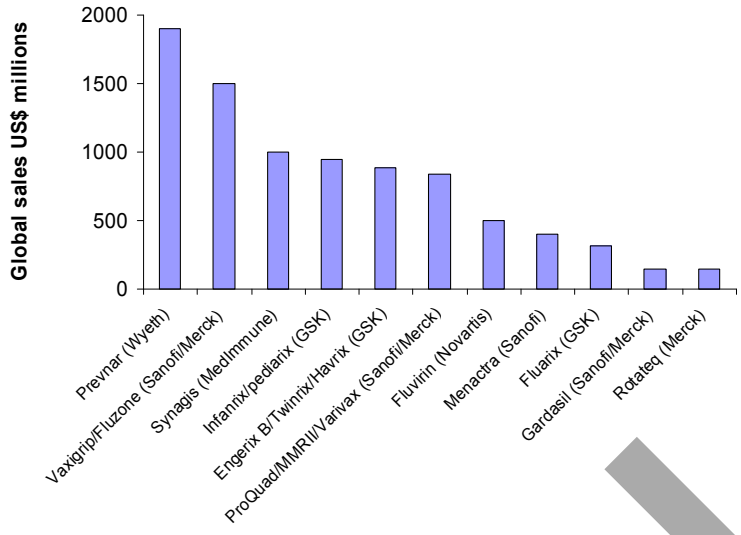
Figure 1.2: Leading vaccine brands 2006

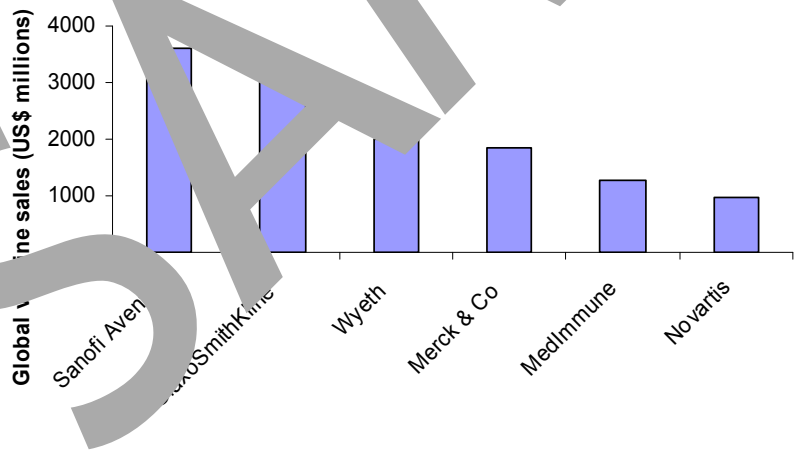


Source: Company data. PharmaVision.co.uk estima

1.2.2 Key pharma players

The vaccine market is dominated by a few companies: & Co., Wyeth, GlaxoSmithKline (GSK), Novartis (formerly Chiron) and Sanofi Pasteur. mmune (no of AstraZeneca) is often excluded from this list, although they supply Synagis, one of fitable va s for the prevention of respiratory syncytial virus (RSV). Total va ne sales for th comp are sum rized in Figure 1.3.

Figure 1.3: Leading companies' les (20



Source: Company data

With the exception of Novartis, these leading companies are anticipating that vaccines will play an increasingly important role in their future sales (Table 1.1).

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3 Leading vaccine delivery companies

Novel vaccine technologies are allowing the development of new and improved therapeutic and prophylactic vaccines that will target a wide range of disease. The tables below summarize vaccine delivery companies, their technologies and products that are approved or in clinical development (Table 3.1).

Table 3.1: Leading vaccine delivery companies

Company	Technology platform	Route of administration	Vaccine pipeline
Acambis, UK	ChimeriVax™ Virus-like particles	Intramuscular	Intramuscular
Activ-Dry, US	Stable, spray-dried dry powder formulation of live attenuated virus	Intranasal	Preclinical: m[illegible]s
AEterna Zentaris Inc, Canada	Genetically attenuated live bacterial vectors	Oral	Preclinical: p[illegible] ca[illegible], melanoma
Alba Therapeutics, US	Agonists of tight junction biology	Intranasal	Preclinical: vaccine [illegible]vant
Alphavax, US	Alphavirus vectors	Intramuscular	Phase 1: seasonal influenz[illegible] [illegible]tomegalovirus, colon canc[illegible] [illegible]inical: pandemic influenza, HIV, bo[illegible]m toxin, Marb[illegible]irus, smallp[illegible]SARS, en[illegible]alomyelitis viruses, p[illegible]te c[illegible]
Altea Therapeutics, US	PassPort™ patch	[illegible]nsdermal	Preclinical: [illegible]a
Antares Pharma, US	Mini-needle injector	Intr[illegible]al	Research
Antigenics, US	Delivery system a[illegible]vant Stimulon® (QS-21) and Heat shock protein adjuva[illegible]	Intram[illegible]	Intramuscular
AstraZeneca, UK	Acquire[illegible] MedImmu[illegible]	[illegible]ntranasa[illegible]	Influenza vaccine FluMist (approved 2003) Phase 1: Respiratory syncytial virus/ parainfluenza virus type 3
Avant Immunotherapeuti[illegible] US	VibrioVec® and [illegible]oVec™ ge[illegible]-attenuate live *Cho*[illegible]d *Salmonel*[illegible]ve	Oral	Phase 2: cholera, typhoid fever Phase 1: HIV Preclinical: anthrax, *E coli, Shigella, Campylobacter*, pandemic influenza
[illegible]arian Nordic, Denmark	[illegible]VA[illegible]® [illegible]ed vaccinia A[illegible]ra virus vectors	Intramuscular	Phase 2: smallpox Preclinical: measles, HIV, respiratory syncytial virus
[illegible]N Immun[illegible]	M[illegible]BN®	Intramuscular	Phase 3: breast cancer Preclinical: prostate cancer
CSL Ltd, Australia	Delivery system adjuvant Iscomatrix™	Intramuscular	Phase 2: human papillomavirus, hepatitis C virus, melanoma Preclinical: influenza ISCOMATRIX licensed to Merck 7 Co. and Wyeth
Coley Pharmaceuticals, US	VaxImmune™ TLR7/8/9 agonists	Intramuscular	Phase 3: lung cancer (with GSK) Phase 1: melanoma (with GSK); anthrax (with DARPA) Outlicensing agreements with Merck & Co., Novartis, GSK and DARPA.

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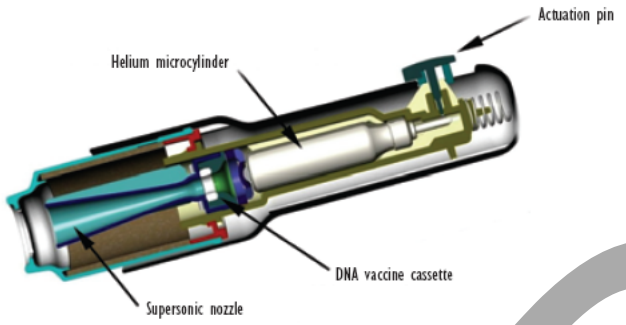
backing of some big pharma companies, Ichor's device has the major advantage of combining and automating the injection and electroporation procedures. The device is likely to be preferred by patients and improvements in the reliability and reproducibility of administration may also improve efficacy results.

5.4.2 Case Study: PowderJect technology (PowderMed, acquired by Pfizer)

PowderMed's technology delivers DNA vaccines to the epidermis. The technology, known as Particle Mediated Epidermal Delivery or PMED™, involves the precipitation of DNA onto microscopic gold particles that are then propelled by helium gas into the epidermis (Figure 5.3). The formulation is stable at room temperature and uses 1000 times less DNA than needle/injected vaccines, reducing the DNA cost per dose.

Figure 5.3: Schematic diagram of the PowderJect device configured for preclinical



Source: Liu, 2006[23]

The company is developing a range of DNA ines using its ED™ system, as shown in Table 5.12. Its lead product is currently in Phase 2 trials for pand luenza[24].

Table 5.12: PowderMed's va e pipeline

Indication	C tatus	es
Pandemic influenza	Pha	
AIDS	Phase	oration with GSK
Hepatitis B	Phase 1	R xpected in 2007
HPV vaccine	Preclinica	Clinica ials expected in 2007
Herpes simplex vi	Phase 1	Novartis has an option for US rights
NY-ESO-1 positive non-small cell lung c er	e 1	In collaboration with the Ludwig Institute for Cancer Research

No these data were lished i 006[25]. However, Pfizer's current pipeline does not include these nes.

owderJect Pharmaceutic as originally spun out of Oxford University in 1993 and developed a large vaccine ortfolio inc the high ccessful Fluvirin® influenza vaccine. Chiron Corporation acquired PowderJect als i 3 for 888 million and spun out PowderMed in 2004 to further develop the PMED™ technology. Chiron v acquired by Novartis in April 2006. Pfizer acquired PowderMed for an undisclosed sum in October 2006.

In our opinion r's acquisition, as well as previous clinical stage partnering deals (GSK and the Ludwig Institute for C er Research), reinforce the potential of PowderMed's technology. 2007 will be a critical year with results expected for Phase 1 studies with Hepatitis B vaccine and initiation of Phase 1 for an HPV vaccine. If these results are favorable, the company will be able to reap the rewards of expertise and backing that come from a parent company the size of Pfizer.

[23] *http://www.touchbriefings.com/pdf/1859/liu.pdf*
[24] *http://media.pfizer.com/files/investors/presentations/Weiner_112906_part1.pdf*
[25] *http://www.pharmaprojects.com/company_analysis/powermedstable.htm*

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6.1.1 Case study: polycationic liposomes (NasVax)

Cationic liposomes have been widely investigated for the delivery of DNA vaccines. One of the challenges with conventional cationic liposomes is their toxic activity, which has limited their use as a systemic delivery vehicle (Dokka *et al*, 2000). Few studies have investigated the use of polycationic liposomes as carriers for protein antigens (Joseph *et al*, 2006).

NasVax Ltd is developing a polycationic lipid adjuvant delivery system. The system comprises a biocompatible polycationic sphingolipid, D-Erythro-N-palmitoyl sphingosyl-1-0 carbamoyl-spermine, which is mixed with cholesterol to form liposomes. The formulation is generated by mixing the dry adjuvant with protein antigens in an aqueous suspension. The antigens coat the surface of the liposomes as well as being internalized. The use of positively charged particles increases the uptake of antigen by negatively charged antigen presenting cells, leading to an enhanced immune response systemtically and at the mucosal surface.

NasVax has demonstrated that:

- Intramuscular and intranasal delivery using the polycationic liposomes generates significantly enhanced systemic immune responses in mice and in aged mice, rats and ferrets.
- Intranasal delivery using their delivery system leads to significantly enhanced retention in the nasal cavity compared to delivery in the absence of adjuvant.
- Intramusclar or intranasal immunization does not lead to systemic adverse events in rats or rabbits. A mild inflammatory response is observed in the nasal cavity/sinuses and lungs of mice and rabbits vaccinated intranasally (Joseph *et al*, 2006). Their delivery system is known to be safe after intranasal administration in humans to date.

Unlike many adjuvants in development, NasVax vaccine suspensions can be delivered via a variety of routes including intranasal, intramuscular and subcutaneous. The company recognizes the potential enhanced efficacy of intramuscular and intranasal vaccines for some diseases and its influenza program is investigating both intramuscular and intranasal delivery. For the intramuscular formulation, a Phase 1 study in healthy adult volunteers is being completed and a study in elderly adults is ongoing (due to be complete in 2008). An initial Phase 1 study for the intranasal formulation is complete and a multi-dose study is planned. The company also has hepatitis B and pandemic influenza vaccines in pre-clinical trials and is undertaking feasibility studies for an anthrax vaccine.

In our opinion, this technology could represent a useful method for increasing the immunogenicity of vaccines delivered via a variety of routes. Although as yet proven, the increased efficacy of their delivery system may enable the antigen dose to be reduced 4 to 5 fold. Given the problems encountered with other polycationic liposomes, further investigation of the safety of the delivery system is required. Despite the early stage of their influenza program, the company aims to have a marketable intramuscular vaccine available within the next 5 years as the influenza antigen is already licensed. Development of the intranasal formulation will take longer.

6.1.2 Case study: Modulation of Tight Junction Biology (Alba Therapeutics)

Alba Therapeutics is developing small molecule antagonists and agonists that close and open tight junctions via a receptor mediated signaling process (Figure 6.2). Opening of the tight junctions allows macromolecules, such as antigens, to move across a range of paracellular barriers. Alba's compounds are therefore suitable for delivery of drugs or vaccines to any mucosal surface.

> ***According to Dr Sefik Alkan, Executive Vice President of Discovery at Alba Therapeutics,***
>
> ***The company's initial focus will be on intranasal delivery due to the simplicity of administration and the company's current expertise. "However, oral, inhaled, transdermal and rectal/vaginal delivery remain viable options," said Dr Alkan, stressing that "vaccines work best when delivered directly to the point of initial infection. Since the great majority of infections occur at mucosal surfaces, our approach with vaccines is to target mucosal immunity." In Dr Alkan's opinion, this concept is beginning to gain acceptance within the vaccine development community.***

Alba's lead agonist compounds are based on the protein sequences of zonula occludens toxin (Zot) from *V. cholera* that allow for permeability modulation of tight junctions in a transient and reversible manner. Alba's

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