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Summary of oral evidence: Stephen Gardner, Novartis Vaccines (formerly Chiron Vaccines).

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Stephen Gardner is Divisional Vice President of Flu and Respiratory Planning, Novartis Vaccines (formerly Chiron Vaccines). Novartis Vaccines is the world's fifth largest vaccines company and the world's second largest manufacturer of flu vaccines. They produce the adjuvant MF59, which improves the potency of the immune response. Their program to develop a cell culture system for influenza vaccine production is currently in Phase III trials in the EU.

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

Science into policy making

Mr Gardner stated that a multifunctional group was involved in preparing the evidence provided by Chiron Vaccines (now Novartis Vaccines) to the study. The comments are not specifically UK-oriented and can be applied to a number of countries.

Mr Gardner was asked about the interactions between his company and the Department of Health and the extent to which he considered that science is considered in policy-making. The UK Department of Health has held talks with Novartis Vaccines about the supply of pandemic influenza vaccine, and Novartis is one of two companies supplying stockpile H5N1 vaccine to the UK government. Novartis Vaccines does not have major scientific collaborations with the UK government, although it carries out work with the NIH in the USA on vaccine clinical trials. The UK Department of Health have not put together a major pandemic vaccine testing programme, such as that that has been established in the US.

Vaccine Design and Dosage

The vaccine being provided by Novartis Vaccines to the UK government is based on the Vietnam strain, which is an inactivated strain of the H5N1 avian subtype. It will be provided in a 7.5 μg dosage with the addition of their adjuvant MF59 in the formulation.

Mr Gardner said that the award of pandemic contracts to Chiron Vaccines (now Novartis Vaccines) from Department of Health was based on their good scientific and clinical data to date with other pandemic strains. Novartis Vaccines has undertaken studies which demonstrate that an H5N3 vaccine incorporating MF59 and demonstrated good levels of immune response, antibody persistence up to 16 months as well as cross reactivity to H5N1 antibodies (ref Professor Nicholson).

Governments are currently 'placing bets' on which H5N1 vaccine to opt for by reviewing the limited data available. By the end of the year, governments will have H5N1 trial data to guide them from the vaccine trials currently being performed by the manufacturers.

The dose range being tested for H5N1 vaccines adjuvanted with MF59 is 7.5 – 15 μg, which is lower than the recent results achieved by other companies with alum adjuvanted vaccines (30μg). There are practical difficulties when going down to doses lower than 5μg, because the assays used to test the product for

quality control (QC) purposes are not sensitive enough. Mr Gardner said that it is possible to mix the adjuvant MF59 at the bedside as it is with alum and this being tested in some NIH clinical trial studies, although this may not be practicable in a pandemic scenario. Novartis Vaccines plans to scale-up the production of MF59 and is exploring the possibility of stockpiling the adjuvant.

In the design of vaccines, Novartis are producing mainly subunit vaccines. In order to change the approach (eg to whole virus), the process for normal seasonal influenza vaccine production would need to be changed. This is a significant undertaking, which Novartis does not believe would result in significant yield improvements for their process; it also believes that potential gains in immunogenicity from such a change in antigen type are likely to be smaller than those obtained by use of the MF59 adjuvant.

Mr Gardner is a member of the Influenza Vaccine Supply manufacturers task force, which has two sub-groups based on technical and policy issues. The website of the International Federation of Pharmaceutical Manufacturers and Associates (www.ifpma.org) contains a list of all vaccine clinical trial studies being undertaken worldwide, of which there are 31 studies in total. Manufacturers have been asked to pool information on clinical trial programmes, to share results with other companies and to publicise results. Novartis have a number of clinical trial studies, including a Phase II H5N1+MF59 study in Europe and in the US there is planned a study by NIH comparing MF59 and alum adjuvanted H5N1 vaccines.

CSL and sanofi pasteur have announced their results recently, they may have not yet published in journals but they have made public announcements of their results.

Vaccine Manufacture

Novartis Vaccines is one of a number of companies pursuing a flu cell culture programme. One advantage of a cell culture system is that vaccine production can be started more quickly as manufacturers can use wild virus, rather than waiting to obtain a new vaccine strain from WHO which can take several months. The vaccine can be produced continuously and it would be possible to construct large fermenters, but this could prove uneconomic if the facilities were not fully utilised for seasonal flu vaccine production. With the egg based production system, it is challenging to set up a continuous production system because the chickens cannot maintain production of eggs for continuous periods. If fermenters were built specifically for the production of pandemic flu vaccine, it is unlikely that they could be used easily for the production of other medicines, due to the specific design of the system or regulatory controls that would have to be put in place for licensing purposes.

Two companies have pursued licence applications in the Netherlands but they have not brought products to the market yet and are seeking EMEA approval. It is expected that these new vaccines will come to the market in the next 2 to 3 years, but for the coming 5 to 10 years the egg-produced system will supply the major dosage output.

There was a discussion about the manufacture of seasonal influenza vaccine and how capacity could be increased to enable the production of a pandemic vaccine. Mr Gardner said that manufacturers usually stop making seasonal vaccine in October and so there is down time between seasons, some of which is taken up by necessary maintenance. Pandemic stockpile vaccines are normally produced during this period.

Vaccination Strategy

If a pandemic were to occur, the spread of disease could be so fast that it is possible that the pandemic would be over before a vaccine was produced (ref: Professor Ferguson). Therefore, it seems logical to have already vaccinated individuals to give some level of protection to populations at the outset of a pandemic, or have stockpiled vaccine in place for immediate use.

Several vaccination strategies have been proposed for pandemic pre-vaccination. These include a 2-dose and a prime boost method. The 2-dose method is likely to be the more effective but its effectiveness depends upon how well matched it is to the actual pandemic strain.

Surge capacity will be a problem in a pandemic situation, another reason in favour of pre-vaccination approaches. Currently 20-30% of the population receive a seasonal flu vaccine in developed countries, which corresponds to about 350 million doses at a global level. In a pandemic situation, production would need to increase to 5 or 10 times that amount and industry cannot build and maintain the facilities at the state of constant readiness required solely for use every 20 or 30 years. It is very difficult to re-commission a facility after long periods of time. One way to increase capacity is for the Government to increase funding to ensure that seasonal flu vaccination is increased. A pandemic pre-vaccination strategy would also increase capacity but a significant amount of work is required to develop an effective vaccine.

In Mr Gardner's view, the US (notably NIH) is the driver of pandemic vaccine research globally. The CDC is aiming to vaccinate 50% of the US population for seasonal flu by 2010, which will increase production capacity.

Novartis Vaccines is currently working on the development of new adjuvants. Global needs of influenza vaccine in the future will require extreme dose sparing so adjuvants will be of major importance.