THE ROYAL SOCIETY

The Academy of Medical Sciences

Summary of oral evidence: Dr Alison Webster, Dr Margaret Tisdale, Dr Hillar Kangro and Dr Chris Worth, GlaxoSmithKline (GSK).

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Dr Webster and Dr Tisdale work in antivirals clinical development at GSK and are involved with the development of Relenza, the first neuraminidase inhibitor, which is administered by inhalation. Dr Kangro is involved with the European vaccine and influenza strategy and Dr Worth is the UK vaccines medical director.

Members of the working group present were: Sir John Skehel, Professor Glynis Breakwell, Professor Barry Furr, Professor Neil Ferguson, Dr John McCauley, Professor Andrew McMichael, Professor Karl Nicholson, Dr Geoffrey Schild and Mr Richard Stubbins.

Key points

Antivirals – Relenza (Zanamivir)

Relenza, the antiviral drug produced by GSK, is licensed in 67 countries for the treatment of influenza and can also be used in prophylaxis and for paediatric use. It has not been widely used to date and is seen as a less preferable option to oseltamivir, probably because the diskhaler inhalation method of administration may be seen by some healthcare professionals as a disadvantage.

The manufacture of Relenza involves primary and secondary manufacturing processes. The company has built up stockpiles of the active substance and the main impediment currently to expanding production is getting the secondary manufacturing processes up and running. A minimum 6-9 month time period would normally be required to ramp up production capacity and over the past 9 months GSK has been able to increase the manufacturing capacity for Relenza more than 20 fold by increasing the number of shifts at production plants and opening a new manufacturing site in Australia.

GSK is currently examining the feasibility of developing an intravenous (IV) formulation of Relenza, and is in discussion with the regulators. It was agreed that the availability of an IV formulation of antiviral medication in an ITU setting would be important in the event of a pandemic.

GSK has had limited discussions with the UK Department of Health about production capacity, but other countries such as the USA have been more actively involved. Last year GSK saw a big increase in demand and large orders for Relenza were received from Germany and France. This has put pressure on manufacture and capacity.

GSK provided a fact sheet on Relenza to all governments and asked whether they were interested in purchasing quantities of the drug. GSK has now received orders from over 50 countries, including an order from the UK Department of Health. Countries usually have ordered enough Relenza to contribute 10-20% of their total antiviral stockpiles.

The Neuraminidase Inhibitor Susceptibility Network has published details of baseline susceptibility to antivirals and they are looking at transmission and susceptibility of influenza isolates obtained worldwide from four different WHO centres. Dr Webster said that the H5N1 resistance seen with oseltamivir does not appear to be

cross-resistant with Relenza and orders have increased since then. GSK is in discussions with the WHO about donations of Relenza.

GSK does not have plans to develop novel antiviral drugs for influenza, though it is developing different formulations of Relenza. Relenza has not been found to reduce the immune response (as measured by antibody titre) in patients suffering from seasonal influenza.

Vaccines

GSK has influenza vaccine manufacturing plants in Dresden and Canada. At the plant in Dresden it would only be possible to manufacture candidate pandemic (pre-pandemic) influenza vaccine during a short time period because this plant manufactures seasonal flu vaccine for both the northern and southern hemispheres, so there is a very short break between the seasons. In the plant in Canada, there could be a 15-16 week window when pre-pandemic vaccine could be produced. GSK is increasing manufacturing capacity in the coming years to meet anticipated demand for such vaccine(s).

It will probably only be possible for GSK to work with one strain of vaccine at a time, in accordance with recommendations from International authorities. In terms of testing for cross-reactivity between strains, GSK has carried out animal studies and is in the process of conducting clinical trials. The results of these studies will be published in due course.

GSK has submitted a mock-up file for production of a pandemic flu vaccine to EMEA, which is based on a formulation of whole virus and alum adjuvant. The proposed dosage of whole virus will be 3.75 μg for young adults and 7.5 μg for adults, in a two-dose study. GSK has had discussions with the UK Department of Health with regard to pandemic influenza vaccines.

The development of new adjuvants is regarded as critical by GSK and the company is currently working on developing a stronger adjuvant system. The use of adjuvants enhances the immune response, the response is broader and there is evidence of cross-protection against antigenic drift strains of influenza.

Diagnostics

GSK has no current plans for the development of diagnostics for influenza. Diagnostics may be useful but GSK has found in the past that it is difficult to develop a diagnostic in parallel with a drug. GSK has found in clinical trials that GP diagnosis of influenza is quite good, when influenza is known to be circulating in the community. During the clinical trials for Relenza, diagnostic tests were carried out to see what proportion of patients that were enrolled in the studies actually had influenza. Influenza was confirmed in 70-75% of these patients.

Scientific and policy issues

GSK is collaborating with academic institutions in several countries to carry out the further development work on both Relenza and influenza vaccines. GSK does not have the right containment facilities to carry out work on avian influenza in the UK.

The group were asked whether clear guidelines are being given from WHO about H5N1 strains. They replied that there is continuous and ongoing dialogue with WHO and they were not aware of any issues with this, GSK work with the information that is provided.

The group were asked whether they feel there is enough support and information for companies, to enable them to respond in a pandemic situation. The group replied that there has been co-operation but there is more that could be done. There is an element of competition between companies when tendering for large

vaccine contracts. GSK has recently submitted applications to a Multi-centre Research Ethics Committee (MREC) and received fast-tracked approval for the study, which was found to be helpful. In relation to vaccines, there are areas such as pharmacovigilance and assay methods where co-ordination and combined efforts are needed.

GSK does not see the development of pandemic influenza vaccines as a commercial activity; it is led by public health need. A combined effort will clearly be required between the EU, WHO, governments and industry to respond to a pandemic flu situation.