Information on the Company

We are a public limited liability company incorporated in Leiden, the Netherlands with the legal and commercial name Crucell N.V., 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 agent in the U.S. is CT Corporation, 111 Eighth Avenue, New York, New York 10011.

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, the fully-liquid vaccine for protection against five important childhood diseases; Hepavax-Gene, the recombinant vaccine against hepatitis B; Epaxal, the only aluminium-free hepatitis A vaccine; Vivotif, the only oral anti-typhoid vaccine; Dukoral, the only internationally licensed oral vaccine with documented efficacy against diarrhea caused by cholera; and Inflexal V, the virosomal adjuvanted influenza vaccine for all age groups. We have manufacturing facilities in the Netherlands, Switzerland, Korea, Spain and Sweden.

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

We believe that each of our selected products either targets unmet medical needs, improves current medications, or is perceived as a marketable product due to predictive study models and/or perceived favourable 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 leads.

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, ebola, HIV, malaria, tuberculosis, human monoclonal antibodies against rabies, H5N1 antibodies, pandemic influenza virus. Our R&D activities are concentrated in our headquarters in the Netherlands. Product development is concentrated in our Swiss operations in Bern. Our R&D facilities are located in the Netherlands, Switzerland, Korea and Sweden.

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 we have 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 exposed to seasonal variations, and the majority of our sales are made 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, but also our travel vaccines are subject to seasonal travel patterns.

Vaccine markets

Our core product portfolio currently consists of six marketed vaccines in three leading segments of the vaccine market: paediatric vaccines, travel vaccines and respiratory vaccines.

Paediatric vaccines

Our core paediatric vaccines are Quinvaxem and Hepavax-Gene.

Quinvaxem

On March 27, 2006 the Korea Food and Drug Administration (KFDA) awarded a licence to Quinvaxem, a fully liquid pentavalent (five-component) vaccine we produce in Korea. Following WHO prequalification in September 2006, Quinvaxem was made available to supranational purchasing organizations. Supranational organizations are major customers for combination vaccines, which are used in large vaccination programs. Quinvaxem combines antigens for protection against five deadly 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 to reach the market, offering a clear advantage in terms of convenience of use. Quinvaxem was co-developed with Novartis (formerly Chiron), which provides four of the five components as bulk.

In December 2006 we were awarded contracts totalling over $ 230 million for our Quinvaxem and Hepavax-Gene paediatric vaccines by supranational organizations. The contracts provide for the supply of these vaccines through 2009, with the awarded amount growing over those three years. In addition, a Latin American supranational organization ordered 7 million doses of Quinvaxem, which we will deliver in 2008.

Hepavax-Gene

Hepavax-Gene is a Hansenula polymorpha-based recombinant hepatitis B vaccine. Since its launch in 1996, more than 590 million doses of Hepavax-Gene have been commercially distributed in more than 90 countries, making it the third most used hepatitis B vaccine in the world. A key competitive advantage for Hepavax-Gene is our stable and efficient production system. The vaccine is produced in Korea.

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, and the exchange of body fluids between an infected mother and a new-born baby during birth.

Market researcher Datamonitor assesses the HBV drugs market at $ 431 million in 2006 across seven major markets and expects the market to nearly triple in size by 2016. Data monitor predicts rapid growth until 2011 that will slow down in the following years as a result of the introduction of generics and the impact of routine HBV vaccination.

The key participants in the HBV market for the developed world are GSK and Merck & Co. Main competitors for sales to supranational organizations are LG, Shanta and SII.

Travel and endemic vaccines

Our core travel vaccines are Epaxal, Vivotif and Dukoral.

Travel vaccines include all vaccine products that protect against diseases which are not native to the region travelers are from but are present in the regions they travel to. 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 endimicity could also be characterized as routine or paediatric vaccination. Furthermore, even in some European countries where endemicity is low, childhood vaccination against Hepatitis A is recommended. Use of vaccines in this manner represents a large potential upside for vaccine manufacturers as these vaccines are not restricted to travel vaccination,

but are also applied in other vaccine markets. Our HAV vaccine Epaxal may be used this way.

Epaxal
Epaxal is the only virosome-adjuvanted vaccine for hepatitis A (HAV). The vaccine has a superior tolerability thanks to the virosomal technology replacing aluminium. The virosome has a unique mechanism of action and mimics the natural process. No aluminium or thiomersal has to be added, resulting in the only bio-degradable HAV vaccine in the world. The vaccine is highly effective, offering protective immunity within a few days following the first dose and, following the second (booster) dose, providing immunity for up to 20 years. The product is currently licensed in more than 40 countries world-wide under the brand names Epaxal and HAVpur and in most of these countries is licensed for adults and children over the age of one year. We currently market Epaxal for HAV in Europe, Latin America and Asia.

The paediatric dose of Epaxal (Epaxal Junior) showed in a Phase III study to be effective in combination with other children's vaccines, providing immediate and long lasting protection. The product's registration dossier has been filed with the Swiss Health Authorities and has been approved. The product is currently under registration in selected countries.

HAV is a highly contagious infection that causes acute inflammation of the liver. HAV is generally contracted orally through and is considered the least dangerous form of hepatitis because it does not lead to chronic inflammation of the liver. HAV commonly spreads through improper handling of food, contact with household members, sharing toys at day-care centres, and eating raw shellfish taken from polluted waters.

The key participants in the HAV market are GSK, Merck and sanofi pasteur. In addition, GSK markets Twinrix, a combination vaccine for HAV and HBV, while sanofi pasteur and GSK have introduced combination vaccines for HAV and typhoid fever.

Vivotif
Vivotif is a live attenuated typhoid fever vaccine administered orally. It is the only oral vaccine indicated for use against salmonella typhi, the most prevalent of the typhoid fever-causing bacteria. Vivotif consists of a live strain of salmonella typhi that has been altered so that it stimulates an immune response, but not the disease. The bacteria are enclosed in coated capsules that dissolve in the intestines, releasing the live organism. Vivotif exhibits high tolerability and efficacy. Vivotif has an stablished track-record for safety, having been on the market for over 20 years. The vaccine is indicated for adults and children over the age of five. Vivotif is currently licensed in 44 countries, including the U.S. Recent results suggest that Vivotif may be unique in also protecting against salmonella paratyphi, a similar but milder variant of typhoid.

Typhoid fever is a debilitating and life-threatening illness caused by the bacteria salmonella typhi. Symptoms of typhoid fever include fever, stomach pains, weight loss, loss of appetite, delirium, severe diarrhea (in children) and constipation (in adults). A similar but generally milder disease is paratyphoid fever, which is caused by any of three serotypes of salmonella paratyphi, A, B and C.

Typhoid fever is transmitted by faecal contamination of food or water, or by person to person contact. Approximately 17 million people worldwide develop typhoid fever each year and approximately 4% of patients with typhoid fever die. The disease is endemic to Africa, Asia (except Japan) and Latin America.

The key participants in the typhoid market are sanofi pasteur and GSK, with their injected vaccine products TyphimVi and Typherix respectively.

Dukoral
Dukoral is an oral vaccine that protects against cholera and the enterotoxigenic Escherichia coli (ETEC) and is registered in more than 50 countries excluding the U.S.. Dukoral is also registered in many of those countries (excluding the European Union and Australia) to protect against ETEC, which is the main cause of travelers' diarrhea. The vaccine is indicated for immunisation against disease caused by vibrio cholerae in adults and children from two years of age who will be visiting endemic/epidemic areas. Dukoral acts by inducing antibodies against both the bacterial components and cholera toxin (CTB).

Cholera is an acute, diarrheal illness caused by infection of the intestine with the bacterium vibrio cholerae. The infection is often mild or without symptoms, but sometimes it can be severe. 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 Centers for Disease Control and Prevention cholera has been very rare in industrialized nations for the last 100 years; however, the disease is still common today in other parts of the world, including the Indian subcontinent and sub-Saharan Africa.

There is no other cholera and ETEC combination vaccine in the world except for Dukoral. Regarding the cholera indication there is no competition in the developed world. There are some cholera vaccines produced locally in the developing world.

Respiratory vaccines

Our core respiratory vaccine is Inflexal V.

Inflexal V
Inflexal V is a virosome-adjuvanted influenza vaccine administered by injection. Due to our virosome technology, the vaccine has a high tolerability. In addition, it has a good immunogenicity profile, making it particularly effective with high-risk patients, such as the elderly, in whom the immune response is generally weaker. Inflexal V was originally introduced in 1997 and was successfully registered through the Mutual Recognition procedure in most European markets in October 2001. The vaccine is currently registered in 43 countries.

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, following infection, the incubation period ranges from one to three days.

The influenza vaccine market is one of the fastest growing vaccine markets. Global sales of influenza vaccine are, according to market research (BCC Research) expected to grow from an estimated $ 2.9 billion in 2005 to $ 7.1 billion in 2010, with average annual growth estimated at 20%.

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 vaccine markets.

The key participants in the market are sanofi pasteur, GlaxoSmithKline (GSK), Novartis and Solvay. Fluad, Novartis' adjuvant flu vaccine, is the main direct competitor of Inflexal V, our influenza product.

Complementary vaccines

Our core vaccines business also includes a range of vaccines for special indications that we offer in our key markets. The company has distribution rights for various vaccines, including Avaxim, Pneumo 23, Stamaril, Gardasil, MMR II, Pentavac and Vaxigrip by sanofi pasteur MSD, Influvac by Solvay Pharma, and Encepur by Novartis' Vaccines. See also 'Marketing and sales partners' in this section.

Protein products

In the field of proteins, the Company entered into two distribution agreements in 2007.

Prolastin
Since April 2007, we act as the exclusive distributor of Talecris' Prolastin in nine Western European countries. Prolastin is a therapeutic protein, indicated for chronic augmentation therapy of individuals having hereditary deficiency of alpha-1 proteinase inhibitor. Proteinase inhibitor treatments are currently sold across Europe and North America.

Cofact
In November 2007 the Company announced the start of a marketing and distribution agreement with Sanquin, the Dutch Blood Supply Foundation. The Company has the exclusive distribution rights of Cofact-Sanquin's prothrombin complex of blood factors II, VII, IX and X which is currently in a mutual recognition procedure (MRP) registration, which we expect to be completed in 2009, in a number of Crucell's key markets including Norway, Sweden, Denmark, Spain and Italy. Crucell will also have a

right of first refusal for China, Korea and a number of Eastern European countries. Cofact is a market leading product in the Netherlands and Belgium with approximately € 10 million in sales annually in these countries alone. Cofact is aimed at promoting blood-clotting for patients treated with anti-coagulants that have bleeding as a result of trauma or urgent surgery, or for prophylacticly treating patients with Factor II, VII and X deficiencies.

Research and Development pipeline

Overview

Our product development programs comprise vaccines against yellow fever, influenza, ebola, HIV, malaria, tuberculosis, human monoclonal antibodies against rabies, H5N1 antibodies, pandemic influenza virus as well as blood coagulation factors.

Overview of our late-stage pipeline

Yellow fever vaccine
Yellow fever is an infectious disease transmitted by mosquitoes, prevalent in tropical regions of Africa and South and Central America. Approximately 200,000 cases and 30,000 fatalities occur each year. Endemic areas have increased over the past 20 years. Also there is a worldwide shortage in the supply of yellow fever vaccines. Since 1963, one of the most reliable vaccines against yellow fever has been produced by the Robert Koch Institute in Berlin. Over 2.5 million doses of the vaccine have been distributed. The vaccine is safe, highly immunogenic and well tolerated. Protection starts from ten days after a single dose and persists for ten years. In 1999 we acquired the rights and know-how for this vaccine from the Robert Koch Institute. Given the successful sales of the MoRu-Viraten vaccine for measles/rubella, to avoid capacity constraints in the production of MoRu-Viraten, we decided to postpone the registration submission of the yellow fever vaccine in Switzerland.

Overview of our early-stage 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 in the future enter into collaborative and/or strategic alliance arrangements with third parties to co-develop and market products that we may develop.

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:

- PER.C6 – An influenza vaccine, in collaboration with sanofi pasteur is being developed using our PER.C6 technology.
- PER.C6 and AdVac – Our ebola, malaria and TB vaccines candidates are recombinant vaccines based on PER.C6 technology that also use AdVac technologies.
- PER.C6 and MAbstract – Our candidate rabies and H5N1 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.

A short description of our main potential products in the early-stage pipeline, and the diseases those products target, follows:

Influenza
Each year approximately 10%-20% 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.

Influenza vaccines are 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 easily scalable, permitting the production of cost-efficient vaccines in large quantities. PER.C6 cells possessing the different receptors required for the production of both human strains and the avian strains that may present a pandemic threat can produce all influenza strains.

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 GMP master cell bank already completed. Currently, we are working to develop a pandemic flu vaccine as well as an interpandemic, or seasonal, flu vaccine under this contract. A Phase II testing of the cell culture-based seasonal influenza vaccine was initiated in the U.S. and started in the fourth quarter of 2007. The Phase II trials, which involve healthy adult volunteers, will focus further on the safety profile and immunogenicity of the cell-based vaccine. Submission is planned for 2010.

H7N1/FLUPAN
A collaborative research project by research institutions, universities and our partner sanofi pasteur, funded by the European Commission, began a Phase I clinical trial for a pandemic flu vaccine with 60 healthy adults in Norway. The trial is the first to assess safety and ability to generate an immune response of a split, inactivated pandemic H7N1 vaccine produced on our PER.C6 cells.

H9N2
We have proprietary virosomal subunit technology which we also license to third parties. In May 2006 we commenced a large clinical trial aimed at assessing the safety, tolerability and immunogenicity of different dosages of H9N2 vaccines formulated as whole virus vaccine, alum-adjuvated whole virus vaccine, and virosomal adjuvanted subunit vaccine in healthy volunteers. In this H9N2 pandemic vaccination study, that has been completed in Q4 2007, all formulations were well tolerated in high dosages. For all vaccine formulations and ages a dose response relation was seen after the first and second dose.

Tuberculosis
Mycobacterium tuberculosis (TB) represents one of the most prevalent infectious diseases throughout the world. It is estimated that 2 billion people are infected with TB, representing a third of the world's population. Each year sees 8 million new cases and 2 million deaths as a result of the disease according to the World Health Organization.

TB is spread when people who have the active form of the disease cough or sneeze and people nearby breathe in these bacteria and become infected. Only 5-10% of infected but otherwise healthy people develop an active TB disease. Most people who carry the bacteria suffer no obvious symptoms and cannot pass on the disease to others during this latent phase of the infection. But if the immune system is weakened, active TB disease can occur. This occurs most in people infected with HIV/AIDS, which severely weakens the immune system.

The increased incidence of TB is a consequence of the spread of HIV/AIDS, the emergence of multi drug resistant strains of TB and variability in protective efficacy of the only currently available vaccine, Bacillus Calmette-Guérin (BCG). Although the BCG vaccine offers protection against the most serious forms of TB in childhood, its efficacy wanes over a period of 10-15 years after the vaccination. A need for an alternative vaccination approach has emerged in the last two decades.

In March 2004 we announced a new collaboration with the Aeras Global TB Vaccine Foundation on the pre-clinical and clinical development of candidate TB vaccines, called AERAS-402. The Crucell-Aeras TB vaccine program is focusing on improvement of BCG, using our PER.C6 and AdVac technologies. We began Phase 1 clinical trials of the AdVac-based tuberculosis vaccine in the fourth quarter of 2006. The trial is an open-label study that is testing the vaccine in a dose-escalation trial involving 32 healthy volunteers. The trial is funded and managed by Aeras. The main parameters under examination are safety, tolerability and immunogenicity. The Phase I clinical trial indicated that the vaccine candidate is safe in healthy adults. A second study in progress in healthy adults in South Africa appears to be showing safety, tolerability and immunogenicity of AERAS-402.

In December 2007 Aeras and Crucell announced the start of a tuberculosis vaccine clinical trial in the U.S. Crucell will receive up to $ 5 million from Aeras to support the advanced development of the candidate AdVac- and PER.C6 technology based tuberculosis vaccine. Crucell and Aeras also announced the launch of a new Phase I BCG-Ad35 prime boost clinical trial of the AdVac-based tuberculosis vaccine. This trial will be conducted in St. Louis, Missouri, U.S.. The main parameters under examination in the trial will be the immunogenicity and safety of BCG prime followed by two AERAS-402 boost doses administered at three to six month intervals after BCG in healthy adults. The trial will be conducted as double-blind, randomized, placebo-controlled study in 32 healthy adult volunteers.

Ebola

Ebola fever is one of the most lethal viral diseases, with a mortality ranging from 50% to 90% according to the World Health Organization. Ebola outbreaks occur regularly in tropical Africa, affecting both human and great ape populations. To date, approximately 2,000 cases have been reported since the virus was first discovered in 1976. The ebola virus belongs to the group of 'hemorrhagic fever viruses', which also includes the highly pathogenic Marburg and Lassa viruses. Ebola virus causes a disease characterized by high fever and massive internal bleeding. Because no vaccine or therapy is presently available, ebola virus is on the Centers for Disease Control (CDC), National Institutes of Allergy and Infectious Diseases (NIAID), and U.S. Department of Defense Category 'A' list of bioterror agents. In 2003 the U.S. government announced that once available, an ebola vaccine may be stockpiled as part of its preparedness for bio-terror attacks under Project BioShield, a comprehensive effort to develop and make available modern, effective drugs and vaccines to protect against attack by biological and chemical weapons.

In May 2002 we entered into a Collaborative Research and Development Agreement (CRADA) with the VRC to develop jointly, 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. The recombinant vaccine will encompass the glycoproteins and the nucleoprotein of ebola virus, but cannot replicate in humans. This method thus provides a very important safety advantage, while ensuring that a strong humoral and cellular immune response is elicited against the ebola virus.

In March 2005 we extended the CRADA with the U.S. National Institutes of Health (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 experiments conducted by the VRC together with the U.S. Army Medical Research Institute of Infectious Diseases (U.S.MRIID) 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. All pre-clinical material was produced at our FDA-compliant production facilities in Leiden.

Phase I clinical testing commenced in the third quarter of 2006. In the randomized, double-blind, placebo-controlled study in 48 healthy volunteers the single-shot vaccine is being tested in a dose-escalation trial. The start of the trial follows the successful completion of the Investigational New Drug (IND) application process required by the Food and Drug Administration (FDA). The Phase I study is being carried out by the VRC at the NIH Clinical Center in Bethesda, Maryland and was ongoing at year-end 2007.

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 one of today's top three killers among 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 one to three 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.

Currently there is no commercially available vaccine to protect against malaria. Our candidate malaria vaccine is based on our AdVac technology and produced using our PER.C6 technology. 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 a collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), part of NIH for the support of the development of our candidate malaria vaccine. In September 2006, we extended the collaboration with the NIAID by signing a clinical trial agreement. The clinical trial started in January 2007 and is a randomized, double-blind, placebo-controlled study that will test the vaccine in a dose-escalation trial involving 96 healthy volunteers. The Phase I trial is funded by NIAID and conducted by researchers at Vanderbilt University, one of NIAID's Vaccine and Treatment Evaluation Units.

HIV
In August 2005, Crucell along with Harvard Medical School, was awarded a $ 19.2 million grant by U.S. National Institutes of Health (NIH) to develop new adenovirus vector-based vaccines against HIV/AIDS. Having entered into an agreement in early 2004, Crucell and the International AIDS Vaccine Initiative (IAVI) jointly announced November 2004 that they had signed an agreement whereby Crucell would develop AdVac vectors for use in IAVI's AIDS vaccine development program. The Investigational New Drug Application (IND) for Phase I of the trial with Harvard Medical School (supported by the NIH) has been approved by the FDA in January 2008. The trial started in the first quarter of 2008.

West Nile virus vaccine development terminated
In June 2003, we announced our decision to develop a vaccine against the West Nile virus based on our PER.C6 technology. We completed the Phase I safety study with our whole inactivated West Nile vaccine manufactured using PER.C6 technology in January 2007. The Phase I trial demonstrated safety and tolerability. However, in January 2008, we terminated the West Nile Virus Vaccine program as well as our development of human monoclonal antibodies for therapeutic use against West Nile. The commercial and market opportunities for the West Nile Virus have proven to be less then originally anticipated, making the commercial and market opportunities for potential West Nile products not as attractive as other products in our pipeline.

Proteins

Rabies monoclonal antibody cocktail
Rabies is a viral disease of mammals most often transmitted through the bite of a rabid animal. The virus infects the central nervous system, causing encephalopathy and ultimately death if medical treatment is not sought before symptoms appear. 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.

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 affected countries such as India and China grow in affluence.

We have developed a human monoclonal antibody in collaboration with the Thomas Jefferson University (TJU) based in Philadelphia and the U.S. CDC in Atlanta, using MAbstract and PER.C6 technology. The product is a combination of two monoclonal antibodies for the post-exposure prophylaxis of rabies, produced using our MAbstract and PER.C6 technology. Our candidate vaccine demonstrated protection at least equivalent to HRIG in pre-clinical trials. In the fourth quarter of 2006, we began a Phase I clinical study in the U.S., followed by a second Phase I study in India, selected because it is a rabies endemic country.

The 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. The program has been granted a Fast Track designation by the U.S. FDA. Phase II clinical trials began in the U.S. in March 2008.

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 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, co-exclusive distribution rights in China and the rights to sell to supranational organizations such as UNICEF. We received an up-front payment of € 10 million and will be eligible for milestone payments of up to € 66.5 million and additional royalties on products sold.

H5N1 avian influenza antibodies

The Company discovered a set of human monoclonal antibodies that protect against avian influenza (H5N1). These were found to be able to neutralize a broad range of H5N1 viruses of avian influenza that have emerged between 1997 and 2004, which currently presents a global threat. These antibodies may therefore provide a powerful tool in pandemic preparedness.

The set of monoclonal antibodies, which Crucell researchers discovered using MAbstract phage display, showed the potential to neutralize distinct H5N1 viruses. The most potent neutralizing antibody was tested in pre-clinical models for the ability to protect against infection from the highly pathogenic A/Hong Kong/97 H5N1 virus and was also tested for its ability to stop the development of the disease caused by this virus. When the monoclonal antibody was given in a pre-clinical model, one day prior to infection with the H5N1 virus, it resulted in full protection against infection. Treatment with the antibody up to three days after infection resulted in 100% survival and cure of the disease.

Recombinant antibody Factor VL/C

Our research program into the recombinant antibody Factor VL/C, as a potential therapy to stop or prevent serious bleeding, has proven to be more challenging than previously anticipated and pre-clinical research provided mixed results and insufficient evidence of the protective benefit of Factor VL/C as a stand-alone therapeutic product. We do no expect to bring the program into clinical trials in the foreseeable future and the research and development expenditure previously earmarked for this program has now largely been allocated to the research and development of monoclonal antibodies in other disease areas.

Technologies

Proprietary technologies

Our product portfolio is supported through a range of proprietary technology platforms. Our core proprietary technologies are classified as follows:

PER.C6 technology: our core proprietary technology. With over 40 licenses issued, the PER.C6 technology is used widely for the development and manufacturing of vaccines, recombinant proteins including monoclonal antibodies, and gene therapy products.

Vaccine technology: we employ a number of proprietary technologies to develop vaccines against viruses, parasites and bacteria.

Protein technology: we employ a number of other proprietary technologies to develop or manufacture monoclonal antibody products, such as MAbstract and STAR.

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.

As at year-end 2007 we employ 11 (2006: 13) people in our business development operations in the Netherlands and an additional 3 (2006: 2) in the U.S. Our business development strategy has historically involved contacting prospective licensees and partners, 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.

PER.C6 technology

Overview

Our PER.C6 technology provides a manufacturing system that consists of a human cell line that can be used to produce a variety of biopharmaceutical products. We developed the PER.C6 technology from a single source of healthy human retina cells. To obtain the PER.C6 cell line, we inserted an exactly defined fragment of the E1 region of the genome of the adenovirus type 5 into the human retina cell so that the cell can propagate indefinitely. The technology has been successfully adapted to grow without the need for serum components or materials that allow cell attachment (microcarriers) and demonstrates excellent cell densities in bioreactors. These features are important because they allow us to produce safe biopharmaceutical products in sufficient quantities.

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 subunit vaccine.
- 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, which is the PER.C6 Development Center joint venture between us and DSM. PERCIVIA is located in Cambridge, Massachusetts, U.S..

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 human 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:

High yields
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.

Scalability in serum-free conditions
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.

Biologics Master File at the FDA
We have filed a Cell Substrate Biologics Master File (BMF) with the U.S. 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 our licensees or we produce using the PER.C6 technology.

Broad industry endorsement
The PER.C6 technology can now claim to have achieved a broad endorsement within the industry. For a total overview of all licensees reference is made to the 'Overview Licensees and Partners' in this section.

Human-based
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.

Vaccine technologies

As a leading vaccine company, Crucell focuses on developing, producing and marketing vaccines against a wide variety of infectious diseases applying a broad portfolio of technologies in order to meet the specific demands posed by the different pathogens including viruses, parasites and bacteria.

Crucell's vaccine technologies include:

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 adenovirus vectors that do not regularly occur in the human population, such as Ad35. The technology supports the practice of inserting DNA coding for 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 fever (ebola, Lassa, Marburg), malaria (Plasmodium falciparum), tuberculosis (Mycobacterium tuberculosis), AIDS (HIV) and hepatitis C (HCV). While no adenovirus-based recombinant vaccines are currently licensed for human use, AdVac-based vaccines for malaria, AIDS, hepatitis C, hemorrhagic fevers, and tuberculosis 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.
- 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.

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 aluminium 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 offer a tool for developing novel, predominantly synthetic vaccines applicable for 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 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.
- Virosome technology is used in the manufacture of several of Crucell's registered products and as such has an excellent safety record and manufacturing know-how.

Hansenula polymorpha

Overview

The yeast expression technology Hansenula polymorpha provides us with a highly efficient production technology for protein, 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.
- Hansenula polymorpha is easy with regard to genetic manipulation and robust in industrial scale fermentations.

Recombinant Cholera Toxin B subunit technology

CTB, Cholera Toxin B subunit 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 have been shown to be effective i.e. CTB has exerted an adjuvant effect. 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 feeding of antigen coupled to CTB suppress peripheral T-cell reactivity to the coupled antigen. The Company 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 toxic A-subunit.

Protein technologies

We have two main technologies for proteins production: MAbstract and STAR.

MAbstract technology

Overview

Our MAbstract technology can be applied for 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 contacted with pathogens, or cells suspected of carrying the drug target, or if the target is already known in advance, the library may be contacted 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 subtract irrelevant phage antibodies present in the library. Since irrelevant phage antibodies for the target in question are often present in great abundance, the subtraction 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 function in binding but have assessory 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, or 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:

Subtraction method of selection
MAbstract technology selects antibodies for possible therapeutic use and discovers novel drug targets using whole cells, tissues or infectious agents.

No inherent limitation on antibody specificity
MAbstract technology does not have the inherent limitation on antibody specificity.

Production using PER.C6 technology
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 an expression vector technology for the production of recombinant proteins in mammalian cells. 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 biologicals. 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 and royalties. 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.
- The STAR technology typically yields stable mammalian cell clones that produce five- to 10- fold more antibody or other therapeutic proteins as compared to cell clones generated without STAR.

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 October 2000, Crucell granted Merck an exclusive license to use Crucell's PER.C6 technology in developing a vaccine against HIV. Merck discontinued development of this vaccine in September 2007 but this was unrelated to the use of Crucell's PER.C6 technology.

In June 2003, Merck and Crucell expanded a Cooperation Agreement and agreed to work closely on matters relevant to maintenance of the PER.C6 Cell Substrate Biologics Master File. 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 receive 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 to 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 have established a joint PER.C6 R&D Center in Cambridge, Massachusetts, named PERCIVIA. 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 against this disease.

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 as 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.

Other collaborations and agreements

Wyeth
In March 2008, we entered into an exclusive agreement with Wyeth. We will perform contract manufacturing 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 clinical development of the vaccine.

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 specifications 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 of product sales arising out of the collaborations. Generally, these collaborations specify that Crucell provides the applicable university with a specific amount of funding, and in consideration, Crucell receives certain intellectual property rights and access to the results of the university research.

Overview licensees and partners
Per year-end 2007 we have the following licensees and partners:

Vaccines

Partner/licensee	Starting date	Technology	Disease target	Development stage
Acambis	Nov. 2007	PER.C6	HSV	Pre-clinical
ADImmune Corp.	Oct. 2006	PER.C6	Japanese Encephalitis	Pre-clinical
Aeras Global TB Vaccine Foundation	Mar. 2004	PER.C6 and AdVac	Tuberculosis	Phase 1
Bestewil Holding BV	Jan. 2006	Co-micelles	Influenza	Pre-clinical
Harvard School of Medicine	Dec. 2003	AdVac + Ad5HVR48	HIV	Pre-clinical
International AIDS Vaccine Initiative (IAVI)	Sep. 2004	AdVac	HIV	Phase 1
Kimron Veterinary Institute	Jul. 2003	PER.C6	West Nile virus —Veterinary vaccine (avian)	Marketed in Israel
Merck & Co. Inc.	Oct. 2005	PER.C6	Hepatitis C	Pre-clinical
Merck & Co Inc.	Dec 2006	Ad5HVR48	HIV	Pre-clinical
National Institutes of Health (NIH)	Mar. 2002	PER.C6 and AdVac	Ebola, Lassa and Marburg	Phase 1
National Institutes of Health (NIH)	Mar. 2004	PER.C6 and AdVac	Malaria	Phase 1
Neotropix	Mar. 2004	PER.C6	Oncology	Phase 1
Novartis	Dec. 2004	PER.C6	Alphavirus	Pre-clinical
Pfizer animal health	Mar. 2007	PER.C6	Veterinary	Pre-clinical
Sanofi pasteur	Dec. 2003	PER.C6	Influenza	Phase 2
Singvax	Mar. 2005	PER.C6	Japanese Encephalitis	Pre-clinical
Tibotec Pharmaceuticals Limited	Nov. 2005	PER.C6	Undisclosed vaccine	Pre-clinical
Transgene SA	Dec. 2007	PER.C6	Undisclosed vaccine	Pre-clinical
Vaxin, Inc.	Sep. 2004	PER.C6	Respiratory viruses	Phase 1
Wyeth Pharmaceuticals	Jul. 2007	AdVac	Non-disclosed	Pre-clinical

Overview licensees and partners (continued)

Proteins

Partner/licensee	Starting date	Technology	Disease target	Development stage
Abbott	Jan. 2007	STAR	Portfolio antibodies	Pre-clinical
Biotecnol SA	Jan. 2007	PER.C6	Portfolio antibodies	Pre-clinical
Daiichi Sankyo Ltd.	Nov. 2007	PER.C6	Portfolio antibodies	Pre-clinical
Ferring International Research Center SA	May 2005	PER.C6	Women's healthcare	Pre-clinical
Ferring International Research Center SA	Dec. 2005	PER.C6	Women's healthcare	Pre-clinical
Genentech	Feb. 2004	STAR	—	—
Genzyme Corporation	Dec. 2005	STAR	Portfolio proteins	Pre-clinical
Invitrogen Corp.	Sep. 2007	STAR	Monoclonal antibodies	Pre-clinical
ISU ABXIS	Jan. 2008	PER.C6	Portfolio antibodies	Pre-clinical
IQ Corporation	Oct. 2005	PER.C6	Anti-anthrax antibody	Pre-clinical
LFB Biotechnologies	Jul. 2007	PER.C6	Undisclosed antibodies	Pre-clinical
Masterclone	Jul 2007	PER.C6	Undisclosed antibodies	Pre-clinical
Medarex Inc.	May 2005	STAR	Portfolio antibodies	Pre-clinical
Medarex Inc.	Dec. 2007	PER.C6	Portfolio antibodies	Pre-clinical
MedImmune	Oct. 2007	PER.C6 and MAbstract	Anti-bacterial antibodies	Pre-clinical
Merck & Co., Inc.	May 2003	PER.C6	Portfolio antibodies	Pre-clinical
Merus B.V.	Jun. 2004	PER.C6	Portfolio oligoclonics	Pre-clinical
Micromet AG	Nov. 2004	PER.C6	Portfolio antibodies	Pre-clinical
MorphoSys AG	Sep. 2004	PER.C6	Portfolio antibodies	Pre-clinical
Novartis	Sep. 2006	STAR	Portfolio antibodies, Proteins	Pre-clinical
Novartis	Aug. 2004	PER.C6	HCV protein	Pre-clinical
Patrys	Feb. 2007	PER.C6	Portfolio antibodies	Pre-clinical
ProFibrix	Dec. 2007	PER.C6	Portfolio antibodies	Pre-clinical
PR&D Biotech SA (Recepta Biopharma SA)	Nov. 2007	PER.C6	Portfolio antibodies	Pre-clinical
Sartorius Biotech GmbH	Jun. 2007	PER.C6	Portfolio antibodies	Pre-clinical
Synergenics/Synco Biopartners Investments B.V.	Aug. 2004	PER.C6	Portfolio antibodies	Pre-clinical
Taiwanese Development Center for Biotechnology	Mar. 2007	PER.C6	Undisclosed proteins	Pre-clinical
UCB S.A.	Mar. 2006	PER.C6	Portfolio antibodies	Pre-clinical
UCB Celltech	Sep. 2006	STAR	Portfolio antibodies	Pre-clinical
UMN Pharma	Mar. 2006	PER.C6	Undisclosed protein	Pre-clinical
XOMA Ltd	Jan. 2006	STAR	Portfolio antibodies, Proteins	Pre-clinical

Overview licensees and partners (continued)

Gene therapy

Partner/licensee	Starting date	Technology	Disease target	Development stage
Ark Therapeutics	Jan. 2006	PER.C6	Portfolio	Phase II
GeneMax Corp. / TAP-Immune	Aug. 2003	PER.C6	Portfolio	Pre-clinical
GenVec Inc.	Jul. 2002	PER.C6	Cardiovascular	Phase II
Merck & Co., Inc.	Nov. 1998	PER.C6	Portfolio	Pre-clinical
Merial Ltd.	Dec. 2005	PER.C6	Veterinary	Pre-clinical
NeoTropix	Mar. 2004	PER.C6	Oncology	Pre-clinical
Transgene SA	Apr. 2001	PER.C6	Portfolio	Phase I/II
Vascular Biogenics Ltd	Mar. 2005	PER.C6	Portfolio	Pre-clinical

Alliances with contract managers for production

Partner/licensee	Starting date	Technology	Area
Cambrex	Aug. 2004	PER.C6	Medium development
DSM Biologics	Dec. 2002	PER.C6	Therapeutic proteins (including antibodies)
Gene Medicine Japan, Inc.	Oct. 2003	PER.C6	Recombinant vaccines & gene therapy products (Asia)
Hyclone, Inc.	Dec. 2003	PER.C6	Medium development
Invitrogen Corp.	Jun. 2003	PER.C6	Medium development
JRH Biosciences Inc.	May 2004	PER.C6	Medium development
Molecular Medicine BioServices, Inc.	Dec. 2001	PER.C6	Recombinant vaccines & gene therapy products (U.S.)
Sigma-Aldrich Corp.	Dec. 2003	PER.C6	Medium development

Functional Genomics

Partner/licensee	Starting date	Technology	Area
Galapagos Genomics N.V.	Jun. 1999	PER.C6	Genomics

Subsidiaries and other equity investments

Pevion Biotech AG
In 2002 Pevion Biotech was founded as joint venture by Berna Biotech and Bachem AG. The company was dedicated to creating novel virosomal formulated vaccines and bringing them from research into clinical development. On November 5, 2007, Crucell sold all of the 2.9 million shares it owned in Pevion Biotech for € 6.1 million to other Pevion Biotech shareholders. Prior to this sale, our ownership interest had already been diluted from 50% in 2006 to 36% in early 2007. We realized a gain of € 2.2 million on the sale.

Kenta Biotech AG
In 2006, Kenta Biotech AG was founded. Berna Biotech AG contributed investments in kind of € 3.3 million in exchange for shares equal to 36.74% of Kenta Biotech's share capital. Kenta Biotech AG is focusing on the discovery and development of innovative, fully human monoclonal antibodies for the life-saving treatment of patients with serious infectious diseases.

ADImmune Corp.
In March 2007, we announced that we have completed an influenza alliance with Taiwan-based ADImmune Corporation. Under the terms of the deal, ADImmune will use our virosome technology to produce a virosomal adjuvanted influenza vaccine for specified markets: Taiwan, Japan and Macau. Additionally, ADImmune will produce influenza antigen, which we may purchase for the production of our vaccine product, Inflexal V.

In consideration of the rights and licenses granted in respect of the technology, ADImmune paid an amount of € 8.9 million (TWD 394,887,000). We obtained a 20% equity stake in ADImmune for which we also paid an amount of € 8.9 million.

Galapagos N.V.
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. Tibotec and we have agreed not to compete with the activities of Galapagos, which holds the rights to the products and technology that it develops. The Company owns 5.8% as of December 31, 2007 (2006: 6.2%).

Marketing and sales partners

We have our own sales and marketing infrastructure in our markets in the Netherlands, Switzerland, U.S., Korea, the Nordic region, Italy, Canada, Spain, China, Argentina, Indonesia and Vietnam. This sales and marketing infrastructure includes a dedicated sales force for supranational organizations, to ensure broader market access for our products and we have established a strong network of partnerships to commercialize our products. We also distribute and market other companies' products. Through these measures, we have established a global position in both public and private markets.

We act as a marketing, sales and distribution partner for numerous companies, including:

- Sanofi pasteur – MSD. We act as marketing, sales and distribution partner for part of the SPMSD portfolio in Sweden.
- Novartis Vaccines and Diagnostics. We act as marketing, sales and distribution partner for part of the Novartis vaccine portfolio in Sweden.
- Statens Serum Institute Denmark. We act as marketing, sales and distribution partner for a number of SSI products in Spain and Sweden.
- Green Cross Corporation Korea. We act as marketing, sales and distribution partner of GreenCross Corporation's Japanese encephalitis vaccine in Europe.
- Netherlands Vaccine Institute. We act as marketing, sales and distribution partner of part of NVI's product portfolio in the Benelux (Belgium, Netherlands, Luxembourg).
- Talecris Biotherapeutics. We act as marketing, sales and distribution partner of Talecris's product Prolastin in nine Western European countries.

We have developed a network of companies that market and sell our products. The most significant collaborations in terms of current sales value are:

- Baxter International Inc. – A marketing, sales and distribution partner for a certain vaccines in Austria, Germany, Greece and Russia.
- Infectopharm Germany – A marketing, sales and distribution partner for our flu vaccine in Germany.
- Masta UK – A marketing, sales and distribution partner for our travel vaccines in the UK.
- Novartis-Behring – A marketing, sales and distribution partner for our travel vaccines in Germany.
- Sanofi pasteur – A marketing, sales and distribution partner for Dukoral in Canada, Australia and a number of other countries outside Europe and the U.S..
- Sanofi pasteur – MSD – A marketing, sales and distribution partner for our flu vaccine in the UK.
- Kedrion – A marketing, sales and distribution partner for 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 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 U.S. and Europe, as well as in other jurisdictions as appropriate.

In addition to retaining outside patent counsel, we also employ European and Dutch patent attorneys that file, prosecute, defend and enforce patent rights as well as manage our patent portfolio. Our patent portfolio comprises 1,554 active cases (i.e. granted patents in force or pending patent applications) as of December 31, 2007 in total for the Company. 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, 2007, 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.

2007 Patent filings

	Pending	Granted	Total Active
Vaccines[2]	300	502	802
Antibodies[3]	145	54	199
Technology[4]	210	226	436
Gene Therapy	46	71	117
Total	**701**	**853**	**1,554**

[2] 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.
[3] Antibodies patent filings relate to antibodies and/or drug targets, excluding the enabling technologies that are classified as technology.
[4] 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 2007 we filed patent applications for six new inventions, in the fields of vaccines, antibodies and technology. Our new filings in the antibody and vaccine fields in 2007 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 the STAR technology. Since we are not actively involved in gene therapy research and development, no new filings were made in that area during 2007.

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, 2007, we have 52 pending applications in the EU[1], 113 pending applications in the U.S.[2], 18 international patent applications (so-called 'PCT applications'[3]) and 518 applications in the rest of the world[4].

A significant number of our pending patent applications are filed under the Patent Cooperation Treaty (PCT), which offers a cost-effective method to seek provisional worldwide protection in more than 100 countries and territories 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 30 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 Patent Cooperation Treaty (PCT) applications while still in the international phase.
[2] U.S. figures do not include U.S. 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 Patent Cooperation Treaty 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, 2007 we owned or co-owned 539 granted patents in the EU territory, 75 patents in the U.S. and 239 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.

Hepavax-Gene
The active substance of this monovalent recombinant hepatitis B vaccine is HbsAg which is no longer protected by patent in Europe and most countries in the rest of the world. The Supplementary Protection Certificates with respect to Hepavax-Gene are still valid in Sweden, Italy, and France. However, we are not currently considering Western European countries for product registration and marketing. The production technology is based on our proprietary Hansenula polymorpha expression technology.

Quinvaxem
We have no patent protection for the active substances of Quinvaxem.

Vivotif
We have no patent protection for the active substances of Vivotif.

Dukoral
We have no patent protection for the active substances in Dukoral, but certain aspects of manufacturing are subject to patent.

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 activities concentrate on protecting these technologies and any improvements thereof in the main worldwide vaccine markets of Europe, the U.S., 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, patents are filed on a worldwide basis by specialized patent attorneys.

Our patent-related activities do not afford complete protection to our intellectual property rights. Patents in the biotechnology and biopharmaceutical fields involve complex factual and legal questions. Patents may not be issued in respect of our pending applications or in respect of future applications that we file. In addition, a patent that is issued to us may be narrower than our application or found to be invalid. Others may make attempts to copy, reverse engineer or design around aspects of our technology, or to obtain and use information that we regard as proprietary. Our patent filings may be subject to challenges.

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.

In 2005, Probiogen, CEVEC Pharmaceuticals and Serono each individually filed oppositions before 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. Cell Genesys has filed opposition against our European patent related to our AdVac technology. The opposition is still pending before the opposition division.

In 2005 we lodged opposition against a European patent held by Chiron related to certain aspects of the production of influenza viruses in cell culture; the opposition is still pending.

Our subsidiary Berna Biotech Korea Corporation (formerly Green Cross Vaccine Corporation) and our partner Novartis (formerly Chiron) lodged oppositions 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. If the Korean Supreme Court were to reverse the decision of the Patent Court and if GSK were to enforce its patent, Berna Biotech Korea Corp. could be found to have infringed the patent. In this case, we may be forced to delay or even cancel our commercial activities with this vaccine. As a consequence, we would lose revenue and our business would be adversely affected.

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.

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.

Research has been conducted for many years in the fields of biotechnology and biopharmaceuticals. This has resulted in a substantial number of issued patents and an even larger number of patent applications. The U.S. Patent Office maintains patent applications that are filed only in the U.S. in secrecy until patents issue, and publication of patent applications elsewhere and of discoveries in the scientific or patent literature frequently occurs substantially later than the date of the underlying discoveries. Moreover, patents that appear not to affect our activities may be construed broadly. As such, we or our licensees may be found to infringe the patents or violate other proprietary rights of third parties and may be enjoined from pursuing research, development or commercialization of our or their products or be required to pay damages. In these circumstances, licensing or other arrangements for addressing these infringements or violations may not be available, or may not be available on commercially acceptable terms.

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 to 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. 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 Company has licensed adjuvation technology called ISCOMS from Isconova AB for the development, manufacture and commercialisation of improved influenza vaccines.

When licensing our technology to third parties we seek to obtain access to any improvement patents 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.

Industry and scientific overview

Manufacturing systems for biopharmaceutical products

Biopharmaceutical products are therapeutics produced by means of biological production systems. Modified bacteria and yeast were initially used to produce the first generation of biopharmaceutical products for humans. The first available human cell-based production systems employed human cells that spontaneously acquired the ability to divide indefinitely. These cell lines have been successfully used to produce a number of human vaccines including those for rubella, mumps, measles, rabies and hepatitis.

Vaccines
Vaccines are designed to protect people against potentially life-threatening diseases, including those caused by parasites, viruses and bacteria.

Scientific progress in vaccines
Vaccines have contributed significantly to the improvement of global public health in the twentieth century. Smallpox was eradicated through the use of vaccines, and polio is well on its way to eradication. 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 such as HIV;
- Parasites such as those that cause malaria;
- Bacteria such as those that cause tuberculosis; and
- Inherited or acquired diseases such as cancer.

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, subunit 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 defence 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

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

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.

Therapeutic proteins
Proteins are main constituents of the human body. They consist of amino acid peptide chains folded in a specific conformation, and often contain a number of so-called posttranslational modifications (one of the later steps in protein biosynthesis) which include glycosylation, sulphation, phosphorylation, gamma-carboxylation, and others. Since the 1950s, proteins have been increasingly used as therapeutic drugs, especially diseases caused by a deficiency of certain proteins. Hematology, endocrinology and oncology are the main disease areas in which therapeutic proteins are applied.

Scientific progress in recombinant therapeutic proteins
Initially therapeutic proteins were isolated from natural sources such as blood, urine and tissue. Clinical experience with these proteins in the 1960s, and afterwards, revealed a significant risk of transmission of infectious pathogens, particular viruses, from the source material to the recipient. Hence, production of proteins in vitro was investigated. Since the 1970s, developments in molecular biology have made it possible to produce proteins in the laboratory. In addition, transgenics were developed that secrete the protein of interest in milk. Today, there are a number of production platforms for non-mammalian cells such as yeast, as well as mammalian cells.

Mammalian cell-based protein production systems mostly use non-human cell lines such as CHO, BHK and others. The type of post-translational modifications carried out by the platform is often determined by the cell-type used. Current thought holds that recombinant proteins should be produced by cell lines in culture media that are completely devoid of human serum components.

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 its 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 also aware of other human expression technologies such as WI 38 and MRC 5 for licensed and marketed vaccines, as well as human cell lines supporting products in development such as (HEK) 293.

In the area of influenza, we are aware that Solvay has obtained registration in the Netherlands for a vaccine based on MDCK cells. We are aware of other biotechnology and pharmaceutical companies that currently are developing influenza vaccines based

on MDCK cells, including GlaxoSmithKline (including IDB/Shire), Nobilon and Novartis (formerly Chiron). In addition, we are aware that Baxter has obtained approval in Austria for its VERO-based influenza vaccine. For other European markets Baxter appears to have stopped at Phase II in December 2004.

In the area of ebola, we are aware that Vical is conducting Phase I clinical efficacy studies with its DNA-based ebola vaccine and has initiated GMP manufacturing for the NIH with whom they are jointly developing the vaccine. We are aware that Health Canada, a federal government organization, is conducting pre-clinical studies with its ebola vaccine that is based on a live replication competent Vesicular Stomatitis Virus (VSV) vector. We are also aware that the U.S. Army Medical Research Institute of Infectious Diseases (U.S.MRIID) is conducting pre-clinical studies with its recombinant ebola vaccine, which is based on ebola virus-like-particle (VLP) technology. U.S.MRIID is also involved in a CRADA with AVI BioPharma in testing the latter's antisense drugs against ebola. AVI BioPharma received funding from the U.S. Senate Committee on Appropriations in June 2004 to support this and its work on the Marburg virus.

In the area of malaria, we are aware of two companies conducting Phase I/II clinical studies with malaria vaccine candidates based on virus-like-particle (VLP) technology: GlaxoSmithKline Biologicals (GSK) and Apovia. GSK has secured significant funding from NGOs for its malaria vaccine RTS,S. We are also aware that Oxford (The Wellcome Trust Centre for Human Genetics) and GSK are jointly developing a malaria vaccine using live vector technology, and that this vaccine is in Phase I/IIa clinical studies. In addition, Oxford is conducting Phase I/II clinical studies with three additional malaria vaccine candidates based on live vector technology, as well as pre-clinical studies with one additional vaccine candidate based on live vector technology. We are aware that the Pasteur Institute is conducting Phase I/IIa clinical studies with its malaria vaccine candidate, which is based on Long Synthetic peptide technology (LSA 3).

For tuberculosis, a number of companies, government bodies and academic institutes around the world are working on the development of new vaccines. The NIAID in the U.S. is involved in a range of early-stage efforts relating to live-attenuated, subunit and naked DNA type vaccine candidates. Our partner, the Aeras Global TB Vaccine Foundation, is working on various other programs including a live recombinant TB vaccine with the David Geffen School of Medicine at UCLA, which entered its first clinical trial in March 2004. In October 2004 Nature Medicine announced an Oxford University subunit vaccine, designed to work in tandem with the existing BCG vaccine, had successfully completed safety trials with positive T-cell responses.

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. In particular, Merck & Co. research has established methods that may prevent problems relating to pre-existing immunity to adenovirus 5 vectors.

Antibodies

Other biotechnology companies, including Celltech Group plc and Protein Design Laboratories, Inc., currently generate humanized antibodies, and Medarex, Inc., GenMab AG, and Regeneron produce fully-human antibodies from transgenic mice. MedImmune (formerly Cambridge Antibody Technology), 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. For rabies specifically, our antibody product may offer an alternative to the existing rabies immune globulin products, both Human (HRIG) and Equine (HRIG), that are currently paired with rabies vaccine for effective post-exposure treatment.

Production of recombinant proteins and monoclonal antibodies

Monoclonal antibodies and recombinant proteins are produced by other companies on a variety of platforms. Simple proteins that do not demand extensive post-translational modifications are produced in bacterial systems (E. coli). For example, the human recombinant insulin is produced entirely on E. coli.

Monoclonal antibodies and complex recombinant proteins are produced mainly on mammalian cell lines, which are used for commercial production of monoclonal antibodies and other recombinant proteins by companies including Genentech, Biogen, Centocor, Amgen, Lonza and Boehringer Ingelheim. We are aware of a human cell line expression platform used for production of recombinant proteins, the 293 human cell line, which shares some of the advantages of the PER.C6 technology. The 293 human cell line is utilized by Eli Lilly & Company to produce a protein for the treatment of adult severe sepsis. The FDA and the EMEA have approved this product and it is currently available for use. We are aware that scientists have published research describing human cell culture systems that appear to have similarities to our PER.C6 technology.

In addition to microbial and mammalian cell culture systems, transgenics are also exploited for the manufacture of complex recombinant proteins. Transgenic plants are also used as a platform for the manufacture of monoclonal antibodies and complex recombinant proteins. Cell culture systems derived from plants are currently used as well, like moss and cultured plant cells, which are currently used for manufacturing recombinant proteins. None of the products produced in transgenics have reached the market yet.

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 chemicals and radioactive and 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.

Our ability and that of our licensees to commercially distribute biopharmaceuticals depends in part on the extent to which governmental health administration authorities, health insurance companies, government health policies, health maintenance organizations, or HMOs, and other organizations are willing to pay for the costs of these products. The willingness of governments and HMOs to pay for the costs of newly developed health care products is uncertain. There are efforts by governmental payers and HMOs to contain or reduce the costs of health care and we expect that there will continue to be a number of legislative proposals to do so.

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 (EMEA) in the European Union, the FDA in the U.S., 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 EMEA in Europe, the FDA in the U.S. 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 U.S., 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 very 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 his biological origin may result in the imposition of restrictions upon the manufacturing and sale of such product, including at worst withdrawal of the product from the market and/or the revocation of the relevant regulatory approvals.

Prequalification applicable to the biopharmaceutical industry

National and regional governments rely on the prequalification 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 prequalification of approval.

The WHO Prequalification project is carried out to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis.

Prequalification 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 products (i.e. medicines) that have been found to meet the set requirements has come to be seen as a tool for anyone bulk purchasing medicines, including countries themselves and other organizations.

Any manufacturer wishing their medicines to be included in the prequalified 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 which assesses working procedures for compliance with WHO Good Manufacturing Practices (GMP).

The Prequalification 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 financial position 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 the following matters:

Deductibility of research and development costs
In Italy, Berna Biotech Italia Srl. was subject to a tax audit for fiscal years 2001 and 2002. For the year 2001, a settlement was reached with the Italian tax authorities in 2007. For the year 2002, no settlement is reached. The tax authorities issued an assessment that deviates from the assessment in the tax return filed. We are challenging this assessment in court. We made a provision for the costs of additional taxes, penalties and interest, as well as lawyers' fees, which we expect we will have to pay as a result. One of the items in dispute is the deductibility of the research and development costs we make in Italy. In the event that we lose the court case on this subject, the Italian tax authorities may challenge the deductibility of research and development costs for the years 2003 up until 2007. We consider it more likely than not that the research and development cost will be tax deductible.

Complaint filed by Korean landlord
The Group leases the property on which our Korean factory is build from our landlord, Green Cross Holdings Corp under a lease that expires in 2010, and which can be extended for an additional five years at our election. We are the only party entitled to terminate the lease.

Our landlord plans to surrender a portion of the land on which our Korean facility sits, to the local and regional authorities due to construction of a light railway and a subway line extension along with the potential urban development associated therewith. In 2007, we demolished a warehouse that was directly in the path of the construction of the subway line. Currently, none of our property is in the way of the construction projects. Our landlord has advised us it will stop providing utilities to us in early 2009. Furthermore, our landlord filed a complaint against us in November 2007, seeking the demolition of two more of our buildings at the Korean facility and delivery to them of the land on which those buildings are located. The suit alleges that there is an implied lease agreement for those buildings and the land on which they sit, which automatically terminated upon commencement of the subway line extension project. In January 2008, we submitted our answer to the Court, denying the landlord's allegations on the grounds that there was no new (whether implied or express) agreement to demolish the buildings and deliver the relevant land. Such an agreement would be inconsistent with the long-term lease agreement which we and the landlord executed in April 2000. We expect this court case to last several years.

An unfavourable outcome of the court case may have a material adverse effect on our business, financial condition and results of operations.

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 1200 square meters of space adjacent to the corporate main building. In 2007 we closed our pilot plant and production facility, which was located in a separate building in the Leiden BioScience Park.

In 2005, we began to construct a new GMP Process Technology Center of 5.400 square meters in Leiden. This new facility will be a BioSafety Level (BSL) 3 facility, in which two concurrent products can be produced, on either BSL 2 and/or BSL 3 safety level. The building will consist of 1,500 square meters of production space; 220 square meters of quality control labs; 185 square meters BSL 3 research and development labs; 80 square meters filling (up to 2,000 ampoules); 40 square meters of buffer and medium preparation; 310 square meters of offices; 350 square meters of storage and 2,715 square meters for utilities, washing area, waste destruction and sterilization and technical areas.

The new centre is named after Crucell co-founder Dinko Valerio, and is known as PTC Valerio Building. The PTC Valerio Building will give us the in-house capability to support vaccine, protein and monoclonal antibody process design and development, minimizing requirements for outsourcing. Bioreactors of 2, 10, 30 and 100-liter capacities have already been constructed off-site and are installed. There is also room for expansion, with multiple 100-liter wave-bags, disposable stirred tank bioreactors, and large scale down stream processing equipment and scale-up of fill and finish capacity.

When fully operational, the Valerio Building will meet the highest environmental and safety standards recommended for the laboratory activities to be conducted there. The facility must receive 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. The facility is currently scheduled to become operational in the first half of 2008.

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

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

Location	Use
Berne, Switzerland (two locations)	Research and development (including pre-clinical facilities) 8,618 m² and production facilities (12,427 m²); office space (5,635 m²) and storage buildings (15,988 m²) (owned)
Madrid, Spain	Production facilities (1600 m²), storage buildings (2400 m²) and office space/labs (1409 m²) (owned)
Seoul, Korea	Development and production facilities (2,201 m²), pre-clinical facilities (999 m²), storage facilities (1,305 m²), office space (1,819 m²) (leased until 2010)
Stockholm, Sweden	Development and production facilities (4,866 m²), pre-clinical facilities (1606 m²), storage facilities (5,990 m²), office space (2,662 m²) (leased until 2020)

Our manufacturing facilities in Switzerland are FDA/EMEA-approved and are used primarily for the production of Inflexal V, Vivotif, Epaxal and mammalian cell culture-based products. One of our facilities also includes facilities for lyophilization and a Center of Mammalian Cell Culture, which is currently not in use.

Our manufacturing facilities in Korea are World Health Organization-approved and are used primarily for the production of Quinvaxem and Hepavax-Gene and for formulating and filling vials. The manufacturing process used at our Korean facilities are based on the patented Hansenula polymorpha yeast expression technology.

In Spain, the center of our European filling and packaging operations, we operate a filling line for syringes.

In Sweden, our manufacturing facilities are EMEA/WHO-approved and are used for the production of Dukoral and the recombinant protein rCTB.

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

In 2006 € 20,337 was invested in property, plant and equipment compared to € 17,137 in 2005. Investments were mainly related to building and equipping our new GMP production facility in Leiden, the Netherlands.

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 carry 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 break-down 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. has not paid any dividends in 2007. 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 ADSs will be entitled to receive payments in U.S. 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 and us.