

GlaxoSmithKline Biologicals - Influenza Vaccines

Background information

GlaxoSmithKline Biologicals (GSK Biologicals) is one of the world's leading vaccine producers with an active research and development programme targeted at both **seasonal and pandemic influenza**. GSK has recently committed over £1 billion (US\$2 billion) to expand capacity for manufacturing influenza vaccine and its anti-viral influenza treatment Relenza® (zanamivir for inhalation) with continuing vaccine research, development and production taking place at various GSK Biologicals' sites.

In North America, GSK recently acquired a major influenza vaccine manufacturer, ID Biomedical Corporation. This acquisition provides GSK with a significant increase in influenza vaccine manufacturing capacity. The production capacity of the newly acquired Canadian facilities - combined with GSK's expanded vaccines manufacturing plant in Dresden, Germany - is expected to reach around 150 million doses per year by 2008. These numbers are based on production of trivalent (providing protection against three different strains) seasonal influenza vaccine. In the event an influenza pandemic is declared all manufacturing capacity could be switched to producing a monovalent pandemic vaccine and the production capacity can be expected to be significantly higher.

INFLUENZA PREVENTION

Seasonal influenza vaccines

Influenza reaches peak prevalence in winter, with variations in peak time between the Northern and Southern hemisphere creating two influenza seasons each year. Therefore, the World Health Organization (WHO), assisted by National Influenza Centres, identifies prevalent circulating strains relevant either to the Northern or to the Southern hemispheres.¹

The WHO assesses the global influenza viruses, of which there may be 10,000, and makes recommendations on the formulation of the vaccine depending on which strains are the greater threat and considered the most virulent.²

The 2007 analysis, which concluded in February 2007, recommended that vaccines to be used in the 2007-2008 season (northern hemisphere) should contain the following:³

- an A/Solomon Islands/3/2006 (H1N1)-like virus
- an A/ Wisconsin/67/2005 (H3N1)-like virus
- a B/ Malaysia/2506/2004-like virus

These recommendations are used by manufacturers to update the annual composition of the influenza vaccines they produce.

GSK uses these recommendations to make the necessary changes each year to their trivalent inactivated split-influenza vaccines, *Fluarix*® and the vaccine known as *FluLaval*™ in many countries (called *Fluviral*™ in Canada). This composition change reflects the changing nature of the viruses circulating. *Fluarix*® has been available since 1992 and is delivered to over one hundred countries in the northern and southern hemisphere.

Influenza vaccines and the elderly

Recognising the need for research into the use of influenza vaccines for the elderly, GSK recently presented humoral/cellular immunity data⁴ and safety data⁵ from a phase I/II clinical study investigating two novel adjuvanted seasonal vaccine candidates during the International Vaccines for the World congress (IVW) 2006. Further data on the new generation influenza vaccine for the elderly has been presented at the International Symposium of Respiratory Viral Infections 2007 in Hong Kong.⁶

These trials assess the efficacy of influenza vaccines in the elderly. Influenza vaccines are generally less efficient in the elderly population (58%) than in younger adults (80%) due to immunosenescence (decline in humoral and cell-mediated responses).^{6,7,9} The outcomes confirm that GSK Biologicals' novel adjuvant system enhances the immune response to influenza in the elderly when compared to non-adjuvanted *Fluarix*®, with significantly higher humoral and cellular immune response observed in elderly patients.⁴

Avian Influenza – Pandemic and pre-pandemic influenza vaccines

GSK is committed to helping governments around the world meet their needs for pandemic influenza planning. GSK was the first company to submit a 'mock-up' dossier for a pandemic vaccine with traditional alum adjuvant to European regulators in December 2005 and indeed the first company to receive a positive opinion from the CHMP for this candidate alum-adjuvanted

inactivated whole virus vaccine (*Daronrix™*). A variation of a 'mock-up' dossier based on a new virus strain can be submitted to the regulatory authorities to allow rapid registration and production of the new variant vaccine, which would be the case should the WHO declare a pandemic and identify the circulating pandemic influenza strain.

There are many strains of potentially pandemic influenza and the H5N1 has only recently been identified as one of the highest risk. However, GSK has been developing vaccines for potential pandemic strains for many years. An influenza H5N1 vaccine, if effective against different variant or 'drifted' H5N1 strains, could be used to vaccinate populations in advance or immediately following the declaration of a pandemic to provide a degree of immune protection in advance of encountering the eventual pandemic strain.

Recent clinical trials have shown GSK's pre-pandemic proprietary adjuvanted candidate H5N1 vaccine to demonstrate a strong cross-reactive immune response against an evolutionary diverse strain of H5N1 in humans and a cross-protective response in animals¹⁰. Additionally, animal model studies have been carried out to show whether they can be protected against challenge with an H5N1 viral strain that is not identical to the one used to produce the vaccine. GSK found that 100% of all animals given $\geq 3.8\mu\text{g}$ antigen, adjuvanted with GSK's proprietary adjuvant system, were protected from a lethal challenge of a non-identical H5N1 strain. This phenomenon is known as "cross-protection".¹¹

A license application for this new generation H5N1 split antigen pre-pandemic influenza vaccine, containing GSK's novel proprietary adjuvant, has been recently filed in Europe, and was accepted for review by the Committee for Medicinal Products for Human Use (CHMP).

In general, GSK's main objectives of the clinical development programme with H5N1 avian influenza virus in humans clinical trials are:

- to evaluate the immunogenicity of a low-dose adjuvanted influenza pandemic vaccine
- to evaluate the number of doses and vaccine dosage needed to achieve antibody levels to induce protection
- to evaluate the safety of an H5N1 vaccine in a large population to evaluate potential cross-protection

In addition to the vaccines under development, GSK already has an anti-viral product, *Relenza®*, which adds to the armament in the fight against a potential pandemic.

Adjuvant System Technology: GSK's Adjuvant Advantage

GSK Biologicals is actively researching ways to improve existing vaccines through the use of adjuvants, additional active components to a vaccine which provoke a stronger immunity in the human body making it more effective.

GSK is hopeful that a vaccine formulated with their novel proprietary adjuvant system will further enable individuals' immune systems to respond to different influenza virus strains, this may offer some protection against both seasonal and pandemic influenza. Trial data has demonstrated that GSK's novel adjuvant technology elicits a high immune response at a very low dose of antigen (3.8µg)¹². This will help to increase the number of doses the company could make available worldwide.

Cell Culture Vaccine Technology

In addition to the traditional egg-based vaccine manufacturing technology, GSK has recently invested in a new manufacturing plant in the US where cell-culture technology will be developed for the production of future influenza vaccines.

For company information visit:

www.gsk.com

www.gsk-bio.com

¹ <http://www.who.int/csr/disease/influenza/influenzanetwork/en/index.html>

² <http://www.who.int/mediacentre/news/notes/2005/np05/en/index.html>

³ <http://www.who.int/mediacentre/news/notes/2005/np05/en/index.html>

⁴ Leroux-Roels I et al. Adjuvanted influenza vaccines improve anti-influenza humoral immunity impaired in elderly. *Influenza Vaccines for the World 2006*. Study ID Flu-AS25-003, NCT: 00318149. Poster presentation 13

⁵ Leroux-Roels I et al. Reactogenicity and safety of adjuvanted influenza vaccines administered in elderly. *Influenza Vaccines for the World 2006*. Study ID Flu-AS25-003, NCT: 00318149. Poster presentation 12

⁶ Leroux-Roels I et al. Adjuvanted influenza vaccines improve anti-influenza immune response altered in elderly *International Symposium for Respiratory Viral Infections 2007*

⁷ Murasko DM, et al. *Exp Gerontology*. 2002;37:427-39

⁸ Govaert TM, et al. *JAMA*. 1994;272(21):1661-65.

⁹ CDC/MMWR. 2005;54:1-40. (www.cdc.gov; accessed Sep. 08, 2006)

¹⁰ Leroux-Roels I et al. Pandemic influenza preparedness: Cross-reactive immunity with an adjuvanted H5N1 candidate vaccine *International Symposium for Respiratory Viral Infections 2007*

¹¹ Baras B et al. Cross-protection against heterologous H5N1 challenges in ferrets with low dose adjuvanted split H5N1 vaccine. *International Symposium for Respiratory Viral Infections 2007*

¹² Borkowski A et al. Antigen sparing effect of a novel adjuvant system in a split H5N1 pandemic vaccine. *International Vaccines for the World 2006*

FluLaval, *Relenza*, *Fluviral*, *Daronrix* and *Fluarix* are trade marks of the GlaxoSmithKline group of companies.