

# NOVARTIS VACCINES leading through innovation and technology

Every year, vaccines save millions of lives by preventing major human diseases, protecting individuals and those close to them, and offering widespread public defence against disease.

In 2006, Novartis joined the vaccines market when it acquired Chiron, creating a new division called Novartis Vaccines & Diagnostics. This acquisition was significant, as it enabled Novartis to create a new strategic platform for growth, and expand its portfolio to include preventative medicines in the form of vaccines, which will benefit patients and physicians around the world and contribute to meeting emerging public health needs.

Since then, Novartis Vaccines has been striving to ensure that we provide our customers and patients with a safe and effective supply of vaccines. Innovation and technology are at the core of our business. Vaccines are an example of an area where innovation is accelerating across the pharmaceutical industry. The global vaccines market is expected to grow 20% to around \$20 billion by 2009, and the number of Phase I vaccines has more than quadrupled over the past 10 years.

Novartis Vaccines is currently the world's fifth-largest vaccines business and the world's second-largest manufacturer of flu vaccines. It also has important meningococcal, pediatric and travel vaccine franchises. The company's portfolio of products includes vaccines for influenza, meningitis, rabies, tick-borne encephalitis, Haemophilus influenzae B (Hib), polio, diphtheria, tetanus and pertussis (whooping cough).

Our pipeline demonstrates our strengths in developing new strategies for helping to protect against flu and meningitis. We have the potential to

be leading the industry by providing a range of vaccines directed against the most prevalent meningococcal strains.

In the nearly two years since the acquisition, Novartis Vaccines and Diagnostics' net sales almost doubled, and they continue to rise. Seasonal influenza, TBE and pediatric vaccines, as well as diagnostics, are driving growth. Meningitis research and new technologies in influenza research will also be growth drivers. New technologies have made it possible to develop improved vaccines – and Novartis Vaccines is a world leader in this revolution. Novartis provides innovative vaccines alongside a wide range of conventional products to combat diseases across the globe.

It is through demonstrating our leadership in innovation and focusing our efforts on filling the voids that still exist within the vaccines landscape that we hope to revolutionise the vaccines industry, and build Novartis Vaccines' presence.

## **Addressing unmet medical need: a single formulation for Men ACWY for all age groups**

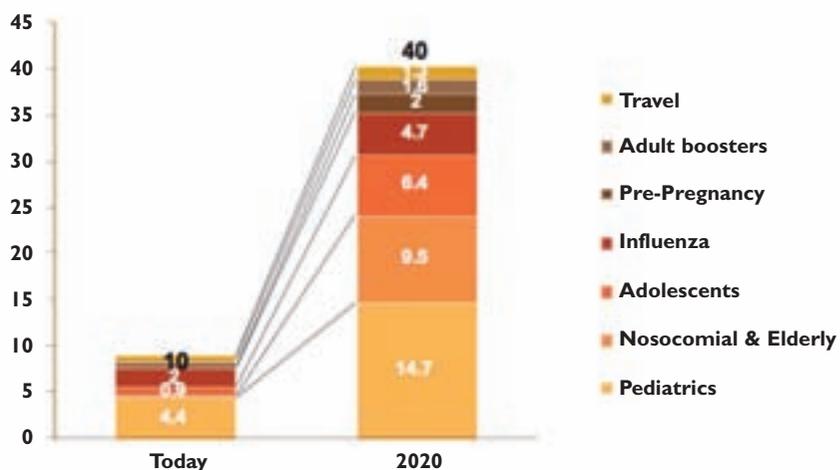
One disease area that presents a clear unmet medical need for a vaccine is meningococcal disease. A rare, but vaccine-preventable disease, invasive meningococcal disease is acute, contagious and potentially life-threatening. The disease-causing bacteria are transmitted from person to person through droplets of respiratory or throat secretions,

**By Dr Joerg  
Reinhardt**

**Corporate Insight**

**The market for prophylactic vaccines is expected to grow substantially in the long term**

Long term vaccines market forecast  
US\$ in bn



Research Day 2007 | Joerg Reinhardt | July 2007



and the symptoms – including sudden onset of fever, headache and stiff neck – progress rapidly. Even with early and appropriate treatment, patients can die within 24-48 hours, causing 50,000 deaths worldwide annually.

Novartis Vaccines recently announced new clinical data for the Novartis development vaccine Menveo™ (MenACWY-CRM), making it the first quadrivalent conjugated meningitis vaccine to demonstrate an excellent immune response in infants as young as six months of age against four common serogroups (or types) of meningococcal meningitis. Menveo is designed to be a single formulation to protect all age groups (infant through adult), infants are considered the highest at-risk group. Currently, there are no vaccines approved in the US to protect children younger than two years of age against serogroups A, C, Y and W-135.

Meningococcal meningitis is a potentially fatal bacterial disease involving inflammation of membranes around the brain and spinal cord. The highest attack rate is in infants three to 12 months old, making meningococcal disease one of the last remaining serious bacterial threats to infants and young children. Despite the best available treatment, the disease is fatal for 5-10% of victims in

industrialised countries, and even higher in the developing world. Between 10-20% of survivors are left with permanent disability such as epilepsy, mental retardation, hearing loss or loss of limbs.

Novartis Vaccines is working to fulfill this significant unmet need by employing cutting-edge technologies and innovative discovery approaches, and is a leading the quest to develop a Men ACWY vaccine.

**Innovation in meningitis research: reverse genomics**

Currently, there is no vaccine available for prevention of serogroup B N. meningitidis (MenB) disease, which is responsible for 32% of all meningococcal disease in the United States and for 45% to 80% of the cases in Europe. This is because sequence variation of surface-exposed proteins and cross-reactivity of the serogroup B capsular polysaccharide with human tissues have hampered efforts to develop a successful vaccine.

Today, Novartis Vaccines is building on its technical expertise in developing meningococcal vaccines to develop a recombinant vaccine against serogroup B.

Novartis scientists, led by Head of Vaccine Research Dr Rino Rappouli, are using an innovative

technique called 'reverse vaccinology'. This technique was pioneered by Dr Rappouli and begins by identifying targets on a completed genome sequence, producing more effective vaccines faster, and providing novel antigens to attack diseases science currently cannot prevent.

Novartis has recently completed Phase II clinical studies for a candidate vaccine for meningitis B. This vaccine, which builds upon Novartis' genomics programme, is designed to offer protection against multiple strains of meningococcus B.

### **Cell culture: applying new technology to seasonal influenza**

Novartis is committed to applying innovative technologies to vaccine research and production extending across disease areas, including influenza. In June 2007, Optaflu, the first influenza vaccine to utilise a Novartis proprietary cell line for the production of viral antigen components rather than the traditional chicken eggs, received European Union approval in all 27 member states, as well as Iceland and Norway.

This was the first major innovation in influenza vaccine manufacturing in more than 50 years. Cell culture-derived influenza vaccine technology is an innovative production process for the manufacturing of flu vaccine on the basis of cell cultures. Cell culture-derived influenza vaccines, commonly referred to as 'flu cell culture' vaccines, use cell cultures rather than chicken eggs for antigen production. Current egg-derived vaccines production requires up to nine months, and this lead time can hinder the response to unanticipated demands such as the discovery of pandemic strains, production failures and seasonal influenza virus strain changes. In contrast, flu cell culture production enables flexible, faster start-up of vaccine manufacturing, providing a particularly important advantage in the event of an influenza pandemic.

As a next generation of products, it also offers the possibility for vaccine seed strain development that more closely matches the original 'wild' virus because cell culture technology eliminates the need for passage through eggs where the virus may be forced to adapt in order to replicate. As a result, the antigen included in the vaccine may express more authentically the surface of the wild type virus, potentially translating into a better immunogenic and effective response.

### **MF59-adjuvant: giving seasonal influenza vaccines a boost**

MF59, the Novartis proprietary adjuvant that is the first and only one to be used with an influenza

vaccine, is another example of our dedication to industry-leading technology.

The addition of the MF59-adjuvant to a conventional vaccine has been shown to augment the antibody response to the vaccination and increase protection of elderly subjects against influenza strains not included in the vaccines (heterovariants).

MF59 is added to both seasonal and pandemic influenza vaccines, and gives rise to greatly improved efficacy, among a number of other benefits. A recent study showed that vaccinating elderly subjects with an MF59-adjuvanted seasonal influenza vaccine (Fluad, from Novartis) resulted in a significant reduction in hospitalisation for major conditions such as pneumonia, acute coronary syndrome (ACS) and cerebrovascular accident (CVA) during the influenza season. In addition, the use of MF59 in Focetria, the Novartis pandemic influenza vaccine, could extend the vaccine supply by allowing for smaller amounts of viral antigens to be used in each dose compared to vaccines without this additive. Finally, our pre-pandemic MF59-adjuvanted H5N1 vaccine currently under review in Europe, could protect against a broader range of viruses in case of an avian flu pandemic situation, and could be used prior to a pandemic outbreak, boosting the immune system's ability to defend against infections from a H5N1 virus strain.

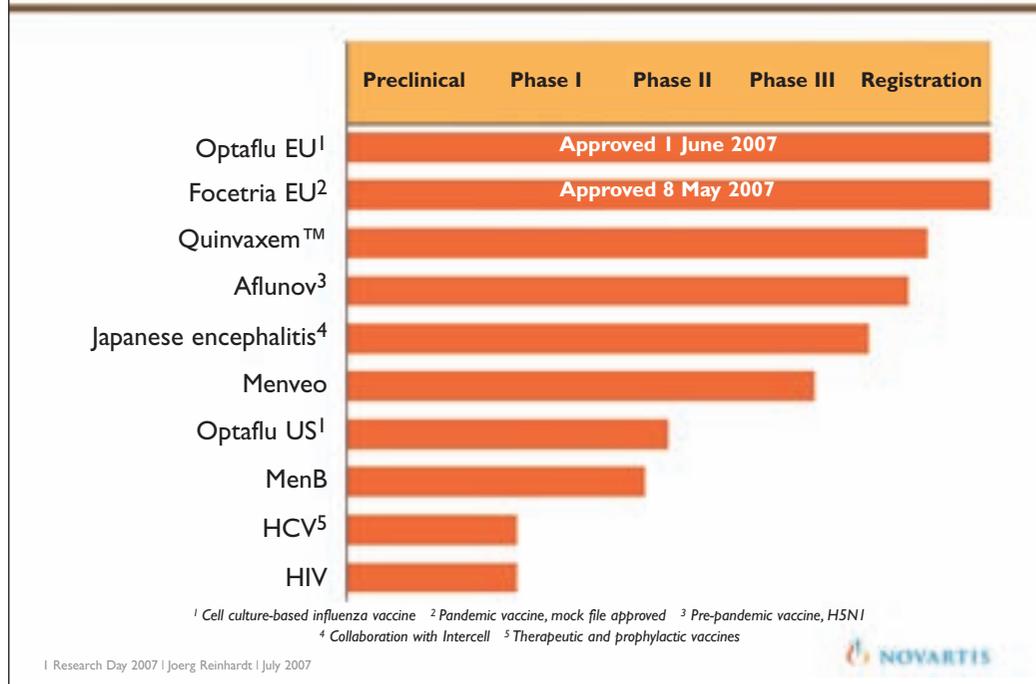
### **Seasonal influenza: meeting the increasing demand for seasonal influenza**

Another significant factor for consideration in the influenza vaccines arena is the growing demand for seasonal influenza vaccines, occurring in large part as a result of the increasing number of people for whom annual influenza vaccination is recommended. The American Center for Influenza Protection recently expanded its recommendations to include children aged six months to five years old (previously was 6-23 months), and continues to discuss their longer-term goal of universal vaccination recommendations. In the not-too-distant-future, the actual demand for influenza vaccine in the United States could exceed 200 million doses annually, a figure well beyond current levels of demand, which are around 100 million doses.

Novartis has undertaken a number of initiatives in order to meet this growing demand. In August, we broke ground on construction of the first cell culture-derived influenza vaccines manufacturing plant in the United States. Once completed, the facility is expected to have an annual production capacity of up to 50 million doses of seasonal

## Corporate Insight

### The development pipeline is showing good progress on highly promising assets



trivalent flu vaccine. In the event of a pandemic declaration, the facility is expected to have a capacity of up to 150 million monovalent doses of MF59-adjuvanted pandemic flu vaccine within six months of the declaration. Completion of the facility in Holly Springs, North Carolina is expected in 2009, and following validation and FDA approval, initial vaccine production at the site is anticipated for 2011.

Additionally, Novartis shipped more than 40 million doses of Fluvirin® influenza virus vaccine for the 2007/08 season to the United States. About seven million of these vaccines were made available earlier than expected, supporting the rollout of annual influenza immunisation programmes nationwide.

According to the Centers for Disease Control and Prevention (CDC), the best defence for people who want to reduce the risk of becoming ill with influenza, or of transmitting the disease to others, is to receive an annual vaccination. Early and sustained availability of influenza vaccine also provides a greater window of opportunity for more people to get vaccinations. Novartis Vaccines is committed to supporting public health efforts by continuing to provide a reliable supply of influenza vaccine as early as possible.

#### Intercell: a strategic alliance

In July, Novartis and Intercell AG formed one of the vaccines industry's most comprehensive and innovative strategic alliances, bringing together the research, development, manufacturing and commercialisation capabilities of Novartis with Intercell's unique research skills and highly-respected pipeline. This novel alliance further leveraged the potential of various Intercell vaccine candidates with the research, development, manufacturing and commercialisation expertise of Novartis.

Several unpartnered projects in the existing Intercell R&D portfolio, which currently includes more than 10 potential projects for which Novartis may choose for further development, will further strengthen the efforts of Novartis to building a broad range of vaccines to prevent life-threatening viral and bacterial diseases as well as strengthen its range of influenza vaccines.

Novartis also secured opt-in rights to all future vaccine candidates discovered by Intercell during the long-term collaboration. The alliance will specifically focus on the development of vaccines derived from Intercell's Antigen Identification Program (AIP), including IC31 adjuvant technology in selected areas. Intercell's AIP approach is

complementary to the Reverse Vaccinology system used by Novartis.

It also expands Novartis' leadership in adjuvanted vaccines through exclusive rights to further develop IC31 adjuvant in influenza – designed to enhance effectiveness

Among the various Intercell projects eligible to Novartis are the IC43 vaccine candidate for use in patients with hospital-acquired pseudomonas infections, which is now in Phase II trials and will expand the range of nosocomial vaccines in the Novartis pipeline, and the pre-clinical vaccine IC47 against pneumonia infections in the elderly and infants.

### Conclusion

Novartis Vaccines is a proven innovator that is not only revolutionising the way that influenza vaccines are made but is also moving the world closer to eradicating one of the world's last bacterial diseases that causes morbidity and mortality in children. We are devoted to exploring many new vaccine technologies and we are prepared to make significant investments in bringing the most promising technologies to fruition once we see advantages in either efficacy or safety. Vaccines promise to play a long term and substantial role in improving world health, and Novartis Vaccines looks forward to leading the way in this relevant and growing industry.

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*Dr Joerg Reinhardt is CEO of the new Novartis Vaccines and Diagnostics Division, which was created from the acquisition of Chiron Corporation's vaccines and blood testing business. He is also a member of the Executive Committee of Novartis. Previously, Joerg Reinhardt was Global Head of Development in the Novartis Pharmaceuticals Division, overseeing clinical, pharmaceutical, chemical and biotechnological product development, drug safety assessment and regulatory affairs. Under his leadership, Novartis achieved an outstanding record in development quality, speed and productivity, resulting in a full product pipeline recognised as one of the most successful in the industry. He joined Sandoz, a predecessor company of Novartis, in 1982 and held various leadership positions in Research & Development for the company. In 1994, he was made Head of Corporate Development. He became Head of Preclinical Development and Project Management for Novartis in 1996, and took the position of Global Head of Development in 1999. Dr Reinhardt chairs the Board of Directors of the Genomics Institute of*

*the Novartis Foundation in La Jolla, California. From 2001 to 2004, he served as a member of the Board of Directors of MorphoSys AG, Germany, a company specialised in research and development of monoclonal antibodies. He received his PhD in Pharmaceutical Sciences from the University of Saarbrücken, Germany.*