



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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EMA/CHMP/508065/2010  
Evaluation of Medicines for Human Use

## CHMP assessment report for the re-assessment of the specific obligations and the benefit/risk profile

**Invented name/Name:** Pandemrix

**International non-proprietary name/Common name:** Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (X-179A)

**AUTHORISED UNDER EXCEPTIONAL CIRCUMSTANCES**  
**EMA/H/C/832/SW/41**

<b>Indication summary (as last approved):</b>	Prophylaxis of pandemic influenza in an officially declared pandemic situation
<b>Marketing Authorisation Holder:</b>	GSK Biologicals

**Assessment Report as adopted by the CHMP with  
all information of a commercially confidential nature deleted.**



### ADMINISTRATIVE INFORMATION

<b>Invented name of the medicinal product:</b>	Pandemrix [D-Pan H1N1v]
<b>INN (or common name) of the active substance(s):</b>	Split virion influenza vaccine of strain, inactivated, containing antigen1 equivalent to: A/California/7/2009 (H1N1)v-like virus 3.75 micrograms per 0.5 ml dose
<b>Pharmaco-therapeutic group (ATC Code):</b>	J07BB01
<b>Pharmaceutical form and strength:</b>	Emulsion and suspension for emulsion for injection The antigen (2.5 ml) and adjuvant (2.5 ml) are mixed before use to provide a 5 ml emulsion for 10 doses.
<b>Marketing Authorisation Holder:</b>	GSK Biologicals
<b>Rapporteur:</b>	Ian Hudson
<b>Co-Rapporteur:</b>	Barbara van Zwieten-Boot

Medicinal product no longer authorised

## **I RECOMMENDATION**

Based on the review of the data submitted by the MAH as evidence of compliance with the specific obligations and having re-assessed the benefit/risk profile of the medicinal product further to the provision of comprehensive data on efficacy and safety such that the grounds set out in Part II.6 of Annex I of Directive 2001/83/EC are no longer applying to maintain the MA under Article 14(8) of Regulation (EC) No 726/2004, the CHMP recommends to change the status of the marketing authorisation outside the scope of Art. 14(8) of Regulation (EC) No 726/2004 for Pandemrix (Influenza vaccine (H1N1)v (surface antigen, inactivated, adjuvanted)).

The CHMP in making this recommendation has taken into consideration that comprehensive information on clinical safety and efficacy have now been provided and that specific procedures in particular concerning safety are no longer required such that the grounds to maintain the licence under exceptional circumstances are no longer considered to apply.

In addition the CHMP, having reviewed all relevant clinical data within the context of Article 21 of Commission Regulation (EC) 1234/2008, considers that adequate information has been supplied to recommend a change of the indication outside of the restricted clinical setting of a pandemic and that the temporary and exceptional nature concerning the approval of the variation introducing the pandemic strain change no longer applies.

As a result of the above the recommended indication now reads as follows: Prophylaxis of influenza caused by A(H1N1) 2009 virus (see section 4.4 of the SmPC). Pandemrix should be used in accordance with Official Guidance thus allowing for further use of vaccine within the EU regardless of whether or not the current WHO pandemic phase is maintained or altered during the coming year. (see section III.3 for more details).

## **II BACKGROUND INFORMATION ON THE MEDICINAL PRODUCT**

Pandemrix is an egg-based adjuvanted inactivated monovalent H1N1v split influenza vaccine, adjuvanted with AS03, which is composed of squalene, DL- $\alpha$ -tocopherol and polysorbate 80.

The CHMP recommended the granting of the marketing authorisation for Pandemrix under exceptional circumstances, because at the time point of authorisation the stage of knowledge of comprehensive scientific information required for the vaccine containing the actual pandemic strain could not be gathered.

The reason for the CHMP's recommendation that a MA under exceptional circumstances should be granted initially was due to the provision of limited safety and immunogenicity data generated with vaccine construct including potential influenza pandemic (mock-up) strain, A(H5N1). This A(H5N1) strain was not circulating in humans and the mock-up vaccine was not intended for use until, firstly the specific influenza virus strain would be identified and included in the vaccine and, secondly the influenza pandemic officially declared (as described in the Annex II.B of the MA).

This implied that, pursuant to article 14 (8) of regulation (EC) No 726/2004, the Marketing Authorisation Holder (MAH) committed to complete ongoing studies, or to conduct new studies, as listed under Specific Obligations (SOBs) in Annex II.C of the MA. Therefore, the recommendation to grant the MA under exceptional circumstances was made on the basis of the MAH undertaking to

submit the Specific Obligations (SOBs) and Follow-up Measures (FUMs) listed in the Letter of Undertaking dated 19 February 2008.

The initial indication for use of Pandemrix (H5N1) was as follows:

“Prophylaxis of influenza in an officially declared pandemic situation. Pandemrix should be used in accordance with official guidance.”

Following the onset of the (H1N1)v pandemic and the declaration of WHO Phase 6 in June 2009, the MAH applied for a variation PU/0017 to change the pandemic vaccine strain composition from A/VietNam/1194/2004 (H5N1) like strain (NIBRG-14) to A/California/7/2009 (H1N1) strain used NYMC X-179A. The recommendation for the approval of the PU/0017 Pandemic Update was adopted by the CHMP on 24 September 2009. The marketing authorisation under exceptional circumstances for the current (H1N1)v vaccine was updated accordingly by the European Commission on 29 September 2009

The revised indication for use of Pandemrix (H1N1) was as follows:

“Prophylaxis of influenza in an officially declared pandemic situation (see sections 4.2 and 5.1). Pandemic influenza vaccine should be used in accordance with Official Guidance.”

The strain change recommendation from A(H5N1) to (H1N1)v was made on the basis of the MAH undertaking further Specific Obligations (SOBs) for Pandemrix (H1N1) which covered for the 2 SOBs previously adopted as well as additional Follow-up Measures (FUMs) that were listed in the Letter of Undertaking dated 24 September 2009.

It should be noted that at time of the variation to include the (H1N1)v strain in the A(H5N1) mock-up vaccine, the CHMP was confronted with an unprecedented situation to recommend the authorisation of a vaccine to be used in a mass vaccination campaign with limited data in accordance with Article 8 of Commission Regulation (EC) No 1085/2004 (repealed by Article 21 of Commission Regulation (EC) No 1234/2008). Therefore at that time CHMP identified a series of Specific Obligations to be addressed by MAH.

It should also be noted that some of these measures exceeded the standard pre-authorisation requirements established for influenza and other vaccines but in the unprecedented circumstances of the Pandemic were considered necessary from a public health perspective.

The application for a change of the status of the Marketing Authorisation outside the scope of Art. 14(8) of Regulation (EC) No 726/2004 was received on 16 April 2010 and contained:

- Listings of SOBs and FUMs for which full or partial responses have been made to date
- Listing of variations completed and ongoing to date
- List of outstanding issues in a revised Letter of Undertaking.
- The latest Product Information (from the last Opinion/CD). The proposed changes related to the change in status of the MA were also included in the submission

This re-assessment of the benefit risk of Pandemrix has reviewed the status of fulfilment of the original and additional SOBs/FUMs based on the extensive experience gained during the 2009 H1N1 influenza pandemic.

### **III SCIENTIFIC DATA PROVIDED BY THE MARKETING AUTHORISATION HOLDER SINCE THE GRANTING OF THE MA UNDER EXCEPTIONAL CIRCUMSTANCES**

III.1 List of all Specific Obligations and Follow-up measures submitted since the granting of the MA under exceptional circumstances

In light of the Marketing Authorisation under exceptional circumstances in the EU and pursuant to Article 14(8) of Regulation (EC) No 726/2004 the MAH agreed to provide CHMP with responses to Specific Obligations (SOBs). These have been addressed as follows:

#### **III.1.1. SOBs**

At the time of approval of the change to include the pandemic strain Specific Obligations required data on immunogenicity and safety collected during clinical trials as well as safety and effectiveness data during routine use.

##### **Clinical SOBs**

The clinical SOBs concerned the reporting of safety and immunogenicity data from sponsored clinical studies with the pandemic vaccine and required reporting of post-dose 1 (PD1) and post-dose 2 (PD2) data (with or without longer-term follow-up and responses to further doses, according to individual protocols) from the ongoing and planned studies that were listed in the Letter of Undertaking agreed at the time of the strain change variation.

In many cases the data required to address these SOBs were provided directly as variations (see next section on variations for details) so that relevant information could be inserted into the SmPC.

The status of the SOBs regarding the D-Pan-H1N1 (Pandemrix) series of studies can be briefly summarised as follows (if filed as variations the reference numbers are shown in brackets):

##### **SOB/048 Study H1N1-021 PD1 (PU/0017) and PD2:**

An abridged report (post dose-1 data) from study H1N1-021 was submitted during the Rolling Review of the variation to include the A(H1N1)v strain (PU/0017). This observer-blinded study was carried out in three centres in Germany to evaluate the safety and immunogenicity of a two-dose schedule of the A/California/7/2009 (H1N1)v-like candidate vaccine adjuvanted with AS03 in adults aged 18 to 60 years. The study compared the AS03-adjuvanted vaccine to a non adjuvanted vaccine containing 15µg haemagglutinin (HA) from the same strain.

The study enrolled 130 subjects and they all received the first dose of vaccine. Before the vaccination, the percentage of seropositive subjects was higher in younger age stratum (44.6% in the 18-40 years group and 29% in 51-60 years). The proportion of subjects seropositive before vaccination did not differ between group A (H1N1 AS03 adjuvanted vaccine) and group B (H1N1 plain vaccine).

At Day 21 the haemagglutination inhibition (HI) seroconversion rate (SCR) observed in the H1N1 +AS03 group was 98.4%. Seroconversion factor (SCF) and seroprotection rate (SPR) were 41.4 and 98.4%, respectively. In the H1N1 (unadjuvanted) group, the SCR was 95.5%, the SCF was 41.4 and the SPR was 97.0%. The CHMP criteria were met in both age strata (18-40 years and 41-60 years) with no appreciable differences between the age strata.

The HI immune responses observed at Day 21 were comparable between treatment groups, which demonstrated the antigen-sparing capacity of the AS03A-adjuvanted vaccine. There was further no impact of prior seasonal vaccination or baseline serostatus on the HI GMTs observed.

The CHMP considered that it was important to include these preliminary data in the SPC at the time of the strain change (PU/0017) to indicate that a single dose may be sufficient in adults.

Solicited local and general symptoms were reported more frequently in the H1N1 + AS03A group compared to the H1N1 group after the first and the second doses. However, the overall reporting rates did not increase after the second dose compared to the first dose of either vaccine. The vast majority of these symptoms were considered to be vaccine-related.

The post dose 2 data showed that there is little or no increment in GMT after the second dose of unadjuvanted vaccine. There were increments in GMTs with the second dose of AS03-adjuvanted vaccine that tended to be greater in magnitude in the older age sub-cohorts. Nevertheless the 95% CI around the post-dose 1 and 2 GMTs and SCFs overlapped and there was no discernible effect on the SPRs and SCRs since they were already so very high after the first dose.

The safety profile of the AS03-adjuvanted vaccine was as expected in this study and did not show increased Reactogenicity after the second dose compared to the first dose.

The product information was updated to reflect the post-dose 1 data from this study within PU/017. This SOB can now be considered fulfilled.

**SOB/049      Study H1N1-021 microneutralisation (MN) assay for neutralising antibody (NA)**

In addressing this SOB the MAH summarised the status of all the NA data available at the time of the submission of this SOB.

In addition to the new NA data post-dose 1 in study H1N1-021 the MAH included the following data in this submission:

Post-dose 1 NA data from study H1N1-009 in children aged < 3 years. These data were already submitted and have been reviewed in variation II/024 and

Post-dose 1 NA data from study H1N1-007 in adults aged from 18-60 years. These data were not previously submitted but have been included in the assessment report on the concurrent variation II/032 regarding post-dose 2 HI and safety from study 007.

Since the MAH's laboratory was still in the course of developing and validating an appropriate method to measure NA against the H1N1v strain, the post-dose 1 sera from studies H1N1-021, H1N1-009 and H1N1-007 were tested by three different external laboratories:

- 1) Samples from D-Pan H1N1-021 have been sent to CDC, R&D laboratory (Dr. R. Donis)
- 2) Samples from D-Pan H1N1-009 have been sent to CDC reference laboratory (Dr. J. Katz)
- 3) Samples from D-Pan H1N1-007 have been sent to Viroclinics (NL)

The CHMP considered that the data cannot be compared across studies or with previously reported data from H5N1 studies due to the fact that sera from these studies were sent to three different laboratories, each with its own assay methodology, for MN testing.

Nevertheless, the results show that a substantial increase in MN titres was observed following vaccination with one dose of D-Pan H1N1 adjuvanted vaccine. The data from study D-Pan H1N1-007 show a further response to a second dose.

In the two studies for which the NA GMTs could be calculated (D-Pan H1N1-009 and D-Pan H1N1-007), these titres were in absolute terms lower than the HI titres obtained by the MAH but the NA responses generally paralleled the HI responses in terms of trends and increases.

Since three independent laboratories have demonstrated that the first dose of Pandemrix (H1N1) elicits a NA response against closely related H1N1 strains the data provide some external validation of the HI responses reported by the MAH. The higher amplitude of the response observed in the MAH's HI assay when compared to the responses obtained in the MN assays underlines the general problems with the large variability in assays for antibody using HI and MN.

SOB-049 can be considered fulfilled as appropriate data have been provided. The MAH was however requested to continue to update CHMP on progress made on developing a fully validated MN assay either in-house or in a contracted facility and to report any additional NA data as FUMs

The CHMP further agreed that there were no implications for the SPC based on these data.

**SOB/050 Study H1N1-007 PD1 (II/019) and PD2 (II/032); adults 18-60**

The CHMP considered that the post dose 1 data from study H1N1- 007 submitted for variation II/019 were in keeping with the results of study H1N1- 021 in which the vaccine used contained a slightly higher amount of HA and was included as preliminary data in the SPC for Pandemrix at the time of the granting of the pandemic strain variation (PU-017). Based on the data from study H1N1-007 the previous SPC advice regarding the possibility of using a single dose in adults aged from 18-60 years was supported.

The CHMP took into account that the baseline serostatus of the subjects in study H1N1-007 was generally comparable with that observed in the subjects in study H1N1-021 (post day 21 results assessed within the pandemic strain variation PU-017) and that, although there was some difference in HI GMTs according to baseline serostatus, especially in the older subjects, there was no impact on satisfaction of the CHMP criteria.

The PD2 data submitted in II/032 showed that there was a clear increment in GMT from D21 to D42 in the adjuvanted vaccine group only and GMTs after each dose showed a trend to decrease with increasing age. The findings were consistent with those reported after the second dose in study H1N1-021 (using a higher dose of HA) as already reported in the assessment of FU2.020.

The limited NA data available from a subset of subjects and derived from an assay performed at Viroclinics showed a baseline imbalance in seropositivity rates. Responses appeared to be generally greater in the AS03 group, including the results by age strata although the responses in the 8 subjects aged 41-50 years were somewhat anomalous. These results must be viewed with some caution but they do demonstrate a good increment in NA titres in the AS03 group after one dose and overall a further increment after the second dose.

The report to D42 from study 007 also indicates that the CD4 T-cell response observed 21 days after dose 2 was higher in the H1N1 + AS03A group compared to the H1N1 group and there were increments from D21 to D42 in the adjuvanted vaccine group regardless of the mode of testing. As observed in the H5N1 studies, there was no effect of vaccination on the CD8 response but this issue has been explored and discussed previously and will not be revisited specifically with regard to H1N1.

The safety profile described with Pandemrix H1N1 in study 007 was generally comparable with that observed after first and second doses in study 021, supporting the previous conclusions that the presence of the adjuvant is much more influential than the HA content in terms of the reactogenicity profile. However, in study 021 there was no consistent trend for higher rates of reporting solicited general symptoms after the second dose although this was observed in study 007 for most symptoms.

As post-dose 1 and post -dose 2 data have been assessed this SOB can now be considered fulfilled.

**SOB/051 Study H1N1-008 PD1 (II/023) and PD2 ((II/038 – under assessment); adults including elderly**

This initial and abridged study report described the preliminary safety and immunogenicity results following vaccination with Pandemrix (i.e. 3.75 µg HA +AS03A) in adults aged from 18-60 years and over 60 years, with a good representation of subjects aged > 60 years (120) of which 45 were > 70 years although only five of these 45 subjects were aged > 80 years.

Based on the HI data at baseline the pre-vaccination seropositivity rates and seroprotection rates were in keeping with those observed in studies 021 and 007 in subjects aged 18-60 years. There was no clear trend to higher baseline rates with increasing age.

The CHMP criteria for HI responses were met in the initial analysis in the strata < 60 and > 60 years. The additional analyses by baseline serostatus, prior seasonal vaccination and detailed age strata also showed that in each analysis the three criteria were met, including the five subjects aged > 80 years, three of whom were seronegative at baseline.

The safety profile of Pandemrix H1N1 appeared to be similar to previously assessed studies (H1N1 021, H1N1-007) generally comparable with that reported with Pandemrix H5N1 in adults aged 18-60 years and in older subjects, in whom reporting rates were generally lower than in the younger cohort. There were no new safety issues raised by these data.

The new data in the elderly merited a cautious reflection in the SPC to allow the option of a single dose. It remains to be confirmed if it is possible to allow this even in those aged > 80 years based on the very limited data in this age group. It is clear from the data that GMTs decreased with age, as observed on previous studies with H5N1 and within the 18-60 years cohort with H1N1v versions of Pandemrix.

However, and in contrast to the experience in this age group with H5N1 vaccine, all five subjects mounted an immune response. None of the five was seroprotected at baseline, although two were seropositive, but all were seropositive at D21 and four of the five were seroprotected. On this basis there does not seem to be any justification for setting an upper limit on the age at which a single dose may be an option, however the limitations of the data need to be taken into consideration (as reflected in section 5.1 of the SPC).

The immediate HI response to Pandemrix was considered highly satisfactory in adults, including the elderly, which confirmed the main recommendation to use one dose in this population. To establish if there could however be any advantages for a second dose in terms of antibody persistence and antibody against potential future drifted variants, the CHMP considered that the outstanding post-dose 1 NA data, the post-dose 2 HI and NA data and the antibody persistence data from this study should be pursued as FUMs.

As post-dose 1 data have now been assessed and further data will be followed up in variations (II-38) and FUMs, this SOB can now be considered fulfilled.

**SOB/052 H1N1-020 PD1 (II/034); PD2 awaited 7/5/2010; Effect of sequential Fluarix**

At 21 days after a first dose of Pandemrix (H1N1) all CHMP and CBER regulatory acceptance criteria were met regardless of whether or not Fluarix had been given three weeks previously. This conclusion also applied within each of the age cohorts 61-70 years, 71-80 years and over 80 years. There was a detectable effect of prior Fluarix vaccination in terms of lower SCRs, SCFs and SPRs at D21 in the group that had received Fluarix compared to the group that had received Placebo at D-21.

The 95% CI did not overlap for the SCRs and SCFs but did overlap for the SPRs. The same pattern was seen in each of the age cohorts 61-70 and 71-80 years. There were too few subjects aged > 80 years (and 5/6 were seropositive against H1N1v at D-21) for any conclusions to be drawn regarding any effect of prior Fluarix on responses to Pandemrix (H1N1).

The reactogenicity profile was comparable to that seen in other studies conducted in adults of this age group and there was no effect of prior Fluarix on the reactogenicity of Pandemrix (H1N1). Overall, and despite the pattern of immune responses observed, the data suggest that there is unlikely to be a clinically important effect of prior vaccination with non-adjuvanted seasonal influenza vaccines on the safety or immunogenicity of Pandemrix in subjects aged > 60 years.

This available data from this study submitted in fulfilment of this specific obligation allowed to conclude that sequential administration of Pandemrix following the seasonal influenza vaccine Fluarix did not lead to any clinically relevant effect in respect to single administration of Pandemrix. The CHMP agreed that additional data awaited on PD2 can be pursued in the form of a FUM, as a one dose schedule for this population can now considered to be most appropriate.

**SOB/053 H1N1-018 PD1 (II/025) and PD2; effect of co-administration with Fluarix**

The abridged study report submitted for II/025 described the preliminary safety and immunogenicity results following vaccination with Pandemrix H1N1 (i.e. 3.75 µg HA +AS03A) coadministered either with Fluarix (F-PAN group) or with saline (PAN-F group) in adults aged >60 years, with a good representation of subjects aged 61-70 years (112) and 56 subjects >70 years. The oldest subject was 85 years.

On assessment of the immunogenicity of Pandemrix H1N1 (whether administered alone or coadministered with Fluarix) the HI data at baseline, the pre-vaccination seropositivity rates and D21 seroprotection rates were in keeping with those observed in study H1N1-008 in those aged >60 years. The CHMP criteria for HI responses were met in the initial analysis in the strata 61-70 years and >70

yrs. The additional analyses by baseline serostatus, prior seasonal vaccination and age strata also showed that in each analysis the three criteria were comfortably met for H1N1.

Further analyses of the data from five subjects aged > 80 years of age and a breakdown of safety into the two age groups (61-70 and > 70 years) for study 018 were provided. These showed that the immunogenicity of Pandemrix in subjects aged > 80 resulted in all seroprotected at D21 compared to only one at baseline and the SCR and SCF CHMP criteria were also met. These data supplement and agree with the results reported from five subjects aged > 80 years in study 008 (see II/023) and do not suggest any interference from co-administration with Fluarix.

Responses to Fluarix were considered difficult to interpret in this small number of elderly subjects due to the baseline seropositivity rates. However in study 018 the responses to Fluarix in the entire age cohort >70 years met the minimal CHMP criteria for seasonal influenza vaccines. The co-administration of Fluarix did not impact on the immunogenicity of Pandemrix H1N1. For Fluarix the responses passed minimal CHMP criteria for seasonal influenza vaccine in this age group. The MAH provided safety data divided into age groups (61-70 years and >70 years). The data show that local reactions occurred much more often at the Pandemrix injection site compared to the Fluarix injection site, as was expected from all previous experience with AS03-adjuvanted influenza vaccines. The rates for local and systemic reactions tend to be lower in those >70 years and Grade 3 reactions occurred in only two subjects.

There was a relatively modest increment in HI immune responses after the second dose of Pandemrix. In contrast to the observations at D21, which suggested slightly better responses when the first dose of Pandemrix was given alone on D0, the overall data showed no difference between the groups that received first Fluarix and then Pandemrix (F-PAN) and the groups that received the vaccines in the opposite order (PAN-F) for HI responses to the pandemic vaccine strain at D42. However, the SPC recommends only a single dose of Pandemrix in this age group (see variation II/023 based on study 008) so that the D42 results are not as relevant as the D21 data.

The additional analyses by age strata and baseline serostatus showed that the increments in HI responses to Pandemrix after the second dose reflected the data for subgroups that were seronegative at baseline. HI responses to Pandemrix were comparable between vaccine groups regardless of vaccine history in terms of SPRs and SCRs while the SCFs tended to be larger in the groups without a history. All values in the various sub-groups exceeded the CHMP criteria.

The safety profile of the first dose of Pandemrix H1N1 when co-administered with Fluarix was comparable to that seen with Pandemrix H1N1 (with saline placebo), and also appeared to be comparable with that reported in study 008 in the older age groups. No difference in the safety profile of Pandemrix H1N1 was seen between the two vaccine groups. This suggests that co-administration of Pandemrix with Fluarix has a similar safety profile (local and systemic, solicited and unsolicited) to that seen with Pandemrix H1N1 vaccination alone. Overall, there were no new safety issues raised by these data.

As noted at D21 co-administration of Pandemrix with Fluarix did not have an unfavourable effect on the overall safety profile when compared with co-administration of Pandemrix with placebo. However, there was a consistent trend to higher rates of local symptoms at the Pandemrix site in the PAN-F group and some general symptoms were also reported more often in this group. Despite these findings the reporting rates for local and general symptoms did not show a consistent trend to higher rates with the second dose and rates of local symptoms rates were lower after the second dose. There was also some suggestion that local reactions were more common at the Fluarix site in the PAN-F group.

Overall, the data suggest that co-administration of Pandemrix with Fluarix was best accomplished at the time of the first dose of Pandemrix. Also, as concluded in variation II-023, the data suggest that co-administration of Pandemrix with Fluarix provides satisfactory responses to both vaccines. It should be noted that in this study all doses of Fluarix were co-administered with a dose of Pandemrix and therefore it is not possible to assess any possible effect of co-administration per se on responses to the seasonal vaccine strains.

As post-dose 1 and 2 data have now been assessed, this SOB can now be considered fulfilled.

#### **SOB/055 Study H1N1-017 PD1 and PD2; Pandemrix compared to Arepanrix**

This data has been assessed for the MA for Arepanrix (see EPAR/CHMP Assessment Report for Arepanrix) and is currently being assessed for Pandemrix.

As adult PD1 and PD-2 data for Pandemrix from other studies have already been assessed (see above), this SOB can now be considered not relevant for Pandemrix anymore Any submissions from this study can therefore be handled as FUMs.

#### **SOB/056 H1N1-009 PD1 (II/024) and PD2 (II/028); half and full doses from some cohorts in children aged 6-35 months; further cleaned data are awaited on 30/4/2010**

##### **Post-dose 1 results**

The abridged study report described the preliminary safety and immunogenicity results following vaccination with one half of the adult dose of Pandemrix (i.e. 1.9 µg HA +AS03B) in 51 children aged 6-35 months. The safety and HI immune response data have been reported according to the three predefined age strata with 17 subjects per stratum.

Based on the HI data three subjects, all in the 6-11 month age stratum, were seropositive at baseline (two of the three were seroprotected). The most likely (but not the only possible) explanation for their baseline serostatus is the persistence of maternal antibody. Details of the immune responses in this

age group for the three seropositive subjects and the 14 seronegative subjects showed that each of these three subjects had a measurable HI response based on the shift in minimum GMT observed and all three were seroprotected at D21.

Therefore, if some children in this age group still have some maternal antibody that reacts with H1N1v in HI assays they still show measurable responses to vaccination. The CHMP highlighted that there are currently no established CHMP criteria for the interpretation of immune responses to influenza vaccines in children. It is not likely that HI titres alone can wholly explain the degree of protection observed and it is not proven that a direct extrapolation of criteria from adults to children is possible. Despite these uncertainties, all the 50 children with Day 21 HI data were "seroprotected", the seroconversion rates were at least 94% and the seroconversion factors were at least 44. The GMT was numerically but not significantly lower in the oldest age stratum but this had no detectable effect on meeting the three criteria (SPR, SCR and SCF). The reverse cumulative distributions by age cohort will be provided and compared when the MAH reports the D42 data. However, it is clear from the GMTs that the majority of children must have achieved HI titres considerably in excess of 1:40.

Thus the D21 HI data suggest that a single administration of half the adult dose may be sufficient for healthy children in the age group 6-35 months. In contrast, and as observed in older children and adults, the data with the corresponding H5N1 vaccine clearly showed that two half or full adult doses (according to age) were needed to achieve the sort of HI responses reported with a single half adult dose of H1N1v vaccine in study H1N1-009. In this regard the assessor notes that in a published study with half the adult dose of an adjuvanted seasonal influenza vaccine (Fluad) in children aged 6-35 months the seroprotection rate to the H1N1 seasonal strain after one dose was from 40-65% in various age sub-groups. There are no such data in this age group with the experimental AS03-adjuvanted seasonal influenza vaccine that might help put the results into perspective.

The limited post-dose 1 NA data CDC support a conclusion that there is a good response to a first half adult dose but likely leave room for a marked increment in NA also to occur after a second dose.

The safety profile of a single half adult dose of Pandemrix H1N1 appeared to be generally comparable with that reported with Pandemrix H5N1 in older children (aged 3-9 years) although redness and swelling appeared to be very common in children aged 12-23 months. General symptoms were most often reported in those aged < 12 months but only one (irritability lasting one day) was of Grade 3.

In addition, in a population that was not apparently given prophylactic antipyretic medication the per subject rates of any fever were < 20%, only three had a fever above 380°C and none had a fever above 390°C. Therefore the tolerability of a single half-adult dose was considered acceptable.

### **Post-Dose-2 results:**

The HI data after each half adult dose submitted for variation II/28 demonstrated a marked immune response to the second dose in terms of increments in GMTs in each of the three age strata. The available data are insufficient to indicate whether a single half adult dose in this age group would be sufficient but this hypothesis cannot be ruled out.

The available data clearly indicate increased reactogenicity with the second half adult dose of Pandemrix H1N1 in children aged 6-35 months but the major concern is the increase in rate of fever, including Grade 2/3 fever, with the second dose. The post-dose 2 findings were unexpected based on the observations made in 3-5 year-old children who received H5N1/AS03 vaccine in the previously reported study. Post-marketing data seem to confirm that fevers are very common after the second dose. Fever also seems to occur commonly or very commonly after the first dose and febrile convulsion has been reported even after the first dose. However, the MAH's assessment suggests that the rate of febrile convulsion may not be unusually high.

Children aged 6-35 months mounted a good immune response to the first half adult dose based on HI and NA data available. It is not known at this time whether the increment in HI antibody observed after the second half adult dose will confer added protection. However, the new safety data post dose 2 throw some doubt on the benefit-risk relationship for a second dose.

At this time the CHMP proposed that SPC section 4.2 should reflect the data, with appropriate cross references, to leave the selection of one or two half adult doses in this age group open. Although the option to give a second dose was still maintained, the SPC was updated in II/028 to state that the option to administer a second dose should take into consideration the safety and immunogenicity information provided in the SPC sections 4.4, 4.8 and 5.1.

As post-dose 1 and post -dose 2 data have been assessed this SOB can now be considered fulfilled.

**SOB/057      H1N1-010 PD1 in children 3-17 years (II/032 and II/033); PD2 awaited  
30/4/2010**

Overall the HI responses to a single adult dose in subjects aged 10-17 years generally resemble those in young adults. In addition, in the table proposed in section 5.1 of the SPC the MAH showed the HI responses separately for children aged 10-17 years who were seronegative at baseline. As expected, these data show satisfactory responses in this subset that far exceeded the CHMP criteria applied to adults. In addition, the safety profile of the first and second adult doses in subjects aged 10-17 years was generally comparable with that observed after each dose in young adults. In subjects aged 10-17 years there were increments in local as well as general solicited symptoms with the second dose compared to the first dose whereas in young adults general symptoms increased with the second dose.

On this basis the CHMP considered that the SPC should continue to recommend a single adult dose from 10 years upwards.

As post-dose 1 data have been assessed and post-dose-2 data were considered of less relevance, given the main recommendation of a single dose, this SOB can now be considered fulfilled and subsequent submissions can be handled as FUMs.

**SOB/058 H1N1-023 PD1 half dose in children 3-17 years (II/033); PD2 awaited 30/4/2010**

In the 10-17 years age group the HI data from study 023 suggest that a single half adult dose might be sufficient. However, the MAH considers that the benefit for a half vs. full adult dose in terms of adverse reactions is limited and therefore proposes to maintain the current recommendation for a single full adult dose at least until such time that more data are available (i.e. microneutralisation assay results, persistence results and heterologous immune response data).

In the 3-9 years age group the HI data from study 023 also suggest that a single half adult dose might be sufficient although the absence of additional serological data limits the confidence that can be placed in the results. Nevertheless, the data lend support to the current dose recommendation in the SPC for this age group, which was made on grounds of caution following the reactogenicity observed after the second half adult dose in children aged 6-35 months in study H1N1-009 (variation II/028) and also taking into account the safety of the first adult dose in children aged 3-9 years reported from study 010. On these grounds, the post-dose 2 safety data from study 023 will be revealing since they may or may not confirm that reactogenicity in children aged 3-9 years is higher after the second half adult dose as was seen in children aged 6-35 months.

Meanwhile, with higher GMTs after a full adult dose in study 010 vs a half adult dose in study 023 in this age group it should be noted that the post-dose 1 rates of local reactions were higher for children aged 3-5 and 6-9 years in study 010 vs study 023 and that rates of general reactions were higher in study 010 for the 6-9 years stratum. Overall, the CHMP did not consider that current evidence indicates any merit in changing the dose recommendations for children aged 3-9 years.

The baseline seropositivity rates in study 023 were low in children aged 3-9 years despite the fact that about half had received prior seasonal influenza vaccination. However, it cannot be ruled out that a proportion of these children could have been primed even though they had no detectable HI at D0. The submission does not provide the HI responses according to influenza vaccination history. In particular the GMTs and SCFs are required since the SPRs and SCRs were anyway at or near 100%. The assessor considers that these tabulations should be provided before reaching a final opinion on this variation in order to confirm that the results at D21 may be extrapolated to other populations with much lower prior exposure to seasonal vaccination.

In terms of safety the data indicate that a first adult dose of Pandemrix H1N1 results in approximately the same safety profile between children aged 10-17 years and young adults. The data raise no particular concerns in this age group.

In the children aged 3-9 years the safety profile associated with a first adult dose could be considered acceptable. However, the second dose is clearly much more reactogenic and results in much higher rates of fevers. In this context it should be noted that some of the spontaneous reports of febrile convulsion have occurred in children aged 5-6 years. Therefore the safety profile would not preclude the option of a single adult dose in this age group.

As post-dose 1 data have been assessed and post-dose-2 data were considered of less relevance, given the main recommendation of a single half dose in this population, this SOB can now be considered fulfilled and subsequent submissions can be handled as FUMs.

**SOB/070 H1N1-024 PD1 modified process vaccine; PD2 currently under assessment**

The statistical tabulations received on the D21 HI data did not indicate any important differences in immune responses to Pandemrix H1N1 manufactured according to the initial process and the new (Triton) process.

The findings support the prior approval of variation II/018 to change the manufacturing process. It should be noted that there are no safety data have been assessed as yet.

There were no implications for the SPC based on these HI data.

As post-dose 1 data have been assessed and as there were no implications for the SPC based on this data this SOB can now be considered fulfilled and any subsequent submissions can be handled as FUMs.

**SOB/073 H1N1-021 neutralising antibody data. This was assessed within SOB 048 – see above.**

The following additional clinical data are awaited

**SOB/054 H1N1-022 half adult dose in adults aged > 18 years; expected 30/4/2010**

As the half dose in adults was not used during the 2009 H1N1 pandemic, this data was considered of minor relevance, however the CHMP considered that any submissions related to this study should be followed up as FUMs.

**SOB/059 H1N1-012 half adult dose in children 2-5 months**

It should be noted that since this SOB was formulated the PDCO has agreed that companies could request a waiver for this population. In addition the MAH notified the CHMP that due to very low enrolment the study was to be terminated. A report is expected on the limited data available. The CHMP agreed that this SOB should be converted to a FUM concerning provision of the limited data obtained.

## **SOB/060**

This concerns collection of vaccine effectiveness data. In fulfilment of this SOB the protocol has been submitted and agreed upon by CHMP and the study is ongoing.

It should be noted that the CHMP in 2003 foresaw the need for effectiveness data, in the context of the development of mock-up vaccines to be used in a pandemic situation. It should also be acknowledged that this goes beyond standard requirements for seasonal influenza and certain other vaccines, whereby immunogenicity data serves as a surrogate marker of efficacy for the assessment of the initial authorisation and clinical data on effectiveness is collected in the post marketing phase. The approach taken for the pandemic vaccines was at the time considered to be appropriate in consideration of all the uncertainties to be faced in a Pandemic context e.g. the virulence of the agent concerned, use in naive population sub-groups and anticipated high morbidity and mortality rates etc.

Overall, the vaccine has shown to be highly immunogenic and besides this, reassuring data from independent evaluation of field H1N1 vaccine effectiveness (including Pandemrix) in European countries indicate that vaccination campaigns have been effective. The CHMP considers further effectiveness data can be collected in the context of a FUM.

## **Pharmacovigilance SOBs**

It should be noted that the listed Pharmacovigilance SOBs exceed standard pre-authorisation requirements for seasonal influenza and other vaccines.

## **SOB/061**

This was a commitment to conduct a post authorisation safety study (PASS) in at least 9,000 subjects in accordance with the RMP. This was carried out in GP practices in England and recruitment was completed in December 2009. Due to the eventual UK immunisation policy, it was not possible to achieve the target sample sizes in the age cohorts of 2-23 m, 2-8 y and 9-17 y, however the CHMP considered that the large amount of available post marketing data in connection with clinical study data in the paediatric population has provided sufficient information to support the position that the safety database in this population can be considered acceptable.

This SOB has been fulfilled as the study was implemented.

The MAH has committed to provide a rolling update on analysis of the uncleaned and preliminary data. In the absence of any clear safety signal arising from the dataset the study was intended to provide a descriptive analysis of AEs compared to the safety profile documented in the sponsored studies with Pandemrix H5N1 and H1N1.

An analysis of the near full study cohort (n=8811 subjects) with 30-day follow-up was recently completed and a preliminary analysis of partially-cleaned data from the full study cohort (30 day FU) was provided. Overall, 12% of subjects in each age cohort reported an event. There was no evidence of case clusters of potential concern amongst the MedDRA terms reported. Two convulsions and three fatal events in elderly subjects with risk factors have been reported. The 7 day follow-up in the reactogenicity cohort revealed relatively high rates of local and general symptoms compared to the H5N1 and H1N1 clinical studies although these have been in the same frequency categories already stated in the SmPC. Grade 3 local symptoms and those requiring medical attention have occurred at very low rates.

This did not identify safety issues. The final study report (30 day FU) is expected on 30 November 2010 and the 6-month FU report is expected 1 April 2011.

Taking into consideration that the protocol has been submitted and agreed by CHMP, that the study is ongoing and that data received to date via interim reports and also safety data generated through post marketing surveillance are extensive and reassuring the CHMP considered that the remaining data from this study can further be pursued as a FUM. It is of note that the requirements for a PASS study goes beyond current standard requirements for safety data for standard seasonal influenza vaccines and was requested in consideration of the exceptional circumstances of a mass vaccination campaign in the context of a pandemic with an unknown epidemiological development. Based on the actual epidemiological development of the 2009 H1N1 pandemic and having considered the totality of the data as described above CHMP considers that any remaining data can be collected in the context of a FUM.

#### **SOB/062**

This was a commitment to implement a pregnancy registry. At time of the strain change pregnancy registries have been added as SOBs to collect data in this risk group despite the fact that these are not normally required pre-authorisation. In fulfilment of this SOB the protocol has been submitted and reviewed by the CHMP and the registry has been established. The MAH has provided the details of the UK pregnancy register and committed to provide the results.

Overall from pharmacovigilance monitoring and data collected so far no safety signal has been detected. For discussion of further data in pregnant women see section III.2.3.2 Clinical Safety below.

Overall taking into consideration the protocol has been submitted and agreed by CHMP the CHMP considered that these data can be pursued as a FUM.

#### **SOB/063**

This was a commitment to establish the mechanisms to promptly investigate issues affecting the benefit-risk balance of the vaccine. The MAH has established routine and enhanced Pharmacovigilance activities both described in the risk management plan and including weekly signalling, evaluation of signals, monthly S-PSUR. In addition for investigating emerging benefit risk issues after the start of the vaccination campaign the MAH has provided different sources that will be use to investigate issues

affecting the benefit risk balance of the vaccine. The method used to analyse the different databases as well as the protocols of the studies have been reviewed and considered acceptable by the CHMP.

This obligation has been fulfilled as the MAH has provided details for a number of data sources that may be useful in evaluating emerging safety issues. These data sources were considered sufficient to fulfil the SOB.

### **Conclusion on SOBs**

The Specific Obligations concerning the evaluation of safety and effectiveness as introduced during the initial authorisation and the variation in order to introduce the pandemic (H1N1)v strain have been sufficiently addressed to conclude on the maintenance of a positive risk/benefit for the use of Pandemrix in the current epidemiological situation. The CHMP considers that the MAH has now provided sufficient comprehensive safety and efficacy data such that grounds to maintain the MA under exceptional circumstances are no longer applicable. In addition specific procedures concerning safety are no longer required in context Article 14 (8) of Regulation (EC) No 726/2004 as these can be achieved in context of the conventional Risk Management Plan.

### **III.1.2. Follow-Up Measures**

Please consult the separate assessment reports that have already been issued for full details.

The status of the FUMs is as summarised below:

#### **Quality FUMs**

##### **Fulfilled**

**FUM 002** Provision of process validation studies.

**FUM 003** Provision of storage data for intermediates.

**FUM 007** Provision of additional process data for adjuvant.

**FUM 008** Confirmation of shelf life of squalene.

**FUM 009** Validation of GC analysis for squalene.

**FUM 010** Provision of shelf life data for adjuvant. This commitment was finalized with the submission in September 2009.

**FUM 011** Revision of sodium deoxycholate limit in antigen bulk. A limit at NMT 100 µg/mL is accepted.

**FUM 012** Investigation of sensitivity of Triton X-100 HPLC assay.

The MAH has satisfactorily investigated the insensitivity of the HPLC method for determining levels of Triton X-100, and adapted the method appropriately.

**FUM 013** Confirmation of suitability of container closure system for H5N1 bulks and final containers.

**FUM 014** Provision of stability data on H5N1 split monovalent bulks (derived from A/Indonesia).

**FUM 015** Provision of stability data for H5N1 final lots.

**FUM 042** Stability data for bulk antigen stored in bags.

The MAH provided the results of the 30-day of the stability study using bags.

**FUM 047** Stability data for bulk antigen stored in bags.

The MAH provided the results of the stability study using batches of H1N1 A/California monovalent bulk stored in bags at +2°C to +8°C.

**FUM 071** Provision of additional data from manufacturing process.

#### **Awaited**

**FUM 004** Confirmation of formaldehyde inactivation of H5N1.

**FUM 005** Provision of PET results if thiomersal falls below specification.

**FUM 006.1** Provision study report feasibility of an additional sterile filtration step.

**FUM 041** Update dossier in line with CHMP/VEG/4717/03 revision.

## Non-clinical FUMs

### FUM 067

This FUM requested a study to evaluate the possible effects of the adjuvant in the presence of antigen when dosed in early pregnancy. A study was conducted and The MAH concluded that neither the full vaccine nor the adjuvant alone had an effect on pre-implantation loss.

### FUM 078

This FUM concerned a study of protection against influenza in ferrets. The AS03-adjuvanted vaccine induced superior antibody responses compared to non-adjuvanted HA, which correlated with the protection observed in response to homologous influenza virus challenge. The protection observed following one dose of adjuvanted vaccine tended to be less than that achieved with two doses.

## Clinical FUMs

The status of these FUMs can be briefly summarised as follows:

### Fulfilled:

#### Pandemrix (H5N1) FUMs

**FUM 017** Study H5N1-002/-030 (D180)/-038 (Years 1, 2 and 3) (consistency & persistence): "Anti-neuraminidase antibodies from 100 subjects "Persistence D180 (-030) "Booster given at D180 data (-030)

The CHMP considered that the neuraminidase present in the vaccine elicits functional anti-neuraminidase antibody as detected by the reference assay method and the results suggest that anti-neuraminidase antibody has some neutralisation activity but the contribution this may make to the overall protective efficacy of the vaccine is unknown. The MAH does not plan any further testing for anti-neuraminidase antibody because of the lack of a standardised high throughput method and the uncontrolled content of neuraminidase in influenza vaccines.

Overall the CHMP agrees with the MAH. Having established that anti-neuraminidase antibody is elicited and makes a variable contribution to the total neutralising activity measured this part of the FUM is considered to be fulfilled.

#### Study H5N1-030

The Month 6 antibody persistence data showed a seroprotection rate in the HN-AS03 group of 40.2% against A/Vietnam but a negligible rate against A/Indonesia. The question of whether immune memory laid down by pre-pandemic vaccination would be sufficient to prevent pandemic influenza or whether it is necessary to maintain a certain level of circulating antibody cannot be answered. However, the data from study

030 do allow for an assessment of immune memory and support a conclusion that the first two doses of AS03-adjuvanted vaccine efficiently elicited priming. These data are in keeping with those reported

from studies 012 and 015 in which response to a heterologous booster strain were also assessed. In addition, the response to a single booster dose in subjects who had previously received adjuvanted vaccine was higher than in the control group at M6 + 21D. This finding is also in keeping with that from study 015.

In the subjects that initially received non-adjuvanted vaccine, a further increase in the response to A/Vietnam and A/Indonesia was observed at M6 + 42D i.e. following the second dose of AS03-adjuvanted A/Indonesia vaccine. However, responses were still significantly lower than those observed at M6 + 21D in subjects primed with the adjuvanted vaccine. Hence, the use of AS03-adjuvanted vaccine for priming and boosting is important.

In terms of safety, more grade 3 general solicited symptoms were observed after the booster in subjects primed with the adjuvanted vaccine (10.9%) compared to subjects primed with the non-adjuvanted vaccine (4.1%). However, rates for grade 3 local reactions were low and there was no difference between groups (5.3% versus 4.1%). The incidence of general symptoms after one booster dose was 78.9% in 030 compared with 64.4% after priming with adjuvanted vaccine in study 002. However, rates for local reactions were comparable (81.9% versus 77.8%). Inevitably the group that had received non-adjuvanted vaccine in study 002 experienced higher rates of local (74.6% versus 17.3%) and general (62.9% versus 37.2 %) symptoms after two booster doses compared to post-primary doses. Following a review of one case of multiple sclerosis (MS), the CHMP further considered that whether or not the use of this vaccine might in some way predispose to the development of MS and/or bring forward the onset of symptoms in those who would eventually develop clinical evidence of the condition must remain under very long-term investigation. No conclusion can be drawn based on one case. The NA data from study 030 and data over years 1-3 are awaited.

**FUM 018** Study H5N1-008/011 (safety): NA data on the remaining subjects (18-60 years): D42 and D180

The data are in keeping with those previously presented. While 21% of subjects in the AS03-adjuvanted group had NA titres of at least 1:80 before vaccination 99% reached this titre after two doses of

15µg/AS03 vaccine (and most reached it after one dose). At D180 71% still had a titre of at least 1:80. The baseline rate of seropositivity against A/Vietnam was comparable with that in study 007 in this age group (1/5-1/3 subjects were NA seropositive at baseline, 10-25% per group had titres > 1:40 and 2-10% had titres > 1:80). In contrast the majority (82-91% per group) of subjects aged > 60 years in study 008 were NA seropositive before vaccination with 69.5% and 67.3% at 1:40 and 44.6% and 40.0% at 1:80. In the 15 µg HA/AS03 group the percentages with > 1:40 and >1:80 at D21 were 99.4% and 93.8%, respectively. At D42 these percentages were 100% and 99.4%. This FUM was considered fulfilled.

**FUM 019** Study H5N1-007 (dose-range): Extended serological follow-up = pre-boost data (M14) of study H5N1-015

This FUM was fulfilled with the submission of the type II variation (II/04) which was received on 14/11/2008.

**FUM 020** Study H5N1-009 (paediatric) - Initial D42 report

The MAH submitted data to D42 from study H5N1-009 in children aged from 3-9 years. It was noted that extended follow-up of this study will include assessment of antibody persistence and safety up to

Month 24 after primary vaccination. According to the timelines identified by the MAH, it is expected that these data will be provided at intervals up to June 2011. Regarding the product information (PI), a variation should be submitted, considering the PI now states "There is no experience in children".

The data were considered insufficient to support an unequivocal recommendation for use of the adult dose in children aged 3-17 years, however the CHMP highlighted that it would seem that some mention of the findings in section 5.1 of the Pandemrix SPC, to be updated as more data emerge, would be potentially useful in case there should be an urgent need to deploy vaccine before adequate data are available. The D42 data point to the potential advantages of using the adult dose in children aged 3-9 years and, therefore, across the age range 3-17 years.

The further follow-up from this study and responses from the MAH to this FUM were assessed within PU/0017 (see EPAR/CHMP AR) and formed the basis for the recommendation in the use in the paediatric indication.

**FUM 021** Study H5N1-010 (elderly): Initial D42 report, D180 data Extended follow-up (24 months) This FUM was fulfilled with submission of variation II/05 received on 14.11.2008.

**FUM 022** Study H5N1 -012 (prime-boost): Initial report (including D180: pre- and post boost 6 months) This FUM was fulfilled with the submission of the type II variation (II/04) which was received on 14/11/2008.

**FUM 023** Study H5N1-015 (booster):Initial D42 report, D180 data, This FUM was fulfilled with the submission of the type II variation (II/04) and variation (II/06), which received positive opinion on 29 May 2009

**FUM 024** Study report(s) from Q-Pan-001 (half-dose adjuvant).

The MAH submitted a full amended clinical study report (CSR) on the D42 data (safety and HI immunogenicity results) from study Q-PAN-001 dated 14 July 2008. The MAH also submitted an annex to the above report dated 18 July 2008, which covers data on safety and HI testing results up to D182.

The data from Q-PAN-001 do not raise any major surprises and were consistent with the previous data from studies H5N1-002, H5N1-007 and H5N1-008 with adjuvanted Dresden antigen vaccine containing A/Vietnam/1194/2004.

Further data and follow-up from study Q-PAN-001 were assessed within the MAA for Arepanrix.

**FUM 025** The MAH commits to provide the CMI data from studies H5N1-009, -010, -012 and -015

In the initial dossier the apparent difference between the observed CD4 and CD8 responses to vaccination could not be explained. The CSFE-LP test system that has since been applied by the MAH demonstrated an expansion of memory CD4+ T cells and CD8+ T cells in the adjuvanted vaccine group. However, as pointed out by the MAH, the pattern of results suggests that the detected CD8+ T

cell response could possibly represent a bystander effect. Therefore, the MAH repeated the LP-CFSE test after CD4+ T cell depletion in experiments.

Further evaluations of CD4+ T cell responses to vaccination continue to indicate that cross-reactive T cell responses occur to different H5N1 subtypes. However, some of the response detected with split virions likely represents recognition of antigens other than HA.

In February 2009 the MAH provided the results of the planned continuation of studies using the LP-CFSE method after CD4 cell depletion.

In addition, in March 2009, the MAH supplied the CMI data from the Paediatric study 009, which have been included in this report.

In the initial dossier the apparent difference between the observed CD4 and CD8 responses to vaccination could not be explained. The CFSE-LP test system that has since been applied by the MAH demonstrated an expansion of memory CD4+ T cells and CD8+ T cells in the adjuvanted vaccine group. However, as pointed out by the MAH, the pattern of results suggested that the detected CD8+ T cell response could possibly represent a bystander effect. Therefore, the MAH repeated the LP-CFSE test after CD4+ T cell depletion.

The results suggest that much of the CD8+ T cell response may represent a bystander effect i.e. is dependent of the presence of CD4+ cells.

The limited data from the study in children 009 indicate that the findings are in line with those reported in adults. The MAH commits to monitor both NA and cellular responses in vaccinees to newer variants of H5N1 that emerge.

**FUM 026** The MAH commits to provide a specific plan for conduct of studies in which NA titres are determined in sera from vaccinees against more recent H5N1 strains.

The MAH has satisfactorily fulfilled this follow-up measure regarding provision of a plan for evaluation of neutralising antibody titres against emerging strains. The FUM should now be converted to request provision of data from any such studies that become possible.

**FUM 030** The MAH commits to repeat User Testing of the PL using the version finally approved by CHMP and to report these results within 6 months of the approval date.

This FUM is closed with the submission of the notification (N/0007) on 02/12/2008.

### **Pandemrix (H1N1) FUMs**

**FUM 065** "The MAH commits to provide the validation of the haemagglutination inhibition assay."

The MAH's HI assay is a validated assay based on the original validation document QVALR-PF-015 with every strain change the Company performs a revalidation of the HI assay. The revalidation includes assessment of assay precision (repeatability and reproducibility), specificity, linearity and stability. Since no international standard serum was available accuracy could not be tested but this will be done once an international standard serum is available. The revalidation was conducted with samples from study D-Pan-H1N1-021 (subjects that have received one dose of an investigational formulation of Pandemrix). Samples from Flu-US-007 were used as the negative controls.

The CHMP considered that this assessment has not provided all details of the original HI assay validation since this has been in operation for some years and has been reviewed previously.

More important are the results of the revalidation exercise using the A/California/07/2009 strain. This appears to have provided results that were well within the required criteria. It was particularly noted that none of the 150 samples from subjects aged 9-15 months were HI seropositive with respect to the new strain, suggesting that the assay has a good specificity.

**FUM 066** Provision of submission dates for other final study reports.

This FUM is fulfilled as the MAH provided the submission dates.

**Awaited (from H5N1 mock-up file)**

**FU2 17.2** Study H5N1-002/-030 (D180)/-038 (Years 1, 2 and 3) (consistency & persistency): Persistence Year 2 (-038), Booster given @ Year 2 data (-038)

**FU2 17.3** Study H5N1-002/-030 (D180)/-038 (Years 1, 2 and 3) (consistency & persistency) Persistence Year 3 (-038), Booster given in Year 3 data (-038)

**FU2 20.2** Study H5N1-009 (paediatric), Initial D42 report, D180 data, extended follow-up (24 Months)

**FU2 21.2** Study H5N1-010 (elderly), Initial D42 report, D180 data Extended follow-up (24 months)

**FU2 23.2** Study H5N1-015 (booster), Initial D42 report, D180 data, extended follow-up (24 months)

**FUM 027** The MAH commits to provide a specific plan for conduct of studies in immunocompromised subjects (overdue)

**FUM 039** From **II/04, II/05 & II/06**: (expected on an on-going basis) With the derivation of a WHO standard since the HI and NA assays were developed, the MAH should inform CHMP of plans to implement use of the WHO standard prospectively and also whether there will be a selection of older samples re-tested in assays that employ the WHO standard.

**FUM 064** Provision of H5N1-009 final study report

The CHMP agreed that the above outstanding FUMs related to the H5N1 mock-up vaccine are considered more relevant for Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals, and are no more requested for Pandemrix (H1N1)v.

## **Pharmacovigilance FUMs**

### **FUM 038**

This FUM related to the assessment of two cases of autoimmune hepatitis (AIH) observed in Q-Pan H5N1 and D-Pan H5N1 clinical studies. The MAH responded to all requests for information and this FUM has been fulfilled within PU/0017. The available information did not provide sufficient evidence to support an association between Pandemrix and AIH or other autoimmune disorders.

### **PSU 031, 032, 033, 034, 035, FU2.035, PSU 036 and FU2.036**

These are completed following sPSUR submissions and addressing subsequent issues raised.

### **PSU 074, 075 and 076**

These PSU commitments concern subsequent sPSURs.

### **FUM 027**

This concerns a request to provide a plan to assess the vaccine in immunocompromised subjects. It may be considered fulfilled in that there is an ongoing assessment of Q-Pan (H1N1)v in immunocompromised subjects in Canada and the MAH will also report data from the study under an Arepanrix FUM, which might be considered supportive.

**FUM 069** This was fulfilled by filing variation IA/001 to update the DDPS.

### **RMP 028, 029 and 068**

These were fulfilled by filing updates to the RMP. These RMPs have been assessed.

**RMP 077** This concerns provision of a further update to the RMP following PU/0017

In summary it can be concluded that the current content of the overall safety database far exceeds the safety data base expected before approval of an influenza vaccine. The data available do not raise any specific safety concern and the safety profile is found to be comparable to that of seasonal influenza vaccines.

It is considered that the remaining commitments for outstanding data related to pharmacovigilance could be converted to FUMs.

### III.1.3. Variations

Please consult the separate assessment reports that have already been issued for full details.

Variations already completed are as follows:

#### **Pandemrix H5N1**

#### **Quality Variations:** II/001, II/009, II/010, II/011, II/012

On 20 November 2008 the CHMP adopted a positive opinion to allow the use of an additional filling and packaging site for the adjuvant (Variation II-001), this variation received a positive Commission Decision on 15 December 2008.

On 25 June 2009 the CHMP adopted a positive opinion to allow changes to the manufacturing process of the H5N1 antigen (Variations II-009, II-010) these variations received a positive Commission Decision on 1 July 2009.

On 20 August 2009 the CHMP adopted a positive opinion to allow the use of alternative shipping containers for the active substance (Variation II-011) and to update the pharmaceutical dossier (Variation II-012) these variations received a positive Commission Decision on 8 September 2009.

#### **Clinical Variations:** II/004, II/005, II/006

On 29 May 2009 the CHMP adopted a positive Opinion on three type II variations based on additional clinical data to update sections 4.2, 4.4, and 5.1 of the SmPC.

Variation II-004 involved the possibility of administering one dose of Pandemrix after primary immunisation with vaccine of the same formulation and approved for pre-pandemic use containing H5N1 antigen from a different clade of the same influenza subtype.

Variation II-005 involved use in subjects aged 61 years and above.

Variation II-006 involved an update of section 5.1 regarding the use of a much longer dose interval for primary vaccination.

These variations received a positive Commission Decision on 10 July 2009.

The Pandemic Update variation to change the strain was numbered PU/II/017. See Section II for details of this variation.

## **Pandemrix H1N1**

**Quality Variations:** II/008, II/015, II/018, II/020, II/021, II/022, II/027, II/029, II/030, II/031, II/035, II/036, II/037, II/039 is currently ongoing

These variations have received a positive Commission Decision between 5 October 2009 and 3 February 2010. The submissions related to changes in the manufacturing process of the active substance, the finished product and the adjuvant. Also further sites were added for the processing of the active substance, finished product and the adjuvant. The variation applications are summarised below:

**II/008** Changes to the manufacture of the adjuvant introduced.

**II/015** Changes to the storage of the antigen were introduced.

**II/018** Changes to the manufacturing process of the H1N1 antigen were introduced.

### **II/020 and II/035**

Additional sites for manufacture of the antigen finished product were introduced.

**II/029** An additional site for the manufacture of the antigen was introduced.

### **II/021, II/022, II/027, II/030, II/031, II/036 and II/037**

Additional sites for the manufacture and testing of the adjuvant were introduced.

**Clinical Variations:** II/019, II/023, II/024, II/025, II/026, II/028, II/032, II/033, II/034,

### **II/038**

All of these variations were filed and completed between 29 September 2010 and the April 2010 CHMP meeting. The data comprised safety and immunogenicity data derived from various clinical studies in subjects aged from 6 months to > 80 years. The status of these SOBs and FUMs can be briefly summarised as follows:

## **II/019 and II/032**

Data from study 007 (PD1 and PD2) in adults aged 18-60 years

II/032 also included data in adolescents from study 010

## **II/023 and II/038**

Data from study 008 (PD1 and PD2) in adults aged from 18 - > 80 years

## **II/024 and II/028**

Data from study 009 (PD1 and PD2) concerning half and full adult doses in children aged 6-35 months

## **II/033**

Data from study 010 (PD1) full dose in children 3-17 years and PD1 data from study 023 half dose in children aged 3-17 years

## **II/025**

Data from study 018 (PD1) on the effect of co-administration with Fluarix in adults

## **II/034**

Data from study 020 (PD1) on the effect of sequential administration of Fluarix in adults

## **II/026**

This concerned an update to section 4.8 of the SmPC only to add information gained from post-marketing reporting of ADRs

The ongoing variations at the time of requesting this switch to full MA are II/38 (clinical), II-39 (quality) and IA/40 as described above.

## **III.2 Other Scientific Data provided relevant for the assessment of the benefit/risk balance**

### **III.2.1. Quality**

The relevant quality data generated as part of the H5N1 mock-up licence were considered supportive for the H1N1v pandemic strain version of Pandemrix. Additional supporting quality data required

specifically for the strain change were provided 22 September 2009 and satisfactorily demonstrated the quality of the vaccine.

Since the pandemic strain change, a number of additional antigen/adjuvant manufacturing sites have been introduced and also the antigen manufacturing process has been amended. There are no quality SOBs for the Pandemrix dossier. Those FUMs that remain to be fulfilled relate to the vaccine manufactured with H5N1 antigen.

The CHMP agreed that the outstanding FUMS related to the H5N1 mock-up vaccine are considered more relevant for Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals, and are no more requested for Pandemrix (H1N1)v.

In conclusion, the CHMP considered that from a quality perspective there are no outstanding concerns regarding conversion to a full MA.

### III.2.2 Non-Clinical

The MAH has responded to the two FUMs. The data have been assessed and RSIs were adopted at the April 2010 CHMP meeting. The additional data on efficacy in ferrets will need to be added to section 5.1 of the SmPC by means of a variation that will follow conclusion of the FUM.

### III.2.3. Clinical

The clinical SOBs and FUMs already fulfilled or partly fulfilled are listed in section III.1 The outstanding clinical issues in terms of data that are awaited in response to SOBs or FUMs are listed in Annex II of the Product Information.

#### III.2.3.1 Clinical Pharmacology and Clinical Efficacy

The assessment of the expected safety and potential protective efficacy of Pandemrix (H1N1)v was initially based on the data obtained with the mock-up vaccine containing H5N1 strains (either A/Vietnam or A/Indonesia) together with very limited and preliminary data from the first reported study (021) in adults aged 18-60 years with an early formulation of Pandemrix (H1N1)v.

The available data on the H5N1 mock-up vaccine before it was approved came from three studies in adults, including elderly subjects. Safety data were available from approximately 5000 subjects exposed to at least the dose of HA/AS03 that was approved and with a substantial proportion of vaccinees followed up to at least 6 months.

After first approval the MAH provided data from three additional studies with the mock-up vaccine, including a study in the elderly, one in children aged 3-9 years only and one in adults that evaluated priming with one or two doses and boosting with a version manufactured using H5N1 virus of a different clade. The MAH also provided the follow-up data from one of the first three studies in which a third (booster) dose was given. All the data with the mock-up vaccine pointed to the need for two priming doses in all age groups. Two half adult doses appeared to be sufficient in children aged 3-9 years. There were no major safety concerns with the second dose except that children aged 3-9 years who had received two adult doses showed higher AE rates (and especially fever) after the second compared to the first dose.

The data from all the studies with the mock-up vaccine were reflected in the SmPC and PL for Pandemrix H5N1. The prescribing information for Pandemrix H5N1 was then used as the basis for drafting the first version of the SmPC and PL for Pandemrix (H1N1)v.

In September 2009, just before approval of the strain change variation (PU/II/017) to the mock-up vaccine, the MAH provided preliminary data from a study (H1N1-021) conducted with Pandemrix (H1N1)v manufactured using a pandemic virus strain approved by WHO and CHMP for vaccine production. The antigen content in the vaccine was slightly higher than that in the final pandemic vaccine because a preliminary method for estimating the antigen content had been used. The data were limited to HI responses at 21 days after a single dose. These data indicated that it was very likely that a single dose might be sufficient for adults aged 18-60 years and the results were taken into account in drafting the first approved SmPC and PL for Pandemrix (H1N1)v.

The SOBs concerning data from sponsored clinical studies with the pandemic vaccine required reporting of post-dose 1 and post-dose 2 data, with or without longer-term follow-up and responses to further doses (according to individual protocols), from the ongoing and planned studies that were listed in the Letter of Undertaking agreed at the time of the strain change variation.

In summary, the data have confirmed that a single adult dose is suitable for subjects aged from 10 years upwards (including subjects aged > 80 years) regardless of their baseline serostatus and seasonal influenza vaccination history. There was an increment in rates of some AEs after the second dose observed in some, but not all, studies in adults but this has not been so marked that the safety profile would preclude a second dose if this was considered desirable (e.g. perhaps in the immunocompromised).

The data have also shown that a single half adult dose elicits a marked immune response with an acceptable safety profile in children aged from 6 months up to and including 9 years. The data indicated a very marked increase in HI antibody GMTs after a second dose and this was accompanied by higher rates of AEs, including fever, in children under 3 years compared with the first dose. There were also increments in frequencies of certain AEs in other age groups after the second compared to the first half adult doses.

As one of the limitations of the current database the CHMP identified that the MAH has been unable to develop and validate an in-house NA assay against the pandemic H1N1V strain and therefore has been unable to fulfil all the commitments made to provide NA data. However, some NA data have been generated by the MAH from three outside laboratories using a range of methods and these data strongly support a conclusion that a single dose of the vaccine elicits a robust NA response. In addition, there has been an assay of NA in a selected subset of sera by independent laboratories that demonstrate large increments in titres after a single dose. Further NA data are expected to be submitted as FUMs as described above.

### III.2.3.2 Clinical Safety

Safety data from completed and ongoing clinical studies

All the data received thus far have been fully assessed and reflected in the SmPC by means of a series of variations as considered necessary. The safety data from clinical studies has been discussed in the section on SOBs above. Additional data will be submitted and assessed along with the immunogenicity data as also listed above.

Post-Marketing Experience

Six simplified Periodic Safety Update Reports (sPSURs) have been submitted by the MAH.

According to the MAH, the cumulative number of doses distributed as of 28 March 2010 (the data lock point of the last sPSUR) was 127,335000 in the EU and 15,543000 in the rest of the world. It is more difficult to estimate the actual number of doses administered. Based on data returns from individual EU MS at least 30 million EU subjects have been vaccinated. Age and risk group-stratified exposure data are not currently available on an EU level. As of 28 March 2010 and since the date of launch on 12 October 2009, the MAH has received 17,885 ADR reports (5098 serious) of which 171 described a fatal outcome.

The majority of ADR reports relate to the post-vaccination signs and symptoms that were reported from clinical studies and already listed in the SmPC. These have included headache, nausea, vomiting, diarrhoea, abdominal pain, dizziness, fever, myalgia/arthralgia, fatigue, malaise, asthenia, chills, sweating, allergic ADRs (including dyspnoea and generalised rashes), lymphadenopathy and injection site reactions (including pain, swelling and localised paraesthesia or numbness). The available data do not allow for an assessment of any change in the expected severity or frequency of such events as compared to the clinical studies.

#### **Serious case clusters**

Since many countries prioritised subjects with chronic underlying illnesses for vaccination there have been several clusters of ADRs in specific SOCs (e.g. cardiac disorders, respiratory disorders, obesity and diabetes-related disorders, kidney disorders) that likely relate to pre-existing conditions. There is

currently no suggestion of specific safety signals arising from such case clusters. However, several clusters of events (e.g. pregnancy outcomes, afebrile seizures, neuropathies, demyelinating disorders) remain under close review via ongoing observed vs. expected analyses conducted by the MAH and by regulatory authorities.

### **Febrile seizures**

Several cases of febrile seizures in young children have been reported across the EU. In light of the evidence that emerged from the paediatric clinical trials regarding fever rates, particularly post-dose 2, section 4.8 of the Pandemrix SPC was amended to include febrile seizures as a potential risk.

### **Fatal events**

There have been 171 events with a fatal outcome reported and the MAH has provided narratives of all cases. The MAH has conducted an 'observed vs. expected' analysis of cases with a fatal outcome, stratified by country. So far it is concluded that overall and by country death rates in vaccinees are below the expected rates. The majority of deaths, more than half of which were in elderly patients, appeared to be most likely due to concurrent illnesses. There remains no clear evidence to suggest that the vaccine has contributed to any of these deaths.

### **Completed safety reviews**

During the review of the four sPSURs the MAH was asked to provide a more detailed assessment of cases of eye disorders, herpes zoster infection, facial palsy, pregnancy-related outcomes (see below), paediatric safety review (see below), cyanosis, paralysis/paresis, hypoaesthesia, respiratory obstruction, administration errors, autoimmune haemolytic anaemia, hearing disorders and arthropathies. These analyses have revealed no specific safety signals or cause for concern.

### **Pending safety reviews**

Two reviews considered to be a high priority are also ongoing - Guillain Barre Syndrome (GBS) and afebrile seizures.

### **Guillain Barre Syndrome (GBS)**

The MAH stated that 72 cases of suspected GBS have been reported in association with Pandemrix. Seventeen of these cases do not fit the Brighton Collaboration case definition for GBS. A further 40 cases contain insufficient clinical detail to assign a level of diagnostic certainty. On the assumption that 30 million persons have been vaccinated with Pandemrix, the MAH's analysis suggests the number of cases observed has been broadly in line with expected numbers of cases.

On 31 March 2010 the EMA convened an expert meeting to discuss the current O/E analyses of GBS and the ongoing surveillance systems and studies within Europe, Canada and the United States to assess GBS following vaccination. It was agreed that, based on results of O/E analyses performed in five countries, the currently available data are reassuring and there is no indication of a risk of a similar magnitude as that found in the pandemic situation of 1976. Taking into consideration the level of evidence currently available, a possible association between the pandemic A/H1N1 vaccines and GBS cannot conclusively be ruled out but, if there is an increased risk, the relative risk in vaccinated individuals as compared to non-vaccinated ones would probably lie between 1 and 2 (i.e. a similar magnitude found in some studies of seasonal influenza vaccines).

It was agreed that the spontaneous data and O/E analyses will not allow this issue to be resolved. It was considered that the ongoing epidemiological studies can provide valid estimates of the risk of GBS associated with the A/H1N1 vaccines. The main issue will be the power of these studies to detect a small increase in risk (i.e.  $<2$ ) as the number of reported cases at this stage and the vaccination

coverage are lower than expected. Given the fact that the main problem of ongoing epidemiological studies will be the lack of statistical power, an objective to be achieved is the pooling of data collected in the different studies. The VAESCO consortium will pool data from eight countries. It was also agreed that there are no additional studies or data that can be reasonably collected or currently requested from vaccine manufacturers to assist in the assessment of this issue.

The CHMP considered that, as there remains no clear evidence of an association between any of the vaccines and GBS, an update of the SmPCs would not be appropriate at this stage. It was agreed that the findings of the EU and VAESCO studies should be awaited before considering any such action. Even if an increased risk up to 2 was confirmed, it was agreed that the balance of risks and benefits would remain favourable.

### **Non-febrile seizures in known epileptics**

There have been three fatal cases of non-febrile seizures in known epileptics with onset < 48 h post-vaccination in the EU. In one case, the patient had a recent history of poor epilepsy control. An O/E analysis has suggested that in order to observe two coincidental deaths due to epilepsy within 48 h of vaccination in the UK approximately 300,000 epileptic patients would need to be vaccinated. At the time of the cases, it was not at all likely that this many epileptic patients had been vaccinated in the UK and therefore this was considered to be a signal requiring thorough evaluation.

Nevertheless, based on an assumption (due to a lack of information on the number of epileptics vaccinated) that the proportion of epileptics in the vaccinated population is the same as in the general population (4.9/1000) the MAH's O/E analysis indicates that the occurrence of three fatal cases would be near to the expected number.

The MAH's assessment (data lock 21 December 2009) identified 119 non-fatal cases of non-febrile seizures following Pandemrix. In 104/119 cases the seizure occurred within 3 days of vaccination. Of 76 cases with sufficient clinical details, 34 had a history of seizure disorder. The MAH's O/E analysis of non-fatal seizures in epileptic subjects suggested that 798 cases might be expected within 2 days of vaccination. To assess the issue properly would require a formal study using available electronic data sources. The MAH has proposed to conduct a self-controlled case analysis of seizures using a Swedish database. A draft protocol for this study has been submitted and results are expected in August/September 2010.

### **Other Adverse events of special interest (AESIs)**

The available data on cases of anaphylaxis do not indicate that reporting rates are greater than the generally-expected (with other vaccines) rate of 1 to 10 cases per million doses. Anaphylaxis was included in section 4.8 of the SPC during the marketing period. Available O/E analyses of cases of Bell's palsy indicate that case reports are well within the expected incidence rate. No signals are apparent for any other AESIs.

### **Age-specific or risk group-specific events**

To address the gap in paediatric recruitment in the PASS study (see below), the MAH provided a detailed assessment of all available paediatric safety data from clinical trials and post marketing. This has identified no specific safety issues in children. Other than the issue of high fever rates post dose 2 in children (see below), there remains no clear evidence of any specific safety issues in any age group or clinical risk group.

### **Safety in pregnancy**

Pregnant women are a target vaccination group in many EU countries. The MAH has provided a detailed analysis of safety in pregnancy. As of 28 March 2010, at least 150,000 pregnant women have

been vaccinated with Pandemrix in the UK while up to 260,000 have been vaccinated with any licensed pandemic vaccine in the EU (the latter may be a considerable under-estimate). No safety signals have so far emerged from spontaneous reports of vaccine exposure in pregnancy. For example, the UK data indicate no excess risk of spontaneous abortion, intra-uterine death or stillbirth in vaccinated pregnant women.

In addition the 9000-subject PASS study enrolled 275 women known to be pregnant at the time of vaccination of whom 18%, 40% and 40% were in the first, second or third trimester, respectively. Although it will be a few more months before the outcomes of all pregnancies are reported it is currently reassuring that 111/119 have resulted in a healthy infant with 7 spontaneous abortions and one elective termination (with no apparent congenital defect) accounting for the remainder.

Although pregnancy was an exclusion criterion for participation in sponsored studies there had been 11 pregnancies reported in the Q-PAN-H1N1 clinical programme up to 17 January 2010. Of three pregnancy outcomes currently known there were two elective and one spontaneous abortion without any apparent congenital defect.

These data and analyses do not raise any specific concerns at present given the known background rates of spontaneous abortion and still birth.

#### **Data from PASS study**

As described above (see SOB 061), the study did not identify safety issues and there was no evidence of case clusters of potential concern amongst the MedDRA terms report from the latest preliminary submission covering 8811 subjects.

The CHMP further considered that the large amount of available post marketing data in connection with clinical study data in the paediatric population would provide sufficient information to support the position that the safety database in this population can be considered acceptable.

In the context of the RMP and as for any other vaccine the safety profile will continue to be monitored.

#### **Risk Management Plan Update**

The MAH provided version 4 of the RMP for Pandemrix in November 2009. The assessment of the RMP raised the points below:

The risk of coring should be included as a potential risk.

Post-authorisation sections of the safety specification should be updated with exposure information and a summary of any important adverse event data.

Milestones for reporting results should be provided for the Swedish cohort study and PGRx GBS monitoring study.

An English study protocol should be provided for the German Embryotoxicology Pharmacovigilance Centre study.

Version 5 of the RMP for Pandemrix dated 5 February 2010 has addressed all these points.

The RMP that was submitted in February 2010 has been updated in order to include the change to a 6-monthly PSUR cycle and provision of monthly data in forms of tables/line listings and the details of the Pharmacovigilance SOBs that are now being changed into FUMs (SOBs 060, 061, 062). The MAH submitted this RMP version 6 on 30 June 2010.

### **III.3 Product Information**

#### **III.3.1. Summary of Product Characteristics, Labelling and Package Leaflet**

The MAH's proposals for the SmPC and PL reflect completion of all the clinical variations listed in III.1.

It should be noted that:

##### **1. Change in indication and additional statement in section 4.4**

##### **4.1 Prophylaxis of influenza caused by A(H1N1) 2009 virus (see section 4.4).**

Pandemrix should be used in accordance with Official Guidance.

##### **4.4 The vaccine can only be expected to protect against influenza caused by A/California/7/2009**

The initial approval for Pandemrix limited its use to WHO Phase 6 in accordance with CHMP guidance and taking into account the paucity of data available on safety and immunogenicity at the time. Since September 2009 Pandemrix has been administered to many millions of people across a wide age range, providing a substantial safety database. In addition, data have been provided from clinical studies in persons aged from 6 months to over 80 years and the SmPC has been amended on several occasions to reflect these data.

While no further pandemic waves are predicted within the EU the usual feature of pandemics is that the influenza A strain and its drift variants persist as the most common cause of seasonal influenza up to the time of the next pandemic. For this reason it has already been recommended that suitable strains should be used in the manufacture of the trivalent seasonal influenza vaccines for the winter 2010-2011.

Uptake of pandemic influenza vaccine has been variable across EU countries thus far. A substantial proportion of the population, including those in groups at risk of complications from influenza, may still be unprotected by means of naturally-acquired or vaccine-induced immunity.

Since all relevant non clinical and clinical data within the context of Article 21 of Commission Regulation (EC) 1234/2007, have been submitted as part of either FUMs/SOBs or variations, such provision is therefore considered adequately fulfilled and the exceptional and temporary nature of the variations to the terms of the Marketing Authorisation for Pandemrix as initially granted in September 2009, not anymore required. Consequently the indication can now be read as stated above.

Thus the proposed change in indication allows further use of vaccine within the EU regardless of whether or not the current WHO pandemic phase is maintained or altered. The addition to section 4.4

is intended to underline the difference between Pandemrix and the forthcoming trivalent seasonal vaccines.

## **2. Updates to other sections**

Several other sections of the Pandemrix SmPC were updated during this procedure so that the emphasis is now placed on the substantial data obtained with the vaccine itself, allowing the H5N1 data to be removed and replaced. In addition, the changes involve removal of the cautionary statements regarding the limits of data from clinical studies in various age groups and replacement with references to section 5.1 where the limited numbers formally assessed for safety and immunogenicity during clinical studies are clearly displayed.

### **III.3.2. General Conditions for the Marketing Authorisation**

#### **B. CONDITIONS OF THE MARKETING AUTHORISATION**

##### **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

##### **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The MAH shall agree with Member States to measures facilitating the identification and traceability of the A/H1N1 vaccine administered to each patient, in order to minimise medication errors and aid patients and health care professionals to report adverse reactions. This may include the provision by the MAH of stickers with invented name and batch number with each pack of the vaccine.

The MAH shall agree with Member States on mechanisms allowing patients and health care professionals to have continuous access to updated information regarding Pandemrix.

The MAH shall agree with Member States on the provision of a targeted communication to healthcare professionals which should address the following:

The correct way to prepare the vaccine prior to administration.

Adverse events to be prioritised for reporting, i.e. fatal and life-threatening adverse reactions, unexpected severe adverse reactions, adverse events of special interest (AESI).

The minimal data elements to be transmitted in individual case safety reports in order to facilitate the evaluation and the identification of the vaccine administered to each subject, including the invented name, the vaccine manufacturer and the batch number.

If a specific notification system has been put in place, how to report adverse reactions.

## **OTHER CONDITIONS**

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

### **Pharmacovigilance system**

The MAH must ensure that the system of pharmacovigilance, as described in version 3.6 (dated 09 November 2009) presented in Module 1.8.1 of the marketing authorisation application, is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

The MAH will submit periodic safety update reports on a 6-month cycle, unless the CHMP decides otherwise.

### **Risk Management Plan**

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version RMPv2 (dated September 2009) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

### **Follow-up Measures**

The MAH agrees to undertake the following Post-Authorisation Commitments requested by the CHMP and commits to submit the data listed below within the specified timeframe.

<b>Area</b>	<b>Description</b>	<b>Due Date</b>
Clinical	The MAH commits to provide the results of the clinical effectiveness study.	already provided on 16 June 2010
Pharmacovigilance	The MAH commits to provide the results of the prospective cohort safety study in at least 9,000 patients in different age groups, including immunocompromised subjects, in accordance with the protocol submitted with the Risk management Plan. Observed-to-Expected analyses will be performed.	Final reports will be provided in November 2010, April 2011, and January 2012

Pharmacovigilance	The MAH commits to provide the results of a study in a pregnancy registry	Data analysis and report of outcomes for A (H1N1)v vaccination in pregnancy April - June 2011
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Area	Description	Due Date
Pharmacovigilance PSUR	<p>The MAH commits to provide monthly update in the form of tables/line listings as outlined below:</p> <ul style="list-style-type: none"> <li>- a frequency table of all spontaneous cases per country, stratified according to type of report (medically confirmed or non-medically confirmed) and seriousness, for the period covered by the report and cumulatively</li> <li>- a frequency table of all spontaneous adverse reactions by SOC, High Level Term (HLT) and Preferred Term (PT), stratified according to type of report (medically confirmed or non-medically confirmed) and including the number of fatal reports, for the period covered by the report and cumulatively.</li> <li>-an ICH E2c line listing of Adverse events of special interest (as defined in the CHMP Recommendations [EMA/359381/2009]) reported from countries world wide.</li> </ul> <p>The MAH commits to provide 6-monthly PSURs, with the first PSUR covering 6 months from the data lock point of the last sPSUR (6th sPSUR).</p>	<p>Next PSUR due date (28 November 2010, the PSUR will cover 29 March through to 29 September)</p>

Final Study Reports and follow-up report submissions

<b>Clinical Studies</b>	<b>Clinical study report - study timepoint</b>	<b>Submission date</b>
Study H1N1-021	Clinical Study Report, Month 6	06 August 2010
	Annex Report, Month 12	February 2011
Study H1N1-007	Clinical Study Report, Month 6	01 October 2010
	Annex Report, Month 12	April 2011
Study H1N1-008	Clinical Study Report, Month 6	01 October 2010
	Annex Report, Month 12	April 2011
Study H1N1-009	Clinical Study Report, Day 42	30 April 2010
	Annex Report, Month 12	April 2011
Study H1N1-010	Clinical Study Report, Month 7	Early November 2010
	Annex Report, Month 12	April 2011
Study H1N1-017	Clinical Study Report, Month 12	May 2011
Study H1N1-018	Clinical Study Report, Month 12	April 2011
Study H1N1-020	Clinical Study Report, Month 12	April 2011
Study H1N1-022	Clinical Study Report, Month 6	10 September 2010
	Annex Report, Month 12	April 2011
Study H1N1-023	Clinical Study Report, Month 7	Early November 2010
	Annex Report, Month 12	May 2011

\* Clinical Study Report for study D-Pan-H1N1-012 (2-5 months) has been removed since only 8 subjects were enrolled and not valuable data will be generated (see also section on SOB/059 above)

A number of FUMs have been submitted since the revision of the opinion of the switch of MA status. Assessment of these FUMs is ongoing and Annex II reflects the FUMs that are still pending. FUMs submitted since the revision of the opinion include:

D-Pan H1N1-020 (Fluarix effect, > 60 yrs) - post dose 2 abridged report (immunogenicity data, solicited and unsolicited symptoms, SAEs)

Study D-Pan H1N1-009 (paediatric data for 6-36 months age) - post dose 2 abridged report (first full dose data on cohort of 50 subjects; immunogenicity, solicited and unsolicited symptoms, SAEs)

Study D-Pan H1N1-010 (paediatric data for 3-17 yrs) - post dose 2 abridged report (immunogenicity, solicited and unsolicited symptoms, SAEs Study D-Pan H1N1-023 (paediatric data 3-17 yrs, half dose antigen + half dose adjuvant: 1.9 µg + AS03).

#### **IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT IN THE CONTEXT OF THE NEW INDICATION AND CHANGE TO FULL MA**

The overall benefit/risk of Pandemrix in the prophylaxis of influenza caused by A(H1N1) 2009 virus (see section 4.4) is considered favourable.

The CHMP considers that there is no major concern.

##### **Benefit profile**

In contrast to the immunogenicity data obtained with the mock-up vaccine Pandemrix H5N1/AS03 all the experience with Pandemrix (H1N1)v has demonstrated the likelihood that a single dose (full adult or half adult according to age group) may be sufficient. The longer-term follow-up of subjects in study 008 will eventually provide data from adults that may demonstrate whether there is any possible benefit in the longer term of two vs. one priming doses.

Currently there are very limited neutralising antibody data available although titres generated in contracted laboratories from subsets of sera have generally demonstrated robust immune responses to a first dose. In addition, taking into account the considerations regarding the validity of applying the CHMP criteria used to assess HI responses to seasonal influenza vaccines to responses to a pandemic strain, the CHMP considered that the SmPC should not preclude the administration of a second dose of Pandemrix (H1N1)v in any age group for which a dose regimen is provided in the current SmPC. Nevertheless, due to the reactogenicity of a second dose in children, the SmPC carries details of fever rates and rates of other reactions to the second compared to the first doses in children by age subgroups.

##### **Risk profile**

In view of safety, following six months of marketing experience with Pandemrix (H1N1)v the substantial data indicate that the safety profile is acceptable. This body of evidence is thought to reflect vaccination of at least 30 million individuals across the EU. The majority of ADRs reported relate to the signs and symptoms of the listed and expected side effects of Pandemrix. Since approval of the strain change variation febrile convulsion was included as a possible side effect in the SmPC and anaphylaxis was moved to the section of ADRs actually reported with the vaccine. The available data do not indicate any excess risk of anaphylaxis. There is currently no evidence of any risk of vaccination during pregnancy.

Afebrile seizures in known epileptics and Guillain Barre Syndrome (GBS) remain under very close review. There is currently no suggestion of an excess risk of GBS of the magnitude observed with swine influenza vaccines in the 1970s. An ad hoc expert group was convened in March 2010 to consider ways to more formally evaluate the GBS signal. At present, these are unconfirmed safety signals. The available data from the PASS study indicate that some local and general solicited

symptoms may have occurred at a higher frequency than was observed in clinical studies. However, rates of Grade 3 symptoms and those requiring medical attention have been very low.

Re-assessment of B/R profile in the context of the revised indication and switch to a full MA

The Specific Obligations concerning the evaluation of safety and effectiveness as introduced during the initial authorisation and the variation in order to introduce the pandemic (H1N1)v strain have been sufficiently addressed to conclude on the maintenance of a positive risk/benefit for the use of Pandemrix in the current Community epidemiological situation.

The CHMP considered that the MAH has now provided sufficient comprehensive safety and efficacy data such that grounds to maintain the MA under exceptional circumstances are no longer applicable. In addition specific procedures concerning safety are no longer required in context Article 14 (8) of Regulation (EC) No 726/2004 as these can be achieved in context of the conventional Risk Management Plan.

Furthermore the safety data presented in additional studies submitted since the initial approval and in the sPSURs have been satisfactory. Overall a favourable benefit-risk assessment continues to be applicable to use in the population for which Pandemrix is indicated.

## Conclusion

Based on the review of the data submitted by the MAH as evidence of compliance with the specific obligations and having re-assessed the benefit/risk profile of the medicinal product further to the provision of comprehensive data on efficacy and safety such that the grounds set out in Part II.6 of Annex I of Directive 2001/83/EC are no longer applying to maintain the MA under Article 14(8) of Regulation (EC) No 726/2004, the CHMP recommends to change the status of the marketing authorisation outside the scope of Art. 14(8) of Regulation (EC) No /2004 for Pandemrix (Influenza vaccine (H1N1)v (surface antigen, inactivated, adjuvanted)).

The CHMP in making this recommendation has taken into consideration that comprehensive information on clinical safety and efficacy have now been provided and that specific procedures in particular concerning safety are no longer required such that the grounds to maintain the licence under exceptional circumstances are no longer considered to apply.

In addition the CHMP, having reviewed all relevant clinical data within the context of Article 21 of Commission Regulation (EC) No 1234/2008, considers that adequate information has been supplied to recommend a change of the indication outside of the restricted clinical setting of a pandemic and that the temporary and exceptional nature concerning the approval of the variation introducing the strain change no longer applies.

As a result of the above the recommended indication now reads as follows: Prophylaxis of influenza caused by A(H1N1) 2009 virus (see section 4.4 of SmPC). Pandemrix should be used in accordance with Official Guidance thus allowing for further use of vaccine within the EU regardless of whether or not the current WHO pandemic phase is maintained or altered during the coming year. (see section III.3 for more details).