

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.