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Pandemic influenza A(H1N1)v vaccines authorised via the core dossier procedure

Explanatory note on scientific considerations regarding the licensing of pandemic A(H1N1)v vaccines

Objectives and Scope

As part of pandemic preparedness planning, the European Commission (EC) and the European Medicines Agency (EMEA) introduced a procedure to allow the submission and evaluation of core pandemic dossiers (for 'mock-up' vaccines) during the inter-pandemic period leading to marketing authorisations which could only be used during an officially declared pandemic (World Health Organization [WHO] Phase 6). The procedure foresees the fast track assessment of the data for replacing the strain in the mock-up vaccine with the recommended pandemic strain as a variation to the MA (Marketing Authorisation).

The objective of this document is to provide details on the scientific rationale which the Committee for Medicinal Products for Human Use (CHMP) has used in order to reach its conclusions on the benefit-risk balance for the concerned vaccines, following the update procedures to insert the pandemic A(H1N1)v strain. It also addresses various aspects of the conditions of use for these vaccines In particular it explains the CHMP's rationale in making extrapolations from existing clinical trial experience with the mock-up vaccines to the use of the pandemic vaccines with particular emphasis on specific populations i.e. use in children and use in pregnant women.

Background

An influenza pandemic is a global outbreak of influenza disease that occurs when a type A influenza strain to which the majority of the population, or the majority in some age groups of the population, have little or no immunity. Seasonal outbreaks of influenza are caused by influenza A and B strains that are closely related to those that have been circulating in previous years, so that much of the population may have some degree of immunity to one or more of the viruses. In contrast the influenza A viruses that cause pandemics are antigenically distinct from the circulating seasonal strains and are new subtypes or are descended from subtypes that have not circulated among people for a long time.

In April 2009, a new strain of human influenza A(H1N1)v was identified and characterised.
On 11 June 2009 the WHO declared Phase 6 of the influenza pandemic. The declaration reflected sustained transmission of the virus from person to person in several WHO regions. WHO and other international agencies are calling the disease **pandemic (H1N1) 2009**. For the virus the nomenclature **influenza A(H1N1)v** (where v indicates variant) has been chosen.

* Updated with information about Celvapan

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The attack rate for the A(H1N1)v virus strain has been estimated to be higher than for recently circulating seasonal strains because of the lower levels of pre-existing immunity in the population. Current estimates for the attack rate associated with the influenza A(H1N1)v virus over the first major wave of infection vary from approximately 10 to 30 % in different geographical areas. As a result, the actual numbers of clinically apparent infections, cases that require hospitalisation and deaths in the pandemic period is expected to be higher than the numbers seen in recent years for seasonal influenza. These estimates may change (upwards or downwards) during the course of the pandemic.

The course of each pandemic is influenced by properties of the virus, including any drifted variants that occur during the pandemic period, and the degree of pre-existing immunity in different segments of the population. Attack rates and case fatality rates vary accordingly from pandemic to pandemic. The severity of the illness may also change during the pandemic and may differ according to age groups and to underlying conditions that pre-dispose to complications of the infection.

So far, in the current pandemic only 2% of confirmed cases have occurred in people over 65 years of age. In Europe the median age has been 25 years in those who acquired the infection during travel and 13 years in those domestically infected. Nearly 80% of cases are in individuals under 30 years of age. Deaths have occurred in previously healthy subjects as well as in those with underlying conditions or pregnancy that would predispose them to complications of influenza. For more information about the known clinical features of the disease caused by influenza A(H1N1)v virus please see the updated Risk Assessment report from European Centre for Disease Prevention and Control (ECDC) on the ECDC website[1].

Given this public health threat, the aim of the CHMP was to ensure vaccines were made available as soon as possible based on a robust assessment of the data, before the beginning of the Northern hemisphere flu season 2009-2010.

Two Regulatory Authorities from outside the EU, i.e. the US Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA), have recently approved non-adjuvanted vaccines for A(H1N1)v.

Only centrally submitted vaccines are evaluated by the CHMP. The authorisation of A(H1N1)v vaccines based on nationally authorised influenza vaccines, is within the remit of Member States.

Concept of Core dossier approval based on mock-up vaccines

Specific guidance has been developed for the fast track assessment procedure for pandemic influenza vaccines[2], which can only be used once the WHO and the European Union (EU) have officially declared the pandemic (WHO Phase 6). The procedure involves the submission and evaluation of a core pandemic dossier during the inter-pandemic period, followed by a fast track assessment of the data for replacing the strain in the mock-up vaccine with the recommended pandemic strain as a variation to the MA.

This guidance is based on a *Proof of Principle* approach by which safety and immunogenicity data are generated with mock-up vaccine 'constructs' containing subtypes of influenza A to which the majority of the population is naïve. These data can be extrapolated to the same construct containing the A(H1N1)v pandemic strain.

[1] http://ecdc.europa.eu/en/healthtopics/Documents/0908_Influenza_AH1N1_Risk_Assessment.pdf

[2] *Guideline on Submission of Marketing Authorisation Applications for Pandemic Influenza Vaccines through the Centralised Procedure* (CPMP/VEG/4986/03).
Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisations Application (CPMP/VEG/4717/03).

These principles are based on:

- The immune responses to a specific mock-up vaccine containing a strain to which subjects within a specific age range were immunologically naïve is expected to predict responses to the same vaccine construct containing an alternative strain of the same subtype or an alternative subtype of influenza A in a comparable population.

- The safety data generated with a specific mock-up vaccine in clinical studies is expected to predict the safety profile observed with the same vaccine construct containing an alternative strain of the same subtype or an alternative subtype of influenza A in a comparable population.

- The "Mock-up" pandemic influenza vaccine (core dossier) is a vaccine that mimics the future pandemic influenza vaccine in terms of its composition construct (antigen content, excipients, and adjuvant system, if used), manufacturing and control. The mock-up vaccine is produced in the same way as is intended for the final pandemic vaccine but it does not contain antigen from the actual pandemic strain.

There is prior experience with the manufacturing processes and formulations of the mock-up vaccines. These have been, where possible, based on, or in many respects are similar to, established methodologies for producing seasonal influenza vaccines. The use of established processes has the advantage that the manufacturers' experience and existing data can be used, compared to completely novel manufacturing processes and formulations.

On the basis of these underlying principles, the mock-up/core dossier construct allows for insertion of the pandemic strain into a vaccine construct and enables a rapid approval of the pandemic vaccine, where all the data obtained with the corresponding mock-up vaccine together with specific data relating to the pandemic strain are taken into account.

Further clinical data are expected over the coming weeks and months for A(H1N1)v versions of each of the vaccine constructs approved via the core dossier procedure. Data from ongoing and planned clinical trials that are specified in the agreed pharmacovigilance and risk management plans (RMPs) will be reviewed as they are submitted. The Summary of Product Characteristics (SmPCs) summarise the existing clinical data and will be updated on an ongoing basis as new data are submitted and assessed.

Extrapolation of experience with mock-up vaccines to A(H1N1)v pandemic vaccines

In the three core dossiers that have led to an approval of a mock-up vaccine almost all of the clinical data were generated with vaccine constructs that included an influenza A (H5N1) strain. For each of the three vaccines approximately 500-5,000 subjects were exposed in clinical studies.

The considerations for extrapolation of the clinical data include the following:

a) The immunogenicity data available for the approved mock-up vaccines were generated using a strain to which the majority of subjects were immunologically naïve based on pre-vaccination testing for antibody that inhibits haemagglutination and in most studies the majority were also naïve based on neutralising antibody tests. Therefore the H5N1 mock-up vaccines represent to a certain extent the most demanding scenario in terms of expected immunogenicity for a potential pandemic vaccine.

b) The safety profiles observed with the mock-up vaccines are expected to be generally applicable to the corresponding constructs containing the A(H1N1)v pandemic strain. Rare

adverse reactions that might be specific to the A(H1N1)v pandemic strain can only be evaluated during extensive usage, and through post marketing follow up.

According to all available preliminary data with A(H1N1)v both adjuvanted and non-adjuvanted vaccines, immune responses after administration of a single dose to healthy adults (at least 18 years and mostly < 60 years) are of greater magnitude than what was observed after single doses of various H5N1 vaccines. The responses observed following a single dose of A(H1N1)v vaccine appears sufficient to achieve in the majority of subjects an immune response that would be considered acceptable for a seasonal influenza vaccine. This may reflect some degree of background priming of the immune system in a proportion of adults for the pandemic strain and/or a difference in immunogenicity between strains. If these early data are confirmed, they point to the possibility that a single dose, at least in adults, may lead to a similar degree of immune response to that which was seen after two doses of H5N1 vaccines. It is not yet known whether the same pattern of responses will be seen in children.

Based on all the considerations above, it is expected that insertion of the pandemic A(H1N1)v strain in a specific vaccine construct would not have a substantial effect on safety. Furthermore, the immune responses are not expected to be of lower magnitude compared to the corresponding mock-up vaccine when used in a similar population.

It has to be acknowledged that waiting for conclusive A(H1N1)v clinical data would significantly delay the availability of the vaccines.
It is considered that the benefit to public health of authorising A(H1N1)v vaccines based on all currently available data justifies the use of these vaccines in accordance with the SmPCs..

Assessment of data (rolling review)

The Commission and the the EMEA have taken preparatory and temporary measures to enable the accelerated assessment of applications for marketing authorisation of pandemic A(H1N1)v vaccines and variations thereof. The practical mechanism established is to perform the evaluation as soon as data from vaccines' manufacturers is made available through expedited rolling assessments. Such rolling process has therefore been established with upfront identification of two-week review cycles with corresponding specific submission dates for identified products.

Rapporteurs and Co-Rapporteurs and Core Expert group Members were identified from the European expert network in the field of vaccines. All these experts were part of the EMEA Task Force (ETF) which also included other representatives such as the chairs of the CHMP, Biologics Working Party (BWP), Vaccine Working Party (VWP), Pharmacovigilance Working Party (PhVWP) and Paediatric Committee (PDCO)[3], the lead clinical assessors from the Rapporteur's teams and other relevant experts in quality, virology, epidemiology, non-clinical, clinical, paediatrics and pharmacovigilance/Risk management.

Throughout this process, quality, non-clinical, clinical, pharmacovigilance (RMP) data and labelling information were submitted by the Marketing Authorisation Holders (MAHs) and reviewed by the ETF/CHMP on a rolling basis for the three pandemic mock-up vaccines leading ultimately, once the data was considered adequate and sufficient, to the formal submission of the variations to include the A(H1N1)v pandemic strain to the original (H5N1) mock-dossier/Marketing Authorisation.

The pandemic A(H1N1)v strain change variation for each of the mock up vaccines was submitted on 22 September 2009 and through an expedited CHMP review of the overall data set submitted, taking into account the assessments of the data during the preceding rolling review cycles, the mock-up concept and extrapolation of the available data where possible, the CHMP was able to adopt positive opinions for Pandemrix and Focetria on 24 September and Celvapan on 1 October 2009

[3] http://www.emea.europa.eu/htms/general/contacts/CHMP/CHMP_WPs.html

recommending the variations to the terms of the Marketing Authorisations with identified specific obligations.

Risk Management and Post marketing Surveillance Activities

In order to have sufficient supplies of pandemic vaccines to initiate vaccination in Europe by the fourth quarter 2009, before the start of the influenza season in the coming autumn and winter months, and bearing in mind the lead times to produce vaccine and also the vast numbers of doses required by the global public health Authorities, manufacturers started production and filling as soon as the required strains and reagents were made available by the WHO. As a consequence of this imperative need to commence production as soon as possible, the initial production batches and the various labelling elements utilised e.g. Package Leaflet, vial labels etc. as they were established at that time, taking into consideration global supply uncertainties and in advance of both the CHMP completing its assessment of the introduction of the pandemic strain change, and the CHMP finalising labelling recommendations to Healthcare Professionals (HCPs). In the exceptional circumstances to ensure that authorised vaccines are made available at the earliest opportunity, it has been agreed that this approach is acceptable.

Extensive amounts of safety and efficacy data will be received in a very short space of time after the initial authorisation of the pandemic strain change variation. Thus it is considered essential that in addition to the normal communication tools to the healthcare professionals, additional methods are introduced to supplement these tools in view of the very dynamic nature of what is known about the use of these vaccines and the evolution of the pandemic. This includes references to websites containing the very latest information updates as well more proactive delivery of updated information to HCPs and efforts to reinforce traceability of the products and stimulate adverse event reporting.

Only limited data on safety and immunogenicity of influenza A(H1N1)v vaccines will be available when Member States start to use the vaccines. In addition, due to the potential mutation of the influenza virus, the effectiveness of the vaccines will need to be followed. Active monitoring of the vaccines is needed to detect and assess adverse events following immunisation. For each vaccine, the frequency and severity of these will be balanced against the available information on their effectiveness.

European collaboration has been established for these activities, taking into account that different vaccines may be used in different Member States. The CHMP will closely and continuously follow up on the progression of data collection.

During the course of vaccination safety and effectiveness data may also be generated by hospitals, academic research institutions, sentinel networks and other groups. These data are important for identification and evaluation of any new issue that may arise during the vaccination.

Post-marketing surveillance commitments are in place for all centrally authorised vaccines in their Risk Management Plans as follows:

- For each vaccine, the company will perform a study on 9,000 patients across all age groups, recruited at the start of the vaccination campaign.
- Each company will provide every month a comprehensive report (simplified Periodic Safety Update Report [PSUR]) on all adverse reports notified by patients and HCPs.
- Adverse events as well as adverse events of special interest (e.g. neurological disorders) that have been identified based on experience with similar vaccines will be specifically monitored for the pandemic vaccines together with other adverse events.
- Special population groups, such as pregnant women, children and immunocompromised subjects will be specifically monitored, using existing or newly established registries and networks of healthcare professionals.

Analysis of new or changing safety issues will also be carried-out by Member States and the EMEA based on different sources of data. The EMEA will produce on a weekly basis Reactions Monitoring Reports synthesising information received in EudraVigilance[4] for each vaccine over one week period. These reports will be communicated to all Member States.

The European Strategy for influenza A(H1N1)v vaccines benefit-risk surveillance has been developed by EMEA and ECDC. It has been approved by the CHMP during its September 2009 meeting. It describes:

- The activities to be performed post-authorisation for the protection of public health in relation to the administration of A(H1N1)v vaccines in the EU.
- The roles and responsibilities of all involved parties (vaccine manufacturers, Member States, European Agencies, public health institutions and research centres).
- The studies to be carried out to ensure continuous evaluation of the safety and effectiveness of the vaccines in European countries.

CHMP is in regular communication with international partners from countries such as the USA, Canada, Australia and Japan, in order to facilitate rapid detection and evaluation of any emerging issue affecting the risk-benefit balance of the vaccines.

Together these measures will ensure rapid, robust and continuous post-authorisation benefit-risk monitoring.

Areas of special consideration:

Adjuvants

Adjuvants are used to enhance the immune response in a population expected to be mostly naïve to the antigens and to increase the amount of vaccine that can be produced ('antigen-sparing': less antigen is needed, when the immune response can be enhanced by the adjuvant). Improving production capacity is in line with the international efforts to make the vaccine available for large population groups in the world. Indeed, the WHO supported the use of adjuvants as a dose-sparing approach for the development of pandemic vaccines. Other potential benefits of using adjuvants include better cross-protection against drifted influenza strains as suggested by results with H5N1 vaccines.

Two out of three mock-up pandemic vaccines authorised in the EU so far, contain adjuvanting systems. Focetria (Novartis) contain MF59C.1, a squalene based emulsion. Pandemrix (GSK Biologicals) contains AS03, a squalene based emulsion)]. Formulating mock-up (H5N1) vaccines with novel adjuvanting systems greatly improved the immune responses to a range of haemagglutinin (HA) doses compared to the same doses of HA alone. For example, these two oil-in-water based adjuvant systems allow reduction of the HA amount per dose by a factor of at least two to four (7.5 µg to 3.75 µg/ dose) compared to seasonal vaccines, (strain-specific antigen content = 15 µg/ dose).

MF59C.1

MF59C.1 is an oil-in-water emulsion, the oil being squalene, a natural component of cell membranes. A seasonal vaccine with the MF59C.1 adjuvant, Fluad, has been licensed for use in elderly in the EU and used in some countries since 1997. More than 45 million doses of Fluad have been distributed since 1997. It is currently under evaluation in children.

Clinical trials with several MF59C.1 adjuvanted vaccines have been performed in different age groups including children from 6 months onwards without raising safety concern while showing increased immunogenicity of the combination of the adjuvant with the antigen. The non-clinical experience with MF59C.1 either alone or combined with a variety of antigens is also sufficient and has not raised concerns

AS03

[4] http://eudravigilance.emea.europa.eu/highres.htm

The AS03 adjuvant of GSK is also an oil-in-water emulsion. The oil phase contains two oils, squalene, the same main component as MF59C.1 (natural component of cell membranes), and DL-α-tocopherol (vitamin E). Non-clinical data are mainly derived from rodent studies, and raise no concern. GSK has generated a significant amount of clinical data in adults and the elderly and limited data in children aged 3-9 years with the H5N1 mock-up vaccine. The AS03 adjuvanting system was associated with greater reactogenicity compared to corresponding doses of HA alone but the safety profile is still considered to be acceptable.

So far no safety signals have been detected that indicate an increased risk of autoimmune disease following the use of these adjuvants.

Paediatric populations

Influenza is an important infection among children. Young children or children with chronic medical conditions are at increased risk for complications and death from influenza. During seasonal influenza outbreaks, the vast majority of excess deaths occur in person aged 65 years and older. However, the attack rates of influenza during annual epidemics are consistently higher in children and young adults. Children are also the main transmitters of influenza in the community. For these reasons, some countries recommend vaccination of children older than 6 months as a routine each year while others recommend vaccination for children with conditions that put them at high risk of complications from influenza.

With respect to the current A(H1N1)v pandemic, ECDC has reported that the observed age distribution is unusual and different from seasonal influenza, being skewed towards younger age groups, with a marked under-representation of infections in people over 65 years of age, who make up only 2% of reported cases. In Europe, among the reported cases, the cases tend to be young: median age being 25 years in those who acquired the infection during travel, and 13 years in those domestically infected. Nearly 80% of cases are in individuals under 30 years of age. Based on these figures, ECDC in its recommendations has included young children (especially those below 2 years) in the risk groups for 2009 pandemic influenza and WHO has included children above 6 months, particularly those with chronic conditions, among the priorities for vaccination.

Summary of paediatric immunogenicity and safety data

With respect to pandemic influenza vaccines, limited data have been collected in children within the development plans of mock-up vaccines, generally testing vaccination with a H5N1 strain. Only two paediatric studies have been evaluated, one with Pandemrix and one with Focetria. Paediatric studies with A(H1N1)v are currently ongoing with all pandemic vaccines, and will become available soon. A(H1N1)v vaccines are to be tested in children in parallel with adults, but for vaccines with a new adjuvant the age range will depend on previous experience with the adjuvant in the paediatric population. A moderate increase in reactogenicity with these vaccines compared to non-adjuvanted seasonal vaccines might be expected.

Pandemrix

Pandemrix use in a paediatric population is currently supported by one study, H5N1-009, in which the H5N1 Vietnam strain was tested. The study comprised 300 children from 3 to 9 years of age and evaluated full and half dose of the vaccine. Two doses were administered 21 days apart. The immune responses in the half dose group were high and comparable to those seen in adults. The adverse event profile reported with the adult dose showed increased incidences of general symptoms compared with the half dose, including 37% fever, and 10-14% (different age strata) being fever of grade 3. The frequencies of fever were lower with the half dose. Therefore, the CHMP concluded that the half dose is sufficient for use in children aged 3 to 9 years.

No data are available in children less than 3 years and children 10-17 years. For children under 3 years, the choice of dose for should take into account the available data on safety and immunogenicity collected with H5N1 in children aged from 3-9 years, and therefore the half-dose would be suggested.

For the 10-17 years, the full dose as in adults is suggested. Consideration to the data collected in the 3 to 9 years could be taken into account as well. Additional data in children from both A(H1N1)v and (H5N1), including data using half dose vs. full dose, will be submitted in the coming months.

Focetria
Clinical trials with MF59C.1 adjuvanted H5N1 vaccine have shown that the vaccine is adequately immunogenic in children older than 6 months up to 17 years with an acceptable safety profile. Moreover, in terms of immunogenicity and overall safety profile, no remarkable differences were noted across the different age strata. Additional data in children from both A(H1N1)v and (H5N1), including data using half dose vs. full dose, will be submitted in the coming months.

MF59C.1 seasonal influenza vaccine (Fluad) is licensed for use in elderly in the EU and is currently being evaluated also for children for seasonal influenza vaccination, in addition to A(H1N1)v pandemic vaccination. Studies with this vaccine in children 6-36 months of age showed high titres to all three strains and high heterotypic cross protection.

Based on available data, the CHMP considers that the full dose is appropriate across the age range 6 months to 17 years for time being.

Celvapan
No results of clinical studies using Celvapan in a paediatric population are available. Whole-virion seasonal vaccines have been studied in children in the past and they demonstrated to be immunogenic and well-tolerated. Should vaccination be considered necessary, the experience with similarly constructed vaccines suggests that dosing in accordance with the adult dose may be appropriate.
Data in children using A(H1N1)v will be submitted in the coming months, that will allow for more refined recommendations.

Conclusion
The following points based on currently available information should be taken in considerations:

As all mock-up vaccines have been tested with (H5N1) and mainly in naïve adults, therefore, using a naïve -population model, an extrapolation of immunogenicity data to children, who are more likely to be naïve to pandemic strains including A(H1N1)v, would be possible at least for the current situation, whilst awaiting results from the ongoing paediatric studies with A(H1N1)v vaccines.

Based on the clinical experience with the mock-up vaccines, the Committee is currently recommending vaccination with two doses, at an interval of three weeks for all three vaccines. Ongoing clinical studies will provide more information on the optimal dosing of the vaccines.

For the mock-up vaccines, Pandemrix and Focetria, paediatric data with (H5N1) are available and the response rates are in good agreement with that seen in adults. The reactogenicity profiles for Pandemrix and Focetria are considered acceptable in children. For Celvapan, there is no clinical experience in children, but experience with whole-virion vaccines indicate a good safety profile. Considering the lack of clinical experience in children below 6 months of age, even with seasonal influenza vaccination, currently it is not possible to determine the benefit risk ratio in this age group.

Pregnant women

Disease burden
According to several studies, in pregnant women the risk for complications due to seasonal influenza increases with the duration of pregnancy, the risk being lower in the first trimester, but not negligible. The risk was highest during the third trimester. Moreover, the presence of co-morbidities in a pregnant woman strongly increased the risk of complications, and also this risk increases as pregnancy progresses.

From April 15 to May 17, 2009 in the USA, 553 confirmed or probable cases of pandemic A(H1N1)v have been reported to the US CDC (Center for Disease Control and Prevention). The estimated rate of hospital admission for pandemic A(H1N1)v virus infection in pregnant women was higher (approximately 4 fold) than in the general population in the first month of the outbreak. Of a total of 266 deaths reported between April 15 and July 29, 2009, there were 15 pregnant women. All of them had developed pneumonia. These data indicate that as in other pandemics, pregnant women appear to be at increased risk for severe complications from the pandemic A(H1N1)v virus infection.

The burden of disease in pregnant women during epidemics and pandemics has been consistently shown to increase with the progression of pregnancy and the presence of co-morbidities.

Based on the observed and the expected epidemiological pattern, ECDC and WHO have recommended the inclusion of pregnant women, regardless of the stage of pregnancy, amongst priority groups for pandemic vaccination.

Experience with non-adjuvanted influenza vaccines
The benefit of influenza vaccines has rarely been assessed specifically in this population, and there are few data from clinical trials in pregnant women. Most knowledge comes from seasonal influenza inactivated vaccines utilised in the general population.

The benefit for the newborn of vaccination with seasonal inactivated influenza vaccines during pregnancy relies on the placental transfer of maternal antibodies. Although this transfer has been demonstrated, rendering possible an indirect protection of the newborn, there is limited evidence available.

Safety data of inactivated (non-adjuvanted) seasonal influenza vaccines in pregnant women that has been collected within clinical trials is very limited. However, these data on pregnant women vaccinated with different inactivated, non-adjuvanted seasonal vaccines indicate no malformative or foetal/ neonatal toxicity. Moreover, there is extensive experience from seasonal influenza vaccination in all trimesters of pregnancy, since such vaccination has been recommended for several years in some countries. For instance, from the years 2000-2003, two million pregnant women were vaccinated in the USA, and available safety data from passive surveillance and epidemiological studies have not raised concerns. The adverse events profile from vaccinated pregnant women is similar to that for vaccinated adults.

Experience with pandemic vaccines
For the three pandemic vaccines (Celvapan, Focetria and Pandemrix), no clinical data are available in pregnant women. Clinical trials with the mock-up vaccines and to some extent the A(H1N1)v strain provide immunogenicity results in women of childbearing age. Based on experience from other influenza vaccines, it is assumed that immunogenic responses in non-pregnant women can be extrapolated to pregnant women.

Celvapan
Reproductive and developmental animal toxicity studies have been performed. The serological responses to the vaccine and exposure of foetuses to specific antibodies were demonstrated. According to the data presented, no vaccine-related harmful effects were seen on mating performance or female fertility, embryo-foetal survival or development, or on pre- and post-natal development. Clinical experience with whole-virion vaccines does not suggest any harmful effects for the foetus.

Focetria
The non-clinical program included studies where the MF59C.1 adjuvant was given alone, or in combination with non-influenza antigens. This included specifically designed studies with administration before pregnancy, at the time of mating, as well as later during pregnancy in rabbits. It was shown that the doses of MF59C.1 applied did not induce reproductive toxicity for the dam or the foetuses. Experience with these adjuvants in pregnant women is very limited. In the pregnancy clinical database of Novartis, a limited number of pregnancies occurred in females of childbearing potential

exposed to at least one dose of a MF59C.1 adjuvanted vaccine (either influenza vaccine or not). No occurrence of congenital abnormalities was reported, but the experience is too limited to draw conclusions.

Pandemrix
Non-clinical studies with regard to female fertility, embryo-foetal and postnatal toxicity (up to the end of the lactation period) were conducted in rats with the Pandemrix mock-up vaccine containing the AS03 adjuvant. There was no cause for concern identified in this study. No data are available on administration around the implantation phase of the embryos. There are no data in pregnant women with a vaccine that contains the AS03 adjuvant.

There is no indication at the present time that inclusion of adjuvants in vaccines is associated with adverse outcomes on pregnancy.

Serological studies exploring the immunogenicity suggest that antibody response to influenza vaccine is similar in pregnant women and non-pregnant women. Therefore it is expected that these vaccines will be adequately immunogenic in pregnant women. Although currently available safety data are very limited, non-clinical data with the current vaccines/adjuvants and experience from other types of vaccines (both non-adjuvanted and adjuvanted) do no raise concerns with respect to use during pregnancy.

Furthermore, vaccine safety in pregnant women and effectiveness will be closely monitored, as part of the RMP. Observational studies using established pregnancy registries are planned.

Persons with deficient immunity (congenital or acquired)
Immunocompromised patients are considered a risk group for both seasonal and pandemic influenza.
In an recently published study of 553 probable and confirmed infections with A(H1N1)v, 30 people were hospitalised because of needing care. Nineteen of the 30 patients had underlying chronic conditions, including also persons with altered immunocompetence.
Killed or inactivated vaccines do not represent a danger to immunocompromised persons and generally should be administered as recommended for healthy persons. However, the immune response of immunocompromised persons to these vaccine antigens may not be as good as that of immunocompetent persons.

Currently there are no data available either with any mock-up H5N1 vaccine or with A(H1N1)v vaccines. However, post-authorisation measures are in place to collect data from vaccination of immunocompromised patients.
At present the benefits of vaccination need to be assessed on individual basis by healthcare professionals.

Coadministration with other vaccines
For the mock-up vaccines with H5N1 strains there are data on co-administration of non-adjuvanted subunit influenza seasonal and Focetria (H5N1) in adults. These data did not reveal any immune interference between the seasonal and the H5N1 strains. There were no differences in serious adverse events (SAEs) between groups, and all SAEs were unrelated. There are no such data for Pandemrix (H5N1) or Celvapan (H5N1).

There are no data on co-administration of Celvapan, Pandemrix and Focetria A(H1N1)v vaccines with seasonal influenza vaccines, or other vaccines. Ongoing studies will examine whether giving a pandemic A(H1N1)v vaccine and seasonal influenza vaccine simultaneously or sequentially will affect the immune response to either vaccine.

However, if co-administration with another vaccine is indicated, immunisation should be carried out in separate limbs. It should be noted that the adverse reactions may be intensified.

Thiomersal

Thiomersal is a compound containing mercury that is used as a preservative in medicines. Thiomersal is metabolised into ethylmercury and thiosalicylate, and contains 49.6% mercury by weight. It is often used in vaccines, to comply with the requirements in the European Pharmacopeia for multi-dose containers, where it helps to prevent bacterial or fungal contamination.

The multi-dose presentations of Pandemrix and Focetria contain thiomersal. These vaccines have been authorised with a two-dose vaccination schedule separated by at least a three-week interval. The maximal exposure to thiomersal is two administrations of 50 micrograms per dose (corresponding to 25 micrograms mercury) separated by at least three weeks.

Concerns have been raised in the past because chronic exposure of infants to high doses of methylmercury (a similar compound present in food) may induce neurological adverse events. However, studies have shown that ethylmercury is eliminated faster from the body. In animals its administration is less neurotoxic than that of methylmercury.

Based on a large amount of scientific data, the WHO, the United States Institute of Medicine and the European Medicines Agency have concluded that the evidence favours the rejection of a causal relationship between thiomersal-containing vaccines and autism. Additional publications have underscored the lack of an association between thiomersal and neurodevelopmental disorders.

Most of the knowledge on the exposure of pregnant women to organic mercury is derived from food consumption. Pregnant women (as well as the foetuses they are bearing) are known to be more sensitive to organic mercury than the normal population. Everybody in the population (including pregnant women) is expected to be exposed to small amounts of methylmercury via food, especially fish. The Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives established a provisional tolerable weekly intake of 1.6 microgram per kg for organic mercury from fish (equivalent to 96 micrograms in a 60-kg woman).

These data suggest that vaccination with two doses of Pandemrix or Focetria separated by at least three weeks are considered safe in pregnant women.

Thiomersal is a contact allergen to which approximately 1-5 % of adolescents and adults in Europe are allergic, having the potential to develop skin reactions. There have been case reports in the literature of occurrences of generalised allergic skin reactions to thiomersal after vaccination. However, over 90% of patients who have a contact allergy to thiomersal do not have an allergic reaction after intramuscular vaccination with a thiomersal-containing vaccine. Therefore, these reactions occur very rarely and an existing thiomersal contact allergy is not a contraindication to the use of a thiomersal-containing vaccine.

The CHMP acknowledges that the presence of thiomersal in some vaccines is necessary, either as a preservative in multidose vials of vaccines or due to the use of organic mercury compounds during the vaccine's manufacture. After evaluation of the scientific evidence, the CHMP has concluded that immunisation with vaccines containing thiomersal continues to offer benefits to the general population.