales and distribution partner for:
Sanofi pasteur – MSD	part of the sanofi pasteur – MSD portfolio in Sweden.
Novartis Vaccines and Diagnostics	part of the Novartis vaccine portfolio in Sweden.
Statens Serum Institute Denmark (SSI)	part of SSI's product portfolio in Spain and Sweden.
Green Cross Corporation Korea	Green Cross Corporation's Japanese encephalitis vaccine in Europe.
Netherlands Vaccine Institute (NVI)	part of NVI's product portfolio in the Benelux
Talecris Biotherapeutics	Talecris's product Prolastin in nine Western European countries.

In addition, we developed a network of companies that market and sell our products. The most significant collaborations in terms of current sales value are:

Our partners:	Marketing, sales and distribution partner for:
Zuellig	several vaccines in China.
Baxter International Inc.	several vaccines in Austria, Germany, Greece and Russia.
Infectopharm Germany	our flu vaccine in Germany.
Masta UK	our travel vaccines in the UK.
Novartis	our travel vaccines in Germany.
Sanofi pasteur	Dukoral in Canada, Australia and a number of other countries outside Europe and the US.
Sanofi pasteur – MSD	our flu vaccine in the UK.
Kedrion	our flu vaccine in Italy.

Intellectual property

Our success and ability to compete depends in large part on our ability to protect our proprietary technology and information, and to operate without infringing on the intellectual property rights of others. We rely on a combination of patent, trademark and trade secret laws, as well as confidentiality, assignment and licensing agreements, to establish and protect our proprietary and intellectual property rights. Our policy is to actively seek patent protection of our intellectual property in the US and Europe, as well as in other jurisdictions as appropriate.

We engage European and Dutch patent attorneys that file, prosecute, defend and enforce patent rights as well as manage our patent portfolio. Our patent portfolio comprised 1677 active cases (i.e. granted patents in force or pending patent applications) as of December 31, 2008. We aggressively protect our inventions and employ a proactive filing strategy with respect to patent applications. Our portfolio management involves active commercialization and enforcement strategies combined with disposal of cases that we no longer consider commercially attractive.

The following table reflects the total number of active cases (pending or granted) through December 31, 2008, organized according to our different fields of operation. All figures include acquired and jointly owned patent cases, but exclude patent positions licensed-in from third parties.

2008 Patent filings

	Pending	Granted	Active
Vaccines ⁽¹⁾	259	367	626
Antibodies ⁽²⁾	141	77	218
Technology ⁽³⁾	268	344	612
Gene Therapy	50	171	221
Total	718	959	1,677

⁽¹⁾ Vaccines patent filings relate to AdVac-based, live viral vector vaccines based on our proprietary measles technology, our virosomal technology and classical whole inactivated virus, split and sub-unit vaccines.

⁽²⁾ Antibodies patent filings relate to antibodies and/or drug targets, excluding the enabling technologies that are classified as technology.

⁽³⁾ Technology patent filings primarily relate to cell-based production technology, adenoviral vector technology, STAR-technology and related technology, functional genomics and target and antibody discovery technology.

Patent filings

In 2008, we filed patent applications for four new inventions, in the fields of vaccines and technology. Our new filings in the vaccine field in 2008 reflect our efforts to further strengthen our patent portfolio in support of product development programs in that area. The new filings in the technology area relate to our continuing effort to protect and commercialize the PER.C6 technology and related uses of the PER.C6 cell lines, as well as our AdVac technology. Since we are not actively involved in gene therapy research and development, no new filings were made in that area during 2008.

We maintain a geographically diversified filing strategy, depending on our technological and business needs, as well as our view of long-term economic trends and developments in legal systems in various parts of the world. As of December 31, 2008, we had 64 pending applications in the EU⁽¹⁾, 110 pending applications in the US⁽²⁾, 21 international patent applications (so called Patent Cooperation Treaty (PCT) applications⁽³⁾) and 523 applications in the rest of the world⁽⁴⁾.

A significant number of our pending patent applications are filed under the PCT, which offers a cost-effective method to seek provisional worldwide protection in more than 100 countries and territories for 30 or 31 months from the filing date. The decision to divide the PCT application into territories in which a granted patent is desired may be postponed until the obtainable scope of protection and the technical and commercial usefulness of the invention becomes clearer. During the pendency of a European patent application, a single application may designate 35 countries but is counted as one pending application. As soon as the European patent application is granted it may be validated for each of the designated countries by filing a translation into the official language of that designated state. Once such a translation has been filed, we count each such patent as a separate patent.

⁽¹⁾ EU refers to filings made under the European Patent Convention. The EU figures do not include European patent applications designated in PCT applications while still in the international phase.

⁽²⁾ US figures do not include US patent applications designated in PCT applications while still in the international phase.

⁽³⁾ Figures reflect PCT applications still in the international phase. Our PCT applications routinely designate all territories and contracting states that are party to the PCT per the international filing date.

⁽⁴⁾ Rest of world consists of Australia, Brazil, Canada, China, India, Israel, Japan, Hong Kong, Mexico, New Zealand, Norway, Russia, Singapore, South Africa and South Korea. Rest of world figures do not include PCT applications designating these countries while still in the international phase.

Patents

At December 31, 2008, we owned or co-owned 601 granted patents in the EU territory, 83 patents in the US and 275 patents in the rest of the world.

The following is a summary of the intellectual property rights related to our major products and product developments.

Epaxal and Inflexal V

Epaxal and Inflexal V are the two virosomal products which are protected by the patent family 'Immunostimulating and immunopotentiating reconstituted influenza virosomes and vaccines containing them', which will expire in 2012. In addition, the hepatitis A strain used to produce Epaxal is claimed in a patent family which will expire in 2012.

Other products

We have no patent protection for the active substances of Quinvaxem, Hepavax-Gene, Vivotif, Dukoral and MoRu-Viraten.

We seek patent protection, whenever possible, commercially feasible and appropriate, in respect of any technology or product development that is important to our business. Together with our affiliates in Switzerland, Sweden, Italy and Korea, we have several platform technologies and consequently our intellectual property (IP) activities concentrate on protecting these technologies and any improvements thereof in the main worldwide vaccine markets of Europe, the US, Canada, Japan and Australia. However, because some vaccine markets are outside these countries, we have also sought protection in other countries, such as Korea, India and China. The IP portfolio is constantly reviewed to decide on maintenance of individual patents or patent families considering parameters such as actual product performance, product development, patent term, options for commercialization or out-licensing of non-core IP. Our IP tasks are coordinated and patents are filed on a worldwide basis by specialized patent attorneys.

Patent enforcement and proceedings

We may need to litigate or institute administrative proceedings such as oppositions to a patent to enforce or uphold our intellectual property rights or determine the validity and scope of the proprietary rights of others. Likewise, from time to time it may be necessary to defend our patents in litigation or administrative patent proceedings such as

opposition proceedings. We believe that litigation can play a significant role in defining and protecting our intellectual property rights. We are aware, however, that legal and administrative proceedings can be costly and time-consuming, and result in a diversion of resources. As an alternative to litigation, we may enter into licensing, including cross-licensing, arrangements as a means of clarifying the status of our intellectual property rights.

Oppositions against patents from the Group

In 2005, each of Probiogen, CEVEC Pharmaceuticals and Serono filed oppositions with the European Patent Office against one or more of our PER.C6 patents. All PER.C6 technology patents were upheld after first instance opposition proceedings. The PER.C6 patents pertaining to protein and virus production are no longer subject to opposition proceedings. The basic PER.C6 patent is currently under appeal, with Crucell as the only appellant and CEVEC Pharmaceuticals as party as of right. The outcome of appeal proceedings can only improve Crucell's position.

Cell Genesys has filed an opposition against our European patent related to our AdVac technology. Following the withdrawal of Cell Genesys from the opposition a swift resolution of the maintain opposition in Crucell's favor is now underway.

In addition to protecting our intellectual property rights, our commercial success also depends on our ability to operate without infringing the intellectual property rights of others. We monitor patent applications to the extent available, patents issued and publications of discoveries in scientific or patent literature to keep abreast of the activities of others in our field and, with the assistance of our internal and external patent counsel and other external advisors, assess whether our activities or products infringe the patents or proprietary rights of third parties. A number of third parties have been granted patents that cover technologies related to ours and similar patents may be granted in the future. We believe that our current activities do not infringe any valid claims of patents or any other proprietary rights of third parties. We will consider the intellectual property rights of others as we continue to identify and develop potential products and may have to enter into licensing or other agreements or use alternative technologies.

Oppositions against patents from competitors

Our subsidiary Berna Biotech Korea Corporation (formerly Green Cross Vaccine Corporation) and our partner Novartis (formerly Chiron) lodged opposition against a patent of GlaxoSmithKline (GSK) in Korea. The patent relates to multivalent vaccine formulations, such as our pentavalent vaccine Quinvaxem. In response to the opposition, the patent was revoked by the Korean Intellectual Property Office in December 2004 on the grounds that the subject-matter claimed in the patent lacks novelty. GSK appealed that decision to the Korean Patent Court. After a hearing which took place in April, 2006, the Korean Patent Court dismissed the appeal in June, 2006. GSK has appealed this decision before the Korean Supreme Court. In 2008, the Korean Supreme Court confirmed the decision by the Korean Patent Court and declared the patent to be invalid. This decision is final.

In 2005, we filed opposition against a European patent held by Novartis Vaccines and Diagnostics (formerly: Chiron) related to certain aspects of the production of influenza viruses in cell culture. The patent was revoked during oral proceedings.

In addition, production of Quinvaxem requires a particular vaccine component that may become the subject of a patent dispute between either GSK and us or GSK and our supplier of that component. The patent on that particular component, held by GSK, is currently under opposition before the patent office and a definitive outcome on the validity of the patent is expected to take a number of years. A negative outcome of this opposition proceeding could lead to infringement proceedings between GSK and us or GSK and our supplier, although we believe that neither we nor our supplier would be held to have infringed or be infringing that patent. The outcome of legal disputes is invariably difficult to predict with accuracy, but in the event GSK were to prevail in infringement proceedings against us, this would adversely affect our business.

Technology licenses from third parties

We licensed numerous technology and patents for specific use as part of our technology platforms from a number of third parties.

We entered into a technology license agreement with Xoma in the field of bacterial expression technology. This license allows us to develop

diagnostic and therapeutic antibodies in the field of infectious disease using phage-display technology. The agreement provides us with options to expand the license to cover additional disease fields. Under the terms of the agreement, we pay Xoma milestone payments and royalties on products as and when developed and marketed using the licensed technology.

We also hold a license under the phage antibody display patent portfolio owned or controlled by MedImmune (formerly Cambridge Antibody Technology) and MRC, a cross-license with Transgene S.A. under which we granted to Transgene a non-exclusive PER.C6 license for the manufacture and sale of certain types of vectors for use in gene therapy, and a license for phage antibody-display technology and part human, or chimeric, binding proteins and molecules from Enzon Corporation's subsidiary, SCA Ventures, Inc.

In the field of vaccines, we have concluded an agreement with the Rockefeller University in New York, US. According to the agreement, we have the exclusive rights to use and exploit the Rockefeller patents related to ex vivo and in vivo targeting of dendritic cells with the use of viral vectors.

The Group has licensed adjuvation technology called ISCOMS from Isconova AB for the development, manufacturing and commercialization of improved influenza vaccines.

When licensing our technology to third parties we seek to obtain access to any improvement patents by our licensees via so-called grant-back provisions to reduce the risk of being exempted from using such improvements for our own benefit, or that of our licensees.

Technology licenses to third parties

We have issued certain licenses on an exclusive basis. These licenses generally state that we will not provide the licensed technology to a party other than the exclusive licensee for use in the area covered by the exclusive license. These licenses also generally provide for higher payments than non-exclusive licenses.

Industry and scientific overview

In this section we discuss the development for the biopharmaceutical areas in which we are predominantly active: vaccines and antibodies.

Vaccines

Vaccines are biological substances that stimulate an immune response that allows a vaccinated individual to resist future infections and disease. The immune system recognizes vaccine agents as foreign, destroys them, and 'remembers' them. When the virulent version of an agent comes along the body recognizes the protein coat on the virus, and thus is prepared to respond by neutralizing the target agent before it can enter cells, and by recognizing and destroying infected cells before that agent can multiply to vast numbers.

Scientific progress in vaccines

Vaccines have contributed to the eradication of smallpox, one of the most contagious and deadly diseases known to man. Other diseases such as rubella, polio, measles, mumps, chickenpox, and typhoid are nowhere near as common as they were a hundred years ago. As long as the vast majority of people are vaccinated, it is much more difficult for an outbreak of disease to occur or to spread. Significant developments include the introduction of combination vaccines and the development of new vaccine technologies that may advance vaccine development. Today, research is under way to develop efficacious and safe vaccines against among others: viruses, parasites, bacteria and inherited or acquired diseases.

Vaccine formats

A variety of vaccine formats are in use today and others are evolving through ongoing research and development efforts. Some of the most common vaccine formats include live-attenuated virus vaccines, inactivated whole-killed virus vaccines, sub-unit vaccines, DNA vaccines, recombinant vector-based vaccines, synthetic vaccines and peptide-based vaccines.

Vaccine technology development

A large variety of vaccine technologies are under development in an attempt to improve safety and overall vaccine efficacy. The key objectives of current vaccine technology research and development are to make safer vaccines without compromising efficacy, to generate new vaccines with stronger and broader

immunogenicity, to make vaccines using more efficient manufacturing processes and to make vaccines easier to administer.

Antibodies

Antibodies are proteins made naturally by cells of the body's immune system. They function as one of the body's principal defense mechanisms against pathogens, which are disease causing agents such as parasites, viruses or bacteria. Antibodies recognize and bind to invading pathogens, ultimately eliminating them, thus playing a crucial role in protecting humans against disease. Because of their binding characteristics, antibodies can distinguish subtle cell differences between healthy and diseased cells. Antibodies are used to develop therapeutic products that can

- Bind to and block a key interaction of a disease-related cell, such as an inflammatory cell;
- Block infectious agents; and
- Trigger the death of a target cell, such as a cancer cell.

Antibodies may also be used to bind and neutralize toxic products, to develop diagnostic products to detect viruses or bacteria and as tools in scientific research such as genomics and proteomics.

Scientific progress in antibodies

Methods for generating monoclonal antibodies have evolved considerably over the last 25 years. The technology originally involved immunizing mice with a target molecule and isolating relevant antibody-producing cells from the mice. Because monoclonal antibodies of rodent origin are recognized as foreign proteins and are rapidly eliminated when applied in humans, methods were developed to produce therapeutic antibodies that are of human origin. These antibodies can be developed either using transgenic mice or by means of phage antibody-display technology. Transgenic mice are genetically engineered mice that carry human antibody genes. This allows the immune systems of mice to generate human antibodies in response to any administered antigenic material. Phage antibody-display technology allows human antibody genes to be cloned into bacteriophages, which are viruses that only infect bacteria. Phages displaying antibody fragments that attach to specific molecules can be selected, enabling isolation of antibodies against targets and/or enabling the identification of target molecules. Phage antibody-display libraries are large

collections of antibody-phages for use in identifying the targets and related antibodies.

Competition in product and technology development

The biotechnology field is one of rapid change and innovation. We expect that this industry will continue to experience significant technological and other changes in the years ahead. We operate in highly competitive markets and we may experience competition from companies that have similar or other technologies, and other products or forms of treatment for the diseases we are targeting. We also may experience competition from companies that have acquired or may acquire technology from universities and other research institutions. As these companies develop their technologies, they may develop proprietary positions in the areas of our core technologies or obtain regulatory approval for alternative technologies or commercial products earlier than we or our licensees do. Other companies are developing products to address the same diseases and conditions that we and our licensees target and may have or develop products that are more effective than those based on our technologies. We also compete with our licensees in developing new products.

Vaccines

Other biotechnology and pharmaceutical companies that are focused on developing vaccines against infectious diseases include Wyeth, sanofi pasteur, Merck & Co., GlaxoSmithKline, Novartis, Acambis, Baxter, GenVec, Bavarian Nordic, Baxter, Solvay, Vical and Nobilon.

With respect to vaccines, other companies use alternative non-human expression platform technologies. We are aware of licensed vaccines that are produced in cell substrates such as MDCK (Madin Darby Canine Kidney cells) and VERO as well as on production platforms based on embryonated chicken eggs. There are also mouse brain-derived inactivated vaccines that are produced in several Asian countries. We are aware of other human expression technologies for licensed and marketed vaccines, as well as human cell lines supporting products in development.

Adenoviral vector technology and other recombinant vectors

With respect to vector development, we are aware of several competing technologies, including those of GenVec and Merck & Co., which may pose a threat to the commercial viability of our AdVac technology.

Antibodies

Other biotechnology companies, including UCB Celltech and PDL BioPharma, currently generate humanized antibodies, and Medarex, Inc., GenMab, and Regeneron produce fully-human antibodies from transgenic mice. MedImmune, MorphoSys AG and Dyax generate fully-human antibodies using phage antibody-display libraries that are similar to ours. Companies such as XOMA and SCA Ventures, Inc., a subsidiary of Enzon Corporation, are also working in the field of phage display libraries and related technologies.

In the area of infectious disease antibodies, potential competitors include serum antibody companies such as CSL and Baxter, and monoclonal antibody companies like MedImmune.

Regulations applicable to the biopharmaceutical industry

We operate in a highly regulated industry. Our products require approval of government health authorities before they can be sold, and require significant pre-clinical testing before approval will be granted. Our research and development and production activities involve the use of hazardous materials, including biological materials, many of which we need special approval to obtain and all of which are subject to regulation regarding their handling and disposal. Environmental laws and regulations and laws and regulations relating to safe working conditions, laboratory conditions, and laboratory and manufacturing practices also apply to our operations. We conduct our operations in a manner designed to comply with applicable regulations and we believe that we have all the licenses and permits required to carry out our current activities.

Obtaining product approval is a costly and time-consuming process. All of our potential products, and those of our licensees, are either in research or development. Any products our licensees or we develop will require regulatory clearances prior to clinical trials and additional regulatory clearances

prior to being produced and distributed commercially. These regulatory processes are generally stringent and time consuming. We expect the European Medicines Agency (EMA) in the European Union, the FDA in the US, the College ter Beoordeling van Geneesmiddelen (CBG) in the Netherlands and comparable agencies in other countries to subject new biopharmaceutical products to extensive regulation. These regulatory requirements with which we and our licensees will have to comply will evolve over time due to the novelty of the biopharmaceutical products and therapies currently under development. Fortunately, the harmonization of these requirements is promoted at an international level (International Conferences on Harmonization (ICH)) to avoid unnecessary repetition of studies when seeking approval in various countries. Under the current definitions, we believe that products developed using our technologies will be regulated either as biological products or as drugs.

Before marketing a (bio) pharmaceutical product, companies require regulatory approval from the relevant authorities. To obtain this approval, pre-clinical and clinical trials must be conducted to demonstrate the safety and efficacy of the product candidates. Clinical trials are the means by which experimental drugs or treatments are tested in human volunteers. New therapies typically advance from laboratory research testing through pre-clinical testing and finally through several phases of clinical human testing. On successful completion of the clinical trials and demonstration that the product can be manufactured in a safe and consistent manner, approval to market the biopharmaceutical may be requested from the EMA in Europe, the FDA in the US or their counterparts in other countries.

Clinical trials are normally done in three phases:

- **Phase I:** First clinical trial of a new compound generally performed in a small number of healthy human volunteers, to assess clinical safety, tolerability as well as metabolic and pharmacologic properties.
- **Phase II:** Clinical studies that test the safety and efficacy of the compound in patients with the targeted disease with the goal of determining the appropriate doses for further testing and evaluating study design as well as identifying common side effects and risks.
- **Phase III:** Large-scale clinical studies with several hundred or several thousand patients to establish safety and effectiveness for regulatory

approval for indicated uses and to evaluate the overall benefit/risk relationship.

Our research and development and production activities are undertaken in a number of countries around the world. These activities are subject to strict regulatory requirements of national and supranational authorities in the countries in which they are undertaken such as requirements governing the testing, manufacturing and marketing of pharmaceutical products. In most countries, it is necessary to obtain an approval to market a pharmaceutical or medical product. The grant of such an approval is subject to a detailed evaluation of data submitted by the applicant related to the quality, safety and efficacy of the product. Many countries, including member states of the EU and the US, impose extensive testing and data submission requirements and conduct rigorous technical appraisals of product candidates. In addition, different regulatory authorities may impose different conditions upon the marketing of a given product or may refuse to grant or require additional data before granting an approval to market a product even though the product may have been approved by another regulatory authority. Pre-clinical testing, clinical research and regulatory approval of a pharmaceutical or medical product is a lengthy and costly process.

Once a product is approved, the manufacturing and marketing of the product remains subject to periodic review. Changes in applicable regulations, breaches of regulatory requirements or the discovery of problems related to the manufacturing, safety, quality or efficacy or stability as well as changes in the characteristic of a product inherent to its biological origin may result in the imposition of restrictions upon the manufacturing and sale of such products, including at worst withdrawal of the product from the market and/or the revocation of the relevant regulatory approvals.

Pre-qualification applicable to the biopharmaceutical industry

National and regional governments rely on the pre-qualification granted to biopharmaceutical products by evaluative bodies such as the WHO and, in some cases, simply elect not to purchase products which have not been granted pre-qualification of approval.

The WHO Pre-qualification project is carried out to facilitate access to medicines that meet unified standards of quality, safety and efficacy.

Pre-qualification was originally intended to give United Nations procurement agencies, such as UNICEF the choice of a range of quality medicines. With time, the growing list of medicines that have been found to meet the set requirements has come to be seen as a tool for anyone purchasing medicines in bulk, including countries themselves and other organizations.

Any manufacturer wishing their medicines to be included in the pre-qualified products list are invited to apply. Each manufacturer must present extensive information on the product (or products) submitted to allow qualified assessment teams to evaluate its quality, safety and efficacy. The manufacturer must also open its manufacturing sites to an inspection team that assesses working procedures for compliance with WHO Good Manufacturing Practices (GMP).

The Pre-qualification project does not intend to replace national regulatory authorities or national authorization systems for importation of medicines.

Additional information on the Company

Legal proceedings

In the ordinary course of business, we have been and may become involved in disputes. Neither we, nor any of our subsidiaries, has been party to any legal or arbitration proceedings that may have, or have had during the 12 months preceding the date of this document, a significant effect on our results of operations or any of our subsidiaries nor, as far as we are aware, are any such legal proceedings pending or threatened, except for those disclosed in 'Intellectual Property – Patent Enforcement and Proceedings' in this section and those disclosed in section '5.18 Provisions, commitments and contingencies – legal proceedings' in the financial statements.

Property, plant and equipment

Our corporate offices and research activities are located in facilities of approximately 8,700 square meters in Leiden, the Netherlands. The section of this building that we use in Leiden includes 3,500 square meters of laboratories, with BioSafety Level (BSL) 1, BSL 2 and BSL 3 labs. The remainder of the main building is divided into 2,800 square meters of office space and 2,400 square meters for storage, technical areas, washrooms, waste destruction and sterilization. In addition, we lease 1,200 square meters of space adjacent to the corporate main building.

In 2008, the construction of the Valerio building, which was named after Crucell co-founder Dinko Valerio, was completed. The Valerio building is a GMP Process Technology Center of 5,400 square meters in Leiden. This new facility can be operated as a BSL 3 facility, in which two concurrent products can be produced at the BSL 2 and/or BSL 3 safety levels.

The Valerio Building meets the highest environmental and safety standards recommended for the laboratory activities to be conducted there. The facility has received approval from the Dutch government to produce material for use in humans. Extensive precautions will be taken to ensure safety and continuity of operations. Product quality will be strictly monitored, maintained and administered in-house.

Since our 2006 acquisitions, we also have office space, laboratories, production facilities, pre-clinical facilities and storage space in Switzerland, Spain, Sweden, Korea and Italy.

The following sets out information regarding our main facilities outside the Netherlands.

Bern, Switzerland (owned)

Crucell has two facilities located in the canton of Bern. These facilities are FDA/WHO/EMEA approved and are the primary sites for the manufacturing of Inflexal V, Vivotif, MoRu-Viraten and Epaxal. The combined facilities have a floor space of 45,000 m², 33,000 m² of which is manufacturing space. The facilities in Bern have the technology to manufacture both viral and bacterial vaccines using various manufacturing platforms within BSL 1 and BSL 2 environments.

In addition to the manufacturing, the facilities also have all the necessary support capabilities including Clinical Affairs, Regulatory Affairs, Quality Control, Quality Assurance, Operations, Finance and Process Development.

The Process Development group has a pilot plant of approximately 2,500 m². This facility is GMP certified and allows for work to be carried out on BSL 2 products. The capabilities within this facility are cell banking, up and downstream manufacturing, formulation, filling and lyophilisation for bacterial vaccine production. This facility is currently being used for life cycle management activities as well as conducting CMO activity for one of Crucell's partners.

Seoul, Korea (leased)

Our manufacturing facilities in Korea are KFDA/WHO approved and are used primarily for the production of Quinvaxem and Hepavax-Gene and for formulating and filling vials. The facilities include 3,201 m² of production and development space, 1,305 m² of storage space and 1,818 m² of office space.

In October 2008, we announced that we will relocate the Korean production facility from Yongin City to the Incheon, Free Economic Zone. The investments in the new facility are expected to total approximately €50 million, with the majority of spending in 2009. We entered into a mortgage loan facility in Korea for an amount of KRW 50 billion to partly finance the investments in the new Korean facility in 2009.

Madrid, Spain (owned)

Crucell has its main center for filling and packaging operations in Madrid as well as local distribution. The facility is EMEA approved and it has the capability to fill syringes on two filling lines, primarily used to fill Inflexal V and Epaxal. The total facility consists of 2,130 m² of manufacturing space, 1,000 m² of office/laboratory space and 2,610 m² of warehousing.

Stockholm Sweden (leased)

In Sweden, our manufacturing facilities are EMEA/WHO approved and are used for the production of Dukoral and the recombinant protein rCTB. The manufacturing capabilities consist of large scale cGMP manufacturing of bulk, comprising both bacterial and mammalian systems, formulation and filling, visual inspection and packaging in vials. The site has a total of 4,866 m² of GMP development and production space, 5,990 m² storage space and 2,662 m² of office space.

In August 2008, we announced the intention to move Dukoral and rCTB bulk production, formulation and fill/finish activities from Sweden to other sites within the Crucell organization. The Group is now going through a feasibility study to determine the scope and timing of the move.

In 2008, € 15,787 was invested in property, plant and equipment compared to € 27,156 in 2007. The investments in 2008 mainly related to our new Korean production facility in the Incheon, Free Economic Zone, investments in our facilities in Bern, Switzerland that will improve current production processes and allow in-house production of materials currently acquired from third parties and investments in our new filling line in Madrid, Spain.

In 2007, € 27,156 was invested in property, plant and equipment compared to € 20,337 in 2006. The investments in 2006 and 2007 mainly related to our new GMP production facility in Leiden, the Netherlands and investments in our facilities in Bern, Switzerland.

Raw materials

We require a reliable supply of materials for the production of our products, including starting materials, like the serum-free medium in which we grow our PER.C6 cells, and antigens that are present in certain of our final products. Some of these materials are provided by a limited number of third party suppliers. Our ability to conduct research and to launch new products also depends on a steady supply of these raw materials. Any adverse changes to our existing supplier relationships will thus likely adversely affect our overall results. Prices for our raw materials are volatile and may change significantly over time. Some of our raw materials are purchased in foreign currencies and are subject to foreign currency exposures. We try to mitigate these exposures by entering in long term purchasing arrangements and by hedging the foreign currency exposures on our purchases.

Insurance

We have in place general third party public and product liability insurance. Our policy has a limit of liability and has certain additional conditions to coverage and deductibles. We do not insure our phage antibody display library or PER.C6 master cell bank, though identical copies of the same cell bank are stored in multiple locations in Europe. We believe we carry adequate insurance relating to theft, fire and damage to the moveable assets within our facilities and other customary insurance coverage for most of our activities, including liability insurance coverage for the members of the Management Board, Management Committee and the Supervisory Board.

Employees

For a breakdown of the employees by function and geography reference is made to note 5.1 'Personnel expenses' in the financial statements.

Material contracts

As of the date of this Annual Report, we are not party to any contracts (not entered into in the ordinary course of business) that are considered material to our results, financial condition or operations.

Dividends and dividend policy

Crucell N.V. did not pay any dividends in 2008. We do not intend to pay dividends on our ordinary shares for the coming years, and thereafter only on the condition that our financial performance is adequate and it is in the shareholders' interest to pay dividends instead of investing the proceeds into the company. Any payment of future dividends and the amounts thereof will depend upon earnings, statutory and financial requirements and other factors deemed relevant by our Management Board, and will be subject to withholding tax in the Netherlands. In the event that we pay dividends in the future, holders of our American Depositary Shares (ADSs) will be entitled to receive payments in US dollars in respect of dividends on the underlying ordinary shares in accordance with a deposit agreement dated October 26, 2000 between The Bank of New York Mellon, as depository, and us.

Risk Factors

Our Management Board is responsible for designing, implementing and operating the Company's internal risk management and control systems. The purpose of these systems is to manage in an effective and efficient manner the significant risks to which the Company is exposed. For a more detailed description please see 'Internal risk management and control system' in the Corporate Governance section of this Annual Report.

An integral part of our internal risk management process is the identification of risks that could prevent us from reaching our objectives. To identify these risks we performed a corporate risk assessment with the Disclosure Committee of the Company in 2008. The outcome has been discussed in the Audit Committee and was taken into account in the risk factors described below. We have classified these risk factors in accordance with the categories of objectives identified in the COSO model, an integrated internal control framework established by the Committee of Sponsoring Organizations of the Treadway Commission.

You should carefully consider these material risk factors. The risks we face are not limited to the risks listed here. Some risks are not yet known to us and some of the risks that we currently do not believe to be material to our operations could prove to be material at a later date. All of these risks can materially affect our business, financial condition and results of operations.

Strategic

Concentration of sales

We are dependent on a limited number of products and customers for a majority of our revenues and expect this dependence to continue in the foreseeable future. Our core product portfolio consists of seven vaccines, namely Quinvaxem, Hepavax-Gene and MoRu-Viraten (paediatric vaccines), Inflexal V (influenza), Dukoral, Epaxal and Vivotif (travel vaccines). The aggregated revenues for our core product portfolio represented a significant part of our total product sales in 2008. The sales to our largest customers, which are in the paediatric vaccines area, represented a considerable part of our net product sales in 2008. In particular, we are highly dependent on sales of Quinvaxem and Inflexal V. If these products were to become subject to any problem such as unexpected side effects, product liability litigation, loss of patent protection, supply interruptions, regulatory proceedings,

publicity affecting doctor or patient confidence or pressure from competitive products, or if a new more effective treatment is introduced, we could experience a significant decrease in revenues and an adverse effect on our financial results.

Additionally, our results may fluctuate as a result of seasonality in our business. In particular, the market for flu vaccines is highly seasonal so a majority of our distribution and sales tends to occur in the second half of the year. Delays in any step of our regulatory approval, production or distribution processes could result in a significant sales reduction.

Strategic alliances

If our current or prospective partners or licensees do not use our products or technologies, we may not be able to continue to realize revenues related to those partners or licensees. In particular, our current or prospective licensees or partners may use or develop alternative technologies or competing products, independently or in collaboration with others, including our competitors. If any of our licensees or partners becomes involved in a business combination or other major corporate transaction, this could cause a strategic shift in their business focus and lead them to discontinue the use of our products and technologies.

Furthermore, we may have disagreements with our licensees over royalty payments owed to us and may have difficulty collecting these payments. Our existing license arrangements generally entitle us to receive royalty payments for any products developed using our technology. We depend on our licensees to inform us when they develop products using our technology. If our licensees fail to inform us of these developments, we may not otherwise learn of payments to which we are entitled. In addition, our licensees may have difficulties making payments to us given the current economic climate or other factors. We may also incur significant expenses in collecting royalty payments, or in some instances, may not succeed in collecting these payments at all.

Competition and pricing pressures

We face competition from other companies in the development, marketing and licensing of new technologies and products. We operate in competitive markets and compete with companies that have their own technologies, products or other forms of treatment for the diseases we target.

Companies may develop proprietary positions in the areas of our core technologies or obtain regulatory approval for alternative technologies or commercial products earlier than we or our licensees do. Other companies, including our own licensees, may already have or may in the future develop products that are more effective or more effectively marketed and sold than those based on our technologies. We may not be able to compete effectively with these companies, and such competition could hamper our ability to bring products to market or to license and derive revenue from our technologies.

Our existing products may experience pricing pressures from competition with other products on the market. Pricing pressures may further increase due to the introduction of new products, the expansion of production capacity, or decreases in demand. We cannot predict with accuracy the impact of such events on our revenues. Products that compete with Quinvaxem have already been introduced to the market and still others may yet be introduced. Increased competition from these products could result in further pricing pressure on Quinvaxem and a substantially negative impact on our revenues.

We experience pricing pressures in the public markets for our products, which typically operate via a tender system. In a tender system, national governments or supranational organizations request proposals for the terms under which a vaccine manufacturer will provide a large quantity of one or more vaccines. The awarding of the contract is typically based on a number of factors, including price, supply reliability and product quality. Failure to win one of these public contracts may cause us to be ineligible to supply a national government or supranational organization for a period of time, resulting in a negative impact on our revenues. Pricing pressures may have a material adverse effect on our business, results of operations and financial condition.

Operational

Product development and clinical trials

All of our products and those of our licensees and partners may fail at any stage of development or even after market introduction due to factors beyond our control. Such failures could have a material adverse effect on our business and prospects.

Pre-clinical testing, clinical research and regulatory approval of a pharmaceutical or medical product is a very lengthy and costly process, and there is a significant risk of failure at each stage of the process should issues arise with respect to the efficacy or safety of a product. In particular, because pre-clinical and early clinical studies cannot ensure efficacy for humans, actual human studies are required for vaccine development. Such studies may, however, fail to prove the efficacy of the product candidates and are at constant risk of suspension for posing unreasonable health risks. There can be no assurance that any product candidate in our product pipeline will reach or successfully complete the clinical research phase of product development. Although a product that reaches a later stage of development offers a reasonably high probability of success relative to products in earlier stages, the chances of failure remain significant throughout the development process. We have had products fail at later stages of development in the past. Any or all of our current later-stage products could fail to be shown sufficiently safe or effective to be brought to market, or could otherwise fail to receive necessary regulatory approvals.

Regulators have granted certain of our products provisional or conditional marketing approval, requiring us to do follow-up studies to assess the safety and efficacy of the product in all or part of the target population. Poor results in any of these studies may give rise to the withdrawal of market authorization for some or all indications, in part or in all of the targeted population. Even if the products currently in later-stage development are introduced to the market, there can be no assurance that demand for such products will develop or be sustained. If a market does develop, there can be no assurance that our existing facilities and resources will be sufficient to meet demand. Accordingly, there can be no assurance that we will realize any potential benefits that may be associated with our later-stage development product portfolio.

Our success depends on a sufficient pipeline of new products and technologies. We therefore commit substantial resources and efforts towards research and development. We have no assurance that these efforts will succeed. Failure to maintain a healthy flow of new products through our pipeline could result in higher costs without a proportional increase in revenues.

To a certain extent, we are dependent on third parties with whom we contract to perform clinical trials of our products. If we fail to adequately manage the work of these third parties, a regulatory authority may determine that they have not complied with applicable regulations and therefore may not approve a product candidate of ours.

To continue to develop our core technologies and new products, we will need access to biological materials such as virus and tissue samples, which may be in limited supply. If we lose or do not obtain access to these biological materials, or if tighter restrictions are imposed on their use or on the information generated from their study, we could be restricted or prevented from conducting certain research and product development.

Interrupted product supply

Supply interruptions, product recalls or inventory losses caused by unforeseen events such as manufacturing or distribution interruptions or regulatory actions, may reduce sales, delay the launch of new products and adversely affect our operating results and financial condition.

Our products are manufactured and distributed using technically complex processes requiring specialized facilities, highly specific raw materials and other production constraints. The complexity of these processes as well as strict Group and government standards for the manufacture of our products may expose us to risks affecting our production process. Defects in the manufacturing process, including equipment malfunction, labor problems, regulatory action, power outages, natural disasters and environmental factors may all affect production output. The new EU regulation (EC 1907/2006, REACH), requiring registration of all chemical materials by us and our suppliers, may cause supply interruptions of raw materials that may in turn cause production delays if we need to change our sources of certain raw materials or marketing delays due to new validation activities to demonstrate similarities, or differences in comparability studies between old and new suppliers. Our vaccine products in particular are subject to the risks of manufacturing problems and inventory loss because of the difficulties inherent in the manufacture of biological materials, whether in our own facilities or in the facilities of our suppliers. Vaccine components cannot be sterilized nor can preservatives be added to the manufactured vaccine. Contamination of our products could result

in the loss of entire batches of finished vaccine, which could lead to lost sales, damage to customer relations, a significant outlay of time and money to investigate the cause of the contamination and possibly a costly product recall if contaminated vaccines have already been shipped to customers. A disruption in the supply of certain key products or our failure to accurately predict the demand for those products could have a material adverse effect on our results.

We rely on a separate facility for the manufacture of each of our products. The marketing and regulatory authorization of biological products, in particular vaccines, is strongly linked to the production facility and equipment that are used to manufacture those products. If any event occurs that interrupts production at one of our facilities we may have to transfer production to a new site, which would be costly and time consuming. Because of the short shelf life of biological products, our existing stocks of product may not be sufficient to supply our customers during such a transition period. For example, our manufacturing facility in Korea is our sole production source of the Quinvaxem vaccine. As such, we are vulnerable to any event that interrupts, reduces or slows production of Quinvaxem at that facility. We intend to relocate our Quinvaxem operations to another site in Korea and preparations for such a move are ongoing. The relocation of the Quinvaxem operations is a complex process, which includes the inherent risk of the new facility not coming online before the old one has shut down. We agreed on the time line and conditions of this relocation with parties involved, enabling a smooth transition to the new production facility, however there can be no assurance that there will be no delay in the transition process.

We require a reliable supply of materials for the production of our products, including starting materials, like the serum-free medium in which we grow our PER.C6 cells, and antigens that are present in certain of our final products. Some of these materials are provided by a limited number of third party suppliers. Any interruption or termination of these supply relationships may have adverse effects on our ability to manufacture and sell products, particularly if we are unable to source new supplies of the same materials or adapt our technologies and manufacturing processes to use different starting materials in a timely manner. Our ability to conduct research and to launch new products also depends on a steady supply of these raw materials.

Any adverse changes to our existing supplier relationships will thus likely adversely affect our overall results.

Regulatory approval

We may be unable to obtain regulatory approval to manufacture and market our new products or may have regulatory approval for the manufacture and marketing of our existing products revoked by regulatory bodies such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the European Commission or other non-governmental bodies such as the World Health Organization (WHO).

These various regulatory authorities have substantial discretion and may impose different conditions upon the marketing of a given product or may refuse to grant, or require additional data before granting, an approval to market a product even though the product may have already been approved by another regulatory authority. National and regional governments rely on the (pre) qualification and/or approval of biopharmaceutical products by evaluative bodies such as the WHO and, in some cases, simply elect not to purchase products which have not been granted (pre) qualification or approval.

Once a product is approved, its manufacture and marketing remains subject to regulatory requirements including industry code of conduct regulations. Changes in applicable regulations, breaches of regulatory requirements or the discovery of problems related to the marketing, manufacture, safety, quality, efficacy or stability of a product, as well as changes in the characteristics of a manufactured product stemming from alterations in its biological origins, could result in the imposition of fines or restrictions upon the manufacture and sale of such product, including in the worst case scenario withdrawal of the product from the market altogether and/or the revocation of necessary regulatory approvals.

Regulatory requirements could make product development based on new technologies highly uncertain because regulatory review of the underlying technologies is generally required.

If regulatory authorities do not approve our new products or other products developed using our technologies, or if they subsequently revoke their approval, that may impact our revenues generated

from the sale of products and/or the licensing of our technologies, which may in turn have a material adverse impact on our business, financial condition, results of operations and prospects.

Intellectual property

Our efforts to protect our intellectual property rights or to defend ourselves against any claims of infringement of third party intellectual property may be costly and, if unsuccessful, we may be barred from using or licensing our technologies, and from developing and commercializing our new products.

Our commercial success depends in part on our ability to obtain and maintain adequate protection of our intellectual property rights, including patents, in our technologies and products in Europe, the US and elsewhere. Our patent-related activities do not afford complete protection to our intellectual property rights. Patents of technology-based enterprises like ours are subject to complex factual and legal issues that may give rise to uncertainty as to the validity, scope and priority of a particular patent. There can be no assurance that we will develop products that are patentable, that patents will be granted under pending or future applications or that patents granted to us or our collaborators will be of sufficient breadth to protect against competitors with similar technologies or products. A patent that is issued to us may be narrower than our application or found to be invalid. Others may make attempts to copy, reverse engineer or design around aspects of our technology, or to obtain and use information that we regard as proprietary. In addition, our patent filings may be subject to challenges. Our inability to adequately protect our products and technologies in emerging economies, such as India and China, may give rise to competition in those countries from manufacturers operating in low-cost economies. Due to compulsory licensing regimes currently in place in many of these underdeveloped and developing jurisdictions, we may not be able to use our intellectual property rights to prevent the low-cost manufacture of competing products. Such competition may adversely affect our ability to maintain viable pricing levels and to sell products in those countries.

In addition, production of Quinvaxem requires a particular vaccine component that may become the subject of a patent dispute between either GSK and us or GSK and our supplier of that component. The patent on that particular component, held by

GSK, is currently under opposition before the patent office and a definitive outcome on the validity of the patent is expected to take a number of years. A negative outcome of this opposition proceeding could lead to infringement proceedings between GSK and us or GSK and our supplier, although we believe that neither we nor our supplier would be held to have infringed or be infringing that patent. The outcome of legal disputes is invariably difficult to predict with accuracy, but in the event GSK were to prevail in infringement proceedings against us, this would adversely affect our business.

For a more detailed discussion of issues surrounding our patent enforcement and related proceedings, see 'Intellectual property – Patent enforcement and proceedings'.

We also endeavor to protect our proprietary technologies, processes, know-how and data by entering into confidentiality agreements with our employees, consultants, partners and certain contractors. We have no assurance that these agreements or other trade secret protections will provide meaningful protection to us.

Our commercial success also depends on not infringing on the patents and other proprietary rights of third parties. As our activities in the biotechnology and biopharmaceutical markets expand and as more patents are issued in the field, the risk that our technologies and products may give rise to claims of alleged infringement increases. Licensing or other arrangements for addressing these infringements or violations may not be available, or may not be available on commercially acceptable terms if we or our licensees are unable to obtain licenses from third parties for the use of their intellectual property in the manufacture of our products, we or our licensees may be unable to develop or market those of our products which are based in part on the intellectual property of others.

Product liability exposure

We may be exposed to product liability and other claims if third parties allege that our technologies or products have caused some harm.

If a third party sues us for an injury caused by our products or by products developed using our technologies, our liability could exceed our total assets. Because our vaccines that constitute our core products are administered to healthy

individuals, any adverse health consequences associated with such administration may be more apparent and perceived as less tolerable than similar side effects associated with the treatment of disease.

Lawsuits against us arising out of clinical trials may increase as more and more licensees utilize our technologies, thereby reducing our control over the manner of their use. We maintain product liability insurance in respect of all of our marketed products. We may seek to obtain additional product liability insurance in the future, though it cannot be assured that such additional insurance will not be prohibitively expensive, or that it will cover all of our potential liabilities. If we are unable to obtain sufficient insurance coverage at an acceptable cost or if we are otherwise unable to protect ourselves against potential product liability claims, we and/or our licensees may be prevented or inhibited from commercializing new products.

Product liability cases, claims and even relatively minor potential health risks associated with our products may give rise to adverse regulatory action, and/or a negative market perception of us and our products, resulting in a material adverse effect on our business, financial condition, results of operations and prospects. Though we believe we have strong defenses in these and other cases, including patent infringement cases, there can be no assurance as to the outcome of these matters and we could incur judgments or enter into settlements of claims that could have a material adverse effect on our results of operations.

Qualified personnel

We may not be able to continue to recruit and retain highly qualified management, scientific, manufacturing, sales and marketing and finance personnel. Competition for qualified personnel could be intense and may limit our ability to attract and retain qualified personnel on acceptable terms and may therefore significantly increase our labor costs. The inability to attract and retain highly skilled personnel on acceptable terms could have a material adverse effect on our business, financial condition, results of operations and prospects.

Hazardous biological materials

Our manufacturing, research and development processes involve the controlled use of hazardous biological materials. Certain of our laboratory

facilities are qualified up to Biosafety Level III (BSL-III), which allows us to work on-site with hazardous biological materials. Our operations may also produce hazardous biological waste. Given the inherently dangerous nature of certain biological materials we may work within our BSL-III laboratory facilities, we cannot eliminate the risk of accidental contamination or discharge or any injuries that result therefrom. Various laws and regulations govern the use, manufacture, storage, handling and disposal of these materials. We could be subject to civil damages and significant adverse publicity in the event of an improper or unauthorized release of, or exposure of individuals to, hazardous materials.

Competition laws

We cannot be certain that our licensing or other agreements are not in breach of applicable competition laws and will not be rendered void by the relevant competition authorities. In the past, we have not notified the European Commission competition authorities of any of our licensing or other agreements or sought clearance from any other competition authority. We take the view that these agreements are unlikely to be found to infringe European Union or other applicable competition regulations. It is possible, however, that current or future licensing or other agreements of ours could be found to infringe applicable competition regulations. If so, among other things, we may be subject to fines and claims of damages and these agreements may be considered void and unenforceable. Under the European Union's 2004 Technology Transfer Block Exemption Regulation, we may be required to review and possibly amend existing license and technology transfer agreements in the future. For example, if certain market share thresholds will be or have been reached in the relevant markets by those third parties that use our technologies to produce their products, the Regulation may require us to revise our agreements with those parties to ensure the agreements are in compliance with applicable European competition law.

Financial

Substantial use of capital

In the past, we have had to raise additional funds to acquire other companies and assets while continuing to research and develop our technologies and products. We also have incurred accumulated net operating losses since our incorporation.

Although the Company generated positive cash flow in 2008, we may have cash outflows and net operating losses in the future due to the occurrence of events that would consume our available capital resources. We may seek additional funding through public or private financing (including debt or equity financing), strategic alliances or other arrangements. We may not have access to additional financing and, if we do, it may not be on favorable terms. If we fail to raise sufficient funds, we may have to forego acquisitions, reduce our capital expenditures, scale back our product development, reduce our workforce and/or license products or technologies to others that we might otherwise commercialize ourselves.

Weakness in the global economy could negatively affect our business

The weakness of the global economy in 2008 was a challenge for many companies worldwide. The ongoing financial crisis became prominent in September 2008 with the failure or near-failure of several United States and European based financial institutions and the resulting deterioration in financial and market conditions spread around the globe. In recent months the financial crisis has adversely affected businesses in many industries and geographical areas all over the world at an unexpected pace.

The weakness of the global economy has not had a significant impact on our liquidity or on our ability to derive revenues from our operations. However, there can be no assurance that our liquidity will not be affected by recent and possible future changes in global financial markets and global economic conditions.

Financial distress and bankruptcies experienced by our customers and suppliers resulting from the recent global economic slowdown could impair their ability, as the case may be, to purchase our products, pay for products previously purchased or meet their obligations to us under supply agreements. This could lead to a material adverse effect in our revenues.

We do not know how long the current financial crisis will continue nor how severe it will ultimately be. In the long run, we may be affected if governmental agencies or supranational organizations decide to realign priorities and allocate fewer funds to public health initiatives. The financial crisis may have

a negative impact on the travel pattern, which is the key driver of our travel vaccines.

Foreign currency risk

The majority of our total revenues in 2008 were in currencies other than our functional currency, the Euro. Currency fluctuations may cause significant economic foreign currency exposure and transactional foreign currency exposure. Fluctuations in the currencies in which we do business relative to the Euro have affected our results in the past and, given the current economic climate and the substantial recent fluctuations in interest rates and currency exchange rates, may do so again in the future. Notwithstanding our efforts to foresee and mitigate the effects of changes in fiscal circumstances, we cannot predict with certainty changes in currency and interest rates, inflation or other factors affecting our business. Because of the variability of currency exposures and the potential volatility of currency exchange rates, we may suffer significant foreign currency losses in the future, particularly if the Euro strengthens relative to currencies in which a significant number of our operations are conducted. We engage on a limited basis in derivative transactions to hedge our foreign currency exposure. See section 3.2 'Foreign currency risk' in the financial statements for further details on our foreign currency risk.

Taxation

We are subject to the tax laws of the countries in which we operate as well as to European tax law. We may incur additional tax charges, including penalties, resulting from changes in tax laws or the interpretation of tax laws or from failure to comply with obligations required by relevant tax authorities. Disputes with tax authorities may arise with regard to the interpretation and application of tax laws. If any of these risks materializes, leading to tax costs associated with particular transactions being greater than anticipated, it could affect the profitability of our business as a whole. See note 5.4 'Income tax' in the financial statements for further details on our taxation.

Compliance and other

Ethical, legal and social issues related to the use of genetic technology

The use of genetic technology and materials derived from human fetal tissue, such as our PER.C6 technology, may raise ethical, legal and/or social

issues that could hinder regulatory approval, patentability or market acceptance of our technologies and the products developed using them. If these risks materialize they could have adverse consequences for our business since they could reduce or eliminate altogether potential markets for our own or our licensees' products.

Protective measures included in articles of association

Protective measures included in our articles of association, in accordance with Dutch law, may prevent corporate action and/or shareholder transactions that might be in the best interests of our Company or the shareholders. Among other things, our articles of association provide that our Supervisory Board may make binding nominations for the election of its members. Only a shareholders' resolution approved by an absolute majority of the votes cast, representing more than one-third of our total outstanding shares, can override those nominations. Furthermore, under Dutch law, we may issue preference shares to a foundation, Stichting Preferente Aandelen Crucell, or the Preferred Foundation, giving it preferred dividend rights, which may dilute the voting rights held by the holders of other classes of shares. The Preferred Foundation has an option to acquire a number of preference shares equal to the number of our total outstanding shares. The chairman of our Supervisory Board, Jan Oosterveld, and four independent members comprise the board of the Preferred Foundation. These and other provisions in our articles of association may have the effect of delaying, deterring or preventing corporate action that might be in the best interest of the Company or our shareholders and/or preventing our shareholders from selling their ordinary shares or ADSs at a premium to the market price. See 'Other information' and 'Articles of Association and Share Capital' for additional information regarding the preference shares and our articles of association.

US and other non-Dutch holders of our ordinary shares may not be able to exercise pre-emption rights.

In the event of an increase in our share capital, holders of our ordinary shares are generally entitled to certain pre-emption rights unless these rights are excluded by a resolution of the General Meeting of Shareholders or a meeting of the Management Board if so delegated by the General Meeting of Shareholders. However, US holders of our ordinary

shares may not be able to exercise pre-emption rights unless a registration statement under the Securities Act is declared effective with respect to the shares issuable upon exercise of such rights or an exemption from the registration requirements is available. No assurance can be given that any registration statement will be filed or, that if filed, it will be declared effective or that any exemption from registration would be available to enable the exercise of a US holder's pre-emption rights.

Shareholders may have difficulty protecting their interests as shareholders as we are a Dutch limited liability Company.

Dutch law and our articles of association govern issues regarding the legal organization, internal constitution, corporate authority and liability of members of our Management Board and Supervisory Board. Most of our offices and assets are located outside the US. In addition, a majority of the members of our Supervisory Board, all of the members of our Management Board and management team are residents of, and most of their assets are located in, jurisdictions outside the US. As a result, it may be difficult to serve process on these persons within the US. It may also be difficult to enforce a US court judgment against them in a US court or in a Dutch court or to enforce a Dutch court's judgment against them in a US court. This can include actions under the US securities laws. In addition, it may be difficult to enforce, in original actions brought in courts in jurisdictions located outside the US, claims under US securities laws. For a more complete discussion of potential difficulties in protecting your rights, see 'Articles of Association and Share Capital – Enforcement of Civil Liabilities'.

Share price volatility

Our ordinary shares and ADSs may have a highly volatile trading price. Shareholders may not be able to resell their ordinary shares or ADSs at or above the price they pay for them, the ADSs may vary in value and our share price may render us vulnerable to a takeover bid. Our ordinary shares are listed on NYSE Euronext Amsterdam and the SWX Swiss Exchange, and our ADSs are listed on the NASDAQ Global Select Market. The trading prices of ordinary shares of biotechnology companies in general have experienced significant volatility in the past and are likely to continue to be volatile. In addition, any negative change in the public's perception of the prospects of biotechnology companies could depress our ordinary share or ADS price regardless of our results of operations. Other broad market and industry factors, such as discussions on business combinations and a weak global economy may affect the trading price of our ordinary shares and ADSs, regardless of our performance.

Operating and Financial Review and Prospects

The following discussions should be read in conjunction with our financial statements and the notes thereto included elsewhere in this Annual Report. We refer to 'Forward-looking statements' as well as to 'Risk factors' for certain factors that may affect our operating results. Unless otherwise mentioned all amounts in this section are in thousands of Euro, except share and option data.

General

We are a fully integrated biopharmaceutical Company, focused on developing, producing and marketing vaccines and antibodies against infectious diseases for private and public markets worldwide. We have a portfolio of well-known vaccines and a pipeline of potential new vaccines and antibodies. We combine proprietary technologies to discover, develop and produce a variety of vaccines and antibodies to combat infectious diseases.

Summary of the full year financial results

Total revenue and other operating income for the year ended December 31, 2008 were € 283,309, which represent a 32.9% increase over the € 213,116 in revenues and other operating income reported in 2007. The increase in total revenues and other operating income is mainly attributable to increased sales of paediatric vaccines, travel and endemic vaccines and higher license revenues.

Total operating expenses amounted to € 129,691 (2007: € 125,918). R&D expenses of € 70,229 (2007: € 63,995) reflect our continued focus on (pre-) clinical development.

We achieved profitability for the full year 2008, reporting a net profit of € 14,586, compared to a net loss of € 42,910 in 2007. This amounted to € 0.22 net profit per share in 2008, compared to a net loss per share of € 0.66 in 2007.

Cash and cash equivalents at December 31, 2008 amounted to € 170,969 (2007: € 163,248).

Our operating cash flow was € 254 negative in 2008, compared to a positive operating cash flow of € 22,194 in 2007. The reduction is mainly due to the build-up of Quinvaxem inventory for sales in 2009.

Segments

We operate in one reportable segment, which comprises the development, production and marketing of products that combat infectious diseases. The Group early adopted IFRS 8 'Operating Segments', which replaces IAS 14, 'Segment reporting', as of January 1, 2007. The Management Board is identified as the 'chief operating decision maker'. The Management Board reviews the consolidated operating results regularly to make decisions about resources and to assess overall performance.

In 2007, our segmentation was based on the two segments that were reported to our Management Board:

- Vaccines: developing, producing and marketing vaccines worldwide to combat infectious diseases; and
- Proteins: leverage our novel, proprietary technologies to develop monoclonal antibodies to combat infectious diseases.

In 2008, the Management Board decided to integrate both business units and reduce the complexity of our organization. In 2008, the separate segments were no longer reported to the Management Board.

Retrospective application of newly adopted accounting policies

We adopted IFRIC 14, 'IAS 19 – The limit on a defined benefit asset, minimum funding requirements and their interactions' in 2008. This interpretation provides guidance on assessing the limit of the surplus in a defined benefit pension plan that can be recognized as an asset. It also explains how a pension asset or liability may be affected by a statutory or contractual minimum funding requirement. Our pension fund in Switzerland has a minimum funding requirement and the application of the interpretation resulted in an increase in the assets recorded on the Group's balance sheet of € 7,853 (2007: € 4,918, 2006: € 746) and a corresponding increase in the Group's equity of € 6,165 (2007: € 3,861, 2006: € 586). As a result of the adoption of IFRIC 14, the result for the year increased by € 2,101 (2007: € 3,037, 2006: € 367). As required by IFRS, all comparative figures were adjusted as if the interpretation had always been applied.

Acquisitions and divestments

In 2006, we acquired a controlling interest in the Swiss biotech Company Berna Biotech AG (Berna Biotech), in a share exchange. In September 2006, we acquired the remaining 1.6% minority interest in Berna Biotech. In October 2006, we purchased the assets and liabilities of Florida-based Berna Products Corp. (BPC) from Acambis plc. In November 2006, we acquired Stockholm-based SBL Vaccin Holding AB (SBL) from the private equity firm 3i and the financial group SEB.

2007 is the first year that includes the consolidated results of the acquired companies for a full year. Our 2006 financial results included one month of SBL's financial results, three months of BPC's financial results and ten months of Berna Biotech's financial results.

Economic and industry-wide factors

Various economic and industry-wide factors are relevant to us and could affect our business, including the factors set forth below.

Our financial strength and ability to adapt to the current market and economic conditions are dependent, in part, on the success of our existing products, the cost of bringing novel products to market and the success of our licensees in developing commercial products using our technology. Our industry is subject to extensive government regulation, and we must make significant expenditures to comply with these regulations. Our business success is dependent in a significant part on our success in establishing intellectual property rights, either internally or through licenses of third-party intellectual property rights, and protecting our intellectual property rights.

Our sales are exposed to seasonal variations, and the majority of our sales is made in the second half of the year. This is specifically the case for our influenza vaccines as vaccination programs mainly take place in the second half of the year. Furthermore, our travel vaccines sales are subject to seasonal travel patterns. The 2008 flu season was comparable to 2007 in our major markets in Europe.

To be successful, we must retain qualified clinical, scientific, marketing, administrative and management personnel. We face significant competition for experienced personnel. In 2008, the number of employees of the Group remained stable at 1,126 employees (2007: 1,126).

The above economic and industry-wide factors are discussed in more detail in the section 'Risk factors'.

Result of operations

Revenues

The table below shows our revenues for each of the years in the three-year period ended December 31, 2008 and the percentage change between these periods.

In thousands of Euro

	Year ended December 31,			% Change	
	2008	2007	2006	08 vs. 07	07 vs. 06
Product sales	226,055	177,569	103,918	27.3	70.9
License revenues	30,202	12,211	16,955	147.3	(28.0)
Service fees	10,900	14,006	10,694	(22.2)	31.0
Total revenues	267,157	203,786	131,567	31.1	54.9

In 2008, total revenues increased by € 63,371 or 31.1% from € 203,786 in 2007 to € 267,157 in 2008. The increase is attributable to an increase in product sales of € 48,486 or 27.3% and license revenues of € 17,991 or 147.3%. The increase is partly offset by a decrease in revenue from service fees of € 3,106 or (22.2%).

Total revenues grew by € 72,219 in 2007 or 54.9 % from € 131,567 in 2006 to € 203,786 in 2007. The increase is primarily attributable to increases in sales of paediatric vaccines by € 41.438 or 115.3 % and travel and endemic vaccines by € 24.210 or 104.9 % and higher revenues related to the acquisitions made in the second half of 2006.

Reference is made to '4.4 Geographical segments' in the financial statements for the breakdown of our revenues by geographic segment.

Product sales

Our product sales by type of product in 2008, 2007 and 2006, as well as the percentage change between the periods, are shown below:

In thousands of Euro

	Year ended December 31,			% Change	
	2008	2007	2006	08 vs. 07	07 vs. 06
Paediatric vaccines	111,039	77,371	35,933	43.5	115.3
Respiratory vaccines	32,474	33,188	40,386	(2.2)	(17.8)
Travel and endemic vaccines	55,572	47,282	23,072	17.5	104.9
Other products	26,970	19,728	4,527	36.7	335.8
Total product sales	226,055	177,569	103,918	27.3	70.9

In 2008, product sales grew by € 48,486 or 27.3%. The increase is primarily attributable to increased sales of paediatric vaccines of € 33,668 or 43.5%, travel and endemic vaccines of € 8,290 or 17.5% and other products of € 7,242 or 36.7%.

In 2008, paediatric vaccines grew mainly due to increased Quinvaxem sales. Supranational organizations awarded us additional contracts for Quinvaxem and Hepavax Gene amounting to \$ 140 million for the period 2008-2009. Travel and endemic vaccines showed considerable growth on an overall basis. 'Other products' include sales of vaccine and proteins trade goods that we distribute for third parties and also sales of conjugates to Wyeth. The increase in other products mainly relates to increased sales under our distribution agreement with Talecris as 2008 includes a whole year of sales under this agreement for the first time.

Our core product portfolio consists of seven vaccines: Quinvaxem, Hepavax-Gene, MoRu-Viraten (paediatric vaccines), Inflexal V (respiratory), Dukoral, Epaxal and Vivotif (travel and endemic vaccines). The aggregated revenues for our core product portfolio amounted to € 191,631 in 2008 (2007: € 151,791, 2006: € 92,144) and represented 84.8% (2007: 85.5%, 2006: 88.7%) of our total product sales.

In 2008, sales to our two largest customers, which are in the paediatric vaccines area, amounted to € 85,142 or 37.6% and € 18,390 or 8.1 % of net product sales. In 2007, sales to these customers accounted for € 45,480 or 25.6% and € 23,457 or 13.2% of net product sales, respectively.

In 2007, product sales grew by € 73,651 or 70.9 %. The growth in revenue from product sales was mainly due to increased revenue from sales of paediatric vaccines of € 41,438 or 115.3%, travel and endemic vaccines of € 24,210 or 104.9 % and sales of other products of € 15,201 or 335.8 %. The increase in product sales was partly offset by a decrease in respiratory vaccines of € 7,198, mainly caused by lower influenza vaccine sales as a result of a mild flu-season in 2007.

The majority of our sales are export sales. Domestic product sales amount to € 3,743 or 1.7% (2007: € 717 or 0.4% and 2006: nil). Almost all of our license revenues and service fees are billed to foreign parties.

License revenues

In 2008, license revenues increased by € 17,991 or 147.3% to € 30,202 compared to 2007. This increase mainly results from milestone payments related to the rabies and influenza programs from sanofi pasteur and upfront fees received from Talecris for the exclusive production rights of two specific proteins.

In 2007, our license revenues decreased to € 12,211, a reduction of € 4,744 or 28.0% compared to 2006, which was mainly due to one-off issuance fees included in contracts with DSM and sanofi pasteur in 2006. The underlying agreements with DSM and sanofi pasteur are still in effect. The decrease was partly offset by recognized issuance fees on contracts signed in 2007 with MedImmune, ADImmune and Wyeth that totaled € 4.3 million and numerous other smaller contracts.

In December 2007, we signed an exclusive collaboration and commercialization agreement with sanofi pasteur related to our rabies monoclonal antibodies. We received a payment of € 10.0 million, which will be recognized as license revenues over the period that the development activities are performed. We will be eligible for additional potential milestone payments of up to € 66.5 million.

Service fees

In 2008, service fees amount to € 10,900, a decrease of € 3,106 or 22.2 % compared to 2007. In 2008, service fees on the sanofi pasteur influenza project were less compared to 2007. Service fees include revenues relating to various collaboration agreements. Typically we do not retain the residual interest on products developed under these agreements. We are more selective in the programs that we want to carry out and we tend to put more focus on the profitability of these types of programs.

In 2007, service fees amounted to € 14,006, an increase of € 3,312 or 31.0% compared to 2006. This increase was mainly attributable to consulting services provided to ADImmune and increased service fees in Sweden realized on miscellaneous projects.

Cost of goods sold

The following table shows our cost of goods sold for each of the years in the three-year period ended December 31, 2008 and the percentage change between these periods.

In thousands of Euro

	Year ended December 31,			% Change	
	2008	2007	2006	08 vs. 07	07 vs. 06
Cost of product sales	138,790	124,557	83,518	11.4	49.1
Cost of service fees	6,965	10,327	6,971	(32.6)	48.1
Total cost of goods sold	145,755	134,884	90,489	8.1	49.1

Cost of product sales

Costs of product sales comprise direct labor, materials, and overhead costs incurred in performing work under various collaboration agreements directly related to product sales. The cost of product sales increased in 2008 mainly due to an increase in product sales of 27.3%. This increase was partly offset by the reduction in purchase price allocation charges in 2008. The 2008 cost of product sales includes additional expenses of € 3,473 (2007: € 10,191) relating to the purchase price allocations of the businesses acquired by the Group. The gross margin on product sales amounts to 38.6% (2007: 29.9%). The percentage increase in gross margin is mainly due to the strengthening of the US Dollar in the second half of 2008, product-mix changes, improvements in production performance and a reduction of the purchase price allocation charges in 2008.

Cost of service fees

Cost of service fees comprises direct labor, materials and overhead costs related to work under various collaboration agreements. We do not retain the residual interest on products developed under the agreements and will normally not have ownership of intellectual property rights on these products.

In 2008, the cost of service fees decreased by € 3,362 or 32.6 % compared to 2007. The decrease reflects the lower level of service fee revenues, which reduced our expenses. The gross margin on service fees was 36.1% in 2008 compared to 26.3% in 2007. In 2008, there has been a shift in strategy to focus more on programs that generate higher margins.

In 2007, the cost of service fees increased by € 3,356 or 48.1% compared to 2006, which is primarily attributable to the increase of the service fee revenues by 31.0%. The gross margin on service fees was 26.3 % in 2007 compared to 34.8% in 2006.

Other operating income

The following table shows our other operating income for each of the years in the three-year period ended December 31, 2008 and the percentage change between these periods.

In thousands of Euro

	Year ended December 31,			% Change	
	2008	2007	2006	08 vs. 07	07 vs. 06
Government grants	5,380	7,086	6,901	(24.1)	2.7
Other operating income	10,772	2,244	2,455	380.0	(8.6)
Total other operating income	16,152	9,330	9,356	73.1	(0.3)

Government grants

In 2008, government grants decreased by € 1,706 or 24.1% compared to 2007. The grants decreased as several projects were completed in 2007. The most significant grants in 2008 were received from NIH and from SenterNovem, an agency of the Dutch Ministry of Economic Affairs, for numerous research projects.

In 2007, government grants were stable compared to 2006. The most significant grants in 2007 were received from NIAID for further research on HIV and from SenterNovem.

Other income

Other income mainly consists of the reimbursement of development costs and funding received from non-governmental agencies. Other income also includes non-core business transactions such as the sale of property, plant and equipment and income generated from training courses. Other income increased by € 8,528 or 380.0% mainly due to reimbursement of development costs on the rabies program, for which the partnership with sanofi pasteur started in 2008, and increased funding from non-governmental agencies in 2008.

The amount of other income in 2007 was stable compared to 2006.

Other operating expenses

The following table shows our other operating expenses for each of the years in the three-year period ended December 31, 2008 and the percentage change between these periods.

In thousands of Euro

	Year ended December 31,			% Change	
	2008	2007	2006	08 vs. 07	07 vs. 06
Research and development	70,229	63,995	67,606	9.7	(5.3)
Selling, administrative and general	64,350	61,752	46,732	4.2	32.1
Restructuring	—	—	3,120	—	—
(Reversal of impairment)/ impairment	(4,888)	171	30,416	(2,958.5)	(99.4)
Total other operating expenses	129,691	125,918	147,874	3.0	(14.8)

Research and development expenses

Research and development expenses consist of personnel expenses, laboratory expenses, technology purchases, patent related fees, technology license fees, depreciation of property, plant and equipment and amortization of intangible assets related to research and development, and lease expenses for lab space and equipment lease. Research and development expenses also include fees we pay to third parties who conduct research on our behalf.

Research and development expenses increased in 2008 by € 6,234 or 9.7% compared to 2007. This increase is mainly attributable to increased expenditures on the rabies program for which two phase II clinical trials were performed.

Research and development expenses comprised 54.2% of total other operating expenses in 2008 (2007: 50.8%). We expect that research and development expenses will continue to be a significant portion of our overall expenses in the future.

In 2007, research and development expenses decreased by € 3,611 or 5.3% compared to 2006, which was primarily attributable to the cost-saving effect of the restructuring program that took place in 2006 to centralize research and development activity in Leiden and phasing out work on both a vaccine candidate as well as on programs at the Center of Mammalian Cell Culture.

Selling, general and administrative expenses

Selling, general and administrative expenses consist of personnel expenses and other operating expenses in marketing and sales, finance, human resources, investor relations, legal and general management.

These expenses increased in 2008 by € 2,598 or 4.2% to € 64,350 in 2008 compared to € 61,752 in 2007. This increase is primarily due to the overall growth of the Group as a whole. Specific items are the increased distribution and sales expenses as a result of increased revenues, annual salary increases and the recognition of specific provisions. The increase in selling, general and administrative programs is partly offset by cost reductions realized through our Healthy Ambition program.

Selling, general and administrative expenses increased in 2007 by € 15,020 or 32.1% to € 61,752 in 2007, compared to € 46,732 in 2006. Selling costs increased as a result of the cost base of the companies acquired in 2006, which are for the first time included for a whole year in 2007. General and administrative expenses also included integration costs of the 2006 acquisitions and additional costs relating to compliance with internal control over financial reporting requirements under US law.

Restructuring

A restructuring program in our Italian subsidiary Berna Biotech Italia Srl. was executed in 2008. A total provision of € 684 was recognized, of which € 610 is recorded in restructuring provisions as per year-end

2008. The majority of this provision was paid in the first quarter of 2009. The costs for the restructuring are included in the applicable operating expenses as they have an operating nature.

There were no restructuring expenses in 2007.

The restructuring expense in 2006 is related to centralizing R&D functions in Leiden and phasing out R&D projects in Switzerland, including the candidate vaccine Aerugen, and the Center of Mammalian Cell Culture. The decision to concentrate R&D in Leiden was made to increase efficiency in R&D spending. The provision was recognized in 2006 as recognition criteria were met at that time. The actual reduction in the number of staff employed was effected in the first quarter of 2007.

Impairment

In the first quarter of 2008, we reversed € 5,219 of previously impaired property, plant and equipment. In 2008, we entered into an exclusive agreement with Wyeth Pharmaceuticals in which we will develop and manufacture certain components of a vaccine for use by Wyeth in clinical studies. The contract manufacturing takes place in one of the two buildings that were impaired in 2006 as described below. We reassessed the recoverable amount of the asset and as the outcome exceeded the carrying value of nil, we partially reversed the previously recognized impairment loss on this building.

In the fourth quarter of 2008, we recognized an impairment charge of € 331 for the animal housing facility in Bern, Switzerland that was not in use anymore. As there was no alternative use for this building for any of the Group's other activities and the building cannot be sold directly to other parties as it is on our campus, the Group impaired the carrying value to zero.

In 2007, we recognized an impairment charge of € 171 for a warehouse in Korea that was demolished to make way for the construction of a light railway.

In 2006, we recognized a total impairment of € 30,416. The impairment related to two buildings in Switzerland including installed equipment, for an amount of € 19,568 and to acquired in-process research and development related to the Tetra vaccine for an amount of € 10,848.

Operating profit/ (loss)

The following table shows our operating profit/ (loss), for each of the years in the three-year period ended December 31, 2008 and the percentage change between these periods.

	Year ended December 31,			% Change	
	2008	2007	2006	08 vs. 07	07 vs. 06
Operating profit/ (loss)	7,863	(47,686)	(97,440)	(116.5)	(51.1)

The movements in operating loss are explained by the operating results discussed above.

Financial income and expense, net

The following table shows our financial income and expenses, net, for each of the years in the three-year period ended December 31, 2008 and the percentage change between these periods.

	Year ended December 31,			% Change	
	2008	2007	2006	08 vs. 07	07 vs. 06
Financial income and expenses	(2,662)	1,378	1,747	(293.2)	(21.1)
Results investments non-consolidated companies	(128)	(996)	(1,956)	(87.1)	(49.1)
Results on disposal non-consolidated companies	1,570	2,186	—	(28.2)	—
Disposal of subsidiaries	(367)	—	—	—	—
Total financial income/ (expense), net	(1,587)	2,568	(209)	(161.8)	(1,328.7)

Financial income and expenses

Financial income and expenses mainly consist of interest income and expenses, foreign exchange losses and other financial expenses.

In 2008, the negative result on net financial income and expenses totaled € 2,662 and consists of interest income of € 5,021, foreign exchange losses of € 3,926, interest expenses of € 2,719 and other financial expenses of € 1,038.

The net financial income and expenses decreased by € 4,040 or 293.2 % compared to 2007. The decrease is primarily attributable to foreign exchange losses of € 3,926. These losses mainly resulted from a weaker Euro in conjunction with Euro receivables in Switzerland, as the Swiss Franc is the functional currency of our subsidiary Berna Biotech AG. In addition, foreign exchange losses were realized on Euro liabilities and losses on US Dollar transactions in Korea.

See – ‘Financial risk management – 3.2 Foreign currency risk’ in the financial statements for more details on foreign currency risk management including the use of hedging instruments by the Group.

Other changes in the net financial income and expenses were:

- A reduction of interest income by € 690, mainly caused by a lower average cash balance in 2008 compared to 2007;
- Increased interest expenses of € 438 as a result of increased finance leases and short-term financial liabilities; and
- An increase other financial expenses of € 292 primarily due to factoring arrangements engaged in during 2008.

In 2007, net financial income and expenses decreased by € 369 or 21.1% compared to 2006. The decrease was primarily attributable to:

- Increased negative foreign exchange results of € 1,142 as the foreign currencies in which we traded lost value compared to the Euro;
- Increased interest expenses of € 544 as a result of additional charges relating to leasing and the full year effect of our 2006 acquisitions; and

- An increase in other financial expenses of € 402 primarily due to factoring arrangements engaged in during 2007. The decrease was partly offset by increased interest income of € 1,993 resulting primarily from higher interest rates in 2007.

Results investments non-consolidated companies

At December 31, 2008, we had one associate, ADImmune Corp and one joint venture, Percivia. In July 2008, we sold our investment in Kenta Biotech AG. The results of investments in non-consolidated companies include the results of Kenta Biotech AG up to the moment of the sale. The results of investments in non-consolidated companies are accounted for under the equity method and amount to a total loss in 2008 of € 128 (2007: € 996). The decrease of € 868 or 87.1% compared to 2007 year is mainly due to the reduced losses on Kenta Biotech AG.

In 2007, the losses from investments in non-consolidated companies were reduced by € 960 or 49.1%. The decrease was primarily attributable to the reduced losses in Pevion Biotech AG and Kenta Biotech AG.

Results on disposal non-consolidated companies

On July 3, 2008 the Group sold all of the 2,625,000 shares it owned in Kenta Biotech AG to Ingro Finanz AG. Prior to this sale, our ownership interest had already been diluted from 37% in 2006 to 22% by the end of 2007. We realized an accounting gain in 2008 of € 1,570 on the sale.

On November 5, 2007 the Group sold all of the 2.9 million shares it owned in Pevion Biotech AG for an amount of € 6,081 to other shareholders of Pevion Biotech AG. The Group realized an accounting gain in 2007 of € 2,186 on the sale.

Disposal of subsidiaries

In November 2008, we sold our fully-owned subsidiary Etna Biotech Srl to Zydus Cadila. The sale resulted in net proceeds of € 182 and an accounting loss on disposal of € 367.

Income tax

The table shows our income tax for each of the years in the three-year period ended December 31, 2008 and the percentage change between these periods.

	Year ended December 31,			% Change	
	2008	2007	2006	08 vs. 07	07 vs. 06
Income tax	8,310	2,208	10,451	276.4	(78.9)

In 2008, tax income increased by € 6,102 or 276.4%. The increase resulted from a change in deferred tax of € 11,503 (2007: € 3,024) that mainly consists of carry forward losses not previously recognized in our subsidiary Berna Biotech AG for € 8,585 and a reduced expected tax realization rate on our deferred tax liabilities of € 3,384 in Korea. The increase is partially offset by current tax charges of € 3,200 compared to € 811 in 2007 as a result of taxable income in Sweden, Korea, Spain and the US.

The Group has a negative effective tax rate of 132.4% in 2008 compared to positive effective tax rates of 4.9% in 2007 and 10.7% in 2006. Our effective tax rate was impacted by numerous items.

The effective tax reconciliation starts with our IFRS profit/ (loss) per subsidiary multiplied by the domestic rate of tax in the country in which our subsidiaries are domiciled. In 2008, our total profit under IFRS of € 6,276 had a negative correlation with our total taxes based on domestic rates of € 820. This effect was mainly caused by a loss under IFRS in our Dutch operation at a tax rate of 25.5% and a profit of our Korean subsidiary at a lower average tax rate of 21.0%.

In addition, the following transactions significantly affected our effective tax rate reconciliation:

- We reached an agreement with the Dutch tax authorities to retroactively change the valuation of our intellectual property, to avoid the evaporation of unrecognized tax carry forward losses. This agreement allows us to recognize € 72,000 of our intellectual property as assets for tax purposes. Under IFRS no deferred tax assets were recognized on these temporary differences, which on a combined basis with the utilization of previously unrecognized carry forward losses in our Dutch fiscal unity in 2008, causes a net negative tax effect of € 6,103;
- We reassessed the valuation of our carry forward losses and recognized previously unrecognized carry forward losses in our subsidiary Berna Biotech AG, which resulted in a taxation gain of € 8,585;
- As of the year 2012, we will benefit from a tax holiday to our investment in the Incheon, Free Economic Zone, Korea, which will significantly reduce the effective Korean income tax rate for a period of 5 years. The reduced expected realization rate for our deferred tax liabilities in Korea resulted in a taxation gain of € 3,384;
- In 2008, we benefited in Korea from a research and development tax credit for an amount of € 2,916; and
- Non-deductible stock-option expenses are recognized in the Netherlands for an amount of € 1,251 in 2008.

See – '1 General information – 1.4 Use of estimates and judgments' in the financial statements section for a description of estimates and management judgments in determining the tax position and '5.4 Income tax' in the financial statements for a numerical reconciliation of our effective tax rates.

Changes in the underlying timing differences in 2007 resulted in a taxation income of € 3,024 in 2007 compared to € 10,922 in 2006.

Liquidity

We have a strong cash position, which we believe makes it possible to continue financing important development programs. Our cash and cash equivalents amounted to € 170,969 and € 163,248 as of December 31, 2008 and 2007, respectively. We believe that our liquidity is sufficient for our present requirements.

In 2009, we entered into a mortgage loan facility in Korea for an amount of KRW 50 billion to partly finance the investments in the new Korean facility.

Cash flows

The following table shows our cash flow statement for each of the years in the three-year period ended December 31, 2008 and the percentage change between these periods.

In thousands of Euro

	Year ended December 31,			% Change	
	2008	2007	2006	08 vs. 07	07 vs. 06
Profit/ (loss) of the period	14,586	(42,910)	(87,198)	(134.0)	(50.8)
Adjustments for non-cash items	18,801	44,593	58,505	(57.8)	(23.8)
Changes in net working capital	(30,381)	24,208	(23,174)	(225.5)	(204.5)
Interest and taxes paid	(3,260)	(3,697)	(2,087)	(11.8)	77.1
Net cash flows from/ (used in) operating activities	(254)	22,194	(53,954)	(101.1)	(141.1)
Net cash flows from/ (used in) investing activities	(8,907)	(24,241)	23,159	(63.3)	(204.7)
Net cash flows from financing activities	16,626	11,244	78,731	47.9	(85.7)
Effect of exchange rates on cash and cash equivalents	256	(3,786)	(1,833)	(106.8)	106.5
Net increase/ (decrease) in cash and cash equivalents	7,721	5,411	46,103	42.7	(88.3)
Cash and cash equivalents at beginning of period	163,248	157,837	111,734	3.4	41.3
Cash and cash equivalents at end of period	170,969	163,248	157,837	4.7	3.4

Net cash flows from/ (used in) operating activities

In 2008, our net cash flow from operating activities decreased by € 22,448 or 101.1% compared to 2007. The decrease resulted from an increase of our working capital by € 54,589 and a reduction in the adjustments for non-cash items by € 25,792. The decrease is partly offset by € 57,496 due to improved results in 2008 compared to 2007.

In 2008, the decrease in changes in the net-working capital compared to 2007 amounted to € 54,589. The year 2008 had relatively stable cash flows on the monetary working capital items compared to positive cash flows in 2007. The decrease in 2008 compared to 2007 mainly resulted from inventories for € 30,993 due to build-up of Quinvaxem inventory for 2009 sales, and other current liabilities for € 22,327.

In 2008, adjustments for non-cash items were reduced by € 25,792. This reduction was mainly caused by:

- One-off cash receipts in 2007 in the amount of € 11,500 in 2007 relating to the non-current deferred revenue on the ADImmune technology license and the rabies program;
- Non-cash revenues realized in 2008 for an amount of € 4,728 that related to the above transactions; and
- Partial reversal of the impairment loss on one of our buildings in Switzerland in 2008 for an amount of € 5,219 as we now perform contract manufacturing at this location.

In 2007, our net cash flow from operating activities increased by € 76,148 or 141.1 % compared to 2006. The increase resulted from a reduction of our working capital by € 47,382 and a reduction of our net loss by € 44,288. The increase is partly offset by a decrease in the adjustments for non-cash items of € 13,912 and an increase in interest and taxes paid by € 1,610 in 2007.

Net cash flows from/ (used in) investing activities

Our cash flow used in investing activities amounted to € 8,907 in 2008, compared to € 24,241 in 2007.

In 2008, the most significant cash flows used in investing activities resulted from investments made in property, plant and equipment for an amount of € 15,787. These investments mainly related to our new Korean production facility, investments in our facilities in Bern, Switzerland that will improve current production processes and allow in-house production of materials currently acquired from third parties, as well as investments in our new filling line in Madrid, Spain.

In 2008, the most significant cash flows from investing activities were from the following transactions:

- Interest received of € 4,395 in 2008 (2007: € 5,274);
- The sale of all shares owned by the Group in Kenta Biotech AG for € 1,570 to Ingro Finanz AG; and
- Restricted deposits that were transferred to cash and cash equivalents for € 1,500.

In 2007, the most significant cash flows used in investing activities were from the following transactions:

- Investments were made in property, plant and equipment for an amount of € 27,156, which mainly related to our new GMP production facility in Leiden, the Netherlands and investments in our facilities in Bern, Switzerland to improve production processes and allow in-house production of materials currently acquired from third parties; and
- The Group acquired a 20% equity-stake in ADImmune Corp. in March 2007 for € 8,553.

In 2007, the most significant cash flows from investing activities were from the following transactions:

- The sale of all shares owned by the Group in Pevion Biotech AG, Switzerland for € 6,081 to other shareholders of Pevion Biotech; and
- Interest received of € 5,274 in 2007.

Net cash flows from/ (used in) financing activities

Our cash flow from financing activities amounted to € 16,626 in 2008, € 11,244 in 2007 and € 78,731 in 2006.

In 2008, the cash flow from financing activities increased by € 5,382 or 47.9% compared to 2007 and, mainly related to:

- Additional short-term financing facilities in Korea for an amount of € 22,222; and
- Finance leases with proceeds of € 12,368 relating to our GMP-facility in Leiden, the Netherlands and our Spanish filling-line.

The most significant cash flows used in financing activities mainly related to:

- Redemption of a Korean Won-denominated privately placed bond in Korea for € 11,869 and a partial redemption of a short-term Euro loan also in Korea for € 1,455;
- Settlement of financial liabilities relating to factored Italian trade accounts receivable by € 5,653 for which the Group did not substantially transfer all the risks and rewards in 2007; and
- Repayment of finance lease liabilities for an amount of € 1,922.

In 2007, the cash flow from financing activities decreased by € 67,487 or 85.7% compared to 2006 as we limited the use of additional financing and funded our operations and investments with our own resources. The cash flow from financing activities in 2007 mainly related to:

- Factoring of trade accounts receivable in Italy for an amount of € 5,653; and
- Finance leases with proceeds of € 4,247. These finance leases mainly related to equipment for the new production and development facility in Leiden.

Critical accounting policies and estimates

The methods, estimates and judgments we use in applying our most critical accounting policies have a significant impact on the results we report in our financial statements. Please see '1 General information – 1.4 Use of estimates and judgments' in the financial statements for further details on our most critical policies and the methods, estimates and judgments used.

In addition to the critical accounting policies and estimates, the Group chooses to disclose the impact of discounts, rebates and returns.

Discounts, rebates and returns

At the time sales revenue is recognized, we also record estimates for revenue deductions, including discounts, rebates and product returns. We report net sales after deducting all sales deductions from gross sales revenue. The following table identifies the items that reduced our gross product revenue as at the end of the periods ended December 31, 2008, 2007 and 2006.

In thousands of Euro

	2008	2007	2006
Product sales, gross	227,791	179,395	105,059
Discounts and rebates	945	626	291
Returns	791	1,200	850
Total discounts, rebates and returns	1,736	1,826	1,141
Product sales, net	226,055	177,569	103,918

Discounts and rebates

Discounts include prompt payment discounts and charge backs. In 2008, our discounts and rebates amounted to € 945.

We generally offer our US wholesalers a prompt-pay cash discount as an incentive to remit payment in full within one month after the date of an invoice. Prompt-pay discount calculations are based on the gross amount of each invoice. We account for these discounts by reducing product sales by the estimated discount amount when the product is sold.

Wholesaler charge backs, customary in our industry, are arrangements that relate to contractual agreements to sell products to Group Purchasing Organizations (GPOs) in the US at fixed prices that

are lower than the list prices we charge wholesalers. When the GPOs purchase our products through wholesalers at these reduced prices, the wholesaler charges us for the difference between the price the wholesaler paid to us and the price at which they sold the products to the GPO. Accruals for wholesaler charge backs closely approximate actual results because charge back amounts are fixed at the date of purchase by the GPOs. As the charge backs are settled within a short time of incurring the liability, the outstanding accruals are relatively low.

We offer rebates primarily in connection with attainment of sales targets by wholesalers and large retailers in contractually agreed percentages. The rebates are accrued as the underlying sales transactions are recognized and are based on reasonable estimates on the attainment of the sales targets.

Returns

Returns that reduce our gross product revenue may arise from the following:

- Customers return of products defective upon delivery;
- Specific right of return in accordance with contractual terms; and
- Returns via the normal distribution channels if the product is in good condition, pursuant to local law in certain jurisdictions.

In 2008, returns amounted to € 791 (2007: € 1,200) or approximately 0.4% (2007: 0.7%) of our net product sales.

The following table shows the percentage of products returned as a percentage of the gross product sales per country during 2008 based on the country from which the products were originally sold.

Country	Returns 2008	Returns 2007	Returns 2006
Spain	3.0%	2.5%	1.7%
Italy	1.1%	1.4%	0.1%
Switzerland	0.1%	0.1%	0.7%
US	2.1%	1.9%	0.9%
Sweden	0.9%	0.1%	0.2%
Korea	—	—	—
Netherlands	—	—	—

Roll-forward information

The table below shows the roll-forward information of our discounts, rebates, and product returns:

In thousands of Euro

	Accrual for discounts and rebates	Accrual for returns	Total
January 1, 2008	(190)	(1,117)	(1,307)
Additions – current period	(945)	(791)	(1,736)
Actual returns/credits – current period	762	240	1,002
Actual returns/credits – prior period	160	975	1,135
Release of accruals – current period	—	—	—
Release of accruals – prior period	—	—	—
Effect of movements in exchange rates	24	18	42
December 31, 2008	(189)	(675)	(864)

Discounts and rebates

We base our estimates for discounts and rebates primarily on historical experience and contractual agreements, supplemented by management's judgment. In 2008, our estimates for rebates based on historical experience did not differ materially from actual results. With respect to discounts, we have limited uncertainties in determining our estimates, because these deductions generally occur within a short time frame of incurring the liability.

For calculating our rebates estimates we make use of quantifiable contractual rebates data. In general, our rebates are based on fixed rebate percentages on product sales to customers that have been granted rebates.

Returns

We base our estimates of product returns on the percentage of returns that we have experienced historically. We may adjust these return estimates if we are aware of other factors that we believe could meaningfully impact our expected return percentages. For example, in respect of our influenza vaccine, we specifically take into account the development of the flu season, in particular, the number and impact of outbreaks. While we do not have a formula that estimates the impact of the

number and impact of outbreaks on the level of the accrual for returned vaccines, an increased number of outbreaks will generally result in a lower accrual for returned influenza vaccines, because it becomes more unlikely that vaccines will be returned. Alternatively, a lower number of outbreaks can result in a higher accrual, because it becomes more likely that influenza vaccines will be returned unused at the end of a mild flu season.

In addition, in our estimates of returns, we take into account other information, such as media coverage of vaccination programs, estimates of inventory levels of our product in the distribution channel, vaccine shelf life and known sales and market trends. These are reflected in the accruals by means of management's judgment.

Increased media coverage of vaccination programs, either by advertising campaigns or coverage of flu outbreaks, results in an increased public awareness. Consequently, this may lead to an increased number of flu vaccinations and fewer unsold doses with our customers, which limits the level of accruals for product returns.

Relatively high levels of inventory of our product in the distribution channel and short shelf life of product sold can be indicators for an increased level of returns.

Sales and market trends are taken into account by reference to the life cycle phase of products. If product sales show a decreasing revenue pattern over time, this can be an indicator for an increased level of returns. We do not rely on quantitative externally sourced information in our calculation of returns estimates. We are not aware of any available external quantitative information or other quantifiable data that would provide us the benefit of a more reliable estimate.

The rate of product returns is quantifiable. We monitor returns primarily on a per country basis based on the country from which the product was sold because our accruals are determined at this level. Within the individual countries, we monitor the returns on a product-by-product basis. In 2008, our estimates for returns did not differ materially from actual results.

Tabular disclosure of contractual obligations

Future minimum payments for all contractual obligations for years subsequent to December 31, 2008 are as follows:

In thousands of Euro

	Total	Less than one year	1-3 years	3-5 years	More than 5 years
Contractual obligations					
Debt obligations (excluding finance lease obligations)	40,225	22,677	2,239	861	14,448
Finance lease obligations ⁽¹⁾	20,526	2,777	6,381	7,911	3,457
Interest payments on debt obligations	12,580	2,105	3,512	2,314	4,649
Derivative financial instruments ⁽²⁾	45,560	45,560	—	—	—
Accounts payable	59,205	59,205	—	—	—
Other liabilities	21,114	20,523	591	—	—
Recognized obligations	199,210	152,847	12,723	11,086	22,554
Commitments					
Operating lease obligations ⁽³⁾	24,662	3,830	6,575	3,498	10,759
Capital expenditure commitments ⁽⁴⁾	20,380	16,163	4,217	—	—
Total commitments	45,042	19,993	10,792	3,498	10,759
Total recognized obligations and commitments	244,252	172,840	23,515	14,584	33,313

⁽¹⁾ Finance lease obligations

Certain of the Group's fixtures and equipment are finance leases. The finance leases relate to equipment for the new production facility in Leiden, the Netherlands and to the filling line in Spain. Interest rates are fixed at the contract date. All leases are on a fixed repayment basis and no arrangements have been entered into for contingent rental payments.

⁽²⁾ Derivative financial instruments are foreign exchange contracts. The contractual obligations are € 45,060. The corresponding receivables are € 46,442.

⁽³⁾ Operating lease obligations

The operating lease obligations include rental obligations. CruCell concluded long-term rental agreements for premises in Sweden and the Netherlands. In addition, CruCell leases certain motor vehicles and items of machinery and equipment.

⁽⁴⁾ Capital expenditure commitments

The contractual commitments for purchases of property, plant and equipment as per December 31, 2008 amount to approximately € 20,380 (2007: € 4,696, 2006: € 11,693).

These commitments mainly relate to our new production facility in Incheon, Free Economic Zone, Korea.

See note '5.19 Short and long-term financial liabilities' in the notes to the financial statements for details on the maturity profile and the interest rate environment of our financial liabilities.

Off-balance sheet arrangements

As of December 31, 2008, we have no unconsolidated special purpose financing or partnership entities or other off-balance sheet arrangements that have or are reasonably likely to have a current or future effect on our financial condition or lead to changes in financial condition, revenues or expenses, results of operations, liquidity, capital expenditures or capital resources, that is material to investors.

The Group has investments in one associate and in one joint venture that are both non-consolidated companies. Details are provided in '5.9 Investments in associates and joint venture' in the financial statements.

Further details on our off-balance sheet arrangements such as our guarantees and covenants are disclosed in note 3 'Financial risk management' in our financial statements.

Quantitative and qualitative disclosure about market risk

Market risk is the risk of loss related to adverse changes in market prices, including currency risk, interest rate risk and risk of financial instruments. During the ordinary course of business, the Group is exposed to various financial market risks, primarily from foreign exchange, interest rates and credit risk. Details on our market risks are disclosed in '3 Financial risk management' in the financial statements.

Impact of inflation

CruCell does not operate subsidiaries in countries with hyperinflation. Sales to customers in hyperinflationary countries are made in hard currency, mainly Euro, US Dollar, Swiss Franc and Swedish Crown.

Corporate Governance

Corporate governance at Crucell

Corporate governance concerns the relationship between management and the shareholders, and more generally the stakeholders, of the Company. It is the formal codification of the manner in which the Company is governed, of the accountability of its management and its supervision, of the manner in which stakeholders, and more particularly shareholders, are able to gain an insight into the state of affairs within the Company, and finally, of the way in which they can influence the decision-making process. With regard to this final issue, voting rights and the manner in which votes can be exercised, play an important role.

As a Dutch corporation, Crucell is subject to the Dutch Corporate Governance Code (the 'Code'). As a foreign private issuer whose ADSs trade on NASDAQ Global Select Market (NASDAQ), we are also subject to US securities laws (including the provisions of the Sarbanes-Oxley Act of 2002) and the NASDAQ rules.

As a foreign private issuer Crucell may follow its home country practice in lieu of the requirements of certain rules of NASDAQ. Our Annual Report discloses those requirements that are not followed and describes the home country practice that is followed instead, see 'Exemptions from certain NASDAQ Corporate Governance Rules' in this section.

Also under the rules of the SWX Swiss Exchange, where Crucell has a secondary listing, it is allowed to apply the Code.

Corporate governance developments

We monitor and assess applicable corporate governance rules, including recommendations and initiatives regarding principles of corporate governance. These include those that have been developed in the US, both by NASDAQ and by the SEC pursuant to the Sarbanes-Oxley Act of 2002, as well as in the Netherlands, through the Code, which came into effect as of the financial year starting on or after January 1, 2004.

Dutch Corporate Governance Code

The Code has been instituted by government decree. According to Dutch law, a public company should include in its annual report a statement about the compliance with the principles and best practice provisions of the Code that regard the

Management Board and Supervisory Board. If a corporation does not, or does not intend to comply with one or more of the principles and best practice provisions, it must explain its motivation in the annual report. According to the Code, substantial amendments to the Company's existing corporate governance structure and compliance with the Code should be submitted for discussion to the General Meeting of Shareholders.

Important principles of the Code are:

- Strengthening the role of the Supervisory Board and its committees and increasing its independence, quality and expertise;
- Strengthening the role of the shareholders with respect to control of the functioning of the Management Board and the Supervisory Board, as well as with respect to nomination and remuneration of members of the Management Board and the Supervisory Board;
- Facilitating and stimulating shareholders to use their voting power and to actively participate in the General Meeting of Shareholders;
- Defining the role of the external auditor vis-à-vis the Supervisory Board as its principal contact; and
- Maintaining an appropriate internal risk and control system.

For an overview of Crucell's conformity with the Code, please refer to our website (www.crucell.com), where the following documents can be consulted:

- Corporate governance at Crucell;
- By-laws of the Management Board;
- Remuneration policy Management Board;
- By-laws of the Supervisory Board; and
- Code of Conduct (Crucell's company code) including whistle-blower policy.

In 2003, we adopted a code of business conduct and ethics (Code of Conduct) that applies to all employees of the Company, including our principal executive officer and principal financial officer. The Code of Conduct underlines that one of the most valuable assets of Crucell is its integrity. The Code of Conduct was amended in 2008 and has been filed as an exhibit to our Form 20-F for the fiscal year ended December 31, 2008. The amended Code of Conduct adheres to the same underlying principles as the original Code of Conduct, but reflects that we are a fully integrated company that operates in numerous countries. No waivers of the Code of Conduct were granted during 2008.

We have a whistle blower policy in place, which encourages employees to report abuses and non-compliance with our Code of Conduct, anonymously if necessary.

Compliance with the Code

In June 2005, the General Meeting of Shareholders approved our current corporate governance structure. Except for the three provisions of the Code referenced below Crucell has fully implemented the recommendations set forth in the Code and incorporated them into its corporate governance policies.

Exceptions to compliance with the Code

The Code contains a 'comply-or-explain' principle, offering the possibility to deviate from the Code as long as any such deviations are explained. Crucell complies with all of the principles and best practice provisions of the Code, except for the following:

Remuneration of Management Board members

Under the Code, the maximum severance pay for a Management Board member should be no more than one year's salary, unless this is manifestly unreasonable. We do not apply this principle in the event of a dismissal arising from an unwanted change of control for Management Board members. The employment contracts of those members of the Management Board that were already in place as at 1 January 2004 (the date on which the Code took effect) remain unchanged. In other cases agreed severance payments can be higher if otherwise this would obstruct the recruitment of the right person for a Management Board position.

Loans to the Company's management

We do not apply the provision in the Code that no personal loans shall be granted to a company's Management Board member because, prior to the Code's development and passage of similar legislation in the US, loans were made to Management Board members and one such loan currently remains outstanding. Reference is made to note 5.23 'Related parties' in the financial statements. We have not granted additional loans to Management Board members since 2002.

Remuneration of Supervisory Board members

We do not apply the provision that remuneration of the members of the Supervisory Board should not include share grants. Crucell deems this form of

remuneration adequate because this is customary among biotechnology companies operating internationally, and it helps attract well-qualified supervisory directors with specific expertise in biotechnology and international business fields.

Exemptions from certain NASDAQ corporate governance rules

NASDAQ rules provide that NASDAQ may provide exemptions from the NASDAQ corporate governance standards to a foreign issuer when those standards are contrary to a law, rule or regulation of any public authority exercising jurisdiction over such issuer or contrary to generally accepted business practices in the issuer's country of domicile. We are exempt from certain NASDAQ corporate governance standards that are contrary to the laws, rules, regulations or generally accepted business practices of the Netherlands. These exemptions and the practices followed by our Company are described below:

- We are exempt from NASDAQ's quorum requirements applicable to meetings of shareholders. In keeping with Dutch law and generally accepted business practice, our articles of association provide that there are no quorum requirements for the general meeting of shareholders.
- We are exempt from NASDAQ's requirements regarding the solicitation of proxies and provision of proxy statements for meetings of shareholders. We inform shareholders of meetings in a public notice, but we do not solicit proxies for the General Meeting of Shareholders. Dutch law does not have a regulatory regime for the solicitation of proxies and the solicitation of proxies is not a generally accepted business practice in the Netherlands. In connection with our American Depositary Shares (ADSS), the Bank of New York Mellon, as depositary, distributes proxy materials to holders of our ADSS.
- NASDAQ requires shareholder approval or prior to the issuance of securities when a stock option or purchase plan is to be established or materially amended or other equity compensation arrangement made or materially amended, pursuant to which stock may be acquired by officers, directors, employees, or consultants. Under Dutch Company law and the Code shareholder approval is only required for equity compensation plans (or changes thereto) for members of the Management Board and

Supervisory Board, and not for equity compensation plans for other groups of employees. Our articles of association provide that a resolution of the General Meeting of Shareholders to amend our articles of association, to dissolve the Company, or to merge or demerge the Company shall only be adopted on a proposal of the Supervisory Board.

- We do not distribute Annual Reports to all of our shareholders in accordance with NASDAQ rules. As our shares are bearer shares, according to Dutch law we are not required to distribute copies of annual and interim reports to all shareholders. Copies of such reports are available to shareholders at our corporate headquarters, and are filed with NASDAQ and the Bank of New York Mellon as depositary under our depositary agreement relating to our ADSs. Upon request the Bank of New York Mellon distributes our Annual Reports to holders of our ADSs.
- The Company has a two-tiered board structure, in contrast to the one-tier board structure used by most US companies. In the Netherlands, a public limited liability company has a Management Board as its management body and a Supervisory Board which advises and supervises the Management Board. In general, Management Board members are employees of the company while members of the Supervisory Board are often former state or business leaders and sometimes former members of the Management Board. Members of the Management Board and other officers and employees cannot simultaneously act as members of the Supervisory Board. The Supervisory Board must approve certain specified decisions of the Management Board. Under the Code all members of the Supervisory Board with the exception of not more than one person, shall be 'independent'. The definition of 'independence' under the Code however, differs from the definition of 'independence' under the NASDAQ listing standards (e.g. employment by the Company in the three years prior to the appointment as member of the Supervisory Board versus five years under NASDAQ and the Code respectively).
- Dutch law requires that the external auditors be appointed at the General Meeting of Shareholders and not by the Audit Committee.
- Our Audit Committee currently consists of two Supervisory Board members whereas the NASDAQ listing rules require three. The Company is currently recruiting a third Supervisory Board member with financial expertise to fill the vacancy in the Audit Committee.

Directors, senior management and board practices

Crucell has a 'two-tier' governance structure, in which executive and supervisory responsibilities are clearly segregated. Our Management Board is responsible for managing the Company's daily affairs and business and, as such, is responsible for achieving Crucell's goals, strategy, policy, and results.

Supervisory Board

The Supervisory Board, which consists solely of independent directors, supervises the Management Board. In the execution of their duties, the members of the Supervisory Board must be guided by the best interests of Crucell and its stakeholders.

The Supervisory Board reports to the General Meeting of Shareholders with regard to the corporate governance of Crucell, its structure and the compliance with applicable internal and external rules and regulations.

The principal duty of the Supervisory Board is to supervise the policies of the Management Board and to provide advice. The Supervisory Board oversees the corporate strategy, the risks inherent in the Company's activities and supervises the structure and operation of the internal risk management and control systems, the financial reporting process and the Company's compliance with relevant legislation and regulations.

Our Supervisory Board must approve certain categories of resolutions of our Management Board, which categories are specified in our articles of association. In addition, our Supervisory Board may give our Management Board written notice of other corporate actions that it wishes to approve. The division of duties and the procedures within the Supervisory Board are set forth in the by-laws of the Supervisory Board and can be found on Crucell's website (www.crucell.com).

Our articles of association provide that at least three Supervisory Board members must serve on our Supervisory Board. We must fill any vacancies on the Supervisory Board as soon as possible, but until they are filled, the remaining members of our Supervisory Board constitute a competent board. Under Dutch law, Supervisory Board members cannot serve as members of our Management Board.

The members of our Supervisory Board are appointed for terms ending on the date of the first General Meeting of Shareholders that is held four years

after the date of their appointment. They may be reappointed for two additional consecutive terms of four years each. Our Supervisory Board nominates its own members. To be binding, there must be at least two nominees for each vacancy on the Supervisory Board. The nominee earning the highest number of votes of Supervisory Board members becomes a binding nomination. The General Meeting of Shareholders can override these binding nominations by a vote of an absolute majority of the votes cast. This vote must represent more than one third of our total issued and outstanding share capital. If the Supervisory Board does not make any nominations within three months after a vacancy has occurred, our General Meeting of Shareholders can fill Supervisory Board vacancies. If the Supervisory Board makes a non-binding nomination (i.e., only one nominee is presented to the Supervisory Board for any particular vacancy), then such nomination can only be overturned by a resolution of the General Meeting of Shareholders taken by an absolute majority of the votes cast, representing at least one third of the Company's total issued and outstanding share capital. The Supervisory Board members retire according to a rotation plan established by the Supervisory Board itself.

Our Supervisory Board appoints its own chairman and must adopt rules for its own internal governance, including the creation of committees. The Supervisory Board must, in any event, establish an Audit Committee, a Remuneration Committee and a Nomination Committee. Passing Supervisory Board decisions requires a majority of the votes cast at a meeting of our Supervisory Board, unless otherwise provided for in the articles of association or the by-laws of the Supervisory Board. The company secretary assists the Supervisory Board.

A Supervisory Board member can be suspended or dismissed at any time by a resolution of a General Meeting of Shareholders passed by an absolute majority of the votes cast. This vote must represent more than one third of our total issued and outstanding share capital if the resolution to suspend or dismiss a Supervisory Board member is not proposed by the Supervisory Board itself. Within three months after a suspension, a General Meeting of Shareholders must either dismiss the Supervisory Board member, terminate or extend the suspension. The total suspension may not exceed three months.

The General Meeting of Shareholders determines the Supervisory Board members' compensation. In contrast to the provisions of the Code, until the

end of our 2004 fiscal year we paid our Supervisory Board members in options on our ordinary shares as well as in cash. Starting in 2005, we began paying them in ordinary shares and cash, or cash only, at the member's discretion. We also reimburse Supervisory Board members for their expenses incurred in work relating to Crucell. The remuneration policy is intended to be able to attract and retain qualified and expert Supervisory Board members. It is in line with what is customary in the US biotechnology industry and is in line, as much as possible, with the best practice provisions of the Code.

According to the best practice provisions of the Code, an individual may hold a maximum of five Supervisory Board memberships in Dutch listed companies, with the chairmanship of a Supervisory Board counting as two memberships. All members of our Supervisory Board comply with this provision.

All members of the Supervisory Board comply with the criteria for independence as set out in the NASDAQ rules, the Code and the requirements of applicable EU and Swiss rules.

The business address of each Supervisory Board member is the address of our principal executive office in Leiden, the Netherlands. As of April 17, 2009 our Supervisory Board members held an aggregate of 0.17% of our ordinary shares.

As of December 31, 2008 the Supervisory Board of Crucell consisted of:

Name	Age	Position	End of current term
Jan Oosterveld	64	Chairman	2010
Phillip Satow	67	Member	2009
Claes Wilhelmsson	69	Member	2011
Seán Lance	61	Vice-Chairman	2011
Arnold Hoevenaars	59	Member	2009
Steve Davis ⁽¹⁾	51	Member	2012

⁽¹⁾ Mr. Davis was appointed as member of the Supervisory Board at the Company's General Meeting of Shareholders on May 30, 2008.

Mr. Jan Oosterveld has served as chairman of our Supervisory Board since June 2006 and as a member of the Supervisory Board since his appointment at the General Meeting of Shareholders on June 3, 2004. He retired from Royal Philips Electronics N.V. on April 1, 2004, after an international career of 32 years. At his retirement he was responsible for Corporate Strategy, Corporate Alliances and the joint

ventures with LGE, Korea, relating to Cathode Ray Tubes (CRTs) and Liquid Crystal Displays (LCDs). In the latter responsibility, he was the Chairman of the board of LG Philips Ltd, which went public in April 2004, and Vice-Chairman of the board of LG Philips Displays B.V. He was also the CEO of Philips Asia Pacific. He graduated with a degree in mechanical engineering from the Technical University Eindhoven and holds an MBA from the Instituto de Estudios Superiores de la Empresa (IESE) in Barcelona. He was appointed Professor at IESE in 2003. He is also a Member of the Board of Barco, Kortrijk, Belgium, Cookson Group, London, U.K., Candover, London, U.K. and Continental, Hannover, Germany. Mr. Oosterveld is a Dutch citizen.

Mr. Phillip Satow has served as a member of our Supervisory Board since our incorporation. He worked 14 years with Pfizer, Inc. where his last position was Vice President, Pfizer Europe. From 1985 to 1997, he was Executive Vice President Marketing at Forest Laboratories, Inc. From 1998 to 1999 he was President of Forest Pharmaceuticals, and Executive Vice President of Forest Laboratories Inc. In addition to the Forest Laboratories Board which he served on from 1999 to 2005, Mr. Satow is a former Board member of Eyetech Pharmaceuticals Inc. Mr. Satow co-founded, and served as Chairman and CEO of JDS Pharmaceuticals LLC, a privately held company that was sold to Noven Pharmaceuticals Inc. in 2007. Mr. Satow is currently a Member of the Board of Directors of Noven Inc. Mr. Satow is a US citizen.

Mr. Claes Wilhelmsson has served as a member of our Supervisory Board since May 2003. He was previously the Executive Director of Research and Development of AstraZeneca plc from 1999 to July 2002, responsible for AstraZeneca's global R&D. He joined Astra in 1985 and held various positions until the company merged with Zeneca in 1999. Prior to working for Astra, he was a lecturer and researcher at the University of Göteborg in Sweden, where he also completed his medical education and PhD. He currently serves on the boards of a number of biotechnology and start-up companies. Dr. Wilhelmsson previously served on the board of AstraZeneca plc. Mr. Wilhelmsson is a Swedish citizen.

Mr. Seán Lance has served as a member of our Supervisory Board since January 2004. Mr. Lance is a former Chairman of Chiron Corporation. He joined Chiron as President and Chief Executive Officer in 1998. From 1985 to 1998 he was employed at Glaxo Holdings where his last position was group Chief Operating Officer and CEO designate. He is a former President of the International Federation

of Pharmaceutical Manufacturers Association. Mr. Lance is a chartered company secretary and administrator and also holds a post-graduate degree in Advanced Financial Management. Mr. Lance is a South African citizen.

Mr. Arnold Hoevenaars has served as a member of our Supervisory Board since June 2005. Mr. Hoevenaars is a chartered accountant in the Netherlands and his previous positions include, among others, Chairman of the Management Board of the Achmea Group; Chairman of the Board of Directors and Chairman/CEO of the Executive Board of Eureka B.V.; and Member of the Management Board and CFO of Royal Boskalis Westminster N.V. Mr. Hoevenaars is a Dutch citizen.

Mr. Steve Davis has served as a member of our Supervisory Board since June 2008. Mr. Davis is a Senior Advisor to McKinsey & Company's Social Sector Office based in Seattle, Washington, US. He is also a Lecturer in Intellectual Property at the University of Washington Law School. He recently served as the Interim CEO of IDRI (Infectious Disease Research Institute) and is now Chairman of its Board of Directors. Previously, Mr. Davis was CEO of Corbis Corporation and presently acts as a senior advisor to the company. He has held positions with the United Nations High Commission for Refugees and several refugee resettlement programs. Currently, he is a member of the Board of Trustees for PATH, a non-profit organization focused on improving public health in the developing world, and the Fred Hutchinson Cancer Research Center, one of the world's leading cancer centers. He also holds board positions with Intrepid Learning Solutions, The Seattle Foundation and Global Partnerships. Mr. Davis holds a Bachelor of Arts from Princeton University, a Master of Arts from the University of Washington and a Doctorate in Law from Columbia University School of Law. Mr. Davis is a US citizen.

Committees

The Supervisory Board appoints from its members an Audit Committee, a Remuneration Committee, a Nomination Committee and a Scientific Advisory Committee. The function of these committees is to advise and assist the Supervisory Board to make decisions.

Audit Committee

Arnold Hoevenaars (chairman) and Seán Lance.

The Audit Committee currently consists of two Supervisory Board members who are independent

within the meaning of the NASDAQ listing rules and the Code. The Company is in the process of recruiting a Supervisory Board member with financial expertise to fill the vacancy in the Audit Committee. The Audit Committee is responsible for, among other things, reviewing our annual and interim reports and accounts and for securing and monitoring our external auditors' involvement in that process. The Audit Committee is the first point of contact of the external auditor when irregularities are found in the contents of the financial reports. Ultimate responsibility for reviewing our Annual Report and interim financial reporting lies with our Supervisory Board. At the request of the Audit Committee, the chairman of the Supervisory Board may be invited to attend its meetings.

Our Audit Committee is in compliance with all of the relevant rules and regulations of the Netherlands. We believe that the members of our Audit Committee have sufficient financial and other experience to perform their responsibilities on the Committee. Mr. A. Hoevenaars is a 'financial expert' as defined in the rules promulgated under the Sarbanes-Oxley Act of 2002.

Remuneration Committee

Phillip Satow (chairman), Claes Wilhelmsson and Jan Oosterveld.

The Remuneration Committee advises on policies and reviews and determines objectives relevant to the compensation of the members of the Management Board and members of the Management Committee. The Remuneration Committee evaluates the performance of members of the Management Board and Management Committee in view of these objectives and advises on the compensation of the members. In advising on short and long-term incentive compensation, the Remuneration Committee considers, among other factors, our financial and commercial performance, scientific performance and progress and any increases in the value of the Company. External compensation survey data available for the biotechnology industry is also used as a benchmark for determining compensation levels. It is the aim of the Remuneration Committee to position the remuneration packages for members of the Management Board and Management Committee at competitive levels. Bonuses are paid to members of the Management Board in connection with achievement of certain objectives set by the Supervisory Board.

CruCell maintains stock option plans whereby the Remuneration Committee may grant options to

employees and members of the Management Board and Supervisory Board as well as non-employees in exchange for consulting services, subject to approval by the shareholders.

In addition, the Remuneration Committee reviews the general compensation and benefit policies for all of our employees.

Nomination Committee

The Nomination Committee consists of all of the Supervisory Board members. This committee (a) draws up selection criteria and appointment procedures for members of the Supervisory Board and the Management Board, (b) periodically assesses the size and composition of the Supervisory Board and the Management Board and makes proposals of nominees to the Supervisory Board, (c) periodically assesses the functioning of individual members of the Supervisory Board and the Management Board, and reports on this to the Supervisory Board and (d) supervises the policy of the Management Board on the selection criteria and appointment procedures for senior management. The committee also makes proposals for appointments of Management Board members to the Supervisory Board.

Scientific Advisory Committee

Claes Wilhelmsson (chairman).

The Scientific Advisory Committee consists of one Supervisory Board member who is independent within the meaning of the NASDAQ listing rules. This committee is responsible for, among other things, reviewing progress in our research and development activities. The committee reports to the Supervisory Board on a regular basis.

Management Board

Our Management Board manages our general affairs and business, under the supervision of our Supervisory Board. Under our articles of association, the Management Board requires prior approval of the Supervisory Board to:

- Expand into a new, or cease an existing, line of business;
- Participate, sell an interest, change its participation, or otherwise take an interest in, or assume the management of, another business enterprise;
- Enter into, terminate or amend any joint venture or pooling arrangement;
- Acquire fixed assets exceeding price limits set by the Supervisory Board; and

- Enter into financial commitments, other than in the ordinary course of business and/ or exceeding price limits set by the Supervisory Board or for longer than a year.

Under Dutch law, in certain circumstances, Management Board actions may require the approval of the General Meeting of Shareholders.

Our Supervisory Board determines the size of our Management Board after consultation with our Chief Executive Officer. The General Meeting of Shareholders appoints the members of our Management Board from a list of candidates nominated by our Supervisory Board. If the list of members contains the names of at least two persons it shall be binding. However, the general meeting of shareholders may at any time, by resolution passed with an absolute majority of the votes cast representing more than one third of the Company's issued capital, resolve that such list shall not be binding. If our Supervisory Board does not nominate anyone for a specific position within three months after a vacancy occurs, our General Meeting of Shareholders can appoint a member at its own discretion. If the Supervisory Board makes a non-binding nomination (i.e., only one nominee is presented to the Supervisory Board for any particular vacancy), then such nomination can only be overturned by a resolution of the General Meeting of Shareholders taken by an absolute majority of the votes cast, representing at least one third of the Company's total issued and outstanding share capital. A member of the Management Board may be appointed or reappointed for a term of not more than four years at a time.

Our Management Board may establish rules governing its internal organization. Our Supervisory Board must approve the adoption of and any changes to these rules. Our Management Board may charge each member of the Management Board with particular duties. The allocation of duties requires the approval of the Supervisory Board. Resolutions of our Management Board are passed by a majority of votes cast, unless provided otherwise in the by-laws of the Management Board. The Management Board shall appoint a Company Secretary who will assist the Management Board. The appointment and dismissal of the Company Secretary requires the approval of the Supervisory Board.

Each member of the Management Board may be suspended or removed by the General Meeting of Shareholders at any time. A resolution to suspend, remove or revoke the suspension of a member of

the Management Board other than at the proposal of the Supervisory Board may only be passed by the General Meeting of Shareholders with an absolute majority of the votes cast representing at least one third of the Company's total issued and outstanding share capital.

Our Supervisory Board may also suspend (but not dismiss) a member of our Management Board. We must hold a General Meeting of Shareholders within three months after a suspension to either terminate or extend it. Any suspension may be extended one or more times, but may not last longer than three months in the aggregate. If at the end of that period no decision has been taken on termination of the suspension, or on removal, the suspension shall cease.

Our Supervisory Board determines the compensation and benefits of the members of our Management Board, based on a proposal by the Remuneration Committee, within the scope of the remuneration policy adopted by the General Meeting of Shareholders. The business address of the members of our Management Board is the same as the address of our principal executive office in Leiden, the Netherlands.

Pursuant to the Code, members of the Management Board are allowed to hold a maximum of two Supervisory Board positions in other listed companies. The members of the Management Board did not hold any such positions in 2008.

The name, date of appointment and position of the members of our Management Board are:

Name/Position	Date of appointment
Ronald Brus Chairman of the Management Board, President and Chief Executive Officer	May 30, 2008
Leonard Kruimer Chief Financial Officer	May 30, 2008
Cees de Jong Chief Operating Officer	May 30, 2008
Jaap Goudsmit Chief Scientific Officer	May 30, 2008

Management Board service contracts

The contracts for the Management Board members have been entered into for an indefinite period and provide for a notice period of up to six months upon termination by us and a notice period of three months upon termination by the individual. Nominations for a seat on the Management Board members are for a period of four years.

A dismissal arising from an unwanted change of control will result in a severance arrangement limited to a maximum of two years' worth of base salaries for the Management Board members.

The contracts of the Management Board members contain non-compete provisions that would apply for a period of one year after the end of their employment with us.

Management Committee

For its day-to-day operations Crucell has established a Management Committee that is responsible for the design, implementation and management of long and short-term strategy under the ultimate responsibility of the Management Board. The Management Board determines the number of members of the Management Committee. Members of the Management Committee are appointed and dismissed by the Management Board, with the approval of our Supervisory Board. The Management Committee generally meets once a month, and works closely with other members of our management. Our Management Board may establish rules governing its relationship with our Management Committee. Our Supervisory Board must approve the adoption of and any changes to these rules.

The following table sets forth the name, age and position of each of the members of our Management Committee:

Name/position	Age
Ronald Brus Chairman of Management Committee, President and Chief Executive Officer	45
Leonard Kruimer Chief Financial Officer	50
Cees de Jong Chief Operating Officer	47
Jaap Goudsmit Chief Scientific Officer	57
René Beukema General Counsel and Corporate Secretary	44
Björn Sjöstrand Chief Business Officer	40
Arthur Lahr Chief Strategy Officer & Executive Vice President Business Development	40

The following paragraphs contain brief biographies of the members of our Management Board and the members of our Management Committee:

Mr. Ronald Brus is chairman of the Management Board and President and Chief Executive Officer since January 2004, and has been a member of our Management Committee since incorporation. He was Executive Vice President, Business Development at IntroGene from 1997 to 2000 and Chief Operating Officer at Crucell from March 2003 until his appointment as President and Chief Executive Officer. From 1994 to 1996, he was product-planning physician at Forest Laboratories (New York) and from 1990 to 1994 he was medical director for Zambon B.V. He holds a medical degree (MD) from the University of Groningen. Mr. Brus is a Dutch citizen.

Mr. Leonard Kruimer became a member of the Management Board in January 2005. He has been our Chief Financial Officer and a member of our Management Committee since incorporation. He held the same position at IntroGene from 1998 to 2000. From 1996 to 1998 he was an independent consultant with companies such as Pepsico and Royal Boskalis Westminster N.V. From 1988 to 1995, he held senior executive positions at Continental Can Europe, GE Capital/TIP Europe and Kwik-Fit Europe B.V. He was a consultant at McKinsey & Co. and has worked with Price Waterhouse & Co. He holds a Masters in Business Administration from the Harvard Business School, a degree from the University of Massachusetts, Amherst, and is a CPA in New York State. Mr. Kruimer is a Dutch citizen.

Mr. Cees de Jong joined Crucell as Chief Operating Officer in 2007. Prior to joining Crucell Mr. De Jong was with Quest International in Naarden, the Netherlands as a member of the Board and responsible for the Flavours Division. Mr. De Jong has also worked as Managing Director of DSM Anti-infectives. In 1989 Mr. De Jong started his career at Gist Brocades, holding a variety of roles in business development, strategy and general management before the company's acquisition by DSM in 1998. Mr. De Jong holds a Medical Degree from the Erasmus University of Rotterdam and an MBA from the RSM Erasmus University.

Mr. Jaap Goudsmit is a member of the Management Board since January 2004. He was Senior Vice President Vaccine Research from September 2001 until July 2002 and member of the Management Committee from July 2002 as Executive Vice President Vaccine R&D. In September 2002 he was appointed Chief Scientific Officer. He chaired the Academic Medical Center of the University of Amsterdam, the Research Institute for Infectious Diseases and the Institute for Science Education. He was the founding Chairman of the Scientific

Advisory Committee of the International AIDS Vaccine Initiative (IAVI) and the founding co-Chairman of the European Vaccine Effort against HIV/AIDS (EuroVac). Since 1989, he has been a professor at the University of Amsterdam and the Academic Medical Center. He holds a medical degree (MD) and a PhD from the University of Amsterdam. Mr. Goudsmit is a Dutch citizen.

Mr. René Beukema has been our General Counsel and Company Secretary since our incorporation. He held the same position at IntroGene from 1999 to 2000. From 1994 to 1999 Mr. Beukema was senior legal counsel for GE Capital/TIP Europe. From 1991 to 1994, he was legal counsel for TNT Express Worldwide N.V. He has a Masters in Law from the University of Amsterdam.

Mr. Arthur Lahr is Crucell's Chief Strategy Officer and Executive Vice President Business Development. He joined Crucell in April 2001 as Executive Director Business Development, was appointed Vice President Business Development in December 2003, a member of the Management Committee in January 2004; Executive Vice President in January 2006; and assumed responsibility for European marketing and sales and company strategy in 2006. From 1994 to 2001, he was a consultant with McKinsey & Co. Prior to that, he worked with Unilever. He holds a Masters in Business Administration from INSEAD and a Masters in Science, Applied Physics, from the University of Delft.

Mr. Björn Sjöstrand joined Crucell in 2007 and is Crucell's Chief Business Officer. He was Chief Executive Officer of SBL Vaccines before it merged with Crucell in November 2006. Mr. Sjöstrand successfully headed the Crucell-SBL integration committee while directing the travel franchise and the Nordic sales force for the Crucell Group. He initiated and led a management buyout of SBL Vaccin AB funded by 3i and SEB Företagsinvest. At SBL, he successfully turned around the company from loss-making to a growth-focused, profit-making company between 2004 and 2006. Between 1999 and 2001, he was Vice President Operations & IT at Active Biotech, where he was also a member of the senior management team. Mr. Sjöstrand completed a Bachelor of Science (BSc) degree in Economics and Business Administration at the University of Örebro. He also studied Financial Investment Theory and Commercial Law at the same university.

Disclosure Committee

The Disclosure Committee is designed to help senior management, particularly the Chief Executive

Officer and Chief Financial Officer, in the maintenance and evaluation of our disclosure controls and procedures. The Disclosure Committee gathers all relevant financial and non-financial information and assesses materiality, timeliness and necessity of disclosure of such information. The Disclosure Committee is comprised of the members of the Management Committee and selected senior managers. Members of the Disclosure Committee have direct access to our external legal counsel and our external auditor. The Disclosure Committee reports to the Chief Executive Officer and Chief Financial Officer.

The Disclosure Committee is an integrated part of our organization and is essential to our internal control over financial reporting. The Disclosure Committee and additional actions taken to further improve disclosure and internal control are intended to help us comply with the requirements of the Sarbanes-Oxley Act of 2002 and regulations promulgated by the Securities and Exchange Commission under that Act.

Remuneration policy for Management Board and Supervisory Board

The Remuneration Committee advised the Supervisory Board in 2008 to make certain changes to the remuneration policy for the Management Board, based on developments in the market as well as recommendations by the Monitoring Commission on Corporate Governance (Commissie Frijns). The main objectives of these changes are to:

- Decrease the complexity of the existing policy; and
- Re-balance the variable components (Short, and Long-Term Incentive bonus) to better reflect the responsibility of the Management Board to achieve both short-term goals and long-term strategy, following market practice.

The Supervisory Board reviewed the changes in the remuneration policy as proposed by the Remuneration Committee. The general meeting of shareholders in 2008 approved the changes in the existing remuneration policy, which took effect in 2008 and are described below.

Remuneration structure

The Management Board members receive fixed remuneration in the form of a base salary as well as performance-based compensation in the form of a short-term incentive plan and a long-term incentive plan.

The incentive for achieving target performance for the Chief Executive Officer equals 115% of base salary (65% in short-term incentive and 50% in long-term incentive). For other Management Board members the incentive is 90% of base salary (50% in short-term incentive and 40% in long-term incentive). For the Chief Executive Officer, this breaks down to 46.5% of salary in fixed compensation and 53.5% of salary in performance-based compensation. For the other three Management Board members, the breakdown is 52.6% fixed compensation compared to 47.4% performance-based compensation.

Base salary

In 2009, the base salary levels of the Management Board have been increased by 3 to 5% in order to keep up with inflation. Each year the Supervisory Board considers whether base salary levels should be adjusted according to external and internal business factors.

Short-term incentive

At the General Meeting of Shareholders in 2008, our shareholders approved the implementation of short-term cash-based incentive plans (STI). The STI bonus is now payable in cash, which is different from the share-based STI bonus in the previous years. In the approved policy, payment of the bonus begins upon 70% achievement of certain milestones. In order to compensate higher achievement of certain milestones, the payment limit was increased from 100% to 130%.

The STI bonus is linked to the achievement of predetermined collective and individual milestones. The collective milestones are based on predetermined annual goals for research, development, business development, finance, intellectual property and corporate legal affairs. We do not disclose specific details of these goals as this is commercially sensitive information. The individual milestones depend on the specific responsibilities of the individual Management Board member. Milestones linked to the STI bonus plan are revised annually and approved by our Supervisory Board.

The table below shows the relative weight of the collective and individual milestones in the STI bonus plan structure:

Management Board	Collective milestones	Individual milestones
CEO, CFO, CSO, COO	70%	30%

The target bonus of the Chief Executive Officer amounts to 65% of base salary and for the Chief Financial Officer, Chief Operational Officer and Chief Scientific Officer a target bonus of 50% of base salary is applicable. The bonus can be increased with a maximum of 30% in the event performance exceeds expectations to a considerable extent. The Supervisory Board has the discretionary power to increase or decrease the bonus by 25%.

Long-term incentive

At the General Meeting of Shareholders in 2008, our shareholders approved certain proposed changes in the long-term incentive (LTI) plan. The main changes in the LTI plan are as follows:

- Shift from payment in shares to payment in conditionally granted options; and
- Reduction of complexity by removing the circuit breaker and the ranking of the Company on Total Shareholder Return (TSR) in the Goldman Sachs European Biotech Index as performance indicators.

Target LTI compensation levels amount to 50% of base salary for the Chief Executive Officer and 40% for the other Management Board members. The LTI compensation can be increased up to 200% of the target award when achieving maximum performance.

Under the terms of the LTI plan, options are conditionally granted and vest at the end of a four-year performance period. The number of LTI options that vests depends on the fulfilment of the LTI performance condition.

On a vesting date CruCell's Total Shareholder Return (TSR) performance is measured against the performance of the NASDAQ Biotechnology Index during the applicable performance period. The positive difference in percentages, if any, between CruCell's TSR compared to the performance of the NASDAQ Biotechnology Index, determines the number of LTI options which vest, in accordance with the table set out opposite:

NASDAQ Biotech Index Vesting Scheme

Positive difference between TSR performance Crucell and the NASDAQ Biotech Index	Vesting as % of target award
≥ 50	200%
≥ 35 and < 50	150%
≥ 20 and < 35	100%
≥ 10 and < 20	50%
≥ 0 and < 10	25%
< 0	0%

Ad-hoc option grant

At the General Meeting of Shareholders in 2008 the shareholders of the Company approved an additional one-off stock option grant to members of the Management Board. The objective of the additional option grant is to increase the alignment of interests of shareholders and the Management Board and to provide an extra retention incentive.

In total, 800,000 additional options were granted to the members of the Management Board and these options were allocated as follows: the CEO received 300,000 options, the Chief Operational Officer 200,000 and the other Management Board members 150,000.

The options are conditionally granted and vest at the end of a three-year performance period. The options are granted conditionally as they include a predetermined performance condition. The performance condition is a TSR of at least 50% as of the vesting date.

Pension

At the beginning of our 2005 fiscal year a new pension plan for our Management Board was introduced. The plan is a defined contribution plan, with a pensionable age of 65 years. The employee contribution is set at 7% of the pensionable salary (base pay minus an offset). The table below outlines the annual contribution rates, including the employee contribution. The risk premium for the survivor's pension is financed separately by the employer.

Total contribution rates for our Management Board members are:

Age	Contribution rate
25 to 30	8.4%
30 to 35	10.2%
35 to 40	12.5%
40 to 45	15.2%
45 to 50	18.7%
50 to 55	23.0%
55 to 60	28.6%
60 to 65	36.1%

Shareholdings of the Management and Supervisory Boards

As of April 17, 2009 members of our Management Board and Supervisory Board held the following ordinary shares and options.

Name of Holder	Ordinary shares held per April 17, 2009	Options held per April 17, 2009	Year of expiration	Exercise price (€)
R.H.P. Brus	239,202	200,000	2011	3.49
		90,000	2011	2.64
		125,000	2011	5.94
		300,000	2013	12.23
L. Kruimer	28,195	36,170	2016	10.82
		30,000	2011	3.49
		125,000	2011	5.94
		150,000	2013	12.23
C. de Jong	2,406	19,490	2016	10.82
		185,000	2012	14.58
		200,000	2013	12.23
		20,655	2016	10.82
J. Goudsmit	169,276	125,000	2011	5.94
		150,000	2013	12.23
		23,388	2016	10.82
		Totals	439,079	1,779,703
J.P. Oosterveld	12,000	10,000	2009	8.81
		10,000	2009	11.55
S.P. Lance	12,500	10,000	2011	7.86
		10,000	2009	11.55
P.M. Satow	66,300	10,000	2009	11.55
		22,000	2011	3.49
		10,000	2011	6.48
		10,000	2009	11.55
C.E. Wilhelmsson	10,000	10,000	2011	6.48
		10,000	2009	8.81
A. Hoevenaars	10,000	5,000	2009	8.81
		10,000	2009	11.55
S. Davis	5,000	–	–	–
Totals	115,800	117,000		

During the period December 31, 2008 and April 17, 2009, a number of 250,000 options with an exercise price of € 9.4 were exercised by Ronald Brus and 85,000 options were exercised by Jaap Goudsmit with an exercise price of € 9.4. There were no other changes in the number of options held by members of the Management Board or Supervisory Board.

For additional details on remuneration of members of the Management and Supervisory Boards reference is made to note 5.23 'Related parties' in the financial statements.

Principal accountant fees and services

Deloitte Accountants B.V. audited the accompanying consolidated balance sheets of Crucell N.V. and subsidiaries (the 'Group') as of December 31, 2008 and 2007 and the related consolidated income statements, shareholders' equity, and cash flows for the years then ended.

The Sarbanes-Oxley Act of 2002 requires that Audit Committees pre-approve all services provided by the Company's external auditor. This process is critical to the auditor maintaining independence. Our process requires that all services provided by the external auditor are pre-approved by the Audit Committee.

During 2008 and 2007, we paid the following amounts to our external auditors for audit services, audit related services and tax services.

Year ended December 31,	2008	2007
Audit fees	840	904
Audit related fees	75	64
Fees for services related to Consultations on tax matters	—	—
Total	915	968

Audit fees include fees associated with the annual audit, interim reviews, required statutory audits and services that only the external auditor can reasonably provide, such as services associated with documents issued in connection with securities offerings.

Audit-related fees include accounting consultations on financial and accounting reporting standards.

Responsibility statement

Crucell's Management Board, as required by section 5.25c paragraph 2c of the Dutch Act on Financial Supervision (Wet op het Financieel Toezicht), confirms that to the best of their knowledge:

- The financial statements of 2008 give a true and fair view of the assets, liabilities, financial position and the profit or loss of the Group;
- The Annual Report gives a true and fair view of the Group's position and the state of affairs as per December 31, 2008; and
- The Annual Report contains a description of the material risk factors that the Group faces.

Controls and procedures

Internal risk management and control system

Crucell's Management Board is responsible for designing, implementing and operating the Company's internal risk management and control systems. The purpose of these systems is to manage in an effective and efficient manner the significant risks to which the Company is exposed. Crucell's internal and risk management and control systems with respect to financial reporting are in line with the guidance set forth in the COSO model, an integrated internal control framework established by the Committee of Sponsoring Organizations of the Treadway Commission. The Company's internal risk management and control systems are designed

to provide reasonable assurance that strategic objectives can be met. Such systems can never provide absolute assurance regarding achievement of Company objectives, nor can they provide an absolute assurance that material errors, losses, fraud, and the violation of laws or regulations will not occur. A summary of the risks that could prevent Crucell from realizing its objectives is included in the section 'Risk Factors' of this report.

Our internal risk management and control systems make use of various measures including:

- Annual strategic evaluations of our business;
- Periodic operational review meetings of the Management Board with the Management Committee;
- Quarterly financial planning meetings of the Management Board with the Supervisory Board;
- A planning and control cycle consisting of annual, quarterly and monthly procedures, including subsequent follow-up on achievements of targets set;
- Advice of Crucell's Disclosure Committee to our Chief Executive Officer and Chief Financial Officer with respect to the timely review, disclosure and evaluation of periodical (financial) reports as well as with respect to the maintenance and evaluation of disclosure controls and procedures;
- Letters of representation that are signed by selected key-management members on a quarterly basis in which they confirm that for their area of responsibility based upon their knowledge:
 - An effective system of internal controls and procedures is maintained; and
 - The financial reports fairly present the financial position, results of operations and cash flows;
- Management letters and audit reports provided by our external auditor;
- Crucell's standardized and formalized working practices, including the Biological Safety Manual which was developed in-house to meet the specific needs of Crucell's working environment; and
- The Code of Conduct of Crucell.

The Management Board has discussed the internal risk management and control system with the Audit Committee and the Supervisory Board.

As a result of its listing at NASDAQ, Crucell is also obliged to comply with Section 404 of the Sarbanes-

Oxley Act of 2002 and related regulations (Section 404). Section 404 addresses the responsibility of the Management Board for establishing and maintaining an adequate system of internal control over financial reporting. Internal control over financial reporting is a process to provide reasonable assurance regarding the reliability of our public financial reporting.

Evaluation of disclosure controls and procedures

We have evaluated, with the participation of our Chief Executive Officer and Chief Financial Officer, the effectiveness of our disclosure controls and procedures as of December 31, 2008. There are inherent limitations to the effectiveness of any system of disclosure controls and procedures, including the possibility of human error and the circumvention or overriding of the controls and procedures. Accordingly, even effective disclosure controls and procedures can only provide reasonable assurance of achieving their control objectives. Based upon our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that the disclosure controls and procedures as of December 31, 2008 were effective to provide reasonable assurance that information required to be disclosed in the reports we file or submit under the US Securities Exchange Act of 1934, as amended, is recorded, processed, summarized and reported, within the time periods specified in the applicable rules and forms, and that it is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate to allow timely decisions regarding required disclosure.

Management's Report on Internal Control over Financial Reporting

Management of the Company is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the US Securities Exchange Act of 1934. The Company's internal control over financial reporting is designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. The Company's internal control over financial reporting includes those policies and procedures that:

- Pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect

the transactions and disposition of the assets of the Company;

- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the Company are being made only by authorized employees in accordance with documented authorizations; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of the Company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness for future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with policies or procedures may deteriorate.

As required by Section 404 of the Sarbanes-Oxley Act of 2002, Management assessed the effectiveness of the Company's internal control over financial reporting as of December 31, 2008. In making this assessment, Management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control-Integrated Framework.

Based on its assessment and those criteria, Management concluded that the Company maintained effective internal control over financial reporting as of December 31, 2008.

Deloitte Accountants B.V., the independent registered public accounting firm that audited the financial statements included in this Annual Report, has issued an attestation report on the effectiveness of the Company's internal control over financial reporting as of December 31, 2008 as stated in their report beginning on page 116 of this report.

Changes in internal control over financial reporting

There has not been any change in the internal controls over financial reporting of the Company that occurred during the period covered by this report that has materially affected, or is reasonably likely to materially affect, such internal controls over financial reporting.