

Flu urges vaccine rush

The threat of avian flu is fuelling an already growing interest in the vaccines market

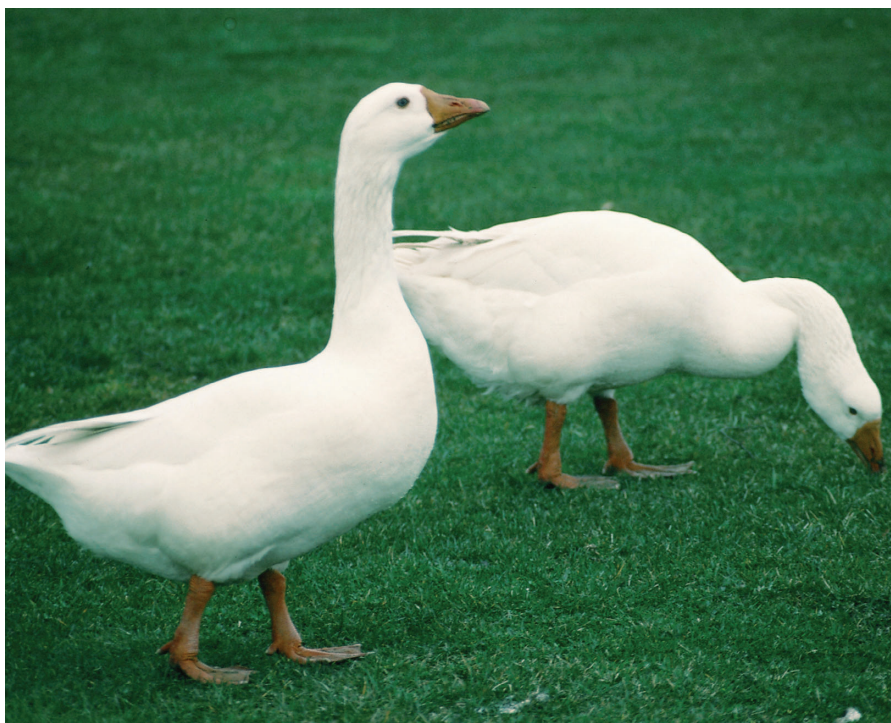
It's early in the flu season and the board of directors at vaccine and biopharma company Chiron has approved a merger agreement with Novartis, worth \$5.1bn.

With the deal agreed, Novartis immediately announced the integration of Chiron's biopharmaceutical activities into its pharma division, creating a new pharma development team; a move that gives Novartis its first foothold in the global vaccines market.

What have we witnessed here?

For one reason or another, vaccines have been covered in the news a great deal in the last few years. Severe acute respiratory syndrome (SARS), the threat of bioterrorism, debate over the combined MMR vaccine and the increasing prevalence of infections, such as HIV and TB, have all grabbed headlines.

Nevertheless, vaccines remain a small part of the overall drug market – less than 3 per cent globally.



“...developing vaccines is more predictable, cheaper and faster than for small-molecule drugs”

The biggest obstacle vaccine makers have faced is a small risk: return ratio, since many products have traditionally been purchased in bulk by governments and other public health authorities, such as humanitarian agencies, which demand low prices.

Vaccine manufacturers also continue to face liability problems and low payments from health insurers.

Finally, compared to the blockbuster drug model, which has been the industry mainstay and typically relies on chronic administration, vaccines also present one obvious but significant difference: most patients only need to take them once.

Rising interest

Why the upsurge in interest from big pharma? The industry is suffering a well-known productivity gap, with fewer new products reaching the market. While there are challenges on the revenue side of the business, the process of developing vaccines is more predictable, cheaper and faster than for small-molecule drugs.

Feathered friend or foe? The current mortality rate of H5N1 in infected humans is 50 to 75 per cent

There has also been a shift in focus from childhood vaccines towards adult vaccines for diseases such as cancer.

The latter are presumed to be one of the key drivers for growth of the vaccine sector, with overall sales expected to more than double in the next five years to in excess of \$20bn annually.

Then, of course, there is avian flu (H5N1). Unfortunately, the latest in an apparently endless series of global panics has a very real precedent, with recently revised estimates putting the death toll from the 1918 Spanish flu epidemic at anything up to 100 million individuals.

Even the much less severe 1968 Hong Kong outbreak still led to at least one million deaths. Many dire warnings about the potentially devastating effects of an H5N1 pandemic are now being issued from even conservative scientific and political authorities.

Spanish flu had a worldwide infection rate of 50 per cent and a mortality rate of 5 per cent. By contrast – although its infection rate is unknown – the current mortality rate of H5N1 in infected humans is running at 50 to 75 per cent.

If this virus was to start efficiently transmitting person-to-person, the resulting

worldwide pandemic would see infrastructure in developed countries stretched to breaking point while, as things stand, medical help in underdeveloped countries would be almost non-existent.

“There has also been a shift in focus from childhood vaccines towards adult vaccines...”

Unsurprisingly, drug companies have been quick to respond (see sidebox on opposite page).

Good company

With the Chiron deal, Novartis joins the ranks of a few other big pharma companies that already have a presence in vaccines.

Merck, for instance, is heavily involved with a portfolio that includes HIV, hepatitis and MMR vaccines among others. Three novel vaccine candidates are in phase III trials, with Food and Drug Administration (FDA) approval expected next year for Rotateq for rotavirus and Zostavax for shingles.

The jewel however is a papillomavirus vaccine, Gardasil, for the prevention of cervical cancer. According to some estimates, it could be the largest selling vaccine ever, with peak sales of around \$2bn following launch, which could be as early as mid-2006.

Phase III studies showing 100 per cent efficacy with no apparent side effects position it well against GlaxoSmithKline's (GSK) experimental HPV vaccine, Cervarix; the subject of a lengthy battle over patent rights only resolved in February of this year when a cross-licence and settlement arrangement was reached between the two companies.

"...a worldwide pandemic would see infrastructure in developed countries stretched to breaking point"

For its part, GSK has a solid vaccine portfolio, which through subsidiaries and licensing deals, includes more than 20 pipeline candidates, according to Thomson Pharma.

It also has a suite of marketed products that contribute just under 6 per cent to topline revenues and include a range of hepatitis vaccines, such as Havrix (hepatitis A), Engerix-B (hepatitis B), Twinrix (combined hepatitis A and B vaccine), and Infanrix (diphtheria, tetanus and pertussis).

GSK also markets Priorix, an MMR vaccine, Typherix, a vaccine for protection against typhoid fever, Varilrix, a vaccine against varicella or chickenpox, and Mencevax, a range of vaccines to prevent meningitis.

Vaccines are also strongly represented at sanofi-aventis, which has the most advanced H5N1 candidate, as indicated in the sidebar.

As it is, the company already has 55 per cent of the world's capacity of flu vaccine, and clinical trials with its H5N1 vaccine have now begun.

Out in the cold

Notably, the world's largest pharma firm, Pfizer, has little in its portfolio to indicate a strategic interest in vaccines, despite being instrumental in the development of a polio vaccine in the 1950s.

Should the company wish to expand into this area, then, like Novartis, it will almost certainly be achieved through acquisition.

The Author

Dr Peter Robins is editorial and content manager for drug information at Thomson Scientific. This article was written using data from the Thomson Pharma database (www.thomson-pharma.com)

Avian flu – the vaccine makers' response

Antigen Express

Antigen Express has designed 24 li-Key/H5 hybrid H5N1 vaccine candidates, using in silico predictions to identify those with the greatest chance of being active in diverse populations. T-helper cells from mice immunised with recombinant H5 protein or H5 DNA have produced interferon and interleukin-4 in response to three of the candidates.

Carrington

Carrington's inactivated, intranasal powder vaccine against H5N1 is being formulated using GelVac technology. A double-blind, three-way crossover phase I study in 15 volunteers found two particle sizes of GelVac to be safe and well tolerated, with powder delivered to the nasal cavity consistently and reproducibly.

Chiron

The US government has awarded Chiron a \$62.5m contract to supply up to 20 million doses of H5N1 vaccine for the Strategic National Stockpile. In 2004, the company was initially contracted to produce 8,000 doses of the vaccine to allow the National Institute of Allergy and Infectious Disease (NIAID) to conduct clinical studies exploring the safety and immunogenicity of two different doses (Aventis-Pasteur was similarly contracted at this time).

Chiron, again under contract from the NIAID, has also investigated a vaccine against H9N2 – another avian influenza strain – in 96 patients.

ID Biomedical

ID Biomedical's H5N1 vaccine is based on a genetically modified reference variant of the strain from the National Institute for Biological Standards and Control. The company is optimising the conditions for development of the variant in chicken eggs and plans to develop a virus seed bank for future vaccine production before initiating clinical trials.

The programme stems from an October 2001, 10-year contract with the Canadian government to assure a state of readiness in case of an influenza pandemic, through the development of infrastructure and capacity.

Nobilon/NV Organon

Akzo Nobel subsidiaries Nobilon and NV Organon are investigating a recombinant protein vaccine against H5N1. Clinical trials are planned for 2006, using material obtained from cell culture technology, rather than embryonated chicken eggs.

PowderMed

PowderMed has cloned the H5 gene from the circulating virus strain into its DNA vaccine backbone, to produce a vaccine scheduled for clinical trials in mid-2006. The product uses the same DNA backbone as the company's annual influenza vaccine, and is delivered using PowderMed's PMED device, which propels gold particles coated in the vaccine into the skin using high-pressure helium.

Sanofi pasteur

Sanofi pasteur, the vaccine arm of sanofi-aventis, currently has the most advanced H5N1 vaccine. The company recently signed a \$100m agreement to provide H5N1 influenza vaccine to the US Department of Health and Human Services (HSS) following an earlier \$13m contract from the HSS to produce two million doses.

The vaccine is to be manufactured from a weakened version of the wild-type virus, provided by the NIAID.

Sinovac

Chinese biotech Sinovac, together with the Chinese Centre for Disease Control and Prevention, is investigating an injectable H5N1 vaccine. Preclinical work is ongoing, boosted by the recent granting of a GMP (Good Manufacturing Practice) certificate to Sinovac for its seasonal flu vaccine, Anflu.

Other approaches

Alternative biological approaches to developing an avian flu vaccine that are being pursued include dsRNA (Ampligen from Hemispherx) and antisense (AVI Biopharma's NeuGene).