EXECUTIVE INFORMATIONAL OVERVIEW

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Developing Biopharmaceuticals for Infectious Diseases

Snapshot

May 26, 2004

Crucell N.V. is a development-stage biopharmaceutical company that employs proprietary technology to discover, develop, manufacture, and commercialize vaccines and antibodies targeted at a variety of infectious diseases. The Company's unique technology utilizes a human **cell line** production system called PER.C6®, which may facilitate products with greater safety, **efficacy**, and cost-efficiency than those currently marketed. Crucell is developing four vaccines to treat and prevent **influenza**, **Ebola**, **West Nile virus**, and **malaria**. To assist in its efforts, Crucell has recently entered into an agreement to develop and commercialize its influenza vaccine with Aventis Pasteur S.A.; has a Collaborative Research and Development Agreement (CRADA) and vaccine production contract in place with the U.S. National Institutes of Health (NIH) for its Ebola vaccine; and is working with GlaxoSmithKline PLC, New York University (NYU), and the Walter Reed Army Institute of Research (WRAIR) to develop its malaria vaccine, which has been funded up to the clinic by the National Institute of Allergy and Infectious Diseases (NIAID). To fund internal research and development (R&D) and ensure a constant and consistent revenue stream, the Company offers its PER.C6® technology to biotechnology and pharmaceutical companies worldwide for a variety of indications. Licensees for the technology include Merck & Company Inc. for a human immunodeficiency virus (HIV) vaccine, Biogen Idec, GenVec Inc., Pfizer, Inc., Schering AG/Berlex, MedImmune Inc., Transgene S.A., and Selective Genetics. These are among a total of more than 30 licensees. Furthermore, Crucell has alliances with contract manufacturing organizations (CMOs), such as DSM Biologics, to boost revenues and further establish the PER.C6® technology as the industry standard biopharmaceutical production system.

Recent Financial Data

Ticker (Exchange)[1]	CRXL (NASDAQ)
Recent Price (05/25/04)	$7.20
52-Week Range	$9.25-2.22
Shares Outstanding (mm)	35.9
Market Cap. (mm)	$258.5
Average 3-month volume	155,181
Insider +5% Owners	12%
Institutional Owners	30%
EPS (as of 12/31/03)	($0.82)
Employees	183

[1] *All amounts are in U.S. dollars (USD) unless otherwise stated.*

Key Points

- Crucell has a portfolio of proprietary products that enables the Company to be competitive with other biopharmaceutical companies while extending Crucell beyond the simple classification of a technology company. Each of Crucell's products addresses an important unmet medical need in the area of infectious diseases. These products are perceived as highly marketable due to predictive and available study models and/or potentially favorable regulatory conditions, which may speed the time to market.
- The Company's recent partnership with Aventis Pasteur changes the position of Crucell by endorsing its cell-based influenza product as an attractive vaccine and places Crucell as a principle participant in the worldwide vaccine market. Along with other agreements, such as the NIAID's coverage of preclinical costs in support of Crucell's malaria vaccine, it also reduces the Company's risk profile.
- Crucell's revenue model benefits from the government grants and licensing fees based on its PER.C6® technology. This offers investors the opportunity to invest in the potential of the drug candidates developed both internally as well as by its licensees since Crucell receives upfront payments and annual fees from each licensee.
- Crucell's market-oriented management team has a solid track record that reflects a mix of business, science, and logistical product development experience and expertise. This is complemented by an independent, non-executive Supervisory Board.
- The Company's balance sheet is solid, with a cash position of $107.4 million as of March 31, 2004.

†**BOLD** WORDS WITHIN TEXT ARE REFERENCED IN GLOSSARY ON PAGES 58-60.

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Executive Overview

Crucell N.V., headquartered in Leiden, The Netherlands, is a development-stage biopharmaceutical company that employs proprietary technology to discover, develop, manufacture, and commercialize vaccines and antibodies targeted at a variety of infectious diseases. The Company's unique technology utilizes a human cell line production technology called PER.C6®, which may produce products with greater safety, efficacy, and cost-efficiency than those currently marketed.

Crucell is currently developing four vaccines to treat and prevent influenza, Ebola, malaria, and West Nile virus using its PER.C6® technology. To assist in its internal development efforts, Crucell has recently entered into an agreement to develop and commercialize its influenza vaccine with Aventis Pasteur (AVE-NYSE). The Company also has a Collaborative Research and Development Agreement (CRADA) and vaccine production contract in place with the U.S. National Institutes of Health (NIH) for its Ebola vaccine. Furthermore, Crucell is working with GlaxoSmithKline PLC (GSK-NYSE), New York University (NYU), and the Walter Reed Army Institute of Research (WRAIR) to develop its malaria vaccine, which is fully funded up to the clinic by the National Institute of Allergy and Infectious Diseases (NIAID). Table 1 provides a snapshot of the Company's proprietary product pipeline as well as estimates of the size of each relevant market.

Table 1
Crucell N.V.
PIPELINE AND MARKET SIZE

Virus	Market Size (estimate)
Influenza (new process)	$1.2 billion+
Ebola (recombinant)	$260 million+
West Nile (whole-killed)	$400 million+
Malaria (recombinant)	$200 million+

Source: Crucell N.V.

Internal Product Development

Influenza. In January 2004, Aventis Pasteur and Crucell entered into a strategic agreement to develop and commercialize novel influenza vaccine products based on its PER.C6® cell line technology. The agreement covers both **pandemic** and **epidemic** influenza vaccines, which up to now have been part of Crucell's in-house product development program. The agreement could provide Crucell with a solid position in the vaccine market, provide a more solid overall financial position in the near- as well as long-term, free up resources for its other in-house development programs, and provide technology recognition for PER.C6® as the industry standard for vaccine production.

Ebola. In May 2002, Crucell signed a CRADA with the Vaccine Research Center (VRC) of the U.S. National Institutes of Health (NIH) and the U.S. Army to jointly develop and manufacture a preventative Ebola vaccine. Additionally, Crucell signed a manufacturing contract with the NIH to develop and manufacture an outbreak vaccine against Ebola. Both vaccines are based on Crucell's PER.C6® technology. Due to of the deadly nature of this virus and the fact that no vaccine or therapy is presently available, the Ebola virus is on the NIAID, Centers for Disease Control and Prevention (CDC), and U.S. Department of Defense Category "A" list of bioterror agents. In August 2002, the CRADA with the VRC-NIH covering a preventative Ebola vaccine was extended to cover the development of vaccines against other **hemorrhagic** fever viruses (**marburg** and **lassa**) as well.

West Nile virus. Crucell is developing a human vaccine against the West Nile virus. To date, the Company has conducted preclinical studies using geese, which are considered the best animal model for testing a potential West Nile virus vaccine. These initial tests successfully demonstrated disease-free survival in geese vaccinated with an experimental version of the Crucell vaccine following a lethal dose of the West Nile virus. Based on these results, the Kimron Veterinary Institute in Israel has licensed the PER.C6® technology to develop a veterinary vaccine. Kimron expects to register the veterinary vaccine in early 2004. Crucell has the exclusive rights to market the PER.C6®-based West Nile virus veterinary vaccine in the United States. Additionally, in December 2003, Pfizer Inc. (PFE-NYSE) took an option on Crucell's PER.C6® technology for the development and commercialization of a West Nile virus veterinary vaccine for horses.

Malaria. Crucell announced at the end of October 2003 that it is developing a malaria vaccine in two collaborative programs involving three leading malaria research organizations: New York University, GlaxoSmithKline Biologicals, and Walter Reed Army Institute. The malaria vaccine candidate is based on Crucell's patented AdVac® adenovirus vector technology (page 33), and is produced using the Company's PER.C6® technology. In March 2004, the NIAID agreed to support the development of Crucell's candidate malaria vaccine, in effect covering the full preclinical costs.

Licensing Agreements for PER.C6® Technology

Due to the versatility of the PER.C6® technology and its applicability to a wide range of human diseases, it is rapidly becoming an industry standard for the production of biopharmaceuticals. This is accomplished through Crucell's active solicitation and licensing of the PER.C6® technology to third parties, which has increased awareness and acceptance of the technology throughout the biopharmaceutical industry. In addition, by increasing the number of third party licenses, the number of products derived from the technology may increase, resulting in the potential for additional licensing and royalty income. Table 2 provides a snapshot of some of the Company's key licensees and collaborators, with descriptions below. Details on each collaboration are provided on pages 35-40.

Table 2
Crucell N.V.
PER.C6® LICENSEE PIPELINE

Licensee	Indication	Category	Phase
Aventis Pasteur S.A	Influenza	Vaccine	Preclinical
Biogen Idec	Undisclosed	Anti-virals	Preclinical
GenVec	Cardiovascular	Gene therapy	II
Merck & Co.	HIV-1 vaccine	Vaccine	I
ML Laboratories	Oncology	Gene therapy	I
Schering AG/Berlex	Cardiovascular	Gene therapy	Phase I/II
Selective Genetics	Tissue repair	Gene therapy	Phase I/II
Transgene S.A.	Oncology	Gene therapy	Phase I/II

Source: Crucell N.V.

Aventis Pasteur S.A. In December 2003, Crucell entered into a collaboration and license agreement with Aventis Pasteur to research, develop, manufacture, and market influenza vaccine products based on the PER.C6® technology. Under the terms of the agreement, Aventis Pasteur was granted an exclusive license in exchange for an up-front payment, milestone payments, annual payments, research and development funding, and royalties on future PER.C6®-based influenza vaccine sales.

Merck & Co., Inc. In October 2002, Crucell entered into an agreement with Merck & Company (MRK-NYSE), in which Merck was granted an exclusive license to use Crucell's PER.C6® technology to develop vaccines for the prevention and treatment of HIV/**Acquired Immune Deficiency Syndrome (AIDS)**. Currently in Phase I, clinical trials of the vaccine have seen the study expand to more than 1,000 people. Scientists hope that the trial leads to the development of a vaccine that would effectively prevent the development of AIDS from HIV infection, as well as treat the HIV infection in infected patients taking anti-retroviral therapy. Merck is implementing an extensively modified **recombinant** adenovirus that is grown using Crucell's PER.C6® technology. In October 2003, Crucell announced that Merck elected to extend its option for exclusivity to develop **hepatitis** C virus vaccines using the PER.C6® technology.

Other Agreements. Crucell's extensive PER.C6® technology licensing program provides an ongoing revenue stream in the form of upfront payments and annual fees, and may provide future revenue in the form of royalties on product sales. More than 30 pharmaceutical and biotechnology companies worldwide have selected Crucell's PER.C6® technology to develop their own products, illustrated in Table 13 (page 35). Several of these products are in various stages of clinical development including Merck's HIV

vaccine candidate as well as other licensees such as Biogen Idec (BIIB-NASDAQ), Centocor/Johnson & Johnson (JNJ-NYSE), and GenVec (GNVC-NASDAQ).

Contract Manufacturing Organization (CMO) Agreements

In addition to the aforementioned license agreements, Crucell has agreements with several contract manufacturing organizations (CMOs) that offer PER.C6® technology to third parties. For instance, Crucell has an alliance with DSM Biologics, a leading contract manufacturer for biopharmaceuticals, for the large-scale production of **monoclonal** antibodies and recombinant proteins based on its PER.C6® technology. Crucell also has an agreement to offer vaccine manufacturing services for clinical grade materials with Novavax, Inc., where Novavax expects to also use Crucell's PER.C6® technology for research on two targeted vaccines. Crucell also has contracts with U.S.-based Molecular Medicine BioServices, Inc. and Japan-based Gene Medicine Japan, Inc. Both companies are involved in license agreements for Crucell's PER.C6® technology, where the companies plan to use the technology to provide manufacturing services for companies, universities, and other institutions researching adenovirus-based **recombinant vaccines** and gene medicine products. Japan's market includes all of Asia, whereas Molecular Medicine provides its services to the global market. Details on Crucell's CMO agreements are on pages 41-42.

Galapagos Genomics

Crucell also holds a 20.8% ownership share in Galapagos Genomics, a Belgian company established in 1999 through a 50/50 joint venture between IntroGene (now Crucell) and Tibotec-Virco., (acquired by Janssen Pharmaceutica, a Johnson and Johnson company). Galapagos conducts functional genomics activities for Crucell using PER.C6® technology in conjunction with Tibotec's robotics technology to generate adenoviral gene libraries for gene-function research. Crucell has provided Galapagos with the necessary cell and adenovirus technologies, and Tibotec has provided Galapagos with **bioinformatics** technology. Under the terms of the joint venture, Galapagos has rights to all the products and technologies it develops.

Management Transition and Appointments

Effective January 26, 2004, Ronald Brus was nominated to the position of President and CEO. He also assumes the role of Chairman of the Management Board. He succeeds Crucell's co-founder, Dinko Valerio, who continues to work for the Company, focusing on corporate and capital market relationships. Jaap Goudsmit, Chief Scientific Officer of Crucell, was nominated as the second member of the Management Board, effective from January 26, 2004.

In December 2003, Jean-Yves Guichoux was appointed Executive Vice President Development. He brings significant product development experience to Crucell, gained over many years at a diverse range of companies, including Afforce Healthcare, Yamanouchi Europe (YNCHF.PK), and Wyeth-Ayerst (WYE-NYSE). He will now be responsible for Crucell's product development programs and will oversee each program from preclinical development through to clinical trials and subsequent product registration.

Headquarters, Manufacturing, and Employees

Crucell N.V. was incorporated in The Netherlands on October 9, 2000 as the legal successor to IntroGene, a biotechnology firm established in 1993. Crucell employs 183 people, with approximately 80% directly involved in R&D activities. Crucell's research facilities and corporate offices encompass 7,240 square meters in the city of Leiden. Its plant and production facilities of 360 square meters are located in a separate building in the Leiden Bioscience Park, which also house 65 square meters of office space.

Growth Strategy

Crucell is focused on developing novel vaccines and antibodies to combat infectious diseases by employing its innovative PER.C6® and AdVac® technology. Currently, the Company is developing vaccines against influenza, Ebola, West Nile virus, and malaria. The Company's antibody programs are in earlier stages of investigation. In the latter part of this decade, Crucell plans to become a profitable enterprise when its proprietary vaccines are marketed and royalties flow from products developed by its licensees.

In areas where Crucell does not aim to develop its own products, the Company licenses its PER.C6® technology broadly to the biopharmaceutical industry. This licensing program provides an ongoing revenue stream in the form of licensing fees, annual and milestone payments, and the potential for future royalties on the net sales of PER.C6®-based products that reach the market. Crucell uses the revenues generated from its extensive licensing program to finance its own product development efforts. In addition, Crucell has agreements with several CMOs that offer PER.C6® technology to third parties. The Company also benefits from government grants based on its PER.C6® technology.

Internal Development

Two of the vaccines in development (influenza and West Nile virus) are based on an **inactivated whole virus vaccine** concept using PER.C6® technology as a cell substrate, or production system. The whole inactivated virus vaccine development concept is a proven method that has a well established record of safety and efficacy. Many of today's best and most widely used vaccines are based on this method, including the Salk Polio and Japanese **Encephalitis** vaccines.

Crucell's two additional vaccine products (Ebola and malaria) are based on the recombinant **adenovirus vector system** and are produced using Crucell's PER.C6® production technology. For its Ebola program, Crucell is developing an adenovirus-based Ebola vaccine under a CRADA with the Vaccine Research Center of the NIH. Crucell believes that it can generate revenues from in-market sales of this product from 2007 onward.

Crucell's malaria vaccine is currently in the proof-of-concept stage of development. The vaccine is based on Crucell's proprietary AdVac® technology and produced using a derivative of the Company's PER.C6® technology. The Company is developing its malaria vaccine in collaboration with three leading malaria research organizations: Walter Reed Army Institute of Research, GlaxoSmithKline Biologicals and New York University. The Company recently received confirmation of support from the National Institute of Allergy and Infectious Diseases, part of the NIH, to cover the full preclinical cost of Crucell's candidate malaria vaccine.

Crucell's AdVac® technology uses a common cold virus (adenovirus) as a **vector** for delivering small parts of the malaria parasite to the immune system, thereby providing strong immune responses and protection against this infectious disease. Since AdVac® technology is based on adenovirus vectors not commonly found in the human population, pre-existing immunity to the vector is rare. By avoiding this problem, AdVac® technology may allow for lower dosage schedules, minimizing the risk of vaccination delivery. Based on a derivative of PER.C6® technology, AdVac® technology could make large-scale manufacturing of recombinant vaccines possible.

In addition to bringing crucial commercial and scientific input to the Company's programs, the partnerships or strategic alliances forged by Crucell, such as the agreement with Aventis Pasteur for the development of a new generation of flu vaccines, significantly reduces the risk profile of the company. The proceeds also become available for the acceleration of other programs. Crucell is aware of the need to expand its future product development pipeline beyond its current programs, as evidenced by a recently announced collaboration with the Aeras Global TB Vaccination Foundation for the preclinical and clinical development of candidate **tuberculosis (TB)** vaccines.

Intellectual Property

Crucell's success and ability to compete depends in large part on its capacity to protect its proprietary technology and information, and to operate without infringing the intellectual property (IP) rights of others. The Company relies on a combination of patent, trademark, and trade secret laws, as well as confidentiality, assignment, and licensing agreements to establish and protect its proprietary and intellectual property rights.

The Company actively seeks patent protection of its intellectual property in the United States and Europe, as well as in other jurisdictions as appropriate. In addition to retaining outside patent counsel, they also employ European and Dutch patent attorneys that file, prosecute, defend, and enforce patent rights as well as manage its patent portfolio.

Crucell's patent portfolio comprises 436 active cases (i.e. granted patents in force or pending patent applications) as of December 31, 2003. The Company aggressively protects its inventions and employs a proactive filing strategy with respect to patent applications. Its portfolio management involves active commercialization and enforcement strategies combined with disposal of cases that are no longer considered commercially attractive.

Table 3 reflects the total number of active cases (pending or granted) and total number of active and inactive cases (cases transferred, abandoned or otherwise disposed of) since the inception of its predecessor company, IntroGene B.V., through December 31, 2003, organized according to the Company's different fields of operation.

Table 3
Crucell N.V.
PATENT FILING STRATEGY[1]

	Pending	Granted	Total Active	Inactive	Total
Vaccines	118	27	145	40	185
Antibodies	64	19	83	37	120
Technology	66	30	96	62	158
Gene Therapy	66	46	112	110	222
	314	122	436	249	685

[1] Total number of pending and granted cases (Active) and total number of cases transferred, abandoned or otherwise disposed of (Inactive) since the inception of Crucell's predecessor IntroGene B.V.

Source: Crucell N.V.

All figures include acquired and jointly-owned patent cases, but exclude patent positions licensed-in from third parties. Patent filings classified under vaccines relate to AdVac®-based and classical vaccines. Patent filings classified under antibodies relate to antibodies and/or **drug targets**, excluding the enabling technologies. Patent filings classified under technology primarily relate to cell-based production technology and, to a lesser extent, adenoviral vector technology, functional genomics and target and antibody discovery technology. Patent filings classified under gene therapy relate to gene therapy technology and developments.

New Filings

Table 4 (page 8) summarizes the most important developments in Crucell's patent portfolio in 2003.

Table 4
Crucell N.V.
FIRST FILINGS AND GRANTED PATENTS IN 2003

	First filings for new inventions	Granted patents
Vaccines	4	4
Antibodies	17	18
Technology	7	20
Gene Therapy	0	5
Total	28	47

Source: Crucell N.V.

The new filings in the vaccine field reflect Crucell's willingness to further strengthen its patent portfolio in support of the product development programs in the field of vaccines. The new filings in the area of antibodies reflect Crucell's intensified R&D in the field of infectious diseases and, to a lesser extent, the completion of programs in the field of target and antibody discovery in the oncology field. The new filings in the technology area relate to Crucell's continuing effort to protect and commercialize the PER.C6® technology and related uses of PER.C6® cell lines. Since Crucell is not actively involved in gene therapy R&D, no new filings have been completed in that area during 2003.

Pending Applications

A significant number of Crucell's 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 for the duration of 30 or 31 months from the filing date.

The Company currently owns or co-owns 66 granted patents in the European Union (EU) territory, 27 patents in the U.S., and 29 patents in the rest of the world (ROW). ROW includes, depending on factors such as the technological or business area, Australia, Brazil, Canada, China, India, Israel, Japan, Hong Kong, Mexico, New Zealand, Norway, Russia, Singapore, South Africa, and South Korea.

During the pendency of a European patent application, a single application may designate 27 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, Crucell counts each such patent as a separate patent.

Management and Supervisory Board

Crucell benefits from the leadership of its focused, market-oriented management team, illustrated in Table 5 and described below. Management's track record is solid and reflects a strong mix of business, science, and logistical product development experience and expertise. Additionally, the Company strives to maintain the highest standards for corporate governance. The Company is listed both on the NASDAQ and Euronext Amsterdam stock exchanges and is fully SEC and NASDAQ compliant.

Management

Table 5
Crucell N.V.
MANAGEMENT

Ronald H.P. Brus	Acting President and Chief Executive Officer
Jaap Goudsmit	Chief Scientific Officer
Leonard Kruimer	Chief Financial Officer
René K. Beukema	General Counsel, Corporate Secretary
Jean-Yves Guichoux	Executive Vice President, Development
Arthur Lahr	Vice President, Business Development

Source: Crucell N.V.

Ronald H.P. Brus, M.D., Acting President and Chief Executive Officer

Ronald H.P. Brus was nominated as Chairman of the Management Board, Acting President and Chief Executive Officer on January 26, 2004, and has been a member of the Company's management committee since its incorporation. He was Executive Vice President, Chief Operating Officer from March 2003 through to his nomination as President and CEO. He was Executive Vice President, Business Development at IntroGene from 1997 to 2000. From 1994 to 1996, he was Product Planning Physician at Forest Laboratories (FRX-NYSE) in New York and from 1990 to 1994, he was medical director for Zambon B.V. He holds a medical degree (M.D.) from the University of Groningen.

Jaap Goudsmit, M.D., Ph.D., Chief Scientific Officer

Jaap Goudsmit was nominated as member of the Management Board on January 26, 2004. He has been Crucell's Senior Vice President for vaccine research since September 2001 and Chief Scientific Officer since September 2002. He has chaired various national and international committees and is a fellow of the NIH and of New York University. He co-founded both the International AIDS Vaccine Initiative (IAV) and Euro Vac, the European Union AIDS vaccine program. Since 1989, he has been a professor at the University of Amsterdam and the Amsterdam Medical Center. He holds M.D. and Ph.D. degrees from the University of Amsterdam.

Leonard Kruimer, CPA, Chief Financial Officer

Leonard Kruimer has been Chief Financial Officer and a member of Crucell's management committee since the Company's incorporation. He held the same position at IntroGene from 1998 to 2000. From 1996 to 1998, he was an independent consultant with companies such as PepsiCo (PBG-NYSE) and Royal Boskalis Westminster N.V. From 1988 to 1995, he held senior executive positions at Continental Can Europe, GE Capital/TIP Europe, and Kwik-Fit Europe B.V. He was a consultant at McKinsey & Co. and has worked with Price Waterhouse. He holds a Masters in Business Administration from Harvard Graduate School of Business Administration, a degree from the University of Massachusetts, Amherst, and is a CPA in New York State.

René K. Beukema, General Counsel, Corporate Secretary

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

Jean-Yves Guichoux, Executive Vice President, Development

Jean-Yves Guichoux joined Crucell in December 2003 as Executive Vice President of Development. He most recently served as Vice President at Afforce Healthcare. Prior to joining Afforce, he worked at Yamanouchi Europe in The Netherlands, where he headed the clinical research department. Mr. Guichoux also spent over 10 years at the European research headquarters of Wyeth-Ayerst, where he held the position of Vice President, Clinical Research and Development. In this function, he directed Wyeth-Ayerst's Phase I through IV product development programs across multiple therapeutic areas. Previously, Mr. Guichoux spent 11 years as Director of the Medical Department for Wyeth's French affiliate. He also worked as Medical Director Lafon and as Medical Advisor for Lepetit. Mr. Guichoux received his M.D. degree from the University of Rennes in France in 1971.

Arthur Lahr, Vice President, Business Development

Arthur Lahr was appointed Vice President of Business Development in December 2003 and a member of the management committee in January 2004. He joined Crucell in April 2001 as Executive Director, Business Development. From 1994 to 2001, he was a consultant at McKinsey & Co. in The Netherlands and New York. Prior to that, he worked with Unilever (UN-NYSE). Mr. Lahr holds a Masters in Business Administration from INSEAD and a Masters in Science Applied Physics, from the University of Delft.

Supervisory Board

Table 6
Crucell N.V.
SUPERVISORY BOARD

Pieter J. Strijkert	Chairman
Jean Deleage	Supervisory Board Member
Phillip M. Satow	Supervisory Board Member
Patrick Van Beneden	Supervisory Board Member
Claes E. Wilhelmsson	Supervisory Board Member
Sean Lance	Supervisory Board Member

Source: Crucell N.V.

Pieter J. Strijkert, Chairman

Pieter J. Strijkert has served as Chairman of Crucell's Supervisory Board since its incorporation. He also served as Chairman of the supervisory board of IntroGene from 1994 to October 2000 and as Chairman of the supervisory board of U-BiSys from 1998 to October 2000. He currently serves on the boards of Chiron Corporation (CHIR-NASDAQ), a position he has held since 1987, and Paratek Pharmaceuticals, Inc., a position he has held since 1998. He served as chairman of the supervisory boards of Pharming (PHGUF.PK) from 1995 to 2001, and for deVGen N.V. and PamGene B.V. from 2000 to 2003. From 1985 to 1995, he was a member of the managing board of Gist-Brocades N.V. Mr. Strijkert has a Ph.D. degree from the University of Utrecht.

Jean Deleage, Supervisory Board Member

Jean Deleage has served as a member of Crucell's Supervisory Board since its incorporation and served as a supervisory board member of IntroGene from 1997 to October 2000. He is a founder and managing director of Alta Partners, a venture capital firm investing in information technologies and life science companies. Alta Partners was founded in 1996. In 1979, he co-founded Burr, Egan, Deleage & Co., a venture capital firm in San Francisco and Boston, where he is currently a managing partner. He was a member of Sofinnova's initial team, a venture capital organization in Paris, and in 1976 formed Sofinnova, Inc. (The U.S. subsidiary of Sofinnova). Mr. Deleage serves on the boards of Kosan Biosciences, Inc. (KOSN-NASDAQ), Rigel Pharmaceuticals, Inc. (RIGL-NASDAQ), and several private companies. He holds a Master's degree in electrical engineering from Ecole Superieure d'Electricite and a Ph.D. degree in Economics from the Sorbonne. In 1984, he was awarded the Ordre National du Mérite, and in 1993, he was awarded the Legion of Honor from the French government in recognition of his career accomplishments.

Phillip M. Satow, Supervisory Board Member

Phillip M. Satow has been a member of Crucell's Supervisory Board since its incorporation. He spent 14 years at Pfizer, Inc., (PFE-NYSE) where his last position was Vice President, Pharmaceutical Development, Pfizer Europe. From 1985 to 1997, he was Executive Vice President of marketing at Forest Laboratories, Inc. From 1998 to 1999, he was President of Forest Pharmaceuticals, Executive Vice President of Forest Laboratories Inc., and a member of its board of directors. Mr. Satow currently serves on the boards of Forest Laboratories Inc., the Columbia College Board of Visitors and the American Foundation for Suicide Prevention. Mr. Satow received a Masters in Economics from Georgetown University.

Patrick Van Beneden, Supervisory Board Member

Patrick Van Beneden has served as a member of Crucell's Supervisory Board since its incorporation and served as a member of the supervisory board of IntroGene from 1997 to October 2000. He is Vice President of GIMV N.V. and since 1985 has held several positions with this company, including financial analyst, investment manager, senior investment manager, executive senior investment manager, and investment director. He currently serves on the supervisory boards of deVGen N.V., Avalon Pharmaceuticals Inc., Xantos Biomedicine AG, and Crop Design N.V., and on the boards of Ablynx N.V., Astex, Pamgene, Psychiatric Genomics, Neurogenetics, I&I Gent, and the Biotech Fund Flanders.

Claes E. Wilhelmsson, Ph.D., Supervisory Board Member

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

Seán Lance, Supervisory Board Member

Seán Lance is a member of Crucell's Supervisory Board as of January 2004. Mr. Lance is the Chairman of Chiron. He joined Chiron as President and Chief Executive Officer in 1998. From 1985 to 1998, Mr. Lance was employed at Glaxo Holdings where his last position was group Chief Operating Officer and CEO designate. He is a past President of the International Federation of Pharmaceutical Manufacturers Association. He is currently Chairman of the Board of Directors for the Global Alliance for TB Drug Development (GATB), and is a member of the Board of Directors of the California Healthcare Institute (CHI). Mr. Lance is a Chartered Company Secretary and Administrator and also holds a post-graduate qualification in advanced Financial Management.

Core Story

Biopharmaceutical Production

Biopharmaceutical products are biological drugs that can only be produced by means of advanced fermentation with the aid of micro-organisms or cell lines. Biopharmaceutical production has long been plagued by a myriad of restrictions connected to the overall bioavailability (scale), safety (required growth conditions for a given cell or organism), and product specifications (non-human origin) of many emerging product leads.

The first generation of biopharmaceuticals was developed using modified bacteria and yeast production systems. The primary drawback of these systems was their inability to produce proteins that work with similar efficiency in humans, thereby inhibiting their overall versatility and effectiveness. As the global demand for biopharmaceutical products increased, the scientific community worked to employ non-human mammalian cells as production systems to broaden the range of biological products that could be manufactured. However, the first non-human mammalian production systems yielded proteins whose characteristics differed from those in human cells. These protein differences limited the usefulness of these products in humans due to a variety of associated risks, such as the potential to trigger an adverse immune response, a shortened half-life, and diminished therapeutic efficacy.

Non-human production systems also faced a variety of manufacturing-based setbacks, particularly in the area of vaccines. Since many human viruses do not grow on non-human cells, scientists have experienced a high degree of difficulty manufacturing human vaccines on a large scale. Even with many recent improvements in vaccine production, current systems are inherently limited in use due to their non-human characteristics.

The scientific community is now looking toward human-derived cells for the production of entirely new and more effective biopharmaceuticals. Perhaps the most viable candidate for the first generation of human biopharmaceutical technologies comes from the implementation of human cell lines. Human cell lines are production systems that are based on cells that replicate indefinitely.

The first available human cell-based production systems were based on cancer cells isolated from human patients—a technology that raised serious safety concerns. The latest state-of-the-art technology encompasses the use of human-derived cells, also referred to as immortalized cells, as completely healthy human cells are engineered to grow indefinitely without taking on a cancer cell phenotype. To produce this technology, a small portion of the **genome** (E1-gene) is extracted from the benign adenovirus type 5 (the 'common cold' virus to which the majority of the population is frequently exposed) and inserted into normal human cells where it subsequently causes indefinite, stable cell growth. The consequent immortalized cell and its resulting characteristics are a "cell line."

Crucell's PER.C6® technology was designed based upon the belief that a human-based, fully characterized production system may grant scientists the ability to produce a new generation of biopharmaceuticals that does not possess the associated deficiencies of currently used systems.

Vaccines

Vaccines are designed to protect people against potentially life-threatening diseases, including those caused by parasites, viruses, and bacteria. Today's vaccines are based on **naked DNA**, modified microorganisms (bacteria), **modified benign viruses** (classified under **subunit vaccines**), or classical formulations composed of live virus, inactivated virus, or subunit (one protein of a pathogen) vaccines. All vaccines possess the ability to induce a strong and specific immune response, thereby allowing the host to resist future infections and disease.

Next to penicillin, vaccines have made the greatest contribution to public health in the 20th century. Several vaccines have also engendered the eradication of deadly epidemics, such as **smallpox**, while the polio vaccine has almost completely eliminated polio. Today, research is underway to develop efficacious and safe vaccines against viruses such as HIV, influenza, Ebola, SARS, and West Nile virus; against parasites such as malaria; and also against inherited or acquired diseases such as cancer.

While the field of vaccine development has experienced a wealth of innovation and progress, many common diseases continue to elude the scientific community. For example, despite intense research and examination of potential methods to counter HIV/AIDS, the medical community has yet to find an efficacious HIV/AIDS vaccine. The primary drawback is that most vaccines are designed to elicit an immune response based on the formation of antibodies, which are most successful in fighting diseases caused by toxins, bacteria, or viruses that pass through the blood to reach the tissues. Since, for example, the malaria parasite and the HIV virus are more cell-associated, many believe that a cell-mediated response is needed to successfully prevent or treat diseases associated with these pathogens.

Prevention versus Treatment

The most devastating diseases among children in the developing world can be prevented with current or near-future vaccine technology. For example, within the developing world, approximately 20% of deaths of children under 5 years are attributed to acute respiratory infection, including **pneumonia** and influenza. Diarrheal diseases, including those caused by rotavirus, account for another 20% of deaths, while measles alone caused 800,000 deaths in 1999. Malaria, tuberculosis, and HIV/AIDS also represent significant causes of mortality and morbidity among children. In total, approximately 3 million children die each year from vaccine preventable diseases.

There are two aspects to confronting viral diseases: (1) prevention, which includes vaccination and public health measures; and (2) treatment, which includes antiviral drugs. Most of the damage to cells in viral infections occurs very early, often before clinical symptoms of disease appear. This makes treatment difficult and thus prevention a more attractive option. Although prevention of infection is the preferred alternative, post-exposure vaccines can be of great value in modifying the course of some viral infections. However, in order to design effective vaccines, a greater understanding of the immune response to viral infection is needed.

Different Vaccine Formats

Vaccines are currently produced in a variety of ways with many methods using animal material, such as fertilized chicken eggs, mouse brains, or non-human cell lines. Additionally, scientists are now exploring human cell-based vaccine manufacturing systems, which are believed to offer several important advantages over currently used production methods. Research in vaccine technology is predicated upon the desire to generate vaccines that are safer, possess broader immunity, and are more efficiently manufactured. Some of the most common include subunit vaccines, inactivated whole virus vaccines, **live attenuated virus vaccines**, **DNA vaccines**, recombinant vector-based vaccines, synthetic vaccines, and peptide-based vaccines. The more common forms are described below.

1. *Subunit Vaccines.* These are the newest type of vaccines, which have proven to be predominantly safe, except for rare adverse reactions. However, they also tend to be the least effective, with problems including relatively poor antigenicity (especially short peptides) and the need for carriers/adjuvants in the delivery process.

2. *Inactivated Whole Virus Vaccines*. This method of production—exposure to denaturing agent—results in loss of infectivity without loss of antigenicity. These types of vaccines have been shown to be more effective than subunit vaccines (better immunogens) with little or no risk if properly inactivated. Its disadvantages are that it is not suitable for all viruses; denaturation may lead to loss of antigenicity; it is not as effective at preventing infection as live viruses; and it may not protect for a long period.

3. *Live Attenuated Virus Vaccines.* This method uses viruses with reduced pathogenicity to provide an immune response without disease and may be a naturally occurring virus or artificially attenuated. The main advantage of this vaccine is its ability to induce high, sustained levels of immunity. Disadvantages include cumbersome manufacturing, which in some cases leads to an unstable product both biochemically and genetically, the possibility of contamination, and safety concerns associated with provoking an unwanted infection or disease.

The Vaccine Market

The market potential for vaccines in developing countries is quite large. Every year, approximately 64 million infants are born in low-income countries and another 48 million are born in middle-income countries. Over the next 10 years, however, it is projected that the size of the birth cohort for low and middle-income countries could increase by approximately 133 million.

With some exceptions, large multinational firms have not made investments in vaccine development that are equal to the magnitude of the problem. In 1992, only 4% of the US$55.8 billion spent on global R&D went toward disorders that account for most of the disease burdening the low and middle-income countries. The situation had not changed much by 2000, when 10% of global research funds were dedicated to 90% of the diseases that affect the world's poorest people.

While it is true that much of the investment in R&D for industrialized countries furthers platform technologies that will benefit the development of many vaccines, R&D dedicated to the needs of the developing world remains slow. Looking only at pharmaceutical investments specific to the developing world, a 1999 study found that only 1% of drugs to reach market between 1975 and 1997 were approved specifically for diseases relevant to developing countries.

In addition, industrial market producers seem to be moving away from the production of what are typically low-margin vaccines, or vaccines that are used mainly in the developing world. For example, the number of licensed manufacturers of yellow fever vaccine has declined markedly in the past few years. The number of industrial market manufacturers supplying the low-margin vaccines used in industrialized countries is also declining. The United States offers an extreme example of this phenomenon, as from the 1970's to today, the number of FDA licensed vaccine manufacturers to the United States CDC has declined. The trend is true of global manufacturers as well. While new participants are emerging to fill these voids, they have not replaced the multinational manufacturers, in some cases contributing to recent vaccine shortages.

Vaccine Sales

Global revenues from the sale of vaccines are expected to reach nearly $10 billion in 2006, up from $5.4 billion in 2001. The total vaccine market is expected to have a 13% compound five-year sales growth. Comparatively, global drug sales reached only 8% during a 10-month period in 2002. The infant section of the vaccine market had sales of $2.5 billion in 2001 and currently makes up the largest section of the vaccine market. However, this could change as the demand for flu shots for the elderly and vaccines for adult tourists continues to grow. Moreover, with the looming threat of bioterrorism, a new business of supplying smallpox vaccines has emerged in response to fears that the virus might be used as a weapon.

Four large pharmaceutical companies—Aventis Pasteur, GlaxoSmithKline, Wyeth and Merck—currently account for the majority of vaccine sales. Several other smaller companies, including PowderJect Pharmaceuticals, Acambis PLC (ACAM-NASDAQ), Berna Biotech AG (BBITF.PK), and Chiron are beginning to become known.

Demand for Vaccines

The following factors suggest that demand for vaccines could more than double by 2010:

- *Increased population density and animal proximity leads to increased exposure to infectious diseases and an increase in pathogen-caused epidemics (e.g., avian influenza and SARS).* With the global population growing from 2.5 to 5.8 billion over the last 25 years, large urban centers throughout the developing world are overcrowded and have inadequate sanitation, ideal for the emergence of infectious diseases. By 2025, the global population is expected to reach 8.6 billion. In developing countries, this represents an 84% increase, which intensifies overcrowding in these areas.

- *An aging global population that is more vulnerable to infectious diseases.* In industrialized countries, an aging population base, the advent of immunosuppressive medications, and the emergence of HIV are combining to increase the risk for opportunistic infection.

- *Increasing global travel leading to the spread of infectious diseases.* With increased travel, clinicians see increasing numbers of patients with exotic diseases acquired abroad. Recent migration of epidemic diphtheria from the former Soviet Union to Europe and the emergence of multidrug-resistant tuberculosis (TB) in the United States and elsewhere are two examples of infections resulting from international travel. In addition, nearly 70% of the fruits and vegetables consumed in the United States originate in developing countries; disease outbreaks related to imported food frequently go unreported.

- *Unlimited capacity of pathogenic organisms to mutate and rapidly adapt to environmental changes and selective pressures.* Extensive cross-species contact among humans and certain domestic animals can dictate antigenic shifts in influenza viruses. The likelihood of the emergence of a new influenza virus in the near future increases with the growth of the hog population in China. The emergence of new viruses, such as HIV and **filoviruses**, indicates the virtually unlimited capacity of pathogenic organisms to mutate and rapidly adapt to environmental changes and selective pressures.

- *Broadening vaccination recommendations.*

- *Government bio-defense initiatives that include funding for vaccine development and vaccine stockpiling preparedness programs.*

Crucell's Vaccine Development Program

Crucell is employing its PER.C6® technology to develop a range of novel vaccines, including several co-developed products through collaborations and strategic alliances with biotechnology companies, governmental, and non-governmental organizations. Specifically, the Company is focused on creating vaccines against influenza, Ebola, West Nile virus, and malaria. In the sections to follow, we describe each of these conditions and the Company's efforts to create a vaccine to treat the particular virus. We begin with influenza, given Crucell's development agreement with Aventis Pasteur.

Influenza

Influenza, commonly called the flu, is a highly contagious infection of the respiratory tract that spreads from person-to-person through infectious respiratory secretion droplets caused by coughing or sneezing. Influenza outbreaks occur almost every year and their severity varies considerably. One unique aspect of influenza compared with other viruses, is its ability to perpetually change over time, usually by mutation. This characteristic enables the virus to evade the immune system of its host, making individuals susceptible to the flu throughout their entire life. When infected with the virus, an individual develops an antibody that works against that virus. Once the virus changes, however, the previous antibody is unable to recognize it, necessitating an entirely new antibody to fight off the virus. These modifications make it necessary for individuals to receive a different influenza vaccination each year, compared with one vaccination that would grant lifetime immunity.

Influenza viruses can be divided into three distinct groups: Influenza A, B, and C. Influenza A and B cause epidemics of disease nearly every winter, initiating widespread infection and high mortality rates. Strains of influenza A and B viruses, which are set apart by different protein structures, are included in yearly vaccines. Influenza C, which causes only mild respiratory illness, is not treatable through a vaccine. While the type C may yield similar symptoms to types A and B, it does not cause epidemics and, many times, does not cause symptoms at all.

Table 7
LEADING CAUSES OF DEATH, UNITED STATES (2001)

Cause of Death	Number of Deaths	Percentage
Heart Disease	700,142	36.8%
Cancer	553,768	29.1%
Stroke	163,538	8.6%
Chronic Low Respiratory Disease	123,013	6.5%
Unintentional Injury	101,537	5.3%
Diabetes	71,372	3.8%
Influenza and Pneumonia	**62,034**	**3.3%**
Alzheimer's Disease	53,852	2.8%
Nephritis	39,480	2.1%
Septicemia	32,238	1.7%
TOTAL	**1,900,974**	

Note: Most current figures reported by CDC.

Source: CDC.

Demand for influenza vaccines to either prevent or treat this virus is expected to more than double by 2010, driven by risks of a new influenza pandemic, SARS, the world's ageing population, and broader government vaccination recommendations. The U.S. CDC recently lowered the recommended age for vaccination from 65 to 50 and expects to add infants between the ages of six and 23 months in the 2004-5 season. Across Asia, governments already have broadened their vaccination recommendations to minimize confusion between influenza and SARS infections, with Singapore now recommending annual influenza vaccination for the entire population. In Europe, recommendations could also evolve in future years. For example, since the beginning of 2003, influenza vaccination has been encouraged in Belgium for those from 50 to 65 years of age.

Morbidity and Mortality

Each year approximately 10-20% of the world's population contracts influenza. An estimated 250,000 to 500,000 people die annually from influenza-associated complications. Occasionally a major genetic shift in the influenza virus results in a deadly new virus strain to which the human population does not have immunity, and a global pandemic outbreak occurs. The Spanish influenza pandemic, the most severe outbreak of influenza to date, occurred from 1918 to 1920 and caused an estimated 20-40 million deaths worldwide.

While the flu affects individuals of all ages, approximately 90% of flu-related deaths occur among individuals above the age of 65. People with chronic medical conditions and young children are also at higher risk to suffer from complications of influenza. Table 7 (page 16) provides a snapshot of influenza and influenza-related pneumonia's position among the leading causes of death in the United States.

Symptoms

Influenza leads to a variety of symptoms, ranging from mild to severe. While symptoms usually abate within one to two weeks, the virus can often lead to further, life-threatening complications, such as pneumonia. One of the largest misconceptions about influenza is that the stomach flu describes a condition caused by bacteria or parasites that can cause vomiting, diarrhea, and nausea. While it is widely believed that these symptoms are related to influenza, stomach flu is, in fact, a separate condition rarely related to the virus. Table 8 provides a snapshot of some of the most common symptoms of influenza.

Table 8
SYMPTOMS OF INFLUENZA

Fever (usually 100-103° F in adults and often higher in children)
Cough
Sore throat
Runny or stuffy nose
Headache
Muscle aches
Extreme fatigue

Source: MedicineNet.com.

Treatment and Prevention

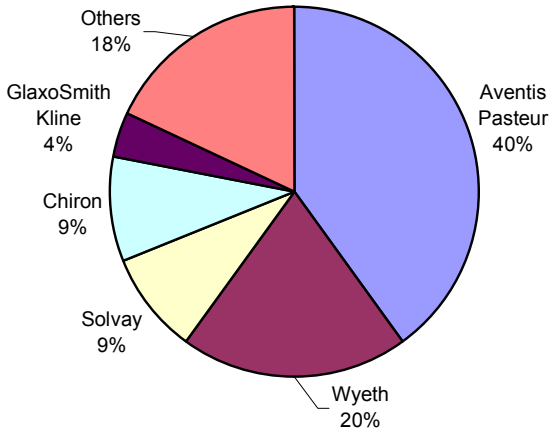
The most effective way to counter influenza is to receive an influenza immunization. Vaccination has shown to be successful in protecting against dangerous influenza-related complications that could lead to hospitalization and death. The overall effectiveness of the yearly vaccine is dependent on its ability to match the strains that cause the illness. According to the National Foundation for Infectious Diseases, the influenza vaccine can prevent disease symptoms in 70-90% of healthy young adults. In very frail elderly individuals, however, success may be as low as 30-40% due to their inability to make protective antibodies.

Current influenza vaccines administered via injection are based on inactivated (killed) whole viruses that are grown in chicken eggs, harvested, chemically inactivated, and processed into vaccines. Throughout the multi-stage manufacturing process, the vaccine is then purified and tested for consistency, safety, and its ability to stimulate antibody production.

Influenza vaccine manufacturers include particular strains of the virus for inclusion in the vaccine, based on annual recommendations received from the World Health Organization (WHO).

The leading influenza vaccine manufacturers currently include Aventis Pasteur (40%), Wyeth (20%), Solvay (SVYSY.PK) (9%), Chiron (9%), GlaxoSmithKline (4%), and others (18%), as shown in Figure 1.

Figure 1
LEADING INFLUENZA MANUFACTURERS



Source: Crucell, Kempen & Co.

Current Influenza Vaccine Efforts

The traditional influenza vaccine is administered with a half-inch to one-inch needle, where approximately one-tenth of a teaspoon of fluid is injected in the upper arm muscle. While only one shot is needed for older individuals, previously unvaccinated children below nine years of age may require two doses, given a month apart. Timeliness is also paramount to thwarting influenza. Individuals are encouraged to receive the vaccine in the fall (October through November), since the epidemic typically peaks in the winter.

Wyeth/MedImmune

FluMist™ Influenza Virus Vaccine Live, Intranasal, was a relatively new entrant to the vaccine market, launched in June 2003. Manufactured by MedImmune Inc. (MEDI-NASDAQ) and marketed by Wyeth, FluMist™ was indicated for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents, five to 17 years of age, and in healthy adults, 18 to 49 years of age. On April 26, 2003, Wyeth announced that it had dropped its rights to the nasal flu vaccine, giving MedImmune Inc. rights to the product after disappointing sales in the last U.S. flu season. The vaccine was very expensive, difficult to store, and not approved for those who needed it most. MedImmune, which is developing an improved version of the vaccine, had previously said that an end to the companies' marketing agreement might be likely. In the latest flu season, MedImmune sold 900,000 doses of FluMist™, of which about 50% were returned because of lack of demand. Sales were disappointing in part because the vaccine needs to be frozen and cannot be prescribed for young children and the elderly, the most important population for flu vaccines. MedImmune is developing a new version that does not need to be frozen and would be available for children and seniors.

Baxter

Baxter (BAX-NYSE) is developing an inactivated whole virus vaccine produced using VERO (monkey kidney) cells, and has obtained product registration in Austria. Product launch is set for 2005. Solvay is also making a cell-based vaccine using MDCK (Madin Darby Canine Kidney cells), and has obtained product registration in the Netherlands. Other competitors with cell-based vaccines such as Shire Pharmaceuticals Group PLC (SHPGY-NASDAQ) and Chiron have either slowed down or stopped their development program. There is increasing pressure from regulatory agencies and the WHO to move away from egg-based flu vaccines and towards high-quality cell-based products. Solvay and Baxter are both developing vaccines using anchorage-dependent cells requiring expensive micro-carriers (small plastic “beads”) for their growth in bioreactors.

Crucell’s Flu Vaccine

In December 2003, Aventis Pasteur and Crucell entered into a strategic agreement to further develop and commercialize novel influenza vaccine products based on Crucell's PER.C6® technology. The agreement covers both pandemic and epidemic influenza vaccines, which up to now have been part of Crucell's in-house product development program. Under the terms of the agreement, Aventis Pasteur receives an exclusive license to research, develop, manufacture, and market cell-based influenza vaccines using PER.C6® technology. Crucell expects to receive milestone payments, annual payments, and R&D funding totaling €30 million (USD $38 million), and high single- up to double-digit royalties on future PER.C6®-based influenza vaccine sales. Crucell retains the commercialization rights for Japan, which accounts for 15% of the global influenza vaccine market which totaled €1.2 billion (USD $1.5 billion) in 2002. For Japan, Aventis Pasteur expects to supply finished vaccine products to Crucell, and Crucell plans to pay a royalty on sales to Aventis Pasteur. Aventis Pasteur is the world leader in the production and marketing of influenza vaccines. In 2002, Aventis Pasteur's consolidated influenza vaccine product sales totaled €460 million (USD $579 million), representing a 40% global market share.

Benefits of Aventis Pasteur Partnership

Aventis Pasteur expects to undertake process development, production scale-up to manufacturing quantities, clinical development and regulatory affairs, while Crucell expects to undertake some parts of upstream process development and pandemic research, and any additional clinical development required for Japan. Aventis Pasteur also plans to fund all of the R&D, except for any development required specifically for Japan, which Crucell expects could primarily be limited to regulatory approval costs.

The Company believes that this partnership validates Crucell's cell-based influenza product as an attractive vaccine and could place Crucell as a participant in the worldwide vaccine market. It also reduces the risk profile of the Company. By combining Crucell's production technology with the manufacturing and marketing strength of Aventis Pasteur, Crucell could benefit in a number of ways:

- Gain a solid position in the vaccine market;
- Strengthen the Company's overall financial position in the short as well as long term;
- Free up resources for other in-house development programs; and
- Endorse PER.C6®'s status as the industry standard for vaccine production.

Additionally, now that Aventis Pasteur pays for the development of the vaccine and makes payments along the way, Crucell can allocate more resources to its existing programs. Crucell made the decision to go forward with its influenza vaccine development program in the second half of 2003. The Company is currently developing upstream processing to support the production of diverse influenza virus strains (epidemic and pandemic flu strains), and is developing a clinical grade purification process for whole-inactivated influenza vaccines. It is expected that use of Crucell's PER.C6® technology could result in a higher quality product with lower cost of goods versus competitive cell-based flu vaccine products.

Benefits of PER.C6® Technology

Based on testing under laboratory conditions, the main advantages of Crucell's PER.C6® technology for influenza vaccine production are ease of scalability, a cleaner, more stable process, greater speed of production, and increased production flexibility. From a safety standpoint, the use of a human cell-based production system addresses concerns over egg-associated allergies, giving the vaccine a key advantage over the current production methods.

Market for Influenza Vaccines

The global market for influenza vaccines in 2002 was €1.2 billion, of which Aventis Pasteur had a market share of 40% (€450 million). Based on this new agreement with Aventis Pasteur, Crucell believes that it is in a solid position to benefit given the value of its PER.C6® production technology combined with the expansion of the global flu vaccine market.

Ebola

Ebola hemorrhagic fever, (also called Ebola HF or Ebola) is a severe, often-fatal disease in humans. It is also fatal in monkeys, gorillas, and chimpanzees. Ebola was named after a river in the Democratic Republic of the Congo in Africa, where it was first recognized in 1976. Ebola HF usually appears in sporadic outbreaks, and spreads within a health-care setting. Researchers do not know exactly how Ebola is spread; however, they have strong reason to believe that the first patient becomes infected through contact with an infected animal. The Ebola virus is then spread from human to human by direct contact with the blood and/or secretions of an infected person or contact with objects, such as needles, that have been contaminated with infected secretions. In Africa, Ebola virus is transmitted from an unknown reservoir (possibly bats) to humans, and between humans through contact with the extremely infectious body fluids of Ebola patients. Humans have also been infected when handling great apes that have died of Ebola fever.

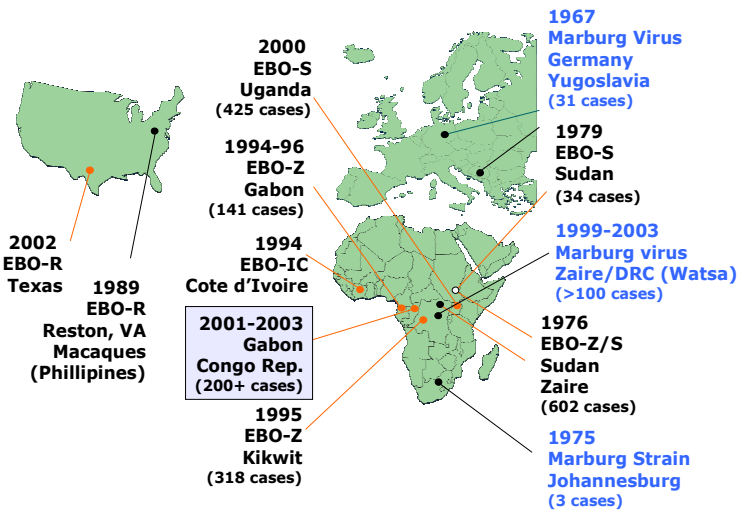
Morbidity and Mortality

Ebola is one of the most feared viral diseases, with a mortality ranging from 50% to 80%. Ebola outbreaks occur annually in tropical Africa, affecting both humans and great apes. To date, approximately 2,000 cases have been reported since the first detection of the virus in 1976. The Ebola virus belongs to the group of "viral hemorrhagic fever viruses", which also includes the highly destructive diseases caused by the Marburg and Lassa viruses. The virus causes a disease characterized by high fever and massive internal bleeding. Since no vaccine or therapy is presently available, the Ebola virus is on the CDC, NIAID, and U.S. Department of Defense Category A list of bioterror agents.

Geographical Distribution

Figure 2

EBOLA AND MARBURG HAEMORRHAGIC FEVER OUTBREAKS



Source: Crucell N.V.

The Ebola virus is a member of the family of **filoviruses**, which cause human disease in remote areas of Central, East, and West Africa, namely Sudan, Uganda, Republic of Congo, Congo, Gabon and Côte d'Ivoire (Ivory Coast), as shown in Figure 2.

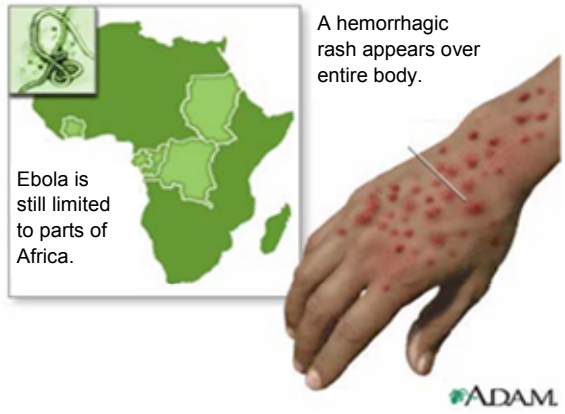
There are three species of the Ebola virus that are pathogenic to man (Sudan, Zaire, and Côte d'Ivoire), and one that is pathogenic for monkeys only (Reston). The Ebola strain that causes disease only in monkeys has been repeatedly imported through the monkey trade, which spans from Asia to the United States and Europe.

Recent Ebola epidemics among gorillas in Central Africa, together with pervasive hunting activities in the region, are capable of pushing these primates to extinction. Even though the Ebola virus is not transmitted as an aerosol (like the influenza virus), its containment requires very strict quarantine measures to prevent large epidemics. There are significant concerns among governments today that the Ebola virus was used to create bio-weapons in secret military programs during the 1970's and 80's.

Symptoms

The incubation period for Ebola is between two to 21 days. After this period, the Ebola virus rapidly spreads throughout the body, infecting nearly all organs, including cells of the immune system. The patient abruptly develops a high fever, headache, muscle pain, abdominal pain, and profound weakness. A rash typically occurs throughout the body as shown in Figure 3 and damage to the inner lining of the blood vessels causes loss of plasma fluid and spontaneous, often massive bleeding into body cavities. The patient eventually dies of low blood pressure and generalized organ failure. A snapshot of the early and advanced symptoms of Ebola is provided in Table 9.

Figure 3
RASH RESULTING FROM EBOLA VIRUS



Source: A.D.A.M.

Treatment and Prevention

There is no specific antiviral therapy for Ebola patients. Although good supportive treatment may reduce mortality rates, it is logistically difficult to install such support measures in Africa and doing so puts the nursing staff at considerable risk of contracting the disease. To date, there is no licensed vaccine for any filovirus infection.

Table 9
SYMPTOMS OF EBOLA

Early	Advanced
Malaise	Conjunctivitis
Fatigue	Generalized rash, hemorrhagic
Headache	Roof of mouth assumes a red color
Sore throat	Genital swelling (labia and scrotum)
Lower back pain	Depression
Nausea	Increased sense of pain in skin
Vomiting	Gastrointestinal bleeding (from mouth and rectum)
Diarrhea	Bleeding from eyes, ears, and nose
Arthritis	Seizures, coma, delirium

Source: University of Maryland.

As the natural source of the Ebola virus remains unknown, refraining from touching dead apes is the only valid recommendation that can be given to prevent accidental human infection in Africa. To prepare for the importation of Ebola patients by air travel, quarantine facilities have been implemented in hospitals of all major cities in industrialized countries. Additionally, as new terrorism concerns emerge, many experts fear that dangerous viruses might be used in future terrorist assaults, against which only emergency vaccination would provide protection.

Due to the Ebola virus' high mortality, human-to-human transmissibility, and the risk of accidental or deliberate spread of the virus, the availability of a vaccine against this deadly agent is currently considered a Public Health priority in the United States. The U.S. government has announced that once available, an Ebola vaccine will 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 or other dangerous pathogens.

Additionally, people living in Ebola-affected regions of Africa would greatly benefit from single shot—emergency vaccinations—that could be given at the onset of a new outbreak. A preventive vaccine using a common "prime-boost" administration schedule would be important for doctors, nurses, aid-workers, and other personnel preparing to work in future Ebola outbreak environments.

Crucell's Ebola Vaccine

Numerous attempts to vaccinate against Ebola virus using inactivated virus or protein-based vaccine modalities have failed in the past, and developing a live attenuated vaccine is considered too dangerous. However, it has been shown that a single-dose immunization with a recombinant adenovirus (expressing Ebola virus proteins) vaccine solidly protects monkeys against a lethal challenge with wild-type Ebola virus. Based on these results, Crucell is developing an Ebola vaccine.

The Company has entered into a CRADA with the Vaccine Research Center (VRC) of the NIH in the United States to jointly develop, test, and manufacture an adenovirus-based Ebola vaccine. Under the terms of the agreement, Crucell has 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 the Ebola virus, which cannot be replicated 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. The vaccine is produced using the Company's PER.C6® technology, making commercial-scale manufacturing of the vaccine possible.

Crucell's Ebola vaccine is targeted toward travelers, government officials, military and healthcare personnel, and people living in Ebola endemic areas in Africa. In addition, the vaccine could provide protection from the lethal virus in the event of biological warfare.

Under a production contract with NIH, Crucell is manufacturing adenovirus Ebola vaccine vectors according to current Good Manufacturing Practice (cGMP) requirements to be used in clinical trials. In 2002, the FDA issued the so-called **"two animal rule"**, which states that efficacy studies in man are not required to obtain a product license for special categories of products as long as efficacy is established in two independent animal models and safety in man.

Crucell's Ebola vaccine may be a candidate for regulatory approval under the two animal rule, as the number of actual cases of Ebola is too limited to obtain sufficient evidence of efficacy in a reasonable period of time. Additionally, outbreaks are often in areas that are difficult to reach rapidly due to location and/or civil unrest. The performance of challenge studies in human beings to demonstrate efficacy is considered unethical for this type of product. The use of the two animal rule could potentially expedite the approval process.

West Nile Virus

The West Nile virus is one of the most pressing global health issues facing the medical community today. Named for the West Nile District of Uganda where the disease was discovered in 1937, the virus possesses the ability to inflict mortality on humans, as well as animals, by manifesting itself as a fatal form of encephalitis, or inflammation of the brain. Health authorities now view the virus as a recurring threat, surfacing every summer with warm and humid weather. Continued efforts are underway to find suitable treatments and vaccines to stop this virus. U.S. public health officials are predicting that the virus could continue to spread to cover the whole country this year. Currently, there is no vaccine available to protect humans against infection with West Nile virus.

Morbidity and Mortality

It is estimated that 20% of the people who become infected with the West Nile virus develop West Nile fever. Persons over 50 years of age have the highest risk of developing a severe disease, such as **meningitis**, an inflammation of the membrane around the brain and the spinal cord, or encephalitis, inflammation of the brain. It is estimated that one in 150 persons infected with the West Nile virus develop a more severe form of disease. Since 1999, the West Nile virus has caused disease in more than 13,000 U.S. citizens, killing over 500.

Geographical Distribution and Transmission

The first known outbreak of West Nile virus occurred in Israel in 1951, followed by subsequent outbreaks in the late 1950's and early 1960's in Egypt and France. Recent epidemics of West Nile fever occurred in Northern Africa, the Middle East, Asia, and Europe between 1994 and 2000. West Nile virus was first detected in the Western hemisphere in 1999 during an outbreak in the New York City metropolitan area involving humans, horses, and birds. Since then the virus has extended its reach through much of the U.S., northern Mexico, and the southern provinces of Canada.

The main route through which humans can contract infection with the West Nile virus is through the bite of infected mosquitoes. Mosquitoes become infected when they feed on infected birds, which may circulate the virus in their blood. The virus eventually gets into the mosquito's salivary glands. Infected mosquitoes can then transmit the West Nile virus to humans and animals while biting to take a blood meal. Figure 4 (page 24) provides a snapshot of the transmission cycle.

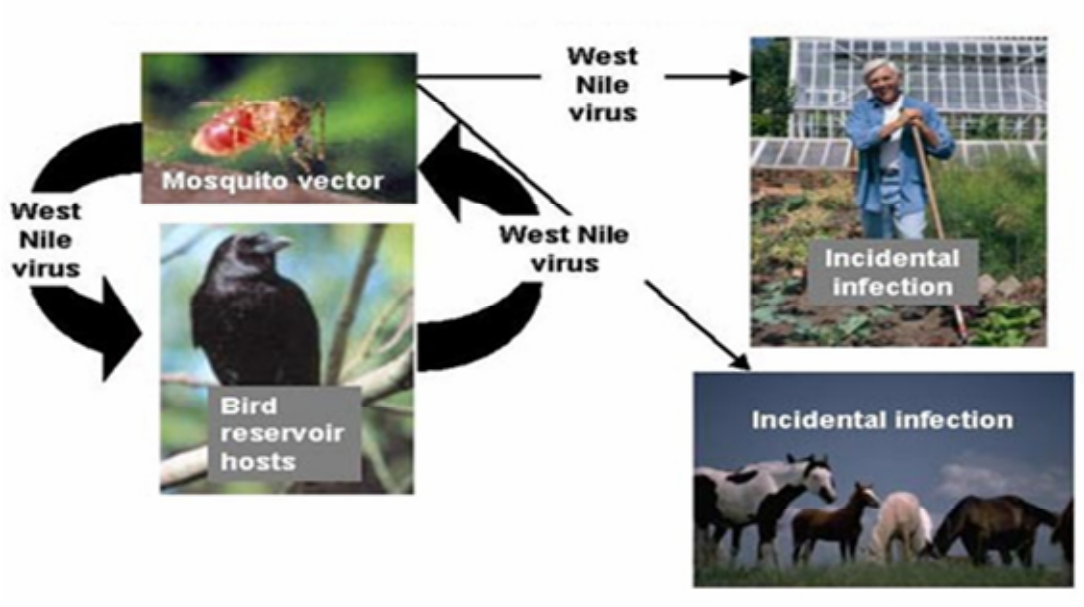
Due to the widespread nature of mosquito populations and the ability of the West Nile virus to replicate in a wide variety of mosquitoes and in over 160 species of birds, the West Nile virus represents a serious global health threat. Table 10 provides an overview of the countries where West Nile virus activity has recently been reported. Figures 5 and 6 (page 25) provide maps of the United States, indicating where cases have been reported, as well as the number of cases and deaths specifically reported through December 2003.

Table 10
RECENT CASES OF WEST NILE VIRUS

Country	Date
Algeria	1994
Romania	1996-1997
Czech Republic	1997
Democratic Republic of Congo	1998
Russia	1999
United States	1999-2001/2001-2003
France	2000

Source: CDC.

Figure 4
WEST NILE VIRUS: TRANSMISSION CYCLE



Source: CDC.

Symptoms

Table 11
SYMPTOMS OF WEST NILE VIRUS

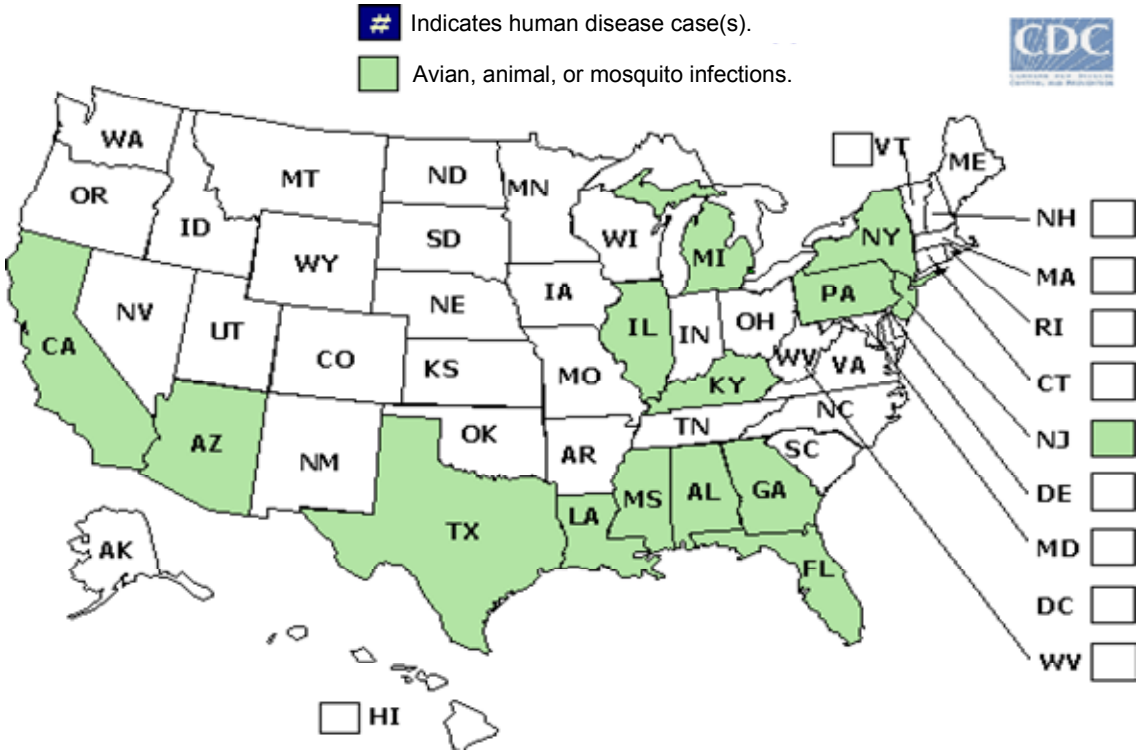
Mild Symptoms	Severe Symptoms
Fever	High fever
Headache	Headache
Back pain	Neck stiffness
Muscle aches	Stupor
Lack of appetite	Disorientation
Sore throat	Coma
Nausea	Tremors
Vomiting	Convulsions
Abdominal pain	Muscle weakness
Diarrhea	Vision loss
	Numbness
	Paralysis

Source: CDC.

West Nile fever usually appears within 3-14 days after infection. It is characterized by mild symptoms, including fever, headache, and body aches and occasionally a skin rash on the trunk of the body and swollen lymph glands. A snapshot of these symptoms is provided in Table 11. The symptoms of severe infection include headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness, and paralysis. Although West Nile fever does not appear to cause any long-term health effects, symptoms of severe disease may last several weeks and neurological effects may be permanent.

Figure 5

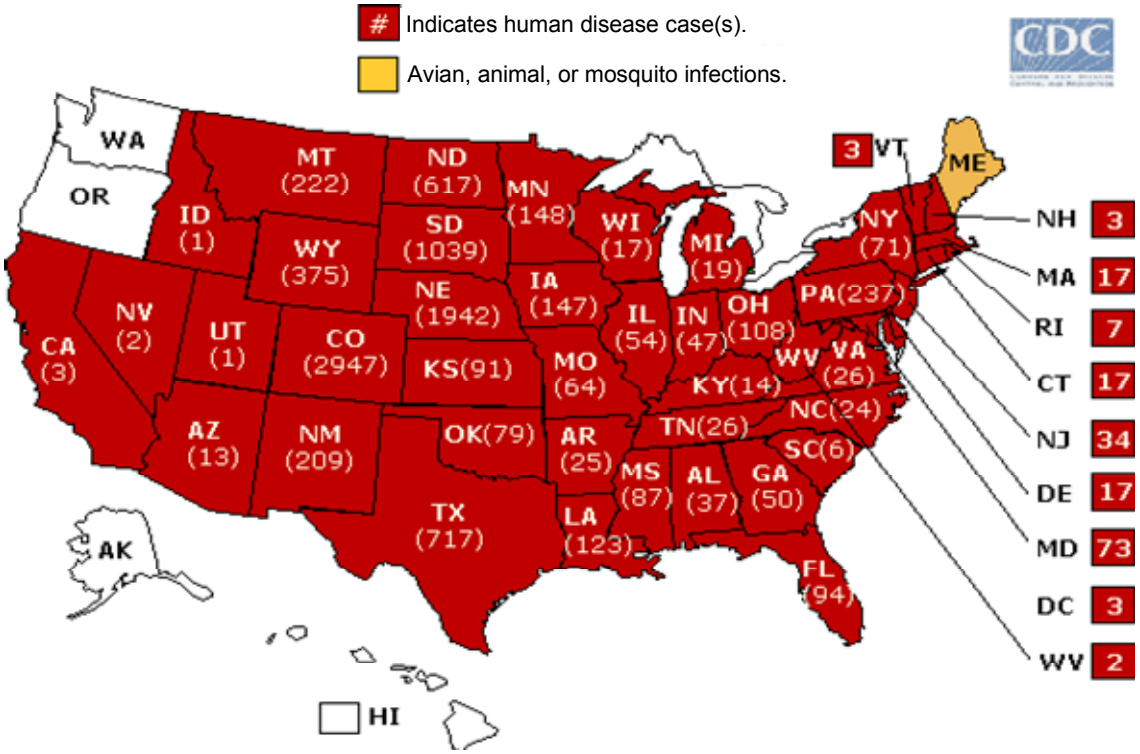
2004 WEST NILE VIRUS ACTIVITY IN THE U.S. (REPORTED TO CDC AS OF MAY 19, 2004)



Source: CDC.

Figure 6

WEST NILE VIRUS: INCIDENCE IN 2003 (THROUGH APRIL 14, 2004)



Source: CDC.

Treatment and Prevention

Since mosquito bites represent the most viable means of transmitting the virus, preventive measures are focused on the avoidance and elimination of the insect. In order to avoid being bitten, individuals are urged to use mosquito repellent and wear long sleeves and trousers. Also, since mosquitoes breed in stagnant water, these areas should be drained and regularly observed. Finally, the use of screens on windows and doors is another advised method of mosquito protection.

In terms of treatment, there are no specific antiviral drug treatments available for West Nile virus. Likewise, there are no licensed vaccines against West Nile virus for prevention of disease in humans. There are, however, a variety of companies and institutions that are actively involved in developing vaccines against West Nile virus. A snapshot of these companies is provided in Table 12, followed by details of these efforts.

Table 12
VACCINES IN DEVELOPMENT FOR WEST NILE VIRUS IN HUMANS

Institution	Headquarters	Technology
Acambis plc	Cambridge (UK) and MA	Vaccines based on live attenuated virus
Baxter-Immuno, Orth/Donau	Austria	Formalin-inactivated cell culture vaccine
Hawaii Biotech	Honolulu, HI	Genetically engineered subunit vaccine
U.S. National Institute of Allergy and Infectious Diseases (NIAID)	Bethesda, MD	Vaccines based on live attenuated virus
University of Queensland	Brisbane, Australia	Vaccines based on live attenuated virus
Vical Inc.[1]	San Diego, CA	Development and pre-clinical evaluation of DNA vaccines

[1] *Cooperative Research and Development Agreement (CRADA) with the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), an agency of the U.S. Department of Health and Human Services, for the development and pre-clinical evaluation of DNA vaccines against the West Nile Virus*

Source: Crucell N.V.

Acambis. Of the companies highlighted above, Acambis is the most advanced in their West Nile virus vaccine development program. The Company is conducting a Phase I clinical safety study in humans with its West Nile ChimeriVax vaccine. This vaccine uses a genetically engineered yellow fever 17D live virus containing the genes encoding the antigens responsible for protection against West Nile virus.

Baxter-Immuno, Orth/Donau. Baxter-Immuno have an inactivated tick-borne encephalitis (TBE) vaccine that is marketed in Europe. TBE formalin-inactivated cell culture contains 2 doses, given 2-13 weeks apart, with a booster after 1 year and a re-boost every 3- 5 years. The TBE vaccine has shown >95% seroconversion after two doses. Using this same technology, a vaccine is being developed for inactiviated West Nile virus.

Hawaii Biotech. The Company's vaccine technology is based on the production of proprietary antigens using the Drosophila expression system. These proteins have native conformational characteristics that, when combined with modern adjuvants, result in protective immune responses in relevant animal models. This technology is applicable to a number of viral diseases including dengue fever, malaria, West Nile, and hepatitis C, although its lead vaccine project is a dengue fever vaccine.

National Institute of Allergy and Infectious Diseases (NIAID). Using similar technology whereby genes in a live dengue virus type 4 were replaced with the corresponding genes of West Nile virus, coding for its protective proteins, NIAID has successfully completed preclinical studies in monkeys with its West Nile virus vaccine. Human clinical trials with this vaccine are expected to begin by late summer 2004, pending FDA approval.

University of Queensland. Australian scientists at the University of Queensland successfully immunized mice against the West Nile virus using a DNA vaccine that led to live and replicating Kunjin virus in the animals. Although Kunjin virus is genetically closely related to the West Nile virus, it only rarely causes disease in humans.

Vical Inc. Vical's DNA vaccines use portions of the genetic code of a pathogen to cause the host to produce specific features of the pathogen that may induce an immune response. This method potentially offers superior safety, ease and reliability of manufacturing, as well as convenient storage and handling characteristics, compared with conventional vaccines that use live, weakened, or dead pathogens to produce an immune response. DNA vaccines have the ability to induce potent T-cell responses against target pathogens as well as to trigger production of antibodies.

Non-human efforts. A veterinary formalin-inactivated vaccine produced on cell culture and developed by Fort Dodge Animal Health, received full-license status from the USDA in early 2003. The vaccine was shown to be safe and effective for prevention of West Nile disease in horses. The same company has also initiated development of a DNA vaccine for horses. An inactivated vaccine approach has also been used by the Kimron Veterinary Institute of Israel to protect young domestic geese against West Nile disease (see section below). The vaccine, produced on the brains of mice, protects 100% of the geese against a lethal dose of the West Nile virus injected directly into the geese's brains.

Crucell's West Nile vaccine

In June 2003, Crucell announced its decision to develop a vaccine against the West Nile virus based on its PER.C6® technology. The Company's vaccine uses an inactivated whole virus concept, which is different from vaccines currently under development by its competitors. Currently, there is no vaccine or antiviral therapy available to protect humans against the West Nile virus. To date, Crucell has concluded preclinical studies in a geese animal model with its experimental West Nile virus vaccine. These initial studies demonstrated disease-free survival in the geese following a lethal challenge dose of the virus. Geese are susceptible to, and usually do not survive, infection with the West Nile virus. The geese animal model, therefore, represents a solid preclinical animal model for testing West Nile vaccines.

The Company has stated that it believes that the results of these preclinical studies are encouraging, demonstrating that a PER.C6®-based vaccine protects against the Israel 1998 Goose strain of the West Nile virus. The fact that this strain is closely related to the New York 1999 strain, which caused the West Nile outbreaks in the U.S., triggered their decision to develop a West Nile vaccine for humans.

Collaboration with Kimron Veterinary Institute. In a separate but related program, Crucell entered into collaboration with the Kimron Veterinary Institute of Israel, wherein they have granted Kimron a license to its PER.C6® technology to develop a West Nile veterinary vaccine for use in geese and other birds in Israel. Kimron intends to replace its existing West Nile veterinary vaccine, which is produced using mouse brain cells, with the PER.C6®-based vaccine. Under the terms of the agreement, Kimron has commercial rights to the PER.C6®-based West Nile veterinary vaccine in Israel, and expects to pay Crucell specific fees based on sales of future product doses. Crucell retains the commercial rights to the vaccine outside of Israel. This veterinary vaccine is targeted for registration in Israel in 2004.

Collaboration with Pfizer Animal Health. Additionally, in December 2003, Crucell entered into an agreement with Pfizer Animal Health (Pfizer) granting Pfizer an option on Crucell's PER.C6® technology for the development and commercialization of a West Nile virus veterinary vaccine for use in horses.

Malaria

Malaria is a life-threatening parasitic disease transmitted by mosquitoes. It was once believed that the disease came from fetid marshes, hence the name mal aria, (bad air). In 1880, however, scientists discovered the true cause of malaria is a one-cell parasite called **plasmodium**. Later they discovered that the parasite was transmitted from person to person through the bite of a female **Anopheles mosquito**, which requires blood to nurture her eggs.

Morbidity and Mortality

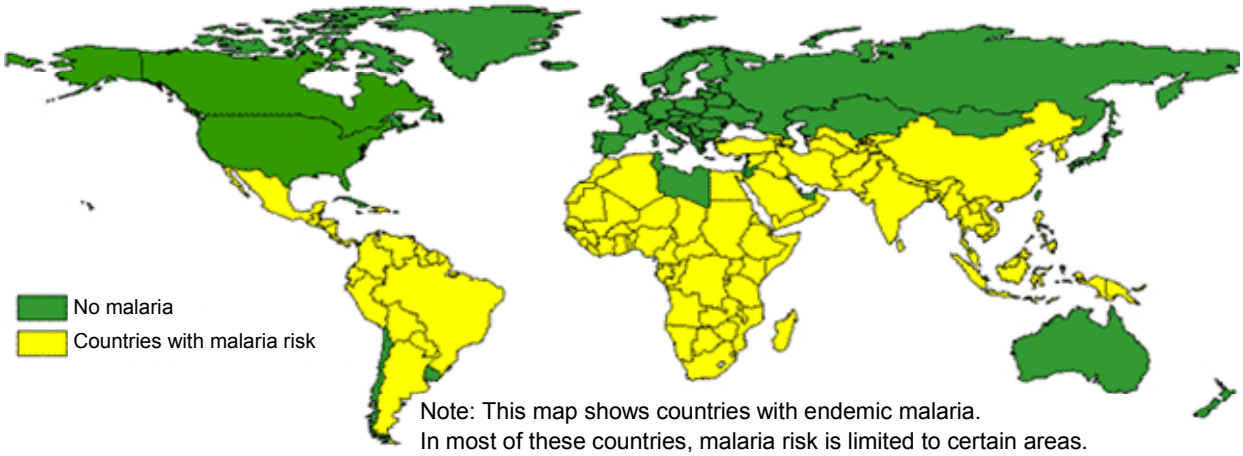
Malaria is one of the top three killers among communicable diseases. Together with HIV/AIDS and TB, malaria is one of the major public health challenges undermining development in the poorest countries in the world. In fact, malaria currently represents one of the most prevalent infections in tropical and subtropical areas, causing severe illness in 300-500 million individuals worldwide, 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, the 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. Each year, approximately 30,000 individuals traveling from industrialized nations to the developing world contract malaria, with more than 1,000 cases of malaria reported to the United States CDC.

Geographical Distribution and Transmission

Currently, approximately 40% of the world's population, mostly those living in tropical and subtropical regions, is at risk of contracting malaria, as shown in Figure 7.

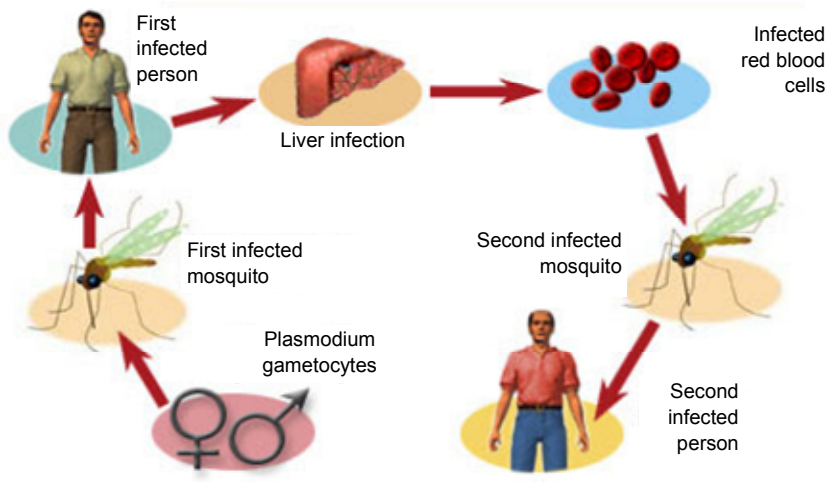
Figure 7
MALARIA-ENDEMIC COUNTRIES



Source: CDC, DPDx.

Malaria parasites are transmitted to humans by the bite of female Anopheles mosquitoes. Infected mosquitoes inject the malaria parasites into the bloodstream, where they remain for a few minutes before invading the liver cells. Once in the liver, the parasites replicate and develop for about one week until released into the bloodstream. The parasites then invade red blood cells, where they undergo several stages of **replication** and development before invading new red blood cells. When susceptible mosquitoes ingest infected blood, the parasite completes its maturation inside the insect's gut, finally migrating to the mosquito's salivary glands. The malaria life cycle, depicted in Figure 8, is perpetuated when the infected mosquito bites a new human host.

Figure 8
MALARIA TRANSMISSION CYCLE



Source: Actonvision.com.

Symptoms

Malarial symptoms appear about 9-14 days after the infectious mosquito bite, although this varies with different Plasmodium species. Typically, the symptoms of infection are flu-like and include chills, fever, and sweating, accompanied by headache, nausea, and vomiting. Life-threatening illnesses associated with severe anemia, impaired consciousness, coma, seizures (cerebral malaria), renal failure, and shock may occur in some infected individuals.

Treatment and Prevention

Malaria can be prevented through interventions that minimize the number of mosquitoes as well as effective chemotherapeutic agents, such as chloroquine and mefloquine. However, the use of drugs remains impractical in the majority of the developing world. Furthermore, the number of drug-resistant parasites and insecticide-resistant mosquitoes is increasing.

Currently, there is no commercially available vaccine against malaria, although the development of vaccines against malaria was initiated more than 30 years ago. Immunization of rodents, non-human primates, and humans with radiation-attenuated sporozoites conferred protection against a subsequent challenge with sporozoites. However, the lack of a feasible large-scale culture system for the production of sporozoites prevents widespread application of such vaccines.

Crucell's Malaria Vaccine

Crucell's candidate malaria vaccine is presently in the proof-of-concept stage of development. To develop an effective and safe malaria vaccine, Crucell has formed two collaborative development programs involving three leading malaria research organizations: NYU, GlaxoSmithKline, and WRAIR. Further, in March 2004, the NIAID agreed to support the development of Crucell's candidate malaria vaccine, in effect covering full preclinical costs.

Crucell's collaboration with NYU has already yielded favorable results. In a study carried out by the university, the efficacy of Crucell's malaria vaccine candidate was tested in NYU's mouse malaria model, which uses the mouse malaria parasite *Plasmodium yoelii*. The study showed that a single shot of a prototype vaccine (a recombinant adenovirus 35 (rAd35) vector expressing CSP) protects mice against infection with the mouse malaria parasite *P. yoelii*. Most recombinant vaccine systems are currently based on adenovirus 5 (Ad5). In contrast to Ad35, antibodies to Ad5 are widespread among humans and are known to lower the immune response to rAd5-based vaccines. In view of the prevalent pre-existing immunity to Ad5 in humans, these results suggest the superiority of the rAd35 vector as a potentially more effective malaria vaccine vector.

The second collaboration is with WRAIR and GlaxoSmithKline. The two parties, together with Crucell, have entered into a CRADA to evaluate Crucell's vaccine candidate directed against the human malaria parasite, Plasmodium falciparum. Crucell's vaccine candidate will be tested as a stand-alone or in combination with GlaxoSmithKline's malaria vaccine candidate, called RTS,S, and formulated in GlaxoSmithKline's proprietary adjuvant, AS01B.

The GlaxoSmithKline malaria vaccine candidate, RTS,S, formulated in a different adjuvant, AS02A, has been shown to confer partial protection to human volunteers in both a laboratory challenge model conducted at WRAIR and under natural challenge conditions in a field study conducted in Gambia. The tests, conducted under the CRADA, are designed to assess whether a combination of the GlaxoSmithKline vaccine candidate with Crucell's vaccine candidate can lead to improved results. The first results from the studies with WRAIR and GlaxoSmithKline are expected in the second quarter of 2004.

PER.C6® Technology

Crucell's cell-based PER.C6® technology represents an attractive option for the manufacturing of biopharmaceuticals. Derived from a single source of healthy human cells in a controlled, fully documented manner, PER.C6® technology employs an immortalized cell line achieved by inserting the E1 gene of an adenovirus into a healthy retinal cell, thereby allowing it to grow indefinitely. This feature enables the cell line to produce biopharmaceutical products in sufficient quantities for commercial production. PER.C6® technology is widely used within the biopharmaceutical industry, and is a key component to Crucell's in-house product development.

Unique Advantages

Designer Cell Line. PER.C6® technology was developed as a designer cell line. This means that all elements of the PER.C6® cell line and its origin are known and all information about the cell line has been carefully documented in a regulatory file kept with the FDA, called a Biologics Master File (BMF).

Biological. The use of a human cell line in PER.C6® technology has several key advantages over traditional production systems, beginning with its biological characteristics. PER.C6® technology can be used to produce fully human biopharmaceuticals, which are believed to demonstrate enhanced biological properties and potentially be more efficacious and less toxic than their non-human counterparts. PER.C6® technology also allows for the production of certain viruses that cannot be produced efficiently using non-human technologies.

Production. From a production perspective, PER.C6® technology holds several advantages. Individual PER.C6® cells can be cultured at high densities and engineered to produce large quantities of biopharmaceuticals. In addition, the cells can be grown in a serum-free medium, without microcarriers, in a closed bioreactor vessel. This allows for easy expansion from laboratory to industrial scale manufacturing and simplifies the purification process which, in turn, allows for reduced expenses. The Company believes that the ability to produce large volumes of easily purified, highly versatile cells could potentially expedite the regulatory approval process.

Potential Applications

Crucell's PER.C6® technology licenses cover the full range of biopharmaceuticals, including vaccines, antibodies and proteins, gene therapy, and functional genomics products. Each of these applications is described below.

Vaccines. PER.C6® technology can be used to develop both classical and recombinant vaccines. The technology produces a classical vaccine by infecting PER.C6® cells with the virus against which the vaccine is meant to protect. The virus is subsequently grown on the PER.C6® cells, yielding a potent starting material that can be processed to produce the final formulation of the vaccine. In the recombinant approach, the PER.C6® technology produces delivery agents called vectors from a basic adenovirus. These vectors have been made replication deficient and are thus only capable of delivering a portion of DNA encoding for a protein from the pathogen into the human body. This results in a strong antibody and T-cell immune response that leads to protection against the disease caused by the pathogen. The DNA inserted into the vector can be derived from a virus, a parasite, or even bacteria, making this technology extremely versatile.

Proteins. PER.C6® technology can be used as a production system for developing and manufacturing antibodies or proteins by inserting DNA encoding for a particular protein into PER.C6® cells. These modified PER.C6® cells are expected to grow further and secrete the desired antibody or protein, which can then be used for preclinical research or developed for administration in humans to fight diseases.

Gene Therapy. The emerging field of gene therapy seeks to treat congenital or inherited human diseases by transferring a therapeutic gene into the cells of a patient where it is needed. The gene can encode for a protein that is either missing or non-functional, or can encode for a protein that counteracts an erroneous biological process. PER.C6® technology's primary function in the field of gene therapy is its

production of adenoviral vectors—a gene delivery mechanism based on a common human virus—that carries therapeutic genes and aids in 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. PER.C6® technology can also be employed to produce libraries of adenoviruses into which individual human genes can be inserted to perform studies of gene functions. The adenovirus libraries carry genes with unknown functions, which can be used to determine the function of genes in a disease process. PER.C6® technology, therefore, represents a key analytical tool in the discovery of new genes and their role in biological pathways and human disease. Galapagos Genomics, a functional genomics company in which Crucell holds a 20.8% ownership share, executes these activities exclusively using PER.C6® technology.

Additional Technologies

AdVac® Technology

AdVac® technology is used in combination with PER.C6® production technology to develop recombinant vaccines. While no adenovirus-based recombinant vaccines are currently licensed for general use, the scientific community is testing the ability of these vaccines to counter viruses (HIV, hepatitis B and Ebola), parasites (malaria), and bacterial toxins, to name a few. Recombinant vaccines are necessary for these diseases since inactivated whole virus vaccine approaches are either ineffective against these particular pathogens, or are too difficult or dangerous to produce.

AdVac® technology was designed to manage the problem of pre-existing immunity in humans against the recombinant adenovirus serotype 5 (rAd5) vaccine vector, without compromising large-scale production capabilities or the immunogenic properties of rAd5. AdVac® technology is based on adenovirus vectors that do not regularly occur in the human population, such as Ad35 and Ad11. The technology supports the practice of inserting immunogenic material into a vector, which then delivers the immunogenic material directly to the immune system. AdVac® technology may also be used to develop *ex vivo* vaccines and gene therapy products.

Unique Advantages

Safety and Efficacy. Because AdVac® technology is based on adenovirus vectors not commonly found in the human population, pre-existing immunity to the vector is rare. This may allow for lower dosage schedules, which could minimize the risk to the subject. Additionally, AdVac® vectors efficiently infect and transduce cells *ex vivo* that play an important role in inducing the required immune response.

Scale and Manufacturing. The cell cultures that complement the AdVac® technology are based on a derivative of PER.C6® technology, and could help make large scale manufacturing of recombinant vaccines possible. Crucell believes that the biopharmaceutical industry requires this capability to meet the global demand for vaccines required for eradication of emerging and existing infectious diseases.

MAbstract® Phage Antibody-Display

MAbstract® technology can be applied for the discovery of novel drug targets—such as cancer markers or proteins from infectious agents including bacteria and viruses—and identify human antibodies against those targets. It employs a human-based antibody-display technology. MAbstract® allows for the production of therapeutic antibodies that have several potential advantages over current technologies that use **transgenic** mice. These unique advantages are described below.

Unique Advantages

Subtraction Method of Selection. MAbstract® technology selects antibodies for possible therapeutic use and discovers novel drug targets using whole cells, tissues, or viruses. The 'subtraction' method of selection is unique, and is not available when generating human antibodies in transgenic mice.

No Inherent Limitation on Antibody Specificity. MAbstract® technology does not have an inherent limitation on antibody specificity, whereas transgenic mice have limitations in their immune systems.

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.

ChromaGenics STAR™ Technology

In March 2004, Crucell completed the acquisition of ChromaGenics B.V., a privately held biotechnology company based in Amsterdam, the Netherlands. ChromaGenics B.V. was founded by UvA Holding B.V., Dr. Arie Otte, and Dr. Niek Roosdorp as a spin-off company of the University of Amsterdam. It is focused on (epi-)genetic discoveries relevant to recombinant DNA protein production in mammalian cells. Dr. Arie Otte discovered genetic elements (STAR™ elements) that are of particular importance to stable and 'high-yield' gene expression. The STAR™ technology is particularly useful for the production of recombinant human antibodies. Dr. Arie Otte, the discoverer of the STAR™ technology (*Nature Biotechnology* 2003 May, 21 (5)) joined Crucell part time as Director Epigenetics Technology, and five members of his team joined Crucell fulltime.

Licensee Agreements

Crucell licenses its PER.C6® and AdVac® technology for its role in the production of vaccines, antibodies and proteins, gene therapy, and functional genomics products. Table 13 provides details of Crucell's licensing partners. Pages 36-40 detail each of these relationships where the information is available.

Table 13
Crucell N.V.
DETAILED LICENSEE PIPELINE

VACCINES

Partner/License	Starting Date	Technology Platform	Disease Target	Development Stage
Aventis Pasteur S.A	Jan. 2003	Undisclosed	Undisclosed	Pre-clinical
Harvard School of Medicine	Oct. 2002	PER.C6® and AdVac®	Undisclosed	Pre-clinical
Kimron Veterinary Institute	Jul. 2003	PER.C6®	West Nile Virus–Veterinary vaccine	—
Medimmune Inc.	May 2002	PER.C6®	Influenza	Pre-clinical
Merck & Co. Inc.	Oct. 2000	PER.C6®	Hepatitis C	Pre-clinical
Merck & Co. Inc.	Oct. 2000	PER.C6®	HIV	Phase I
National Institutes of Health (NIH)	Mar. 2002		Ebola, Lassa and Marburg	Pre-clinical
NeoTropiX	Mar. 2004	Undisclosed	Undisclosed	Pre-clinical
New York University	Aug. 2002	PER.C6® and AdVac®	Malaria	Pre-clinical
Novavax, Inc.	Sep. 2003	PER.C6®	2 Non-disclosed targets	Pre-clinical
Vaxin, Inc.	June 2000	PER.C6® and AdVac®	Rabies	Pre-clinical
Walter Reed Army Institute of Research & GlaxoSmithKline Biologicals	Mar. 2003	PER.C6® and AdVac®	Malaria	Pre-clinical

ANTIBODIES & THERAPEUTIC PROTEINS

Partner/License	Starting Date	Technology Platform	Disease Target	Development Stage
Applied Molecular Evolution, Inc.	Oct. 2002	PER.C6®	Portfolio	Pre-clinical
Centocor Inc. (Johnson & Johnson)	Dec. 2002	PER.C6®	Portfolio	Pre-clinical
Innogenetics N.V.	Jan. 2002	PER.C6®	Portfolio	Pre-clinical
Merck & Co. Inc.	May 2003	PER.C6®	Portfolio	Pre-clinical
Millipore Corp.	Mar. 2003	PER.C6®	Undisclosed	—
NatImmune	Sep. 2002	PER.C6®	Portfolio	Pre-clinical
NatImmune A/S	Aug. 2002	PER.C6®	Manna-binding lectin	Pre-clinical

GENE THERAPY

Partner/License	Starting Date	Technology Platform	Disease Target	Development Stage
Cell Genesys Inc.	Jan. 2001	PER.C6®	Portfolio	Pre-clinical
DirectGene Inc.	Sep. 2000	PER.C6®	Portfolio	Pre-clinical
Eurogene Ltd (Ark Therapeutics)	Nov. 2000	PER.C6®	Portfolio	Pre-clinical
EMD Lexigen Pharmaceuticals	Jan. 2002	PER.C6®	Portfolio	Pre-clinical
GeneMax Corp.	Aug. 2003	PER.C6®	Portfolio	Pre-clinical
GenVec Inc.	July 2002	PER.C6®	Cardiovascular	Phase II
GlaxoSmithKline Ltd.	Feb. 1999	PER.C6®	Portfolio	Pre-clinical
Merck & Co. Inc.	Nov. 1998	PER.C6®	Portfolio	Pre-clinical
ML Laboratories Ltd.	June 1998	PER.C6®	Portfolio	Phase I/II
Schering AG (Berlex)	Sep. 1998	PER.C6®	Cardiovascular	Phase I/II
Selective Genetics Inc.	June 2001	PER.C6®	Portfolio	Phase I/II
Transgene SA	Apr. 2001	PER.C6®	Portfolio	Phase I/II

FUNCTIONAL GENOMICS

Partner/Licensee	Starting Date	Area
Galapagos Genomics N.V.	June 1999	Genomics

Source: Crucell N.V.

Exclusive Licensee Agreements

Crucell has issued certain licenses to licensees on an exclusive basis. These licenses generally state that Crucell will not provide technology similar to the technology licensed to the exclusive licensee, to a party other than the exclusive licensee for use in the area covered by the exclusive license. As such, these licenses generally provide for higher payments. The exclusive licenses that appear to be most important to Crucell's business include its agreements with Aventis Pasteur, Merck, and DSM Biologics. The terms of the Aventis Pasteur and Merck agreements are described below; terms of the DSM Biologics agreement is described under the CMO section, page 41. All of Crucell's other licensing agreements are described on pages 37-40.

Aventis Pasteur S.A.

Crucell and Aventis Pasteur signed a commercial license agreement for manufacturing technology related to viral vaccines. The agreement allows Aventis Pasteur, one of the world's largest vaccine producers, to use Crucell's PER.C6® cell-based vaccine manufacturing technology to develop and commercialize next generation vaccines. It is expected that new cell-based manufacturing technology could replace the existing production methods to provide more flexible manufacturing and potentially yield more competitive products. Under the agreement, Crucell will receive upfront payments, milestone payments, and royalties on future product sales.

On January 7, 2004, Aventis Pasteur and Crucell entered into a strategic agreement to further develop and commercialize novel influenza vaccine products based on Crucell's PER.C6® cell line technology. The agreement covers both pandemic and epidemic influenza vaccines, which up to now have been part of Crucell's in-house product development program. Under the terms of the agreement, Aventis Pasteur receives an exclusive license to research, develop, manufacture, and market cell-based influenza vaccines using PER.C6® technology and Crucell will receive milestone payments, annual payments, and R&D funding totaling €30 million (USD $38 million), and high single- up to double-digit royalties on future PER.C6®-based influenza vaccine sales. Crucell retains the commercialization rights for Japan, which accounts for 15% of the global influenza vaccine market that totaled €1.2 billion (USD $1.5 billion) in 2002. For Japan, Aventis Pasteur will supply finished vaccine products to Crucell and Crucell will pay a royalty on sales to Aventis Pasteur.

Merck & Co., Inc.

Crucell and Merck signed an agreement in October 2000 granting Merck an exclusive commercial license to Crucell's PER.C6® technology to develop vaccines for the prevention and treatment of certain diseases, including HIV/AIDS. The agreement provides for up-front and ongoing fees as well as royalty and milestone payments paid by Merck to Crucell.

Merck is currently utilizing Crucell's PER.C6® technology to develop an HIV-1 vaccine. Merck employs a modified recombinant adenovirus that is grown on Crucell's PER.C6® cell line technology. Currently in Phase I, clinical trials of the vaccine have seen the study expand to more than 1,000 people. Scientists hope that the trial leads to the development of a vaccine that can effectively prevent the development of AIDS from the HIV infection, as well as treat HIV infection in patients taking anti-retroviral therapy.

Phase I data have shown that the vaccine, which generated a substantial and prolonged specific T cell response, is generally well tolerated by the healthy volunteers enrolled. When compared with vaccinations featuring naked DNA, the adenovirus-based vaccine showed a stronger anti-HIV immune response. Additional data released by Merck have demonstrated that the Merck adenovirus-based vaccine protected monkeys against an AIDS-like illness. These results, combined with strong safety data, represent an opportunity to establish the PER.C6® technology as a viable contributor to ongoing efforts to counter HIV and AIDS. Crucell expanded the agreement in June 2003, which relates to its PER.C6® Cell Substrate BMF, BB-MF 8453, in the U.S., and equivalents in other jurisdictions. The BMF is the regulatory dossier filed with the FDA. Licensees of Crucell's PER.C6® technology refer to this BMF for their regulatory filings of PER.C6®-based products.

Other Licensee Agreements

Applied Molecular Evolution, Inc.

Crucell and San Diego-based Applied Molecular Evolution, Inc. (AMEV-NASDAQ) signed a non-exclusive, worldwide PER.C6® research license agreement allowing Applied Molecular Evolution to evaluate the production of monoclonal antibodies on the PER.C6® human cell line technology. Applied Molecular Evolution also has an option for a non-exclusive, worldwide commercial product license to manufacture one or more specified monoclonal antibody products using PER.C6® technology. Additionally, Crucell has granted Applied Molecular Evolution the right to enter into collaborations with third parties for the R&D of monoclonal antibody products produced through Applied Molecular Evolution's programs on the PER.C6® cell line technology. Under the terms of the agreement, Crucell will receive an upfront payment, annual maintenance fees, and royalties on future sales of any products manufactured using the PER.C6® technology.

Biogen Idec

Crucell N.V. signed a non-exclusive PER.C6® technology research and commercialization license agreement with Biogen Idec for the production of recombinant proteins to be used in in-house antibody discovery programs. Biogen Idec is one of the top three biotechnology companies in the United States. Under the terms of the agreement, Crucell will receive upfront and annual payments, as well as royalties on net sales of products discovered using the PER.C6® technology in Biogen Idec's in-house discovery program.

Centocor Inc. (company of Johnson & Johnson)

Crucell has a research license agreement with Centocor Inc., a Johnson & Johnson company, allowing Centocor to evaluate the production of monoclonal antibodies using the PER.C6® human cell line technology. Centocor also has an option for a non-exclusive, worldwide commercial product license to manufacture one or more specified monoclonal antibody products using the PER.C6® technology. Under the terms of the agreement, Crucell will receive an upfront payment, annual maintenance fees, and royalties on future sales of any products manufactured using the PER.C6® technology.

Cell Genesys Inc.

Crucell signed a licensing agreement with Cell Genesys Inc. (CEGE-NASDAQ) for access to its PER.C6® technology. Under the terms of the agreement, Cell Genesys will license Crucell's PER.C6® adenoviral packaging cell line for research purposes, with an option to convert to a commercial license within five years. Cell Genesys, a leading gene therapy company, is focused on the development and commercialization of cancer vaccines and gene therapies to treat major, life-threatening diseases, which include cancer, hemophilia, cardiovascular disease, and Parkinson's disease

EMD Lexigen Pharmaceuticals Corp. (owned by Merck KgaA)

Boston-based EMD Lexigen Research Center has licensed Crucell's PER.C6® technology for research and clinical development of therapeutics in the field of oncology. Crucell will receive upfront and annual payments, while EMD Lexigen has an option for a commercial license. EMD Lexigen is a biotechnology company with a twofold mission of developing treatments for serious and life-threatening diseases and building a pharmaceutical platform that will lead to new therapies. EMD Lexigen is wholly owned by Merck KGaA (no relation to Merck & Co., Inc.) of Darmstadt, Germany.

Eurogene Limited (Ark Therapeutics)

Crucell has a license agreement with London-based Eurogene Limited for access to Crucell's PER.C6® technology. Under the terms of the agreement, Eurogene will license Crucell's PER.C6® adenoviral packaging cell line for research purposes, with an option to convert to a commercial license within five years. In return, Crucell will receive an up-front payment with further annual payments along with royalties on net sales of adenoviral gene therapy products arising from the agreement.

GeneMax Corp.

Crucell and GeneMax Corp. (GMXX-OTC.BB) entered a license agreement for Crucell's PER.C6® cell line technology. Under the terms of the agreement, GeneMax will use Crucell's PER.C6® technology for research in the field of adenovirus-based gene delivery. GeneMax has also obtained an option for a non-exclusive commercial license to use PER.C6® cells to manufacture and sell products in the field of gene delivery. Crucell will receive upfront and annual payments for the research license. If the research license is converted into a commercial license, Crucell will receive additional annual payments and royalties on future sales of PER.C6®-derived products.

GenVec, Inc.

Crucell signed a licensing agreement with GenVec, Inc., a biopharmaceutical company developing gene-based medicines, to use PER.C6® technology in the development of GenVec's lead cardiovascular product candidate, BioBypass® angiogen. Under the terms of the agreement, GenVec will receive a non-exclusive, commercial license to use Crucell's PER.C6® cell line technology for the development of BioBypass®. Crucell will receive an upfront fee and annual payments, as well as royalties on any future net product sales. BioBypass® is intended to induce new blood vessel formation (angiogenesis) and improve blood circulation in tissues with inadequate blood flow. The product is currently in late-stage Phase II clinical trials to evaluate its potential use in the treatment of coronary artery disease.

Innogenetics

Crucell and Belgian biotechnology company Innogenetics (INNX: Nasdaq Europe) entered into a non-exclusive license agreement for the manufacturing of monoclonal antibody products on PER.C6®. Under the terms of the agreement, Innogenetics will use the PER.C6® platform to develop monoclonal antibodies in the context of its therapeutic programs, and will be able to manufacture and market the emerging therapeutic products. Crucell will receive upfront and annual payments, as well as royalties on net sales of marketed products.

Kimron Veterinary Institute

Israeli Kimron Veterinary Institute has a license agreement to use Crucell's PER.C6® technology to develop a West Nile veterinary vaccine. The new vaccine is expected to have improved purity at competitive costs. Kimron has commenced a large trial involving approximately 2,000 geese to test the PER.C6®-based West Nile veterinary vaccine under field conditions. The geese will be vaccinated two times within a 14-day interval followed by direct exposure to the live West Nile virus. Depending on the success of the field trial, the PER.C6®-based West Nile veterinary vaccine could be approved for use in geese in 2004. Geese are natural targets for the West Nile virus and can contract a West Nile virus infection resulting in West Nile fever and possibly neurological disease and death. In Israel, West Nile virus affected the country's goose population resulting in severe morbidity and mortality until vaccination with a West Nile veterinary vaccine was implemented. Kimron intends to replace their existing West Nile veterinary vaccine, which is currently produced on mouse brains, with the PER.C6®-based vaccine. Kimron has commercial rights to the whole-killed West Nile veterinary vaccine in Israel, and will pay Crucell a royalty on sales. Crucell will receive the commercial rights to the vaccine outside of Israel.

Merck & Co., Inc. (Additional Agreement to HIV, page 36)

Crucell and Merck signed an agreement in October 2000, granting Merck an exclusive commercial license to Crucell's PER.C6® technology to develop vaccines for the prevention and treatment of certain diseases. Under the terms of the agreement, Merck obtained an option for exclusivity in three infectious disease fields. Of these options, Merck elected to extend the option for exclusivity to develop hepatitis C vaccines using the PER.C6® technology. The agreement provides for up-front and ongoing fees and royalty and milestone payments paid by Merck to Crucell. This agreement is in addition to the one for HIV and gene therapy (page 36).

NatImmune A/S

Crucell has a research licensing agreement with the Danish company, NatImmune A/S, to evaluate the production of the therapeutic protein, mannan-binding lectin (MBL), on PER.C6® cells. Additionally, NatImmune has an option for a non-exclusive commercial product license to manufacture potential MBL products. Crucell will receive upfront and annual payments, as well as royalties on net sales on marketed MBL products. MBL is a natural human protein that plays a key role in first line immune defense. It is capable of clearing a wide range of bacteria, viruses, fungi, and parasites through binding to the microorganism and activating other parts of the body's immune system. MBL-deficiency affects 35% of the population. However, due to a large amount of overlap in the immune system, an MBL-deficiency does not manifest itself in clinical symptoms, unless the individual is immunosuppressed or suffering from certain diseases.

NeoTropiX, Inc.

Crucell and U.S.-based NeoTropiX, Inc. have entered into a PER.C6® technology licensing agreement for viral therapy in the field of oncology. NeoTropiX will receive a non-exclusive, worldwide license to use PER.C6® technology for research and clinical development of viral therapy products in the field of oncology, with an option for a commercial license. Crucell will receive upfront and annual payments.

Progenics Pharmaceuticals, Inc.

In early December 2003, Crucell announced a service agreement with U.S.-based Progenics Pharmaceuticals, Inc. (PGNX-NASDAQ), whereby Crucell expects to undertake the development of a cell line based on its PER.C6® technology for the production of a recombinant protein product candidate for Progenics. Under the terms of the agreement, Crucell expects to receive payments upon reaching agreed milestones outlined in the PER.C6® cell line technology development program.

Pfizer Animal Health (division of Pfizer Inc.)

Crucell granted Pfizer Inc. an option to develop and commercialize a West Nile Virus veterinary vaccine for use in horses. Under the terms of the agreement, Pfizer would pay Crucell an upfront license fee, milestones, annual fees, and a royalty on sales of the vaccine. This agreement builds on the Israeli Kimron Veterinary Institute agreement to develop a West Nile virus veterinary vaccine for use in geese in Israel. Crucell and Kimron anticipate approval of the veterinary vaccine in Israel in 2004. Pfizer is responsible for the development of the vaccine for use in horses.

Selective Genetics Inc.

Crucell has a licensing and production agreement with San Diego-based Selective Genetics Inc. for access to its PER.C6® technology and for the manufacture of Selective Genetics' therapeutic product for studies in the U.S. Under the terms of the agreement, Selective Genetics receives a non-exclusive license to Crucell's PER.C6® cell line technology. Furthermore, Crucell has manufactured clinical grade batches of Selective Genetics' PER.C6®-derived gene therapy product using its human cell line production platform, PER.C6®. Selective Genetics is focused on the development of highly localized, site-specific gene therapeutics for tissue repair and regeneration. Crucell receives upfront and annual payments for the license and additional fees for the production of preclinical batches. If converted into a commercial license, Crucell receives additional annual payments and royalties on future sales of PER.C6®-derived products.

Vaxin, Inc.

Crucell and Vaxin, Inc. are jointly developing new types of vaccines that could be suitable for administration to patients in a non-invasive (needle-less, injection-less) way. The combination of the two technologies is the starting point for a new generation of vaccines. The two companies will combine Crucell's PER.C6® cell line technology and related vaccination technology with Vaxin's unique skin delivery system for vaccines, known as EasyVax™. This delivery system enables the development of new antiviral vaccines that can be administered non-invasively to the surface of the skin using a patch. This

vaccination system eliminates pain and potential contamination created by using a needle-based system. Under the terms of this joint development agreement, Crucell and Vaxin will collaborate on developing two anti-viral vaccines and will share costs and profits. Research will be performed in Birmingham, Alabama, and in Leiden, The Netherlands. One of the diseases targeted for vaccination development is rabies, which kills 60,000 to 80,000 people in Asia each year. Crucell will select a second vaccine for development.

Contract Manufacturing Organization (CMO) Agreements

Crucell has established alliances with contract manufacturing organizations (CMOs) to boost revenues and further establish its PER.C6® technology as the industry standard production technology for biopharmaceuticals. These alliances include DSM Biologics, a global CMO, U.S.-based Molecular Medicine BioServices, Novavax, and Tokyo-based Gene Medicine Japan among others. Through these alliances, Crucell offers biotechnology and pharmaceutical companies' access to the PER.C6® technology and expertise as well as the large-scale manufacturing capability required to meet commercial demands. A snapshot of these CMO Agreements is provided in Table 14.

Table 14
Crucell N.V.
ALLIANCES WITH CONTRACT MANUFACTURERS FOR PRODUCTION

Partner/License	Starting Date	Technology Platform	Disease Target
DSM Biologics	Dec. 2002	PER.C6®	Therapeutic proteins (including antibodies)
Gene Medicine Japan, Inc.	Oct. 2003	PER.C6®	Recombinant vaccines & gene therapy products (Asia)
Molecular Medicine Bioservices, Inc.	Dec. 2001	PER.C6®	Recombinant vaccines & gene therapy products (USA)
Novavax	Sep. 2003	PER.C6®	Two-non disclosed targets
Invitrogen Corp.	Jun. 2003	PER.C6®	Medium development

Source: Crucell N.V.

DSM Biologics

Crucell has a collaboration agreement with DSM Biologics, one of the world's leading CMOs for biopharmaceuticals, for the large-scale production of monoclonal antibodies and recombinant proteins based on its PER.C6® technology. DSM Biologics contributes the required production expertise and process optimization capabilities. Crucell contributes unique know-how in the form of the PER.C6® cell line technology.

The goal of the agreement with DSM is to prepare new medicines expeditiously and at a lower cost. DSM Biologics obtains, against payment, a license on Crucell's PER.C6® technology under which it is entitled to grant sublicenses to third parties for the development and preparation of the biopharmaceutical proteins. Both companies actively market licenses and share the royalty income. DSM Biologics and Crucell offer pharmaceutical and biotechnology companies the possibility to rapidly test, develop, and produce high-quality products under an easy-to-obtain license. This means that customers can shorten the time-to-market and reduce product costs.

Gene Medicine Japan, Inc.

Crucell and Japan-based Gene Medicine Japan, Inc. are involved in a license agreement for Crucell's PER.C6® technology. Gene Medicine Japan is expected to use PER.C6® technology to provide manufacturing services for companies, universities, and other institutions researching adenovirus-based recombinant vaccines and gene medicine products in Japan and the rest of Asia. The Crucell-Gene Medicine Japan agreement is expected to help boost research activity in Japan and the rest of Asia. Gene Medicine Japan's production facility is scheduled to commence operations on Kobe Port Island in June 2004. Under the terms of the agreement, Crucell expects to receive upfront and annual payments, as well as double-digit royalties on contract manufacturing sales by Gene Medicine Japan.

Molecular Medicine BioServices, Inc.

Crucell and U.S.-based Molecular Medicine BioServices, Inc. have a license agreement for Crucell's PER.C6® technology. Molecular Medicine is to use Crucell's PER.C6® technology to provide global manufacturing services for companies, universities, and other institutions researching adenovirus-based recombinant vaccines and gene medicine products. Crucell and Molecular Medicine BioServices expect that their agreement could boost clinical research activities throughout universities and non-profit organizations worldwide. Molecular Medicine has its fully operational production facility in San Diego, California, and has successfully produced several clinical material batches using the PER.C6® technology. Under the terms of the agreement, Crucell will receive upfront and annual payments as well as double-digit royalties on contract manufacturing sales by Molecular Medicine.

Novavax, Inc.

Crucell and Novavax are involved in a license agreement to offer vaccine manufacturing services for clinical grade materials on Crucell's PER.C6® technology. In addition, Novavax is to use Crucell's PER.C6® technology for research on two targeted vaccines. Under the terms of the agreement, Crucell will receive upfront and annual payments, as well as royalties on contract manufacturing sales by Novavax. Novavax will offer manufacturing services to governments and academia for inactivated, subunit and attenuated viral vaccines produced on Crucell's proprietary PER.C6® production technology. Novavax is a specialty pharmaceutical company engaged in research, development, and commercialization of proprietary products focused on women's health and infectious diseases. The company sells, markets, and distributes a line of prescription pharmaceuticals through its specialty sales force, calling on obstetricians and gynecologists throughout the U.S. In addition, Novavax conducts R&D on preventative and therapeutic vaccines and proteins for a variety of infectious diseases, including smallpox, HIV, SARS, West Nile virus, papilloma, influenza, hepatitis viruses, and therapeutic immunotherapies for prevention of stroke.

Invitrogen Corp.

Invitrogen is a provider of serum-free medium. Crucell has agreed to collaborate with them in order to improve the medium in which they develop PER.C6®. Crucell provides medium producers with its technology and know-how and they are expected to seek to develop an improved medium.

Key Points to Consider

- Crucell has created a portfolio of proprietary products, which enables the Company to be competitive with other biotechnology companies and expands it beyond the realm of merely a technology company.

- The Company is focused on developing vaccines using its proprietary PER.C6® technology to prevent Ebola (developing with the NIH), West Nile Virus, and influenza (developing with Aventis Pasteur). Additionally, Crucell is working with New York University, GlaxoSmithKline, and the Walter Reed Army Institute of Research to develop a malaria vaccine, with the preclinical support of the NIAID. Each of these products contains predictive study models and is poised for either favorable regulatory conditions (Ebola, malaria, West Nile virus vaccines) or has a known development trajectory (influenza vaccine).

- The global vaccine market is expected to grow to $11 billion from $5 billion, and the Company believes that by leveraging its technology, Crucell can become a significant participant in this expanding world market. The Company is developing vaccines that could be approved according to the “two animal rule”, which would imply shorter development lead times and faster time to market.

- Crucell’s PER.C6® technology offers potentially significant competitive advantages in the development and commercialization of its products. PER.C6® technology can be used to produce biopharmaceutical products that may demonstrate enhanced biological properties and prove to be potentially more efficacious and less toxic than products derived from other production systems. The technology is also well suited for the production of certain human viruses that cannot be produced efficiently using alternative technologies currently available. From a production perspective, PER.C6® offers the ability to manufacture biopharmaceutical products in large volumes, which may speed the production process and reduce manufacturing costs.

- The Company’s recent strategic agreement with Aventis Pasteur to further develop and commercialize novel influenza vaccine products based on Crucell's PER.C6® cell line technology is further validation of the potential of this technology to deliver a superior performance. Crucell has also licensed to Merck its PER.C6® technology under an exclusive agreement to develop an HIV-1 vaccine.

- The Company’s ongoing PER.C6® technology licensing program supports the development of its internal product pipeline. It also offers investors an opportunity to invest in the potential of the drug candidates that its licensees are developing based on the PER.C6® technology since Crucell receives upfront payments and annual fees from each partner to compensate for access to its technology. Furthermore, Crucell will receive royalties from future product sales.

- The Company follows a revenue model that benefits from government grants and licensing fees based on its PER.C6® technology. In the later part of the decade, the Company could boost revenue when its proprietary vaccines are marketed and royalties flow from products developed by its licensees.

- The Company benefits from a seasoned management team with a proven track record as well as solid corporate governance, with management and Supervisory Board members experienced in finance, general management, and product commercialization.

- The Company is listed on the NASDAQ and Euronext Amsterdam, and is fully SEC and NASDAQ compliant. Additionally, Crucell’s balance sheet is solid, with a cash position of $107.4 million as of March 31, 2004.

Risks

Some of the information contained in this report relates to future events or future business and financial performance. Such statements can be only predictions and the actual events or results may differ from those discussed due to, among other things, the risks described in Crucell's reports on Forms 10-K, 10-Q, 8-K, and other forms filed from time to time. The content of this report with respect to Crucell has been compiled primarily from information available to the public released by Crucell through news releases, and through Securities and Exchange Commission (SEC) filings. Crucell is solely responsible for the accuracy of that information. Information as to other companies has been prepared from publicly available information and has not been independently verified by Crucell. [Certain summaries of scientific activities and outcomes have been condensed to aid the reader in gaining a general understanding.] For more complete information about Crucell, please refer to the Company's website at www.crucell.com.

Competition

The field of biotechnology is one of rapid change and innovation. Crucell expects that this industry will continue to experience significant technological change in the years ahead. The Company operates in highly competitive markets and may experience competition from companies that have similar or other technologies, or and other products or forms of treatment for the diseases they are targeting. Crucell 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 Crucell's core technologies or obtain regulatory approval for alternative technologies or commercial products earlier than Crucell or its licensees do. Other companies are developing products to address the same diseases and conditions that Crucell and its licensees target and may have or develop products that are more effective than those based on Crucell's technologies. The Company also competes with its licensees in developing new products.

Vaccines

Other companies use alternative non-human expression platform technologies. Crucell is aware of licensed vaccines that are produced in cell substrates such as MDCK (Madin Darby Canine Kidney cells) and VERO (monkey cells), as well as on production platforms based on yeast or embryonated chicken eggs. There are also mouse brain-derived inactivated vaccines that are produced in several Asian countries. Crucell is 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. Other biotechnology and pharmaceutical companies that are focused on developing cell-based vaccines for emerging viruses and/or to defend against bio-terrorism include Wyeth, Aventis-Pasteur, Merck, Chiron, Acambis, Baxter, GenVec, Berna Biotech, Bavarian Nordic, Baxter, Solvay, Shire, Vical, and Nobilon.

- *Influenza.* In the area of influenza, Solvay has obtained registration in The Netherlands for a vaccine based on MDCK cells. There are also other biotechnology and pharmaceutical companies that currently are developing influenza vaccines based on MDCK cells, including Shire and Chiron. In addition, Baxter has obtained approval in Austria for its VERO-based influenza vaccine, which could be commercially available during the course of 2005.

- *West Nile virus.* In the area of West Nile virus, Acambis is conducting a Phase I clinical safety study in humans with its West Nile ChimeriVax vaccine. This vaccine uses a genetically engineered yellow fever 17D live virus containing the genes encoding the antigens responsible for protection against West Nile virus. Vical is developing a DNA-based West Nile virus vaccine that uses portions of the genetic code of a pathogen to cause the host to produce specific features of the pathogen that may induce an immune response. In addition, other parties are working on human West Nile virus vaccine research.

In the area of West Nile virus veterinary vaccine research, Fort Dodge Animal Health's veterinary formulin-inactivated whole virus West Nile vaccine produced on cell culture, received full license status from the USDA in early 2003. This vaccine is indicated for the prevention of West Nile virus in horses. The same company has also initiated development of a DNA-based West Nile virus vaccine for horses. In addition, Merial recently announced their West Nile virus veterinary vaccine program.

- *Ebola.* In the area of Ebola, 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. 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. The U.S. Army Medical Research Institute of Infectious Diseases is conducting pre-clinical studies with its recombinant Ebola vaccine, which is based on Ebola virus-like-particle (VLP) technology.

- *Malaria*. In the area of malaria, two companies are conducting Phase I/II clinical studies with malaria vaccine candidates based on VLP technology: GlaxoSmithKline Biologicals and Apovia. Also, Oxford (The Wellcome Trust Centre for Human Genetics) and GlaxoSmithKline are jointly developing a malaria vaccine using live vector technology, with this vaccine in Phase I/II a 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. 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).

Antibodies

Other biotechnology companies, including Celltech Group plc and Protein Design Laboratories, Inc. (PDLI-NASDAQ), currently generate humanized antibodies, and Medarex, Inc. (MEDX-NASDAQ), and Abgenix Corp. (ABGX-NASDAQ) produce fully-human antibodies from transgenic mice. MorphoSys AG (MPHSF.PK) and Cambridge Antibody Technology Group plc (CATG-NASDAQ) generate fully-human antibodies using **phage** antibody-display libraries that are similar to Crucell's. Companies such as Dyax Corp. (DYAX-NASDAQ) and SCA Ventures, Inc., a subsidiary of Enzon Corporation (ENZN-NASDAQ), are also working in the field of phage display libraries.

Other companies use alternative non-human expression platform technology such as transgenic animals and cell lines derived from animals. Chinese hamster ovary (CHO) and murine myeloma (NS0) cells are widely used for the development and/or commercial production of antibodies and therapeutic proteins by companies including Genentech (DNA-NYSE), Biogen Idec, Centocor, Amgen Inc. (AMGN-NYSE), Lonza Group AG (LZAGF.PK), and Boerhinger Ingelheim.

Crucell is aware of only one human cell-line expression platform used for production of monoclonal antibodies, the 293 human cell-line expression platform, which shares some of the advantages of the PER.C6® cell line. The 293 human cell line expression platform, which is considered to be public domain, is utilized by Eli Lilly & Company (LLY-NYSE) 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.

No product based on the PER.C6® cell line has yet been approved by the FDA or the EMEA. Crucell is aware that scientists have published research describing human cell culture systems that appear to have similarities to the Company's PER.C6® cell line. With respect to vector development, several competing technologies include those of GenVec and Merck, which may pose a threat to the commercial viability of Crucell's AdVac® technology. In particular, Merck research has established methods that may prevent problems relating to pre-existing immunity to adenovirus 5 vectors. If successful, these methods may limit the development of a market for its AdVac® technology.

Regulation

Crucell operates in a highly regulated industry. The Company's activities involve the use of hazardous materials, including chemicals and radioactive and biological materials, and animal testing, all of which are subject to regulation. Environmental laws and regulations, as well as laws and regulations relating to safe working conditions, laboratory conditions, and laboratory and manufacturing practices also apply to the Company's operations. Crucell conducts its operations in a manner designed to comply with applicable regulations and believes that it has all the licenses and permits required to carry out its current activities.

Crucell's ability and that of its licensees to commercially distribute biopharmaceuticals depends in part on the extent to which governmental health administration authorities, Health Maintenance Organizations (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 it is expected that there will continue to be a number of legislative proposals to do so.

All of Crucell's potential products, and those of its licensees are either in research or development stage. Any products the Company or its licensees 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. Crucell expects the EMEA in Europe, the FDA in the United States, the *College ter Beoordeling van Geneesmiddelen* (CBG) in the Netherlands, and comparable agencies in other countries to subject new biopharmaceutical products to extensive regulation. The Company believes that products developed using its technologies will be regulated either as biological products or as drugs.

In both the U.S. and Europe, companies require approval prior to marketing a biopharmaceutical product. To obtain this approval, preclinical and clinical trials must be conducted to demonstrate the safety, efficacy and consistent quality of the product candidates. New therapies typically advance from laboratory research testing through animal preclinical testing and finally through several phases of clinical human testing. On successful completion of the clinical trials, approval to market the biopharmaceutical may be requested from the EMEA in Europe, the FDA in the Untied States, and their counterparts in other countries.

Clinical trials are normally done in three phases.

- *Phase I.* In Phase I, trials are conducted with a small number of patients or healthy volunteers to determine the safety profile, the pattern of drug distribution, and metabolism.

- *Phase II.* In Phase II, trials are conducted with a larger group of patients afflicted with a target disease in order to determine preliminary efficacy, optimal dosages, and expanded evidence of safety.

- *Phase III.* In Phase III, large-scale, multi-center, comparative trials are conducted with patients afflicted with a target disease in order to provide enough data for the statistical proof of safety, efficacy, and potency required by appropriate authorities.

For life-threatening disease, initial human testing generally is done in patients rather than in healthy volunteers. These studies may provide results traditionally obtained in Phase II trials and are referred to as "Phase I/II" trials.

Europe

Obtaining EU approval is a costly and time-consuming process. There is a broad range of legislation in force in member states of the EU governing the testing, manufacturing, and marketing of biopharmaceutical products. EU legislation imposes specific requirements on pre-clinical testing where the data generated in such preclinical testing is to be used for a subsequent application for a product marketing authorization in the EU. In addition, guidelines have been issued by a number of organizations,

including the Committee for Proprietary Medicinal Products (CPMP), with respect to the conduct of preclinical and clinical testing and the operation of laboratories. There are also national laws and regulations within each member state of the EU governing the conduct of research. Each European country has regulations for the conduct of clinical trials with DNA therapeutics. Manufacturers of pharmaceutical products operating within the EU must hold a manufacturer's manufacturing authorization. There are also specific directives and other legislation on, among other things, pricing, distribution, labeling, and advertising of medicinal products.

The "Council Directive 65/65/EEC on the approximation of provisions laid down by law, regulation, or administrative action relating to medicinal products," as amended and subsequent related directives regulate drugs, or medicinal products as they are called in the EU. Medicinal products can only be marketed once the competent authority of an EU member state has issued a national marketing authorization, or once a centralized authorization has been granted for the whole of the EU. Marketing authorizations are granted for five years, and are renewable for further periods of five years.

The centralized procedure is mandatory for medicinal products developed by certain biotechnological processes, such as recombinant DNA technology, which is used in gene therapy. It is optional for certain innovative medicinal products, such as products developed by innovative biotechnology processes or products administered by means of innovative new delivery systems. The other regulatory procedure for obtaining marketing authorizations in EU member states is the mutual recognition procedure. All medicinal products for which the centralized procedure is not mandatory may follow this procedure.

Applicants submit centralized applications to the EMEA, which coordinates the assessment process. The CPMP then assesses and issues an opinion on the product's quality, safety, and efficacy and sends its opinion to the European Commission, which drafts a decision based on that opinion. After consulting its standing committee, the European Commission may grant a marketing authorization, subject to adequate evidence of quality, safety, and efficacy. The marketing authorization granted is valid in all EU member states.

Under the mutual recognition procedure, the applicant submits its product for review to the first EU member state, which is called the reference member state. The reference member state then assesses the medicinal product for quality, safety, and efficacy. Once the reference member state has granted national marketing authorization, a company may then make applications to the other EU member states. The other EU member states may either recognize the marketing authorization of the reference member state or issue objections. If an EU member state maintains its objection, an arbitration process is initiated and the final decision is made by the European Commission on the basis of an opinion by the CPMP. The mutual recognition procedure may be used more than once for subsequent applications to other member states in relation to the same medicinal product.

United States

The Federal Food, Drug, and Cosmetic Act regulates both drugs and biological products, and the Public Health Service Act also regulates biological products. The areas of these two Acts and related regulations govern include testing, manufacturing, safety, efficacy, labeling, storage, record keeping, and advertising and other promotional practices. The FDA must approve a product or provide alternative clearances before clinical testing, manufacturing, and marketing of biologics or drugs may begin.

- *Biologics Master File (BMF).* Crucell has submitted a BMF to the FDA. The companies to which Crucell licenses its PER.C6® technology can take advantage of the BMF that it has filed with the FDA and need not compile their own history of the PER.C6® cell line when they seek regulatory approval of any biopharmaceutical they may produce using it. Crucell is required by regulators to periodically supplement its BMF. This may assist its licensees in applications they may make to the FDA for products manufactured on the PER.C6® cell line technology.

- *FDA Approval.* Obtaining FDA approval is a costly and time-consuming process. Generally, in order to gain FDA pre-market approval, pre-clinical studies must be conducted in the laboratory and in animal model systems to gain preliminary information on an agent's efficacy and to identify any major safety concerns. Applicants submit the results of these studies as a part of an application for

an Investigational New Drug (IND), which the FDA must review and allow before human clinical trials can start. The IND application includes a detailed description of the clinical investigations.

A company must sponsor and file an IND for each proposed product and must conduct clinical studies to demonstrate the levels of safety, efficacy, and potency that are necessary to obtain FDA approval. The FDA receives reports on the progress of each phase of the clinical testing, and it may require the modification, suspension, or termination of clinical trials if an unwarranted risk is presented to patients. Human DNA therapeutics is a new category of therapeutics, and the clinical trial period may be lengthy or the number of patients may be numerous in order to establish safety, efficacy, and potency. After the completion of clinical trials of a new product, applicants must obtain FDA marketing approval. If the product is regulated as a biologic, applicants require a Biologic License Application (BLA). If the product is classified as a new drug, applicants require a New Drug Application (NDA). The NDA or BLA must include results of product development activities, preclinical studies, and clinical trials in addition to detailed manufacturing information.

The FDA subjects NDAs or BLAs to an unpredictable and potentially prolonged approval process. The FDA may ultimately decide that the application does not satisfy its criteria for approval or may require additional pre-clinical or clinical studies. Even if applicants obtain FDA regulatory clearances, the FDA subjects a marketed product to continual review, and subsequent discovery of previously unknown problems or failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or mandated withdrawal of the product from the market as well as civil or criminal sanctions. Before marketing clearance is secured, the manufacturing facility will be inspected for compliance with current Good Manufacturing Practices (cGMPs) requirements by FDA inspectors and will be inspected periodically for continuing compliance by FDA inspectors.

The FDA also regulates animal testing. Safety studies in laboratory animals that are intended to be submitted to the FDA in support of marketing authorization applications generally must comply with principles of Good Laboratory Practice and are subject to inspection and verification by FDA or foreign government agencies with which the FDA maintains mutual recognition agreements.

In addition to the FDA requirements, the NIH has established guidelines for research involving recombinant DNA molecules. These guidelines apply to all recombinant DNA research, which the NIH conducts or supports, including proposals to conduct clinical research involving DNA therapeutics and including Crucell's collaboration with the NIH to develop an Ebola vaccine. The NIH review of clinical trial proposals is a public process and usually involves review and approval of by the Recombinant DNA Advisory Committee of the NIH.

Intellectual Property

Crucell's success and ability to compete depends in large part on its ability to protect its proprietary technology and information to operate without infringing the intellectual property rights of others. The Company relies on a combination of patent, trademark, and trade secret laws, as well as confidentiality, assignment, and licensing agreements, to establish and protect its proprietary and intellectual property rights. Crucell's policy is to actively seek patent protection of its intellectual property in the United States and Europe, as well as in other jurisdictions as appropriate. In addition to outside patent counsel, the Company also retains key employees that file, defend, prosecute and enforce its patent rights, as well as, manage the Company's patent portfolio.

Recent Events

05/10/2004—Announced the nomination of Jan Pieter Oosterveld and Domenico Valerio, Ph.D., to its Supervisory Board. The nominations will be presented at the Annual General Meeting of Shareholders (AGM) on June 3, 2004. The two new members will replace Patrick Van Beneden and Jean Deleage, who will complete their terms having served on Crucell's Supervisory Board since the Company's incorporation.

04/14/2004—Announced financial results for the first quarter of 2004. Revenues for the first quarter were € 4.0 million (US$ 4.9 million) compared to € 2.1 million (US$ 2.6 million) for the same quarter in 2003. The increase relates primarily to revenues recognized from the Aventis Pasteur flu vaccine agreement, as well as to additional licensing and other revenues. Net loss for the quarter of € 7.0 million (US$ 8.5 million), compared to € 3.6 million (US$ 4.4 million) in the same quarter last year, increased primarily due to non-cash expenses related to long-term incentive plans. Cash and cash equivalents increased by € 1.0 million (US$ 1.2 million) to € 88.2 million (US$ 107.4 million) during the quarter.

03/30/2004—Announced that the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health (NIH), will support the development of Crucell's candidate malaria vaccine. In effect, NIAID will cover full pre-clinical development costs of the AdVac®-based vaccine, with the value of the agreement estimated at US$ 3.5 million.

03/24/2004—Announced a collaboration with Aeras Global TB Vaccination Foundation of Bethesda on the pre-clinical and clinical development of candidate tuberculosis (TB) vaccines. The program will focus on improvement of the only currently available TB vaccine, Bacillus Calmette-Guérin (BCG), using Crucell's proprietary PER.C6®- and AdVac®- technologies. Aeras agreed to provide Crucell up to US$ 2.9 million contingent upon meeting certain development milestones. Crucell's early stage TB vaccine development is fully funded up to entering the clinic.

03/16/2004—Announced a PER.C6®- technology licensing agreement with U.S.-based NeoTropiX, Inc. for research and clinical development of viral therapy products in the field of oncology.

03/16/2004—Announced that UK-based ML Laboratories had renewed its PER.C6® technology license agreement, negotiating research and commercial terms for gene therapy products developed and manufactured on PER.C6®- technology.

03/11/2004—Completed the acquisition of ChromaGenics B.V., a biotechnology company based in Amsterdam, adding its STAR™ technology to Crucells' protein production business.

01/26/2004—Announced 2003 financial results. Revenues for the year were € 7.4 million (US$ 9.3 million) compared to € 9.6 million (US$ 12.0 million) for 2002. A significant up-front fee from a commercial contract signed in December 2003 was not included, but deferred for recognition as revenue in future years. Total deferred revenues at December 31, 2003 were € 13.8 million (US$ 17.4 million) compared to € 6.0 million (US$ 7.6 million) for 2002. Net loss was € 23.4 million (US$ 29.4 million), compared to € 55.7 million (US$ 70.0 million) in 2002, which included a goodwill impairment charge of € 30.9 million (US$ 38.9 million).

01/26/2004—Announced the nomination of a new President and Chief Executive Officer, Ronald H.P. Brus, MD, replacing Dinko Valerio as part of a planned management transition. Dr Brus will also assume the role of Chairman of the Management Board, where he will be joined by Chief Scientific Officer Dr Jaap Goudsmit.

01/15/2004—Announced a non-exclusive PER.C6® technology research and commercialization license agreement with Biogen Idec, Inc. for the production of recombinant proteins to be used in their in-house antibody discovery programs. Biogen Idec is one of the top three biotechnology companies in the United States.

01/13/04—Announced that it has granted Pfizer Inc. an exclusive license to develop and commercialize Crucell's West Nile Virus veterinary vaccine for use in horses.

01/07/04—Announced that they have entered into a strategic agreement with Aventis Pasteur to further develop and commercialize novel influenza vaccine products based on Crucell's PER.C6® technology. The agreement covers both pandemic and epidemic influenza vaccines, which up to now have been part of Crucell's in-house product development program.

12/08/2003—Signed a service agreement with U.S.-based Progenics Pharmaceuticals, Inc., whereby Crucell will undertake the development of a cell line based on its proprietary PER.C6® technology for the production of a recombinant protein product candidate for Progenics.

11/21/2003—Presented comprehensive update on the company's in-house product development programs during an on-site Analyst Meeting. Presentations by Crucell's management team highlighted Crucell's commitment to the execution of the company's four key vaccine programs against influenza, Ebola, West Nile virus, and malaria infection.

11/19/2003—Announced the appointment of Jean-Yves Guichoux, M.D., to Executive Vice President, Development. Dr. Guichoux reports to Dr. Jaap Goudsmit, Chief Scientific Officer.

11/14/2003—Presented encouraging study results on the efficacy of an experimental malaria vaccine at Viral Vectors & Vaccines conference held in Las Vegas. The study is part of a close collaboration between Crucell and the Department of Medical and Molecular Parasitology at New York University (NYU) to provide proof of principle that a vaccine based on Crucell's AdVac® technology is able to confer protection against malaria.

10/27/2003—Announced resignation of Supervisory Board Vice Chairman, Mr. Michiel A. de Haan, effective as of December 1, 2003. Mr. de Haan had involved with Crucell since the founding of the Company. He has served as Vice Chairman of Crucell's Supervisory Board since the Company's incorporation in October 2000, and served as a Supervisory Board member of IntroGene, Crucell's predecessor, from 1994 to October 2000.

10/22/2003—Announced that Crucell's vaccine candidate against malaria will undergo testing and collaborative development in two programs involving three leading research organizations, all with a long history of working in the field of malaria. Initial results are expected by the end of this year.

10/14/2003—Announced a license agreement with Japan-based Gene Medicine Japan, Inc. for PER.C6®. Gene Medicine Japan will use PER.C6® technology to provide manufacturing services for companies, universities, and other institutions researching adenovirus-based recombinant vaccines and gene medicine products in Japan and the rest of Asia.

10/13/2003—Announced financial results for the third quarter of 2003. Crucell's revenues for the third quarter 2003 were €1.2 million (US$ 1.4 million) compared to €2.0 million (US$ 2.3 million) for the same quarter in 2002. Operating costs for the third quarter of 2003 were €9.8 million (US$ 11.4 million), compared to €9.4 million (US$ 10.9 million) for the same period last year. Net loss for the third quarter was €7.2 million (US$ 8.3 million) compared to €6.5 million (US$ 7.6 million) for the same quarter of last year.

09/25/2003—Announced that they have entered into a license agreement with Novavax to offer vaccine manufacturing services for clinical grade materials using PER.C6® technology. In addition, Novavax will use PER.C6® technology for research on two targeted vaccines.

09/22/2003—Presented results of a joint study with Harvard Medical School on a novel HIV vaccine vector at the AIDS Vaccines 2003 Conference, which was held in New York from September 18th to 21st, 2003.

09/03/2003—Announced with Israeli Kimron Veterinary Institute that they anticipate approval of a veterinary West Nile vaccine in early 2004. Kimron had previously expected to register the PER.C6®-based West Nile veterinary vaccine at the end of 2004. Based on encouraging results from the initial pre-

clinical studies, Kimron now will conduct a field trial during the 2003 mosquito season to ensure that the licensed vaccine is available before the start of the 2004 mosquito season.

08/12/2003—Announced that it had entered a license agreement for PER.C6® technology with GeneMax, where GeneMax will use Crucell's PER.C6® technology for research in the field of adenovirus-based gene delivery. GeneMax has also obtained an option for a non-exclusive commercial license to use PER.C6® cells to manufacture and sell products in the field of gene delivery.

08/07/2003—Expanded the Research Plan of its Cooperative Research and Development Agreement with the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases (NIAID). The NIAID is part of the United States of America's primary biomedical research institute, the National Institutes of Health (NIH). In May 2002, Crucell entered into an agreement with the NIAID to develop an Ebola vaccine. The Research Plan of this agreement has now been expanded to include the development of vaccines to protect against Marburg and Lassa infections.

07/14/2003—Announced financial results for the second quarter of 2003. Crucell's revenues for the second quarter 2003 were € 1.1 million (US$ 1.3 million) compared to € 2.9 million (US$ 3.3 million) for the same quarter in 2002. Net loss for the second quarter was € 6.2 million (US$ 7.1 million), compared to € 6.1 million (US$ 7.0 million) for the same quarter last year.

06/11/2003—Announced license agreement with Kimron Veterinary Institute of Israel. The program will focus on the development and registration of a whole killed West Nile veterinary vaccine based on the PER.C6® technology. The Kimron Veterinary Institute is the diagnostic and research arm of the Veterinary Services of the Israeli Ministry of Agriculture.

06/03/2003—Signed a PER.C6® technology research license agreement with Merck, allowing Merck to use the PER.C6® cell line to study the production of certain protein products, including monoclonal antibodies.

06/03/2003—Expanded the Cooperation Agreement made with Merck, which relates to the PER.C6® Cell Substrate Biologics Master File (BMF), BB-MF 8453 in the United States of America, and equivalents in other jurisdictions.

04/29/2003—Announced the nomination of Dr. C.E. Wilhelmsson and Mr. S. Lance to its Supervisory Board. The nominations will be presented at the Annual General Shareholders Meeting on May 22, 2003. Upon acceptance of the nominations, Dr. Wilhelmsson's appointment would take place immediately, while Mr. Lance's appointment would be effective January 1, 2004.

04/14/2003—Announced financial results for the first quarter of 2003. Crucell's revenues for the first quarter were € 2.1 million (US $ 2.3 million) compared to € 2.2 million (US $ 2.3 million) for the same quarter in 2002. The net loss for the first quarter 2003 decreased to € 3.6 million (US $ 3.9 million) compared to a net loss of € 5.3 million (US $ 5.7 million) in the same quarter last year. The reduction in net loss is due to lower R&D expenses and to changes to its overall compensation programs which included the exchange of certain stock options in January.

01/27/2003—Announced 2002 financial results. Total revenues for the year ended December 31, 2002 was €9.6 million ($10.0 million), an increase of 4.3% over 2001. A significant payment received from a commercial contract signed in December 2002, was not recognized as revenue, but deferred to future years in accordance with US GAAP accounting principles. Total deferred revenues per December 31, 2002 increased to €6.0 million ($6.3 million) from €2.0 million ($2.1 million) at December 31, 2001.

01/27/2003—Signed a commercial license agreement for manufacturing technology related to viral vaccines. The agreement allows Aventis Pasteur to use Crucell's PER.C6® technology to develop and commercialize next generation vaccines.

01/16/2003—Signed a PER.C6® technology research license agreement with Centocor Inc., a Johnson and Johnson company, allowing Centocor to evaluate the production of monoclonal antibodies using the PER.C6® human cell line. Centocor also has an option for a non-exclusive, worldwide commercial product license to manufacture one or more specified monoclonal antibody products using the PER.C6® cell line.

Historical Financial Data

Crucell was listed as a public company in 2000, with the initial public offering (IPO) bringing in a net €128 million (USD$120 million). Today the company's net cash position amounts to €94 million (USD$109 million), sufficient to finance the required development programs for the foreseeable future. The current cash burn rate is approximately €6 million (USD$7 million) per quarter, and should remain fairly consistent going forward. Crucell's business model benefits from government and other institutional grants as well as from on-going licensing fees, which the company receives on its proprietary PER.C6® technology. Management expects to continue generating revenues from government and non-government grants in the future.

Table's 15, 16, and 17 on pages 52, 53, and 54 provide a snapshot of Crucell's Income Statement, Balance Sheet, and Cash Flow in Euro's. Tables 18, 19, and 20 on pages 55, 56, and 57 provide a snapshot of the same respective financial statements in U.S. dollars, noting that these figures are **not** official but rather are provided for informational purposes only, and correspond to a specific exchange rate noted in the table for a specific time frame.

Amounts in EUROS (€)

Table 15

Crucell N.V.

CONSOLIDATED STATEMENTS OF OPERATIONS

(in thousands, except share/ADS and per share/ADS data)

	Year ended December 31		
	2001	**2002**	**2003**
REVENUES			
License	€ 7,972	€ 6,664	€ 5,204
Government grants and other revenues	1,209	2,911	2,220
Total revenues	9,181	9,575	7,424
COSTS AND EXPENSES			
Research and development	17,392	24,252	22,284
Selling, general and administrative	8,875	10,386	7,606
Developed technology amortization	1,330	1,331	1,330
Goodwill amortization	8,826	—	—
Goodwill impairment	—	30,891	—
Stock option compensation	888	1,371	2,696
Acquired in-process research and development	—	—	—
Total costs and expenses	37,311	68,231	33,916
LOSS FROM OPERATIONS	(28,130)	(58,656)	(26,492)
Interest income	6,205	3,547	2,143
Foreign currency gain/(loss)	463	(54)	(19)
Gain on sale of available for sale securities	—	—	982
Equity in losses of unconsolidated investments	(2,524)	(507)	—
NET LOSS BEFORE PROVISION FOR INCOME TAXES	(23,986)	(55,670)	(23,386)
Provision for income taxes			
NET LOSS	(23,986)	(55,670)	(23,386)
BASIC AND DILUTED NET LOSS PER SHARE			
Net loss per share-basic and diluted	(0.68)	(1.57)	(0.65)
Weighted average shares outstanding-basic and diluted	35,268,457	35,547,635	35,920,626

Source: Crucell N.V.

Amounts in EUROS (€)

Table 16
Crucell N.V
CONSOLIDATED BALANCE SHEETS

(in thousands)	Dec. 31, 2001	Dec. 31, 2002	Dec. 31, 2003
Assets			
Current assets:			
Cash and cash equivalents	€ 120,243	€ 110,645	€ 87,210
Trade accounts receivable, net allowance for doubtful accounts of €100 and €50 at December 31, 2002 and 2001 respectively	3,111	1,009	9,547
Receivable from related parties and employees	239	—	—
Prepaid expenses and other current assets	1,268	2,823	3,658
Total current assets	124,861	114,477	100,415
Notes receivable from employees	1,239	901	662
Investment in joint venture	507		
Plant and equipment, net	13,104	11,153	11,333
Developed technology, net	4,657	3,326	1,996
Goodwill, net	30,891	—	—
Total assets	€ 175,259	€ 129,857	€ 114,406
Liabilities and shareholders' equity			
Current liabilities			
Accounts payable	€ 2,341	€ 2,407	€ 2,087
Accrued compensation and related benefits	1,744	3,033	808
Short term portion of deferred revenue	2,008	2,334	5,371
Accrued liabilities	4,453	5,025	3,450
Total current liabilities	10,546	12,799	11,716
Long term liabilities:			
Long term obligation under capital lease	—	1,951	2,597
Long term portion of deferred revenue	—	3,698	8,448
Total long term liabilities		5,649	11,045
Shareholders' equity:			
Ordinary shares, €0.24 par value; 89,199,990 shares authorized, 35,649,938 and 35,318,188 shares issued and outstanding at December 31, 2002 and 2001 respectively	8,477	8,556	8,642
Additional paid-in capital	334,708	336,652	340,678
Deferred compensation	(4,334)	(3,992)	(4,482)
Accumulated deficit	(174,138)	(229,807)	(253,193)
Total shareholders' equity	164,713	111,409	91,345
Total liabilities and shareholders' equity	€ 175,259	€ 129,857	€ 114,406

Source: Crucell N.V.

Amounts in EUROS (€)

Table 17
Crucell N.V.
CONSOLIDATED STATEMENTS OF CASH FLOWS

(in thousands)

	Year ended December 31		
	2001	**2002**	**2003**
Operating activities			
Net loss	(23,986)	(55,670)	(23,386)
Adjustments to reconcile net loss to net cash used in operating activities			
Depreciation	1,342	2,583	2,712
Loss on disposal of plant and equipment	—	72	460
Amortization of deferred compensation	888	1,371	2,696
Compensation expense related to the insurance of stock options			
Intangible amortization	10,156	1,331	1,330
Goodwill impairment	—	30,891	—
Equity in losses of unconsolidated investments	2,524	507	—
Gain on sale of available for sale securities	—	—	(982)
Revenue recognized in exchange for available-for-sale securities	—	—	(324)
Issuance of warrants to acquire ordinary shares for services	—	—	616
In-process research & development	—	—	—
Issuance of ordinary shares for services	—	—	—
Change in operating assets and liabilities, net of the effects of acquisitions	—	—	—
Trade accounts receivable	(2,738)	2,102	(8,538)
Receivable from related parties and employees	(787)	577	239
Prepaid expenses and other current assets	1,248	(1,555)	(835)
Accounts payable	(4,109)	66	(320)
Accrued compensation and related benefits	827	1,289	(2,225)
Deferred revenues	1,676	4,024	7,787
Accrued liabilities	937	(88)	(1,285)
Net cash used in operating activities	(12,022)	(12,500)	(22,055)
Cash flow from investing activities			
Investment in joint venture	(700)	—	—
Investment in partnership	(145)	—	—
Purchase of plant and equipment	(4,366)	(2,972)	(3,448)
Proceeds from sale of plant and equipment	—	—	96
Proceeds from sale of available for sale securities	—	—	1,306
Merger costs	—	—	—
Cash acquired in business combination	—	—	—
Net cash used in investing activities	(5,211)	(2,972)	(2,406)
Cash flow from financing activities			
Proceeds from the issuance of ordinary preferred shares	436	994	310
Proceeds from sale and lease-back of property and equipment	984	5,349	1,258
Repayment of notes payable and capital lease obligations	—	(469)	(902)
Net cash provided by financing activities	1,420	5,874	666
Net (decrease)/increase in cash and cash equivalents	(15,813)	(9,598)	(23,435)
Cash and cash equivalents at beginning of period	136,056	120,243	110,645
Cash and cash equivalents at end of period	€ 120,243	€ 110,645	€ 87,210

Source: Crucell N.V.

Amounts in USD ($)

The amounts in the table below have been translated for convenience purposes from Euros (€) to U.S. Dollars at a rate of $0.8901 as of December 31, 2001, $1.0485 as of December 31, 2002, and $1.2597 as of December 31, 2003, respectively. These are not official figures, but are presented here for informational purposes only.

Table 18
Crucell N.V.
CONSOLIDATED STATEMENTS OF OPERATIONS

(amounts in thousands of dollars, except share data)

	Year ended December 31		
	2001	**2002**	**2003**
	as of 12/31/2001 (1 Euro=0.8901 USD)	as of 12/31/2002 (1 Euro=1.0485 USD)	as of 12/31/2002 (1 Euro=1.2597 USD)
REVENUES			
License	$7,096	$6,987	$6,555
Government grants and other revenues	1,076	30,530	2,797
Total revenues	8,172	10,039	9,352
COSTS AND EXPENSES			
Research and development	15,481	25,428	28,071
Selling, general and administrative	7,900	10,890	9,581
Developed technology amortization	1,184	1,396	1,675
Goodwill amortization	7,856	—	—
Goodwill impairment	—	32,389	—
Stock option compensation	790	1,437	3,396
Acquired in-process research and development	—	—	—
Total costs and expenses	33,211	71,540	42,724
LOSS FROM OPERATIONS	(25,039)	(61,501)	(33,372)
Interest income	5,523	3,719	2,700
Foreign currency gain/(loss)	412	(57)	(24)
	—	—	1,237
Equity in losses of unconsolidated investments	(2,247)	(532)	—
NET LOSS BEFORE PROVISION FOR INCOME TAXES	(21,350)	(58,370)	(29,459)
Provision for income taxes			
NET LOSS	(21,350)	(58,370)	(29,459)
BASIC AND DILUTED NET LOSS PER SHARE			
Net loss per share-basic and diluted	($0.61)	($1.65)	($0.82)
Weighted average shares outstanding-basic and diluted	35,268,457	35,547,635	35,920,626

Source: Crucell N.V.

Amounts in USD ($)

The amounts in the table below have been translated for convenience purposes from Euros (€) to U.S. Dollars at a rate of $0.8901 as of December 31, 2001, $1.0485 as of December 31, 2002, and $1.2597 as of December 31, 2003, respectively. These are not official figures, but are presented here for informational purposes only.

Table 19
Crucell N.V
CONSOLIDATED BALANCE SHEETS

(amounts in thousands of dollars)	**Dec. 31, 2001** as of 12/31 (1 Euro=0.8901 USD)	**Dec. 31, 2002** as of 12/31 (1 Euro=1.0485 USD)	**Dec. 31, 2003** as of 12/31 (1 Euro=1.2597 USD)
Assets			
Current assets:			
Cash and cash equivalents	107,028	116,011	109,858
Trade accounts receivable, net allowance for doubtful accounts of €100 and €50 at December 31, 2002 and 2001 respectively	2,769	1,058	12,026
Receivable from related parties and employees	213	—	—
Prepaid expenses and other current assets	1,129	2,960	4,608
Total current assets	111,139	120,029	126,493
Notes receivable from employees	1,103	945	834
Investment in joint venture	451	—	—
Plant and equipment, net	11,664	11,694	14,276
Developed technology, net	4,145	3,487	2,514
Goodwill, net	27,496	—	—
Total assets	155,998	136,155	144,117
Liabilities and shareholders' equity			
Current liabilities			
Accounts payable	2,084	2,524	2,629
Accrued compensation and related benefits	1,552	3,180	1,018
Short term portion of deferred revenue	1,787	2,447	6,766
Accrued liabilities	3,964	5,269	4,346
Total current liabilities	9,387	13,420	14,759
Long term liabilities:			
Long term obligation under capital lease	—	2,046	3,271
Long term portion of deferred revenue	—	3,877	10,642
Total long term liabilities		5,923	13,913
Shareholders' equity:			
Ordinary shares, €0.24 par value; 89,199,990 shares authorized, 35,649,938 and 35,318,188 shares issued and outstanding at December 31, 2002 and 2001 respectively	7,545	8,971	10,886
Additional paid-in capital	297,924	352,980	429,152
Deferred compensation	(3,858)	(4,186)	(5,646)
Accumulated deficit	(155,000)	(240,953)	(318,947)
Total shareholders' equity	146,611	116,812	115,067
Total liabilities and shareholders' equity	155,998	136,155	144,117

Source: Crucell N.V.

Amounts in USD ($)

The amounts in the table below have been translated for convenience purposes from Euros (€) to U.S. Dollars at a rate of $0.8901 as of December 31, 2001, $1.0485 as of December 31, 2002, and $1.2597 as of December 31, 2003, respectively. These are not official figures, but are presented here for informational purposes only.

Table 20
Crucell N.V.
CONSOLIDATED STATEMENTS OF CASH FLOWS

(amounts in thousands of dollars)

	Year ended December 31		
	2001	**2002**	**2003**
	as of 12/31/2001 (1 Euro=0.8901 USD)	as of 12/31/2002 (1 Euro=1.0485 USD)	as of 12/31/2003 (1 Euro=1.2597 USD)
Operating activities			
Net loss	(21,350)	(58,370)	(29,459)
Adjustments to reconcile net loss to net cash used in operating activities			
Depreciation	1,195	2,708	3,416
Loss on disposal of plant and equipment	—	75	579
Amortization of deferred compensation	790	1,437	3,396
Compensation expense related to the insurance of stock options	—	—	—
Intangible amortization	9,040	1,396	1,675
Goodwill impairment	—	32,389	—
In-process research & development	—	—	—
Equity in losses of unconsolidated investments	2,247	532	—
Issuance of ordinary shares for services			
Change in operating assets and liabilities, net of the effects of acquisitions			
Trade accounts receivable	(2,437)	2,204	(10,755)
Receivable from related parties and employees	(701)	605	301
Prepaid expenses and other current assets	1,111	(1,630)	(1,052)
Accounts payable	(3,657)	69	(403)
Accrued compensation and related benefits	736	1,352	(2,803)
Deferred revenues	1,492	4,219	9,809
Accrued liabilities	834	(92)	(1,619)
Net cash used in operating activities	(10,701)	(13,106)	(27,783)
Cash flow from investing activities			
Investment in joint venture	(623)	—	—
Investment in partnership	(129)	—	—
Purchase of plant and equipment	(3,886)	(3,116)	(4,343)
Proceeds from sale of plant and equipment	—	—	121
Proceeds from sale of available for sale securities	—	—	1,645
Merger costs	—	—	—
Cash acquired in business combination	—	—	—
Net cash used in investing activities	(4,638)	(3,116)	(3,031)
Cash flow from financing activities			
Proceeds from the issuance of ordinary preferred shares	388	1,042	391
Proceeds from sale and lease-back of property and equipment	876	5,608	1,585
Repayment of notes payable and capital lease obligations	—	(492)	(1,136)
Net cash provided by financing activities	1,264	6,159	839
Net (decrease)/increase in cash and cash equivalents	(14,075)	(10,064)	(29,521)
Cash and cash equivalents at beginning of period	121,103	126,075	139,380
Cash and cash equivalents at end of period	€ 107,028	€ 116,011	€ 109,858

Source: Crucell N.V.

Glossary

Acquired Immune Deficiency Syndrome (AIDS)—The late stage of HIV disease, characterized by a deterioration of the immune system and a susceptibility to a range of **opportunistic infections** and cancers.

Adenovirus vector system—A vehicle used to transfer genetic material based on a group of viruses called adenoviruses, known to cause a variety of respiratory disorders, such as the common cold, pneumonia, and bronchitis. Adenovirus vector systems can be implemented in vaccines used to treat a variety of diseases and is currently being used in Crucell's malaria vaccine product development program.

Adenoviruses—A group of viruses responsible for a wide variety of respiratory disorders, such as the common cold, pneumonia and bronchitis.

Anopheles mosquito—The mosquito most commonly known for carrying malaria.

Bioinformatics—The use of computers to analyze biological data. Bioinformatics technology is commonly used to study DNA and other nucleic acids.

Cell line—A culture of a particular type of cell that can be reproduced indefinitely, thus making the cell line "immortal."

DNA vaccines—These vaccines represent a new means of immunization that is entirely gene-based. By using the recipient's own cells, the vaccine attempts to offer greater control over the immunization process. DNA vaccines are believed to proactively enhance cell-mediated immunity and are currently being tested against TB and malaria.

Drug targets—Molecules to which drugs are directed to interfere with disease processes.

Ebola—Ebola is one of the most lethal viral diseases, with a mortality ranging from 50% to 80%. 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 ''viral hemorrhagic fevers,'' which also includes the highly destructive diseases caused by the Marburg and Lassa viruses. The virus causes a disease characterized by high fever and massive internal bleeding.

Efficacy—In vaccine research, the ability of a vaccine to protect vaccinated people against a specific infection or disease. A vaccine may be tested for efficacy in Phase III trials if (smaller) Phase I and Phase II trials show it to be safe and promising.

Encephalitis—An inflammation of the brain usually induced by viral infection.

Epidemic—The occurrence of more cases of a disease than would be expected in a community or region during a given time period. A sudden severe outbreak of a disease such as SARS.

Filoviruses—A family of viruses that includes Ebola and Marburg. These diseases commonly produce hemorrhagic symptoms and are sometimes fatal.

Genome—A set of chromosomes and genes that an individual inherits from his or her parents.

Hemorrhagic—Causing bleeding.

Hepatitis—An inflammation of the liver. May be caused by bacterial or viral infection, parasitic infestation, alcohol, drugs, toxins, or transfusion of incompatible blood. Although many cases of hepatitis are not a serious threat to health, the disease can become chronic and can sometimes lead to liver failure and

death. There are four major types of viral hepatitis: (1) hepatitis A, caused by infection with the hepatitis A virus, which is spread by fecal-oral contact; (2) Hepatitis B, caused by infection with the hepatitis B virus (HBV), which is commonly passed on to a partner during intercourse, particularly during anal sex, as well as through sharing drug needles. (3) non-A, non-B hepatitis , caused by the hepatitis C virus, which appears to be spread through sexual contact as well as through the sharing of drug needles (another type of non-A, non-B Hepatitis is caused by the hepatitis E virus, principally spread through contaminated water); (4) delta hepatitis , which occurs only in persons who are already infected with HBV and is caused by the HDV virus; most cases of delta hepatitis occur among people who are frequently exposed to blood and blood products, such as persons with hemophilia.

Inactivated whole virus vaccines—Vaccines containing whole virus particles that have been treated (often with formaldehyde) to prevent them from infecting the host. Upon treatment, the virus particles are still able to maintain some unaltered virulent characteristics, thus inducing an immune response.

Influenza—Commonly called “the flu,” influenza is a highly infectious disease caused by viruses that infect the respiratory tract. Influenza often leads to more serious disorders, such as pneumonia, which is often a fatal condition.

Lassa—Lassa fever is an acute viral illness that occurs in West Africa, with the number of cases being as many as 100,000 to 300,000, with approximately 5,000 deaths. Transmitted by a rodent known as the multimammate rat, Lassa fever is highly infectious and in many cases deadly.

Live attenuated virus vaccines—Vaccines containing an active virus that has been weakened so it is no longer dangerous upon administration. The Salk polio vaccine is the best known and most effective attenuated virus vaccine.

Malaria—An infectious parasitic disease transmitted by the Anopheles mosquito or by a contaminated needle. Symptoms of this often deadly disease include headache, vomiting diarrhea, muscle aches, cough, and in severe cases, even kidney and liver failure or coma.

Marburg—A virus that causes hemorrhagic fever affecting both humans and primates. Caused by an animal-borne RNA virus, Marburg is in the filovirus family, which also includes the four species of Ebola virus.

Meningitis—A severe inflammation of the membrane around the brain or spinal cord, producing symptoms such as headache, vomiting, fever, stiff neck, and sometimes death.

Modified benign viruses—A benign virus that is genetically modified for use in a vaccine.

Monoclonal—Made from a single clone of cells with specific binding properties.

Naked DNA—The use of DNA in a vaccine that is injected directly into the patient.

Opportunistic infections—An illness caused by an organism that usually does not cause disease in a person with a normal immune system. People with advanced HIV infection suffer opportunistic infections of the lungs, brain, eyes, and other organs.

Pandemic—An epidemic (a sudden outbreak) that becomes very widespread and affects a whole region, a continent, or the world.

Phage—Short for bacteriophage, a phage is a virus that infects bacteria and possesses the ability to integrate into the genetic material of its host cell.

Plasmodium—The one-cell parasite that causes malaria.

Pneumonia—An inflammation of the lungs usually caused by bacterial infection. Pneumonia is often the result of serious cases of influenza.

Project BioShield—A comprehensive effort to develop and make available modern, effective drugs and vaccines to protect against attack by biological and chemical weapons or other dangerous pathogens.

Recombinant—Genetic material resulting from the splicing and ligation of DNA fragments that are not linked together.

Recombinant vaccines—Weakened viruses or bacteria into which harmless genetic material and other disease-causing organisms are inserted. While no recombinant vaccines are currently licensed for general use in the United States, scientists are testing their ability to counter viruses, such as HIV/AIDS and hepatitis B.

Replication—A complex process whereby the "parent" strands of DNA in the double helix are separated and each one is copied to produce a new "daughter" strand.

Smallpox—A highly contagious disease marked by the high fever and the formation of scarring pustules. While there is a vaccine available, smallpox is widely feared as a potential agent for bioterrorism.

Subunit vaccines—Newest type of vaccines which have shown to be safe, except for rare adverse reactions.

Transgenic—Used to describe an animal that contains genes from a different species. For example, transgenic mice are given human genes for the production of vaccines.

Tuberculosis (TB)—An infectious disease characterized by small rounded swellings that form on the mucous membranes.

Two animal rule—States that efficacy studies in man are not required to obtain a product license for special categories of products as long as efficacy is established in two independent animal models and safety in man

Vector—A vehicle for transferring genetic material.

West Nile virus—A virus transmitted by mosquitoes that causes mild to severe symptoms, some of which can be life threatening. The virus is known for causing West Nile fever, which can lead to paralysis, coma and death. First identified in Africa, the virus has surfaced in North America and Europe in recent years and is spreading across both continents.

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