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Vaccines: growth boosters

► Radical changes ahead in the fast growing vaccines industry

The vaccine market is expected to keep outpacing pharmaceuticals over the next five years (estimated CAGR of 13% versus 6% for Pharma). Although small in size, the vaccine franchises contribute substantially to the overall growth of GSK, Sanofi-Aventis, Merck & Co and Wyeth. The historical flu franchise and new types of vaccines will drive the growth and changing shape of this market.

► Flu vaccine: a key to success for Sanofi-Aventis

Sanofi-Aventis will benefit from its global leading position in the flu arena, which will be driven by both enhanced protection against seasonal influenza and the anticipation of possible pandemics. Flu vaccine players are dramatically increasing their production capacities and trying to revolutionise the production process by moving from fertilised egg production to in vitro cell-based culture.

► New vaccines are also new marketing paradigms

Vaccines against Human Papilloma Virus (HPV) to prevent cervical cancer, pre-cancerous genital lesions and genital warts are a turning point. Merck & Co, Sanofi-Pasteur (its European partner) and GSK will have to deploy considerable resources in "pharma-like" marketing. This underlines the issue of pricing and reimbursement, as more marketing efforts are needed. Merck and GSK are likely to reap the biggest benefits from this new wave of products.

► An oligopoly with room for new players

The vaccines market will remain oligopolistic around Merck, Sanofi-Aventis and GSK, although Novartis (with Chiron) and Wyeth are investing strongly to become part of the oligopoly. Behind the majors, many smaller companies are progressing rapidly and might become major innovation providers, like CSL, Acambis, Crucell or MedImmune. Local players may also manage to keep, or even increase, their share of the pie (for example in India, Brazil or Japan).

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Contents

Stage set for radical changes in the fast-growing vaccines industry	3
The vaccines business model is changing	6
Three categories of players in the field	9
The technology (r)evolution	12
Case study 1: The new HPV vaccines	14
Case study 2: The seasonal and pandemic flu vaccines	16

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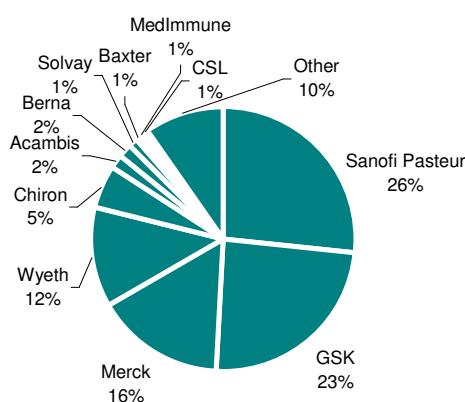
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Stage set for radical changes in the fast-growing vaccines industry

The vaccines market was estimated to be worth USD10bn in 2005 and is growing very fast compared to the pharmaceuticals market (2006-2010 sales CAGR of 13%e for vaccines vs 6%e for Pharma). The vaccines segment will remain relatively small but will continue to grow faster than the market for a long time to come. In addition, new types of vaccine will help sustain operating margins at least at par with the pharma sector average.

Chart 1: Key players in the vaccine market



Source: Bionest partners, Exane BNP Paribas

There are still many opportunities for the vaccine market to expand both in the short term and over the longer term. Innovative vaccines, for example from Merck and GlaxoSmithKline in cervical cancer, which we believe will be commercialized as of 2006, will be a catalyst for market dynamics. Additionally, the possibility of pandemics, such as avian flu, may increase the need for vaccination against new diseases and extend the reach of vaccines.

The large pharma companies most exposed to vaccines are Sanofi-Aventis, Wyeth, Merck and GlaxoSmithKline.

Table 1: Vaccines are a major growth engine

Company	Vaccines as % of group 2005 sales	Vaccines 2005 sales growth (%)	Group 2005 sales growth (%)
Wyeth	8	43	8
GSK	6	15	7
Merck*	5 (+2.0 with SP-MSD)	9	(4)
Sanofi-Aventis*	8 (+1.3 with SP-MSD)	27	9

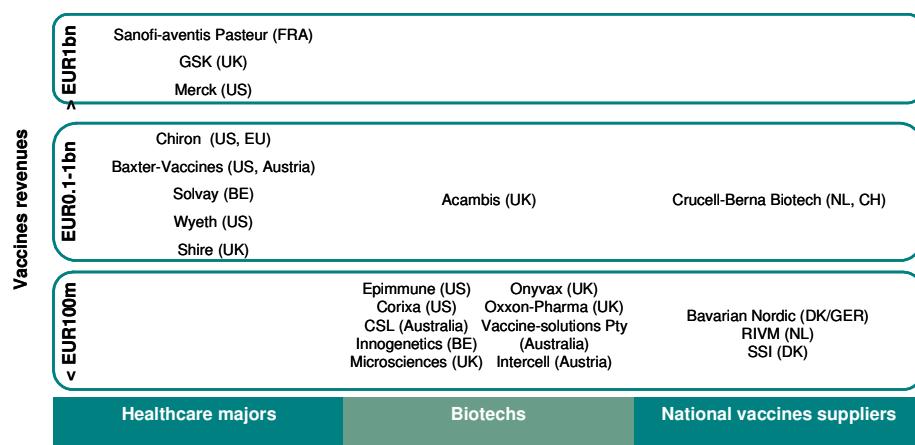
* Sanofi Pasteur MSD, a 50/50 JV between Merck and Sanofi-Aventis in Europe accounted for by equity, reported 6% growth in 2005

Source: Companies

Vaccine business models are likely to evolve rapidly.

- The majors, Merck, Sanofi-Pasteur and GSK will remain oligopolistic leaders with Merck probably dominant. Novartis-Chiron and Wyeth are determined to become major players.
- The arrival of new vaccines will require the makers to develop a new type of sales organisation, similar to that developed for conventional pharma sales. This could give an advantage to players such as GSK and Merck.
- The biotech players are forging stronger links with big pharma and vaccine players, who lack R&D innovation; some biotech companies will emerge as key players (e.g. CSL, Acambis, Crucell, MedImmune).

Chart 2: Major players of the 140 ones involved in the vaccines area



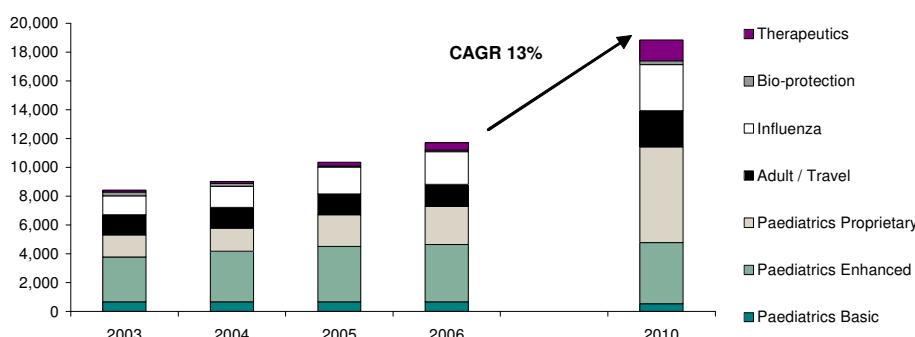
Source: Bionest Partners, Exane BNP Paribas

New vaccine markets will develop

This paper will discuss four themes:

- the dynamics of the vaccine industry and its evolution towards a “Big Pharma” model;
- the technological evolution of vaccines;
- the impact of the launch of Gardasil and Cervarix on the business models of Merck and GSK for vaccines;
- flu vaccination, including the impact of pandemic preparedness.

Chart 3: Vaccine market growth by segment



Source: Bionest Partners, Exane BNP Paribas

Taking two examples, Gardasil and the flu market, we have highlighted the changes likely to occur in the market, both commercial and technological.

Gardasil and Cervarix to build the future vaccine blockbuster model

The advent of Gardasil, approved by the FDA on 8 June in the prevention of cervical cancer, precancerous genital lesions and genital warts due to human papillomavirus (HPV), is a turning point in the history of vaccines. After Wyeth's success with Prevnar, the first ever vaccine blockbuster, Gardasil (and second-in-line Cervarix from GSK) will compete for market penetration and market share in a totally new area in which it confers 100% protection and hence create huge demand among the population at risk. The combination of protection against sexually transmitted diseases *and* avoidance of cancer-related infection has generated tremendous interest. Merck and its European partner, Sanofi-Pasteur, and GSK will be deploying considerable resources to promote their brands.

The major issue for developing these new vaccines into blockbusters will be obtaining satisfactory pricing and reimbursement. This will likely be the case for Gardasil and Cervarix in the "at risk" population. We believe that the strong efficacy of the two products (i.e. 100% protection) will prompt reimbursement even in Europe, either through classical channels, possibly initially for specific population groups and in certain countries, or with the support of private health insurers.

On June 29 2006, the US Advisory Committee on Immunisation Practice (ACIP), a CDC and Public Health Authorities board of experts, will give its opinion regarding the use of Gardasil in paediatric care, and notably for school-aged children. The ACIP is known for having a strong influence on US Public Health, so its position will provide a first sign (be it positive or negative) on the reimbursement status of HPV vaccines in a controversial environment over sexually-transmitted pathologies.

Flu vaccines are far from being a commodity

Another sweeping change that is likely is the broader use of vaccines against seasonal influenza ("flu") infection and government measures to prepare against a possible avian flu-derived pandemic in humans. We expect to see changes at several levels:

- 1) an increase in seasonal flu doses required to protect under-served populations in many countries (including the USA) and to protect countries in the southern hemisphere;
- 2) stockpiling in anticipation of a pandemic, with a resulting threat to production cycles and logistics. Overall production capacity is limited and a trade-off with the production of conventional flu vaccines would be necessary.
- 3) a transition from an egg-based culture to a cell-based culture technology. Flu vaccines are currently produced in fertilized chicken eggs, after a six month culture process. All vaccine players are currently investigating alternative mammalian kidney cell-based cultures (similar to the process for polio vaccines). Major improvements are expected to derive from this research: fewer impurities, no risk of allergic reactions to egg albumin and, above all, much higher quantities, with quicker scale-up. However, the timelines for regulatory approval of cell culture still puts these some way in the future, one important factor being the intrinsic risk carried by these cancerous cells.

The vaccines business model is changing

Today's vaccine business model has many differences with Pharma's

Today, prophylactic vaccines are prescribed to healthy infants, children, adolescents and adults to confer immunity against bacterial and viral diseases.

In developing countries, massive vaccination and advocacy campaigns are carried out under the auspices of such organisations as the WHO Expanded Program on Immunization, the United Nations Children's Fund (UNICEF), the Pan-American Health Organization (PAHO), and the Global Alliance for Vaccines and Immunization (GAVI). In addition, non-governmental organisations (NGOs) such as the Bill and Melinda Gates Foundation also play a significant role in vaccination.

In the western world, the prescription of vaccines is driven by medical practices and vaccination calendars to protect at-risk groups such as the over-65s (influenza), infants (diphtheria, tetanus, tuberculosis, poliomyelitis, etc.), and healthcare professionals (hepatitis B).

Chart 4: Vaccines constitute a distinct segment from pharmaceuticals

	Vaccines	Pharmaceuticals
Regulatory / CTRs*	<ul style="list-style-type: none">Focus on prevention – not patients, but healthy subjectsKey role for the government agenciesVery low acceptance of side effects5,000 to 10,000 subjects before registration (<i>can be up to 67,000 for Wyeth's Rotavirus vaccine</i>)	<ul style="list-style-type: none">Focus on treatment – patient is generally sickKey role for the healthcare playersAcceptance of side effects varies by severity of disease2000 to 3000 subjects before registration
Manuf.	<ul style="list-style-type: none">High manufacturing and supply chain complexity (<i>Cold Chain Management, complex biological processes</i>)	<ul style="list-style-type: none">Medium manufacturing and supply chain complexity (<i>Easier to handle chemical synthesis in most cases</i>)
Marketing / sales	<ul style="list-style-type: none">Small and non-specialized sales forceLimited advertisingDirect sales to physician (U.S.) or pharmacist (E.U.)Very few generic products (<i>Due to manufacturing complexity</i>)	<ul style="list-style-type: none">Massive sales force commitmentExtensive advertisingIndirect sales through physician as prescriberIncreasing generic threat

Source: Bionest Partners, Exane BNP Paribas

New vaccines are poised to change part of the model towards a Pharma one

Over the past ten years, some product innovations have modified the market, e.g. acellular pertussis vaccines. However, most of the innovation has been in the combination of paediatric vaccines, up to seven different valences, to ease injection schedules and confer wide protection to the young population. This enabled vaccine companies to strongly raise their prices on the back of higher convenience.

However, 2006 will see the real start in the development of a new category of proprietary vaccines targeted at specific at-risk populations and with the prospect of blockbuster potential (i.e. sales > USD1bn). The precursor was Prevnar, a vaccine against pneumococcal infections launched in 2002 and dubbed as the first-ever blockbuster vaccine (i.e. USD1bn sales over in 2005).

- Gardasil by Merck has just been approved by the FDA (June 2006) to prevent cervical cancer, precancerous genital lesions and genital warts due to human papillomavirus (HPV) types 6, 11, 16 and 18; Cervarix by GlaxoSmithKline will be filed in 2006 for similar indications to those of Gardasil;
- Rotatet by Merck received FDA approval in February 2006 to prevent rotavirus gastroenteritis, a leading cause of severe infant diarrhoea; GSK's Rotarix was approved in Europe in March 2006 in the same indication;
- Zostavax by Merck was approved by the FDA and in the European Union in May 2006 to prevent shingles in adults of 60 years and older.

The promotion of these new products will no longer be confined to a limited target of paediatricians and specialist physicians, but will emulate the "Big Pharma" model, with massive investment in sales and marketing to gain penetration and market share quickly in totally new markets.

The sales of these few high-price new vaccines (e.g. USD360 for a course of three injections with Gardasil) could rapidly create a market worth over USD5bn. As a comparison, the price of a flu vaccine shot is around USD11.

As a consequence, the vaccine industry is poised to go through a polarisation around two major models.

The traditional Vaccine model

This model remains constituted mainly by paediatric vaccines used to prevent healthy patients from the well-known series of viral / bacterial infections. After having multiplied the number of antigens injected in the same shot (penta, hexa, heptavalent vaccines), it appears the technical changes in this area will be more limited.

The four big players (Merck, GSK, Sanofi-Pasteur and Wyeth) are all established in this model but more and more local players like Indian or Brazilian companies are emerging with state-of-the-art knowledge and industrial capacities.

Emergence of a "Pharma-like" vaccine model

The new vaccines mentioned earlier set the stage for the emergence of a more Pharma-driven business model combining high R&D expenditure, a commercial focus on developed countries and high prices. The focus is no longer just on children but also on adults. This model implies substantially higher marketing and sales expenses but also offers higher expected returns. With Prevnar, Wyeth was the first to enter this new model, now followed by Merck and GSK with HPV vaccines. Sanofi-Aventis is on the sidelines of this evolution (as only through its European JV with Merck) and so far remains entrenched in the traditional model by maintaining a very wide range of paediatric single and combo vaccines, as well as strengthening its leading position in flu by investing in enhanced manufacturing and R&D capabilities.

The Pharma-like model is fuelled on the R&D side by the emergence of biotech companies, with innovative and productive technologies. Some have forged good deals with bigger players and could reach out to the market and become significant players in their own right in the next three to seven years.

Chart 5: Three major vaccine market categories

Market Type	Clients	Geographical areas	Market organization
Commercial Market <i>Biggest markets in value by far</i>	Public or private	Mainly for developed countries, but increasing importance of emerging markets	Strongly regulated market where competition does exist and pricing is implemented in more classical way.
Donor Market <i>Biggest markets in doses but low in Value (with some exceptions)</i>	Managed by International organizations such as WHO, UNICEF, PAHO and GAVI**	Poor or developing countries	International organizations buy mostly EPI monovalent vaccines at a tiered price for routine or mass immunization
Closed market <i>Currently very small markets (but could be huge in the future)</i>	Local clients (Often Non-exportable for regulatory reasons)	e.g. India, Indonesia, China, Brazil, Cuba	Local producers supply the local needs with EPI* monovalent vaccines

*Expanded program on immunization (EPI)

**World Health Organization (WHO), United Nations Children's Fund (UNICEF), Pan American Health Organization (PAHO), Global Alliance for Vaccines and Immunization (GAVI).

Source: Bionest Partners, Exane BNP Paribas

Three categories of players in the field

Vaccine majors: Sanofi-Pasteur, Merck and GSK

Should the success of Prevnar, prove to be a precursor for new proprietary blockbuster vaccines, such as Gardasil, Cervarix, Rotateq, Simplirix, generating blockbuster sales in the next five years, the traditional paediatric vaccines market will be dwarfed. Only flu vaccine sales, shifting to cell-culture based products and with possibly higher volumes due to pandemic, could rival the blockbusters.

So far, large vaccines companies have been part of even larger pharmaceuticals conglomerates.

Table 2: Vaccine business for big pharma players

 The vaccines business of sanofi-aventis Group	"Sanofi-Pasteur, the vaccines business of Sanofi-Aventis, is the largest company in the world devoted entirely to human vaccines."
	"We market over 25 vaccines worldwide to prevent potentially life-threatening or crippling illnesses such as hepatitis A, hepatitis B, diphtheria, tetanus, whooping cough, measles, mumps, rubella, polio, typhoid, influenza and bacterial meningitis."
	"As one of just five major pharmaceutical research companies in the world that is actively pursuing the development of new vaccines, we are making significant inroads in the cause of disease prevention. We expect our vaccine business to continue to provide significant strength to our long-term growth."

Source: Company websites

The vaccine divisions of the main players typically generate operating margins slightly below the pharma average. This is mainly due to lower prices and higher manufacturing costs, despite lower sales and marketing expenditures. Also, the vaccine business is more capex-intensive than the pharma business and has consequently never really been at the forefront of investors' interests.

With the advent of the new blockbuster vaccines, and despite the large investment required in sales and marketing to push these products, some vaccine players are likely to generate margins and achieve growth rates above those obtained in pharmaceuticals.

In terms of organizational efficiency, it is likely that **GSK** and Merck will reallocate "pharma" resources to market their new vaccines. GSK's commercial organisation already allows this type of switch in most countries. **Merck** is in more complex situation as it shares its vaccine activity with Sanofi-Aventis in Europe and will thus probably be unable to pool resources with pharma in the region.

Sanofi-Pasteur is in a very different situation. It operates through a 50/50 joint venture with Merck in Europe and has its stand-alone operation in the USA. The European JV will market the Merck blockbuster vaccines, but the US organization will not. This imbalance creates a competitive disadvantage for Sanofi-Pasteur. Besides, Sanofi-Pasteur's pipeline contains fewer potential blockbusters. The company has a number of interesting, albeit difficult vaccines in development (e.g. HIV, dengue, Respiratory Syncytial Vaccine).

Novartis has been a sleeping shareholder of Chiron prior to taking it over in 2006. Chiron, a leading manufacturer of flu vaccines, encountered a dramatic setback in 2004 due to manufacturing problems for its flu vaccines. As a result the company missed at least two flu seasons in the USA, with the loss of around USD400m in sales. Novartis is willing to become a vaccine major, and is investing heavily in a new vaccines plant in the USA.

Wyeth has been a producer of human and animal biologicals for decades. The company was the first to be able to develop and manufacture a pneumococcal vaccine, where many other companies failed. Prevnar sales have surpassed USD1.5bn, but this is the only salient product in an otherwise narrow portfolio.

Vaccine-focused biotech companies: Acambis, Crucell-Berna, Intercell

This group of companies prospers on the strength of their proprietary technology and ability to bring forward attractive vaccine candidates in their R&D pipeline. They all focus on infectious diseases and develop their own business model.

Table 3: Positioning of vaccine biotechs

Acambis The future of vaccines. Today	"Acambis is a biotechnology company discovering, developing and manufacturing novel vaccines to prevent and treat infectious diseases."
Crucell	"Crucell is a biotechnology company focused on developing products that prevent and treat infectious diseases."
intercell SMART VACCINES	"Intercell AG is a fast growing biotechnology company with a clear strategy and focus on the design and development of novel vaccines for prevention and treatment of infectious diseases with substantial unaddressed medical need."

Source: Company websites

As often with biotechnology companies, the business model is very dependent on the therapeutic area addressed and on the technology. However, vaccine biotechnology companies have several common features:

- multiple alliances with big pharma/vaccine majors to enhance the vaccine portfolio: 1) Acambis with Baxter, Sanofi-Pasteur, Chiron; 2) Crucell-Berna with Sanofi-Pasteur, GSK; 3) Intercell with Novartis, Merck, Kirin Brewery, SciGen, Sanofi-Pasteur;
- strong intellectual property rights allowing the licensing of technology and generation of significant revenues (e.g. PER.C6 cell line of Crucell, a technology which uses a human cell line for the production and large scale manufacturing of viral-based vaccines, monoclonal antibodies, and recombinant proteins);
- a substantial number of vaccine candidates in clinical development: Acambis and Crucell both have five, Intercell has four.

Vaccine-focused biotech companies have a number of specific characteristics.

First, the emergence of bio-terrorism risks has created a new market with governments financing the development of specific vaccines in order to stockpile huge quantities against bioterrorism attacks.

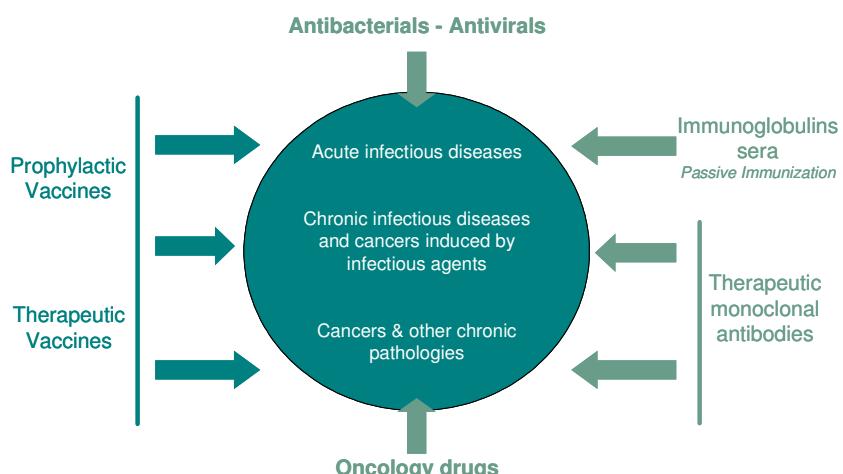
Several companies have been fortunate to be selected, including Acambis (smallpox) and Vaxgen (anthrax). The downside is the risk of bottlenecks in manufacturing and resource concentration that could be detrimental to the rest of the activity.

Second, biotech-focused vaccine companies are at the forefront of technology. They take risks in discovering and developing new components for vaccines of the future: cell lines, recombinant proteins, adjuvants, vectors, etc. Some of the companies are well financed as a result of public listings (e.g. Intercell); others are still heavily dependent upon venture capital financing. All have links with vaccine majors in deals where technology can be levered and financed properly.

Finally, biotech-focused vaccine companies are important players in related fields such as antibacterials, antivirals, therapeutic monoclonal antibodies, therapeutic vaccines (e.g. for cancers). Their science and technology platforms open up many avenues around innate and humoral immunity. Therefore their business models can evolve beyond the traditional vaccination targets (age groups at risk of developing a disease) and extend to established diseases for which medical, regulatory and marketing activities are quite different.

An example of such a company is MedImmune, which is developing a humanized monoclonal antibody currently under evaluation for its potential to prevent serious lower respiratory tract disease caused by RSV in paediatric patients at high risk of RSV disease. MedImmune is also studying the potential for preventing upper respiratory tract infections such as otitis media. This is a case where a monoclonal antibody would be utilized with a preventative objective (similar to a vaccine), but marketed as a highly specialized medicine, for a limited group of patients and with a pharma-like approach.

Chart 6: Indirect competitive environment within vaccine-related therapeutic areas



Source: Bionest Partners, Exane BNP Paribas

Domestic-focused vaccine companies

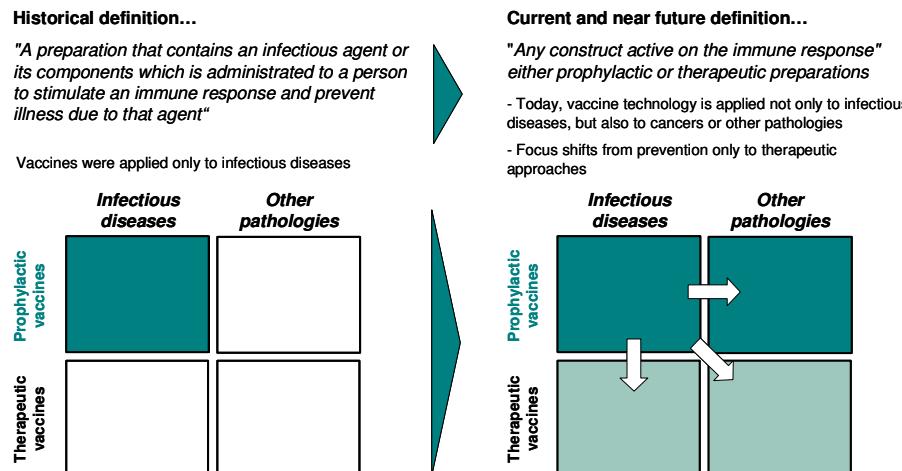
This covers national players, public or public-private, developing in-house capabilities to serve their domestic market and gradually replace western manufacturers, mostly in the traditional vaccine market.

This is particularly the case of Japan, India, Brazil, Mexico, Indonesia, and China with players such as Kaketsukan, Kitasato, Denka Seiten, Biken (Japan), SII, Pinacea (India), Fiocruz, Butantan (Brazil), and Birmex (Mexico).

The technology (r)evolution

A vaccine used to be a biological preparation given to patients likely to be subject to an infectious disease (e.g. Poliomyelitis, Measles, Mumps and Rubella). This is still the case today, especially for children, but vaccine technology is increasingly applied to non-infectious disease areas, as well as for therapeutic vaccines.

Chart 7: Historical and current/near future definition of “Vaccines”



Source: Bionest Partners, Exane BNP Paribas

Therapeutic vaccines have so far proved disappointing, for several reasons:

- no survival benefit (e.g. Apton's Insegia -G17DT, CancerVax's Canvaxin, Biomira's Theratope);
- technological complexity beyond reach (e.g. VaxGen's AIDSVAX);
- commercial limitations of personalized vaccines (e.g. Cell Genesys's GVAX lung and myeloma);
- inferiority to existing therapy (e.g. Progenics's GMK).

It is principally in the area of cancer and HIV that therapeutic vaccines could have a major interest. For example, research communities, opinion leaders and key investigators, interest groups and regulatory agencies are discussing the position of immunotherapy in disease management of HIV. Since the development of a prophylactic vaccine is currently out of reach, there could be an immunotherapeutic approach to reduce the viral load of infected patients.

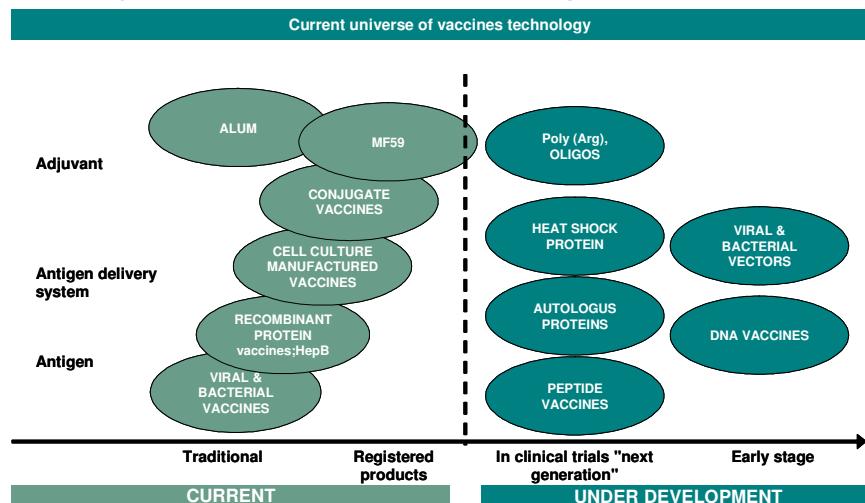
When these therapeutic vaccines reach the market, the big pharma vaccine majors (e.g. Sanofi-Pasteur, GSK, Baxter, Merck, Wyeth) will have to negotiate their commercialization: an oncology therapeutic vaccine is likely to be promoted more effectively by specialized oncology sales forces, which have a history with oncology-prescribing physicians, than by a vaccines sales force.

Vaccinology R&D has enjoyed rapid progress over the past decade. Recent insights in immunology have opened new ways to stimulate different T Cell populations, induce memory, and avoid stimulation of suppressive regulatory cells.

The sequencing of bacterial and viral genomes has accelerated genetics research. For example, sequencing has enabled the production of hepatitis C virus, which could not be cultivated in vitro.

Progress in cellular and molecular biology has permitted the development of new vaccine components, such as recombinant vaccine carriers which induce powerful immune responses.

Chart 8: Very active search for alternative technologies



Source: Bionest Partners, Exane BNP Paribas

More is expected from science and technology in the coming years. The case of DNA vaccines is a good example; if DNA vaccines work in humans, it is theoretically possible to create a universal vector that will carry any possible inserted gene of a disease pathogen.

There is a need for improved production processes in vaccine manufacturing, from early batch production to massive bulk production. A lot of effort is being put into:

- process controls: systematic use of modern methods (e.g. protein sequencing and molecular markers) to control starting materials in vaccine production, ensure manufacturing consistency and to detect potential contaminants;
- product testing: opportunities to replace in vivo testing of vaccine batches by in vitro testing of physico-chemical characterization.

The most difficult microbiological scientific areas to crack are likely to be microorganisms with antigenic variation (HIV), large genome of parasites (malaria), and ineffectiveness of antibodies against intracellular pathogens (chlamydiae).

While these technologies are all promising, the time to actually be converted into marketable products can be a matter of several years. This is similar to the time it is taking the genomic/proteomic advances of the 1990s to lead to new products.

There remain several significant barriers to overcome in manufacturing, including avoidance of product contamination, compliance difficulties and antigen incompatibility in combination.

Table 4: Impact of technology

Vaccine value chain	Major drivers
Antigens	Impact of molecular biology and structural proteomics. Unmet need in many infectious diseases: nosocomial agents (<i>Staphylococcus Aureus</i> , <i>Pseudomonas Species</i> , <i>E.Coli</i>), vector-borne agents (<i>Plasmodium falciparum</i> , dengue fever virus, chikungunya), sexually-transmitted agents (HIV, Chlamydia, HSV Type 2)
Adjuvants and delivery	Aluminium hydroxide is currently the only registered adjuvant widely used registered for influenza with the addition of MF 59, an oil-in-water emulsion. An entire biotech industry sector dedicated to adjuvants is under development. Molecular understanding of innate immune defence mechanisms against pathogens will provide new opportunities for promoting the immune response by developing new adjuvants.
Production systems	Much is expected from mammalian cell cultures that could replace egg-based production of influenza vaccines. Cell culture based systems can be rapidly expanded in times of pandemic; yet their development is extremely complex. Some vaccines, such as polio, are already produced by cell lines.

Source: Bionest Partners, Exane BNP Paribas

Case study 1: The new HPV vaccines

HPV is one of the most common sexually-transmitted infection. The US Center for Disease Control and Prevention (CDC) estimates that about 6.2 million Americans become infected with genital HPV each year and that over half of all sexually active men and women become infected at some time in their lives. On average, there are 9,710 new cases of cervical cancer and 3,700 deaths attributed to it in the USA each year. Worldwide, cervical cancer is the second most common cancer in women and is estimated to cause over 470,000 new cases and 233,000 deaths each year.

In the US, approximately 20 million people are infected with HPV, and approximately 80 percent of females will have acquired HPV by age 50. Certain high-risk types of HPV, if unrecognized and untreated, can lead to cervical cancer. Approximately 10,000 women are diagnosed with cervical cancer every year, and an average of 10 women die each day from the disease. In addition, certain low-risk types of HPV cause genital warts and can lead to abnormal Pap results. Approximately 1 million cases of genital warts occur each year in the US and an estimated 32 million cases occur worldwide. Additionally, there are an estimated 4.7 million abnormal Pap results that require follow-up each year in the US. At least 3 million of these results are caused by some type of HPV. HPV related disease, including screening, follow-up and treatment, costs about USD5 billion per year in the US.

Merck licensed Gardasil technology from the Australian company CSL in 1995. In June 2006 approved the prescription of Gardasil to females 9-26 years of age.

Gardasil is a recombinant vaccine (contains no live virus) that is given as three injections over a six-month period. Immunization with Gardasil is expected to prevent most cases of cervical cancer due to HPV types included in the vaccine. However, females are not protected if they have been infected with that HPV type(s) prior to vaccination, indicating the importance of immunization before potential exposure to the virus. Also, Gardasil does not protect against less common HPV types not included in the vaccine, thus routine and regular pap screening remain critically important to detect precancerous changes in the cervix to allow treatment before cervical cancer develops.

GSK and Merck are going to fight a head-to-head battle to capture the HPV market. Merck is a year ahead, but GSK is determined to transform Cervarix into a blockbuster.

The differences between the two products are not very strong. GSK puts forward the difference in adjuvants (ASO4 vs. aluminium) which will supposedly bring three advantages:

- faster onset of protection;
- stronger protection due to higher antibody titres;
- longer duration of protection.

Merck emphasizes Gardasil: the broader coverage of HPV types:

- Gardasil: types 16 & 18 (high grade cancers) and 6&11 (low grade cancer);
- Cervarix: types 16 & 18 (high grade cancers) only.

It is difficult to predict the outcome of the battle. Since both products claim a 100% protection against risk, it will be the intensity of medical and marketing campaigns that will result in different market shares for this worldwide competition.

In this respect, the HPV battle is a typical “big pharma” competition, not unlike the very large therapeutic classes such as statins and anti-hypertensives.

The major issue for developing these new vaccines into blockbusters will be obtaining satisfactory pricing and reimbursement. This will likely be the case for Gardasil and Cervarix in the “at risk” population. We believe that the strong efficacy of the two products (i.e. 100% protection) will prompt reimbursement even in Europe, either through classical channels, possibly initially for specific population groups and in certain countries, or with the support of private health insurers.

On June 29 2006, the US Advisory Committee on Immunisation Practice (ACIP), a CDC and Public Health Authorities board of experts, will give its opinion regarding the use of Gardasil in paediatric care, and notably for school-aged children. The ACIP is known for having a strong influence on US Public Health, so its position will provide a first sign (be it positive or negative) on the reimbursement status of HPV vaccines in a controversial environment over sexually-transmitted pathologies.

We currently estimate HPV vaccines will reach USD2.5bn in sales in 2012e (implying around 7 million vaccines courses a year in the developed world at a USD360 price per course), split 50/50 between Gardasil and Cervarix. As a reminder, Sanofi-Aventis should get about 25% of profits from Gardasil through the JV with Merck in Europe, while Merck will get the remaining 75%.

Case study 2: The seasonal and pandemic flu vaccines

Some definitions

Seasonal Influenza, commonly called flu, is an acute respiratory illness that affects the upper and/or lower parts of the respiratory tract and is caused by an influenza virus, usually of type A or B. Patients become ill between 18 and 72 hours after being infected. The most common symptoms of uncomplicated influenza are an abrupt onset of fever, shivering, headache, muscle ache and a dry cough.

It can be transmitted from person to person. Most people have some immunity, and a vaccine is available.

Pandemic flu is virulent human flu capable of causing a global outbreak on a worldwide scale.

Influenza epidemics occur virtually every year, although the extent and severity of such epidemics vary widely. The most frequent, extensive and severe outbreaks are caused by the influenza A virus. Illness and death from influenza outbreaks continues to be substantial.

In the interpandemic period, death occurs primarily in individuals with underlying diseases who have been characterized as being at "high risk" for complications of influenza.

It is estimated that approximately 10-15% of people worldwide get influenza each year. During major epidemics, the attack rate of influenza may be as high as 50%.

The viruses in the vaccine change each year based on international surveillance and scientists' estimations about which types and strains of viruses will circulate in a given year.

Avian (or bird) flu is caused by influenza viruses that occur naturally among wild birds. The H5N1 variant is deadly to domestic fowl and can be transmitted from birds to humans. There is no human immunity and no vaccine is available.

What is at stake for Industry?

Several vaccine companies have developed and market flu vaccines (GSK, MedImmune, Sanofi-Pasteur, Chiron-Novartis, Solvay, etc.). The worldwide influenza vaccines market was estimated to be worth between USD1bn and USD1.3bn in 2006. Approximately 350m doses were administered in western markets during the 2005-2006 season.

In the US, only one plant is licensed to manufacture flu vaccines, that of Sanofi Pasteur in Swiftwater, Pennsylvania. Due to manufacturing problems at Chiron, the US market is underserved and there is considerable public and private pressure to increase local production.

Competition is fierce among the few specialists able to supply the US market.

- Sanofi-Aventis has the only US plant labelled to ship flu vaccines. For the 2008/09 season the company plans to have doubled its plant capacity from the 50m doses produced in the 2005/06 season.

- Last season, GSK imported several million doses from its plant in Dresden, Germany, and filed a BLA in March 2006 for FluLaval, its new Type A and B new vaccine developed by ID Biomedical.
- Chiron (Novartis) has the broad flu vaccines range but was temporarily put off market by major manufacturing problems.
- MedImmune has announced major investments.
- CSL has announced a major commitment to supplying the US market, with an increase in capacity at its Melbourne plant to 40m doses. CSL intends to seek FDA approval to ship vaccines for the 2007/08 season

In May 2006, the US Department of Health awarded contracts together worth over USD1bn to develop cell-based flu vaccines. The contracts were awarded to GlaxoSmithKline (USD275m), MedImmune (USD169m), Novartis Vaccines & Diagnostics (USD221m), DynPort Vaccine (USD41m), Solvay Pharmaceuticals (USD299m).

Cell-based vaccine manufacturing – a technology that is used in many other modern vaccines – holds the promise of a reliable, flexible and scalable method of producing influenza vaccines. Currently licensed influenza vaccines are produced in specialized chicken eggs in a technique that has changed little in over 50 years. With increasing demand for seasonal influenza vaccine and with the looming threat of a pandemic, a system that allows surge capacity in an emergency is needed.

Using a cell culture approach to producing influenza vaccine offers a number of benefits. Vaccine manufacturers are able to bypass the steps needed to adapt the virus strains to grow in eggs. In addition, cell culture-based influenza vaccines will help meet surge capacity needs in the event of a shortage or pandemic, since cells may be frozen in advance and large volumes grown quickly. Licensure and manufacture of influenza vaccines produced in cell culture will provide security against risks associated with egg-based production, such as the potential for egg supplies to be unavailable as a result of various poultry-based diseases. Finally, the new cell-based influenza vaccines will provide an option for people who are allergic to eggs and therefore unable to receive the currently licensed vaccines.

It remains unclear when cell-based production will overtake egg-based vaccines. The industry experts we talked to consider it will take several years for the technology to become commercially available and another few years to replace egg-based vaccines.

Therefore the flu vaccination market is a state of flux:

- Will pandemic develop, due to avian flu transmission to man?
- Will there be enough manufacturing capacities to serve the market?
- How will the Industry serve the developing markets, where avian flu scare can increase vaccination needs?
- Will cell culture-based vaccines be successfully developed and licensed to substitute for egg-based culture vaccines in the long run?

The consequences of these uncertainties will substantially modify the competitive intensity of the flu vaccine sector:

- Will Sanofi-Pasteur retain its leadership in egg-based production?
- Will smaller outsiders (MedImmune, CSL) be able to carve out new markets for their flu vaccines?
- Will prices of flu vaccines rise (law of market supply and demand) or fall (customer pressure in view of increasing – not to mention pandemic – quantities, but also the impact of the strong increase in production capacity)?

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Stock Rating (vs Sector)

Outperform: The stock is expected to outperform the industry large-cap coverage universe over a 12-month investment horizon.

Neutral: The stock is expected to perform in line with the industry large-cap coverage universe over a 12-month investment horizon.

Underperform: The stock is expected to underperform the industry large-cap coverage universe over a 12-month investment horizon.

Sector Rating (vs Market)

Outperform: The sector is expected to outperform the DJ STOXX50 over a 12-month investment horizon.

Neutral: The sector is expected to perform in line with the DJ STOXX50 over a 12-month investment horizon.

Underperform: The sector is expected to underperform the DJ STOXX50 over a 12-month investment horizon.

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