IRISH MEDICINES BOARD

Friday, 4th September 2009

Dr. Tony Holohan
Chief Medical Officer
Department of Health & Children
Hawkins House
Hawkins Street
Dublin 2

Re: Marketing Authorisation Application for Pandemic Influenza (H1N1) 2009 vaccines

Dear Tony,

I would like to take this opportunity to bring you up to date on the status of the ongoing process to assess and license the pandemic vaccines, and to highlight the very limited data that is likely to be available when these vaccines are authorised in the EU. Dr. Joan Gilvarry, Director of Human Products Safety Monitoring, IMB, is attending the various advisory groups on our behalf and is updating colleagues on a day by day basis on what is a dynamic situation.

In prudent preparation for a pandemic, so called "mock-up" pandemic vaccines were approved by the European Commission, containing a strain of the influenza virus that was specifically chosen because the population had never been exposed to it. In this case the H5N1 "avian influenza" strain was used. The mock up vaccines were authorised under exceptional circumstances pursuant to Article 14(8) of Regulation (EC) No 726/2004. The mock-up dossier concept provided that in the context of an officially declared pandemic situation (WHO phase 6), the Marketing Authorisation Holders (MAH's) of the mock up vaccines according to Article 8 of Regulation (EC) No 1085/2003 could submit a variation to permit the insertion of the Pandemic Influenza strain (H1N1 2009). These vaccines are all approved centrally by the European Commission on the advice of the European Medicines Agency and the authorisations apply to all European countries.

It is important to recognise that currently available clinical and non-clinical data relates solely to studies involving the H5N1 mock up vaccines and these mock-up vaccines were stand-alone applications relating to 'new' vaccines and not necessarily developed in a similar manner to seasonal flu vaccines.

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The Irish Medicines Board and its European counterparts, coordinated by the EMEA, are at present assessing the available data for the pandemic influenza H1N1 vaccines. In relation to quality data, there are substantial deficiencies in the data at present available for the Baxter product while quality data are not currently available for the GSK product.

The clinical safety and efficacy of the vaccines are also being assessed based currently on extrapolation of data from studies with the H5NI strain. There are no clinical data specific to the use of the H1N1 strain.

In the absence of comprehensive clinical data required to evaluate the benefit-risk of these vaccines, specific Risk Management (Pharmacovigilance) Plans for each of these vaccines are being developed and assessed to assist in minimising the risk in post-marketing use. To date, there are no immunogenicity or safety data available with the H1N1 vaccines, and while Clinical Trials have commenced there are no data yet available from these trials. As data becomes available, it will be assessed and we will update colleagues across the expert advisory groups. Additionally, we must highlight that there are currently no data on use in pregnant women with very limited data for only one of the vaccines to support recommendations in children.

During the course of the mass vaccination programme, various groups are likely to generate large amounts of information on safety and effectiveness of A/H1N1 vaccines. In the context of the Risk Management Plans, vaccine manufacturers will conduct a prospective cohort study to be started as soon as the vaccine is used. Data will also need to be collected in special population groups, on specific adverse events of interest and on the effectiveness of vaccines. These data may be relevant for public health and will need to be quickly identified and assessed in order to evaluate their impact on the benefits and risks of the vaccines and the need for regulatory actions. The IMB will perform this assessment and disseminate the information.

In addition, due to the potential phenomenon of mutation of the influenza virus, the effectiveness of vaccines will need to be constantly measured. Active post-authorisation surveillance of the vaccines will be needed to detect and assess adverse events following immunisation (AEFIs) and, for each vaccine, the frequency and severity of these events will need to be balanced with the available information on their effectiveness. The IMB considers that continuous quantification of benefits and risks and efficient communication between interested parties will be key to protect and promote public health and strengthen citizens' confidence in the ability of authorities to take decisions in their interests.

When the vaccines are licensed and in use the IMB is committed to implementing a pandemic pharmacovigilance strategy which includes the IMB undertaking the following measures:

- Access safety information with and from other Member States and the EMEA, through the use of Eudravigilance (European Safety Database).
- Inform health care professionals regarding the surveillance of adverse events of special interests (AESI), fatal and life-threatening events and other severe unexpected adverse reactions.
- Facilitate the notification of severe adverse reactions by healthcare professionals and patients. A web-based system for reporting adverse reactions to pandemic vaccines has been developed. Appropriate communication documents for healthcare professionals and the public have been prepared.

- Perform signal detection based on spontaneous reports and other relevant sources of information, and circulate and access signals to/from the EMEA via the Signal Management system using the European Pharmacovigilance Information Tracking Table system (EPITT).
- Inform immediately the Rapporteur, Member States and the EMEA of any new information affecting the benefit-risk profile of a pandemic vaccine, using the appropriate communication system, e.g. the Rapid Alert System.
- If appropriate, submit to ECDC and EMEA any safety or effectiveness issue for which a recommendation or opinion is required.
- Communicate with healthcare professionals and the public if deemed necessary to inform them about changes in the benefit-risk profile of pandemic vaccines.
- Keep you and the Department of Health and Children/HPSC/Pandemic Expert group apprised of safety issues as they arise.

The entire process of the approval of the "mock up" vaccines was based on a worst case pandemic scenario. It is likely that at the time of authorisation of the vaccines by the European Commission, only very limited information on the safety and efficacy of the vaccines will be available. On the basis of the current information on this pandemic, the IMB is concerned by the impact of this absence of data on the product information. In particular, the IMB considers that the absence of information on dosage in children and use in pregnant women may be a difficulty for national health authorities when making recommendations for the safe use of the vaccines in these patient populations.

While it is difficult to accurately predict timelines, at this stage it may be that the Baxter vaccine (Celvapan) may be given a positive opinion by the EMEA's advisory committee, the CHMP, at the end of September and the GSK vaccine (Pandemrix) by early/mid October (this may however leave many unanswered questions). In such a scenario a Commission Decision (i.e. an EU license) might be delivered within one week.

I trust this update is helpful and we are hopeful that sufficient data will be made available by the manufacturers to enable a positive opinion on the use of the vaccines. Please feel free to contact me or my IMB colleagues at any time and we continue to be available to advise the expert groups.

Yours sincerely,

Pat O'Mahony
Chief Executive

C.c. Mr. Paul Barron, Assistant Secretary