EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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: Focetria
International non-proprietary name/Common name: Influenza vaccine (surface antigen, inactivated, adjuvanted) a/california/7/2009 (H1N1)v like strain (x-181)

AUTHORISED UNDER EXCEPTIONAL CIRCUMSTANCES
EMEA/H/C/710/SW/24

Indication summary (as last approved):	Prophylaxis of pandemic influenza in an officially declared pandemic situation
Marketing Authorisation Holder:	Novartis Vaccines and Diagnostics S.r.l.

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

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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 Focetria (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 should read as follows: Prophylaxis of influenza caused by A(H1N1) 2009 virus (see section 4.4 of the SmPC). Focetria 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

Focetria is an inactivated monovalent H1N1v influenza vaccine, adjuvanted with MF59C.1. The CHMP recommended the granting of the marketing authorisation for Focetria 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 2 Specific Obligations (SOBs) and 16 Follow-up Measures (FUMs) listed in the Letter of Undertaking dated 22 February 2007.

The initial indication for use of Focetria 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."

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-05) to change the pandemic vaccine strain composition from A/Vietnam/1194/2004 (H5N1) to A/California/7/2009 (H1N1)v like strain (X-179A) recommendation for the approval of the PU-05 was adopted by the CHMP on 24 September 2009.

The revised indication for use of Focetria was as follows:

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

Therefore, the variation(s) to the terms of the marketing authorisation for the medicinal product "Focetria - A/Viet Nam/1194/2004 (H5N1) virus surface inactivated antigen" should exceptionally be accepted, on a temporary basis, in accordance with Article 8 of Regulation (EC) No 1085/2003, and Decision C(2007)2025 should be amended accordingly.

The strain change recommendation was made from A(H5N1) to (H1N1)v on the basis of the MAH undertaking 6 Specific Obligations (SOBs) which cover for the 2 SOBs previously adopted, as well as 5 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 seasonal influenza and other vaccines but both were considered necessary from a public health perspective in the unprecedented circumstances of the Pandemic.

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 the revised Letter of Undertaking dated 22 April 2010.
- The current Product Information showing all the changes that have been implemented thus far.

This re-assessment of the benefit risk of Focetria 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 6 Specific Obligations (SOBs). These have been addressed as follows (please see the Appendix and the individual assessment reports for full details).

III.1.1. SOB

Clinical SOBs

The clinical SOBs concerned reporting of safety and immunogenicity data from clinical studies with the pandemic vaccine and 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 at the time of the strain change variation.

In most of the cases the data were provided as variations in order to insert the relevant information in the SmPC.

SOB 027

SOB27 concerned studies V111_02 and V111_04 performed in adult and elderly subjects.

Study V111_02 was a randomised, single-blind, dose-ranging study in adult and elderly subjects. The objectives of the study were to identify the preferred vaccine formulation, dosage and schedule of the egg-derived (H1N1)v monovalent vaccine in healthy adults.

On 12 October 2009 the MAH submitted variation II/11 to update sections 4.2, 4.4, 4.8 and 5.1 of the summary of product characteristics to reflect immunogenicity and safety results of study V111_02. Based on the post-dose 1 data, inclusion of advice regarding the possibility of using a single dose in adults aged 18-60 years was deemed appropriate in the SPC. Further clarity regarding the posology recommendation was made in the scope of variation II 15 submitted on 17 November 2009 with a commission decision on the 27 November 2009. Considerations were made on the possibility of using a single half dose, however CHMP agreed that this posology was not appropriate. Please refer to the AR of variation II/11 that has already been issued for details of the data provided.

This variation was approved on 11 November 2009 by the European Commission.

Study V111_04 was designed to assess the immunogenicity and safety of 2 injections of 7.5 µg HA A/H1N1 2009 in adult and elderly subjects previously exposed to 2009/10 northern hemisphere (NH) formulation of seasonal influenza vaccine and in those not yet vaccinated.

On 13 November 2009 the MAH submitted variation II/013 to update section 4.5 of the summary of product characteristics regarding administration of Focetria with seasonal influenza vaccine based on results post-dose 1 obtained from study V111_04.

The results in adults aged 18 to 60 years indicated that Focetria may be administered concomitantly with seasonal influenza vaccine. These results also indicated that previous administration of adjuvanted or non-adjuvanted seasonal vaccines and Focetria did not interfere with the immune

response to Focetria. Please refer to the AR of variation II/13 that has already been issued for details of the data provided.

This variation was approved on 27 November 2009 by the European Commission.

On 29 January 2010 the MAH submitted variation II/20 to update sections 4.2, 4.5, 4.8 and 5.1 of the SPC to include safety and immunogenicity information following assessment of the H1N1 data available with Focetria in children, adults and the elderly.

This update was based on further results obtained from studies V111_02, V111_04 and V111_03 (please refer to SOB 028). Regarding study V111_02, the post-dose 2 data did not allow to modify the previous recommendations of administering one full dose in adults aged 18-60 and two full doses above 60. With regards to study V111_04, all data presented, which included post-dose 2 results, supported the previous observation that Focetria may be co-administered with non adjuvanted seasonal influenza vaccine.

The assessment of study V111_03 with a view to establishing any impact on posology were made in parallel in the context of variation II/19 (please refer to SOB 028). However available safety and immunogenicity data from study V111_03 was included in the SmPC within the scope of II 20 in order to make it available to prescribers.

Please refer to the AR of variation II/20 that has already been issued for details of the data provided.

Following variation II/20 which received a positive opinion on 17 February 2010, SOB 027 was considered fulfilled.

SOB 028

SOB 028 concerns study V111_03, a randomized, single-blind, dose-ranging study in infants, children and adolescents from 6 months to 17 years of age aimed to evaluate immunogenicity, safety and tolerability of different formulations of adjuvanted and non-adjuvanted egg-derived, inactivated (H1N1)v monovalent influenza virus vaccine in healthy subjects.

On 17 November 2009 the MAH submitted variation II/015 to update sections 4.2, 4.8 and 5.1 of the summary of product characteristics to reflect the available immunogenicity and safety clinical trial data available in children and adolescents, as requested by the CHMP. Variation II/015 was approved on 27 November 2009 by the European Commission.

Preliminary results from study V111_03 showed that the CHMP criteria were met, and in particular results were considered relevant for children and adolescents aged 9-17 years. The data presented were in favour of the use of a single full dose of Focetria in subjects aged 9-17 years. This was in line with the results seen in adults.

On 16 December 2010 the MAH submitted variation II/18 to update section 4.2, 4.8 and 5.1 of the summary of product characteristics regarding administration of Focetria to children of 3 to 8 years of age based on results from study V111_03. Data at day 22 and day 43 in cohort 1 (children and adolescents aged 9-17 years of age) and cohort 2 (children aged 3-8 years of age) were provided within this variation. The results obtained were considered relevant for an update of the posology related to children aged 3-8 years. The data presented were reassuring regarding the effect of a single full dose of Focetria in subjects aged 3-8 years. However, preliminary data indicated that there was a further immune response to a second dose. Please refer to the AR of variation II/18 that has already been issued for details of the data provided.

This variation was approved on 23 December 2009 by the European Commission.

On the 8 January 2010, the MAH submitted variation II/19 to update section 4.2, 4.8 and 5.1 of the summary of product characteristics regarding administration of Focetria to children of 12 to 35 months of age based on results from cohort 3 (1 to 3 years) and cohort 4 (6 to 11 months) of study V111_03.

Variation II/19 was reviewed in parallel to this procedure. In light of the availability of all the relevant data on the different age groups concerning immunogenicity and safety the CHMP made considerations on the whole data set in order to give a posology recommendation in children. The CHMP reviewed the data on children aged 3-8 years in light of the availability of the full data set in this age group and the overall data set in children. In this age group all CHMP criteria were met after a single dose of the adjuvanted vaccine. A further immune response to a second dose, in terms of GMT values, was observed. The clinical significance of this increase is not known at present. It is the CHMP opinion that overall data on immunogenicity support the use of a single dose of the adjuvanted vaccine in the age-stratum 3-8 years, in line with the current posology recommended for influenza seasonal vaccines. The relevant SmPC sections have been updated to reflect the CHMP opinion. Of note the posology for 3-8 years old is in line with that of the existing posology for 9-17 year olds.

In the 12 to 35 months age stratum immunogenicity results for the adjuvanted vaccine met all three CHMP criteria as early as 3 weeks after the first vaccination, achieving the HI seroprotection threshold of 1:40.

Final data related to the effect of the second dose in the age group 12 to 35 months have been assessed as well as overall immunogenicity data in children aged 6-11 months. Immunogenicity provided by one full dose of Focetria has been shown to induce a satisfactory immune response, achieving the HI seroprotection threshold of 1:40. A further dose has been shown to augment the immune response. This information has been mentioned in the relative sections of the SmPC and the PL has been updated accordingly.

Please refer to the AR of variation II/19 for details of the data provided.

All critical clinical data post dose 1 and post dose 2 are now submitted from study V111_03. Long term ancillary data are expected in August 2011. Therefore this obligation is considered sufficiently fulfilled and it can be perused in context of a FUM.

SOB 029

SOB 29 concerns the commitment to submit the protocol and provide the results of the clinical effectiveness studies carried out in accordance with the study protocols published by ECDC. PASS studies covering both safety and efficacy are being carried out to address this commitment (see also SOB 030). In fulfilment of this SOB the protocol has been submitted and agreed upon by CHMP and the study is ongoing. An interim report is expected by August 2010.

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 suggests that vaccination campaigns have been effective. The CHMP considers therefore that any remaining 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 030

SOB 30 concerns the commitment to submit the protocol and the results of a 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.

PASS studies are being carried out to address these commitments (SOB 029 and SOB 030). Study V111_05 is entitled "Observational cohort study for the evaluation of safety and effectiveness of adjuvanted, egg-derived inactivated novel swine origin A/H1N1 subunit pandemic influenza vaccine after the onset of the pandemic".

In fulfilment of this SOB the MAH has submitted the protocol which has been reviewed by CHMP and the study is ongoing.

The MAH has recently submitted data on 8274 enrolled subjects in this study collected through active surveillance in the 3-week post-vaccination. Additional data from study V111_09, a prospective observational study of safety and occurrence of influenza-like illness following administration of Focetria, has also been provided including a report on 1000 enrolled patients.

The enrolled paediatric population in these studies is less than expected due to immunisation policy at Member state level, in particular for the study V111_05. Approximately 1100 out of more than 4000 planned children have been studied in study V111_05 and 10 out of 1000 enrolled subjects in V111_09 study are children.

In general, the adverse events patterns observed in these studies are similar and can be considered in line with the post marketing surveillance data. Overall, no particular new safety concern has been identified from these interim reports from the two PASS studies.

Taking into consideration that the protocol has been submitted and agreed by CHMP and 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 this 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 future development based on the actual epidemiological development of the 2009 H1N1 pandemic and having considered the totality of the adult data as described above the CHMP considers that any remaining data can be collected in the context of a FUM.

SOB 031

This SOB represents a commitment to implement a pregnancy registry. 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 a first report and more recently a second interim report on 1324 women enrolled.

According to the latest weekly update (9 April 2010) 1534 subjects were enrolled in the registry. Among 1478 recorded subjects (666 vaccinated and 787 unvaccinated) 51 SAE reports were received (28 vaccinated and 23 were unvaccinated). The study is ongoing, although the accrual rate seems to be slowed down when compared with the accrual plan proposed by the MAH. Overall from

pharmacovigilance monitoring and data collected so far from the registries no safety signal has been detected.

Overall taking into consideration the protocol has been submitted and agreed by CHMP and the study is ongoing and also taking into consideration that that these data are not normally requested, the CHMP considered that these data can be pursued as a FUM.

SOB 032
This SOB represents the commitment to establish the mechanism 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 analyze the different databases as well as the protocols of the studies have been reviewed and considered acceptable by the CHMP.

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 Focetria 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 see the documents in the Appendix for a full listing of completed, ongoing and unfulfilled FUMs. Please consult the separate assessment reports that have already been issued for full details.

Quality FUMs

Follow-up measure fulfilled

FUM 3 (H5N1 Mock-up vaccine)
The MAH committed to complete the stability study for the H5N1 strain to support the stability claim for the Monovalent Pooled Harvest of a shelf-life of 1 year at 2-8° C, and to report any confirmed out-of-specification results or unexpected trends. Furthermore, the results of the SDS-PAGE - obtained at 0 and 12 months were to be provided. On 18 October 2007 the CHMP concluded that the MAH had adequately addressed the request and that a shelf-life of one year at 2-8° C for the Monovalent Pooled Harvest was acceptable.

FUM 4 (H5N1 Mock-up vaccine)
The MAH was requested to provide data on compatibility of the components of the vials with the final product. On 30 June 2008, the MAH provided the requested information. The compatibility of the components of the vial with the final product was discussed by the MAH adequately and the stability data provided (18 months for vials and 24 months for syringes) confirmed the good stability of the product.

FUM 5 (H5N1 Mock-up vaccine)
The MAH committed to develop a suitable procedure and specification for polydispersity to further assure the consistency of the Drug Product. The MAH position that the current procedures and the specifications for the Drug Product were sufficient and complied with International Standards was well documented and endorsed by the CHMP on 24 April 2008.

FUM 6 (H5N1 Mock-up vaccine)
The MAH committed to complete the stability study for the H5N1 strain to support the proposed shelf life of 1 year at 2-8° C for the Drug Product in pre-filled syringes and in mono- and multi-dose vials to report any confirmed out-of-specification results or unexpected trends. Based on the data provided by the MAH, the CHMP concluded on 24 April 2008 that a shelf-life of 18 months at 2-8° C may be assigned to the H5N1 Drug Product in pre-filled syringes and that a shelf life of 12 months at 2-8° C may be assigned to the influenza Drug Product in mono-dose vials and in multi-dose vials. The currently approved shelf life for pre-filled syringes and multi-dose vials is 12 months at 2-8° C.

FUM 26 (H5N1 Mock-up vaccine)
The MAH committed to provide the final report concerning the re-validation of ability of formaldehyde to inactivate avian leucosis virus. Based on the data provided by the MAH, the CHMP considered that this FUM was fulfilled on 20 November 2008.

FUM 33
The MAH was requested to provide the revalidation report on the SRD assay performed with the new reference antigen (X-179). On 19 November 2009 CHMP concluded that the data provided indicated that the SRD test was validated for the evaluation of X-179 (H1N1) influenza vaccine antigen content.

FUM 41
The MAH committed to provide additional data on in-use stability of the MDV. The results provided regarding the "worst case scenario", where most of the doses were withdrawn within the first 8 hours, indicated that the product was within specifications after 24 hours. Thus, the FUM 41 has been satisfactorily addressed by the MAH and the commitment from variation II-16 to support the 24h in-use shelf life was considered fulfilled by the CHMP in April.

<u>Follow-up measure partially fulfilled/ongoing evaluation</u>

FUM 7 (H5N1 Mock-up vaccine)
The MAH committed to present proposals for alternative and faster assays for testing extraneous agents on influenza seed virus. A request for a delay to submit this FUM was submitted on 16 March 2009 and based on the justification provided the request was considered acceptable by the CHMP. The submission is planned for December 2010..

FUM 8 (H5N1 Mock-up vaccine)
The MAH committed to present the results of the HPLC assay for the determination of the HA content. Based on results, the HPLC assay developed by the MAH was considered suitable for the determination of the HA content of seasonal influenza vaccines. However, the MAH was requested to provide further

information regarding the validation of the method. The responses of the MAH are awaited for December 2010.

As FUM 7 and 8 are related to the H5N1 mock-up vaccine, they are considered more relevant for Foclivia, Novartis Influenza vaccine H5N1 (surface antigen, inactivated, adjuvanted), and are no more requested for Focetria (H1N1)v.

Follow-up measures currently under evaluation

FUM 43

The MAH committed to provide stability data, both accelerated and at 2-8°c for X-179 derived vaccines and for X-181 derived vaccines. Data on accelerated and real time stability, both on X-179 and X-181 derived vaccines are been provided and evaluated as they became available.

Non-clinical FUMs

Follow-up measure fulfilled

All non-clinical FUMs have been fulfilled by the MAH.

FUM 34

Following variation II/05 and in order to confirm the immunogenicity of Focetria vaccine formulations, the MAH was asked to present the final report of the Focetria mouse study n° BB-0910. This study performed in mice aimed at confirming the immunogenicity of vaccine formulation containing A(H1N1)v antigens made using the Focetria process, with and without MF59 adjuvant, when administered using different regimens. The CHMP was of the view that the report provided confirmed the immunogenicity of Focetria formulation in mice even after a single dose.

FUM 38

The MAH submitted an update of the non clinical sections with data related to the dossier of the monovalent influenza vaccine Aflunov (surface antigen, inactivated, influenza vaccine adjuvanted with MF59C.1). The non-clinical package for Focetria was found to be in accordance with the relevant pertinent guidelines.

Clinical FUMs

Follow-up measures fulfilled

FUM 9 (H5N1 Mock-up vaccine)

The MAH committed to perform a study evaluating Cell-Mediated Immunity (CMI) response to H5N1 vaccine and to submit a final report.

The MAH submitted a clinical study report for the trial V87P2, including a 6-month follow-up after the booster vaccination. Study V87P2 was a phase II, randomised, controlled, observer-blind, single-centre study with the aim to evaluate CMI, immunogenicity and safety of two injections, administered 3 weeks apart, and a booster injection 6 months after the second injection, of two Fluad- H5N1 influenza vaccines containing 7.5 µg or 15 µg of H5N1 influenza antigen and of a non-adjuvanted influenza vaccine containing 15 µg of H5N1 influenza antigen, in adults.

The primary aim was to investigate CMI after six months from the priming and following the booster dose. Results showed a strong CMI response for the adjuvanted formulation and enhancement of the response following the booster dose.

Observations on safety were considered of limited value due to the small number of study subjects. Nevertheless, these observations contributed to the total amount of information to be evaluated in RMP and PSURs.

FUM 9 was considered fulfilled by the CHMP.

FUM 10 (H5N1 Mock-up vaccine)

The MAH committed to review and re-code the data available from clinical studies used for development of Focetria using the same MedDRA coding system on adverse events.

The MAH provided the list of AEs previously coded with the COSTART Thesaurus recoded by MedDRA for all concerned studies on 30 June 2008. The MAH also provided comments on the frequencies of events. After reviewing the data, the CHMP considered the FUM fulfilled.

FUM 13 (H5N1 Mock-up vaccine)

The MAH committed to provide the final study report and to assess the persistency of antibody titres among vaccines at 6 and 12 months from vaccination with Focetria H5N1 (study V87P1). Study V87P1 was a phase II, randomized, controlled, observer-blind, multi-centre study that aimed to compare the two initial formulations of vaccines including different amount of H5N1 antigen in adults and elderly subjects.

Following the submission of the results of this study, the CHMP concluded that a substantial immune response and a satisfactory safety profile of the pandemic vaccine Focetria H5N1 were confirmed.

Follow-up measures partially fulfilled

FUM 12 (H5N1 Mock-up vaccine)

The MAH committed to provide a detailed plan indicating the general strategy and the clinical trials to be performed in children and risk groups with Focetria H5N1. The MAH provided information on the strategy for clinical trials in children and risk group. Further information related to the studies protocols was then requested. However, taking into consideration the WHO Phase 6 declaration in June 2009, other studies have been performed in children with the current (H1N1)v vaccine.

FUM 14 (H5N1 Mock-up vaccine)

The MAH committed to explore alternative and/or condensed vaccination schedules with Focetria H5N1. In order to comply with this commitment, the MAH submitted the protocol of study V87P12, a phase III, randomized, open-label, single-centre study to evaluate the safety and immunogenicity of a FLUAD-H5N1 influenza vaccine in adult subjects using four different vaccination schedules. The protocol was considered in line with the CHMP guidelines. The results of the study have been submitted and are under assessment.

As FUM 12 and 14 are related to the H5N1 mock-up vaccine, they are considered more relevant for Foclivia, Novartis Influenza vaccine H5N1 (surface antigen, inactivated, adjuvanted), and are no more requested for Focetria (H1N1)v.

FUM 36

The MAH committed to submit the dates for which the final H1N1 clinical study reports will be available. The timelines provided by the MAH were discussed by the CHMP and further information was requested on 18 February 2010.

FUM 40

Following variation II/11, the MAH committed to provide the validation reports for HI and MN for H1N1v.

The MAH provided validation reports for both testes which fulfil several validation criteria. However, there were some other parameters and issues which should also have been taken into consideration for future serological determinations and a Request for Supplementary Information was addressed to the MAH on 18 March 2010. The MAH was requested to provide additional data as regards the 2009 pandemic H1N1 strain. Since the influenza vaccines for the season 2010-2011 will include the 2009 pandemic H1N1v strain, and the MAH will perform a small clinical trial to assess immunogenicity of the new formulation, serological assays should be re-assessed on that occasion, at the latest. The MAH was also requested to include the re-testing of seronegative children sera from Focetria clinical trials. Provided the requested information, the FUM 40 can be considered fulfilled.

Follow-up measure currently under evaluation

FUM 35

Following variation II/05, the MAH was requested to provide the final study report of study V87P13 on data collected with the Focetria H5N1. This study was a phase III, randomized, controlled, observer-blind, multicentre study to evaluate the safety, tolerability and immunogenicity of two doses of a Fluad-H5N1 in adult and elderly subjects. Furthermore, the MAH committed to provide a completed pooled analysis of safety data for the H5N1 mock up vaccine.

Overall, 3481 subjects (3089 non-elderly adults and 392 elderly adults) were enrolled in the four Fluad-H5N1 studies included in the pooled Fluad-H5N1 safety analysis. The pooled Fluad-H5N1 safety set consisted of 3011 non-elderly adults aged 18 to 60 years and 387 elderly adults aged >60 years.

Data provided in this analysis confirmed the well known safety profile for both 7.5 µg Fluad-H5N1 and 15 µg Fluad-H5N1 groups. No new concern was raised from this analysis. The Final Report including data at six months follow up and responses to Rapporteur's comments is awaited by 30 April 2010.

Pharmacovigilance FUMs

Follow-up measures fulfilled

FUM 15

The MAH committed to update the risk management plan submitted with the MAA of Focetria taking into account the CHMP recommendations for the Pharmacovigilance plan for Pandemic Influenza vaccines.

FUM 16

The MAH committed to present the pandemic vaccine monitoring board in the first PSUR. This monitoring board was presented by the MAH and considered acceptable by the CHMP.

FUM 17

Whenever the core CHMP recommendation for the pandemic influenza vaccines would be updated the MAH committed to update the pharmacovigilance plan.

sPSUR

At the time of the MA, the MAH committed to provide sPSUR on a monthly basis. Six monthly sPSURs have already been submitted by the MAH. The SmPC was updated within variation II/18. The SmPC updating related to II/20 variation is currently under EC approval.

The marketing Authorisation holder will continue to submit periodic safety update reports on a 6-month cycle. The MAH has also committed to submit on a monthly basis a frequency table of all spontaneous cases, a frequency table of all spontaneous adverse reactions and a line listing of Adverse events of special interest.

Follow-up measures partially fulfilled

FUM 37
Following variation II/05, the MAH committed to provide an update of the RMP. An updated version (1.7) of the RMP has been submitted on 13 April 2010 and is under evaluation.

III.1.3. Variations

Please see the documents in the Appendix for a full listing of completed and ongoing variations.

Variations already completed are as follows:

H5N1 Mock-up vaccine

Quality Variation: II/0001

On 23 July 2009 the CHMP adopted a positive opinion to allow changes to the Drug Substance and Drug Product already approved for the MF59-adjuvanted seasonal influenza vaccine (Fluad), with the aim to increase flexibility in production and logistic. These changes included additional buildings at the Siena site, improvements of operative flows of the Bulk Monovalent Pools, rationalization of the quality tests on the Drug Product and addition of the second manufacturing line for MF59C.1 at the Marburg site (variation I/0001). This variation received a positive Commission Decision on 12 August 2008.

Focetria (H1N1)v

Quality variations: II/0006, II/0007, II/0008, II/0016, II/0014

On 15 October 2009 the CHMP adopted a positive opinion to allow changes in two of the analytical methods used for control of critical steps of the adjuvant MF-59C (variation I/0006), this variation received a positive Commission Decision on 20 October 2009.

On 15 October 2009 the CHMP adopted a positive opinion to allow the addition of a new manufacturing line (Line 3) for the manufacture of the adjuvant MF-59, in the Novartis Marburg facility in Germany (variation I/0007), this variation received a positive Commission Decision on 20 October 2009.

On 22 October 2009 the CHMP adopted a positive opinion to allow to change the reassortant derived from A/Calirfornia/7/2009 (H1N1)v strain from X-179A to X-181 for the manufacturing process of the vaccine substance (variation I/0008), this variation received a positive Commission Decision on 11 October 2009.

On 17 December 2009 the CHMP adopted a positive opinion to allow the change of the product information to include the shelf life of a multidose vial after first dose withdrawal (variation I/0016), this variation received a positive Commission Decision on 23 December 2009.

On 18 February 2010 the CHMP adopted a positive opinion to allow the implementation of the new "rapid sterility test" to be used as the primary sterility test for drug substance and drug product testing (release and in-process) at Novartis Rosia (variation I/0014), this variation received a positive Commission Decision on 02 March 2010.

Clinical variations: II/0009, II/00010, II/00011, II/00013, II/00015

Three variations received a positive opinion on 22 October 2009 and a positive Commission Decision on 11 November 2009. The data comprised safety and immunogenicity data from various clinical studies.

Variation **II/0009** – Update of section 5.1 of the SmPC with H5N1 data on persistence of antibodies in elderly subjects

Variation **II/0010** – Update of section 4.8 of the summary of product characteristics to include the latest H5N1 safety information available as requested by the CHMP.

Variation **II/0011** - Update of sections 4.2, 4.4, 4.8 and 5.1 of the summary of product characteristics to reflect immunogenicity and safety results of a H1N1 study in adults as requested by the CHMP. (study V111_02)

Two variations (variation II/0013 and II/0015) received a positive opinion on 11 November 2009 and a positive Commission Decision on 27 November 2009.

Variation **II/0013** - Update of section 4.5 of the summary of product characteristics regarding administration of Focetria with seasonal influenza vaccine based on results in adults as requested by the CHMP. (Study V111_04)

Variation **II/0015** - Update of sections 4.2, 4.8 and 5.1 of the summary of product characteristics to reflect the currently immunogenicity and safety clinical trial data available in children and adolescents, as requested by the CHMP (study V111_03)

One variation received a positive opinion on 17 December 2009 and a positive Commission Decision on 23 December 2009.

Variation **II/0018** – Update of section 4.2, 4.8 and 5.1 of the SPC regarding administration of Focetria to children of 3 to 8 years of age based on results of a study in children as requested by the CHMP (study V111_03). Section 4.8 was updated to include Adverse Drug Reactions reported in Post Marketing Surveillance for Focetria further to the assessment of sPSUR 1 and 2.

The ongoing variations at the time of requesting this switch to full MA are as follows:

One variation received a positive opinion on 17 February 2010. Variation **II/0020** concerned the update of sections 4.2, 4.5, 4.8 and 5.1 of the SmPC to include safety and immunogenicity information following assessment of the H1N1 data available with Focetria in children, adults and the elderly (Studies V111_02, V111_03 and V111_04). The change of the age cut-off for adult population from 18-60 to 18-65 was not approved by the CHMP. However, the addition of a statement regarding co-administration with trivalent seasonal vaccine non adjuvanted in adult population (18-60 years of age) was approved.

Variation **II/0019** related to the update of sections 4.2, 4.8 and 5.1 of the summary of product characteristics regarding administration of Focetria to children of 12 to 35 months of age as a one dosing schedule based on results of a study in children (Study V111_03). A request for supplementary

information was adopted at the February CHMP. Following the assessment of the responses by the MAH, a final recommendation was adopted at the April CHMP.

Variation **II/0017** to update the Detailed Description of the Pharmacovigilance System to version 11.1 was considered approvable by the CHMP and received a positive opinion on 18 March 2010.

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

III.2.1. Quality

There are still some on-going commitments that the MAH needs to address and, in view of their specific nature, the proposed timelines are considered to be reasonable. Data on accelerated and real time stability, both on X-179 and X-181 derived vaccines has been provided and is under assessment.

The relevant quality data generated as part of the H5N1 mock-up marketing authorisation were considered supportive for the H1N1v pandemic strain version of Focetria. Quality data required specifically for the strain change (X-179A vaccine virus) were provided on 14 August and 4 September 2009 and satisfactorily demonstrated the quality of the vaccine. An additional strain change from H1N1 X-179A to H1N1 X-181 vaccine virus was submitted on 14 October 2009. In this case the documentation presented by the Applicant also supported satisfactorily the variation.

Since the pandemic strain change, an additional adjuvant manufacturing line has been introduced at Marburg site. Changes to the manufacturing process have also been done regarding a) two analytical methods for the control of MF59C.1 adjuvant; b) the switch from the classic sterility test to a new, rapid version.

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

Regarding non-clinical data provided to support the dossier of Focetria, the applicant compiled data emerging from non-clinical studies with the adjuvant alone and in combination with different antigens performed over the last 15 years. The non-clinical data supporting the approval of Fluad and the MF59 non-clinical data package represented the principal support to the (H1N1)v Focetria application.

The challenge testing in the ferret showed that the formulation of vaccine containing either 7.5 µg or 15 µg of A/NIBRG-14 (H5N1) antigen per dose is both immunogenic and efficacious in reducing the viral load and viral shedding. The various disease markers indicated the protective effects of mock-up vaccination with the formulation of the vaccine used.

Immunogenicity studies in young and old mice with H1N1v formulation showed that immunisation with both adjuvanted candidate vaccine and non-adjuvanted vaccine, elicited a dose-related antigen-specific antibody response, regardless of the serologic status at baseline. The presence of MF59 adjuvant resulted in a more immunogenic product, in both young and old mice.

Non-clinical safety data have revealed no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, embryo-foetal and postnatal toxicity (up to the end of the lactation period).

The MAH has responded to all non-clinical FUMs. There are no outstanding issues on non-clinical matter.

III.2.3. Clinical

Clinical SOBs and FUMs are given in section III.1 as well as in the Appendix of the report.

III.2.3.1 Clinical Pharmacology and Clinical Efficacy

The assessment of the expected safety and potential protective efficacy of Focetria (H1N1)v was initially based on the data obtained with the mock-up containing influenza A(H5N1) strains. Clinical trials on protective efficacy for the mock-up vaccine were not possible as the strain causing the current pandemic as well as the subjects with a corresponding infection were not present at that time. Therefore a detailed characterisation of the immunological response has been performed. Immunogenicity of the mock-up strain A/Vietnam/1194/2004 (H5N1) was determined in 458 subjects (297 adults; 161 elderly). For 7.5 µg and 15 µg HA group, seroconversion rate and seroconversion factor in the adult and the elderly population were in compliance with CHMP requirements. In both age groups, the GMTs induced by Focetria (7.5 µg HA) were non-inferior to the GMTs induced by the vaccine containing 15 µg HA. Seroprotection rates in adults and elderly calculated using the SRH assay met the set CHMP requirements. These results were supported also by the microneutralisation assay.

A clinical trial submitted post core-dossier authorisation was conducted with a H5N1 vaccine combined with MF59C.1 adjuvant in 471 children from 6 months to 17 years of age. The results indicated a substantiated immune response.

No further data on clinical efficacy regarding H5N1 strain are awaited.

The SOBs concerning data from sponsored clinical studies with the monovalent (H1N1)v 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.

Data coming from post-approval studies support the use of a single dose of the adjuvanted H1N1 vaccine in subjects from 9 to 60 years regardless of their serostatus at baseline and seasonal influenza vaccination history. In elderly (> 60 yrs), all three CHMP criteria required for pandemic vaccines differently from the seasonal requirements, were met only after the second dose. These data are currently reflected in the relevant posology section of the SmPC.

In children aged 3-8 years all CHMP criteria were met after a single dose of the adjuvanted vaccine. A further immune response to a second dose, in terms of GMT values, was observed. The clinical significance of this increase is not known at present. It is the CHMP opinion that overall data on immunogenicity support the use of a single dose of the adjuvanted vaccine in the age-stratum 3-8 years, in line with the current posology recommended for influenza seasonal vaccines. The relevant SmPC sections have been updated to reflect the CHMP opinion.

In the 12 to 35 months age stratum immunogenicity results for the adjuvanted vaccine met all three CHMP criteria as early as 3 weeks after the first vaccination, achieving the HI seroprotection threshold of 1:40.

Final data related to the effect of the second dose in the age group 12 to 35 months have been recently assessed as well as overall immunogenicity data in children aged 6-11 months.

Immunogenicity provided by one full dose of Focetria has been shown to induce a satisfactory immune response, achieving the HI seroprotection threshold of 1:40. A further dose has been shown to augment the immune response. This information has been mentioned in the relative sections of the SmPC.

When studied, immunogenicity of the non-adjuvanted vaccine was found to be inferior in comparison to the adjuvanted vaccine.

Administration of the half dose in children induced a good immune response; however this response was systematically lower than the full dose.

In summary, immunogenicity data with Focetria (H1N1)v covering subjects from 6 months to > 60 years old are currently available. However, no data are available in subjects under 6 months of age. This is in accordance with the decision of the PDCO, which modified the standard PIP requesting waivers for this age group.

III.2.3.2 Clinical Safety

SOBs and FUMs related to pharmacovigilance and risk management are listed in section III.1 and in the Appendix of the report.

Safety data from ongoing clinical studies

Clinical trials with H5N1 strain

The database on safety on Focetria H5N1 has been increased with the submitted results of study V87P13 (H5N1 Safety Study): "A Phase III, Randomized, Controlled, Observer-Blind, Multicentre Study to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of a Monovalent A/H5N1 Influenza Vaccine Adjuvanted with MF59 (Fluad-H5N1), in Adult and Elderly Subjects". The pooled analysis of safety of the entire safety database did not show reason for concern or previously unexpected events.

Focetria was initially approved based on the information collected in trials conducted with the (H5N1) strain. However, data generated with Focetria including a H5N1 strain cannot entirely predict the safety profile of Focetria including the influenza A(H1N1)v strain since there remains a possibility of ADRs associated with the antigenicity of a specific influenza strain.

Clinical trials with H1N1 strain

Study V111_03 in children

Safety data after first and second dose of Focetria H1N1 (both half and full dose) in children and adolescents 6 months -17 years of age suggested a comparable safety profile with that reported for the H5N1 mock-up vaccine formulation. The use of half dose of vaccine was associated with a slight reduction of local reactogenicity in subjects of any age. Reactogenicity after the second dose was generally lower compared to the first dose.

The data provided in children 12 to 35 months confirmed that vaccine, at any dose of antigen and adjuvant, is generally safe. This was also observed in children aged 6 -11 months. No death and no related severe AE were reported.

Study V111_04 in adults and the elderly

Results in adults aged 18 to 60 years after first and second dose indicated that Focetria may be administered concomitantly with seasonal influenza vaccine. Results in adults also indicated that previous administration of adjuvanted or non-adjuvanted seasonal vaccines and Focetria did not interfere with the immune response to Focetria. The product information was updated to reflect these findings.

Study V111_02 in adults and the elderly subjects

The safety observations were in line with the profile of Focetria. A reduced local reactogenicity but comparable systemic reactogenicity was observed in adults receiving the half dose. In elderly the differences were even lower. The CHMP considered there was no relevant advantage in terms of safety with the 0.25 ml vs. 0.5 ml.

All the available data on safety from clinical studies and routine use suggest that there is no undue risk associated with use of Focetria. These data have been assessed and reflected in the SmPC by means of a series of variations as considered necessary.

Based on the current available data also coming from post-marketing surveillance, the Focetria safety profile could be considered similar to the adjuvanted seasonal influenza vaccine.

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

Post-Marketing Experience

According to the MAH about 85 million doses were distributed worldwide from the launch to 22 February 2010 (data lock point of the fifth sPSUR). The MAH provided an exposure estimation of more than 7 million vaccinated subjects in the EEA. This was in line with the estimation of at least 6.5 million vaccinated subjects in the EEA which was published by the European Medicines Agency within the last Pandemic Pharmacovigilance weekly report (24 March 2010). Age and risk group-stratified exposure data are not currently available.

As of 22 February 2010 the safety database of the MAH contains 4,721 spontaneous reports, of which 781 were serious (33 fatal). As of 14 March 2010, a total of 2,947 reports had been received by Eudravigilance.

The majority of ADR reports related to the post-vaccination signs and symptoms were reported from clinical studies and already listed in the SmPC. These have included headache, nausea, dizziness, fever, myalgia/arthralgia, fatigue, malaise, chills, sweating, allergic ADRs (including dyspnoea and generalised rashes), 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.

Moreover, from post-marketing surveillance further ADRs have been identified and have been included in the SPC: lymphadenopathy, palpitation, tachycardia, asthenia, muscular weakness, pain in the extremity, Cough and diarrhoea. In the fifth sPSUR the AEs vertigo has been found to occur frequently and the MAH has been requested to submit to include it in the SmPC.

Fatal cases

Overall, 33 fatal cases have been reported in the fifth sPSUR, 3 of which were non-medically confirmed. In 7 cases the death were assessed as unexplained and the MAH has been requested to follow up the unexplained deaths.

The majority of deaths, mainly occurred in elderly, seemed to be likely related to severe underlying conditions. There was no clear evidence suggesting that the vaccine contributed to the subjects' death.

Other AE under close monitoring

During the review of the sPSURs the MAH was asked to provide reviews of cases of disturbance in consciousness, cardiac disorders (e.g. arrhythmia), eye disorders, infections (e.g. herpes virus, pneumonia), convulsions, peripheral neuropathies, arthritis, peripheral oedema and pregnancy-related outcomes. These analyses have revealed no specific safety signals or cause for concern.

Adverse Events of special interest

The main issues concerned cases of anaphylaxis and GBS.

With regards to anaphylaxis the MAH was requested to provide a review of all anaphylaxis case (as SMQ) and to analyse them according the standard case definitions and guidelines by Brighton Collaboration Anaphylaxis Working Group. Up to the data lock point of 22 February 2010, a total of 245 cases were retrieved using the narrow SMQs "Anaphylactic reaction" and "Angioedema". Furthermore, 43 cases were found to meet BC's anaphylaxis case definitions based on evidence available in the narratives. Of these anaphylaxis cases, 9 met the definition at BC level 1; 27 at BC level 2 and 7 at BC level 3.

In addition, 12 cases were found meeting the definition at BC level 4 being reported anaphylaxis with insufficient evidence to meet the case definition. In other words, these cases were "unevaluable" using BC based on evidence in the narratives. 190 cases (~78% of the total) were found not to be anaphylaxis (at level 5).

Regarding GBS, cumulatively 21 cases of GBS were included in the sixth sPSUR. Following an analysis performed by the assessors a signal (although weak) of an increased number of observed cases after vaccination with Focetria has emerged. Similar signals has been noted with (H1N1)v vaccines other than Focetria in the context of observed to expected (O/E) analyses performed in Germany, Sweden and United Kingdom.

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.

Age-specific or risk group-specific events

No particular safety concerns have been identified in the paediatric population. Surveillance data in children are in line with safety data coming from ongoing H1N1 clinical trials and from PASS study.

Safety in Pregnancy

No particular safety concerns have been identified for vaccinated pregnant women. It is estimated that 92,000 pregnant women have been vaccinated.

Until the 5th February 2010, 14 cases of intrauterine foetal deaths (after 20 weeks of pregnancy) and 10 cases of miscarriage (or spontaneous abortions, before 20 weeks of pregnancy) have been reported to the MAH. Incidence of intrauterine foetal death has been estimated as 2.6 - 9.1 per 1000 live birth (from 2004 European Perinatal Health Report by Euro-Peristat project in collaboration with SCPE, EUROCAT & EURONEOSTAT). Considering those rates, the number of vaccinated pregnant women who would coincidently experience an intrauterine foetal death would be between 192 and 764.

Incidence of miscarriage in the general population is about 4% (lowest risk in the population) and around 10 to 12% according to published data from the literature (Lancet 19 December 2009; 374: 2115–22). In the 11th Pandemic Pharmacovigilance weekly update on 17th of February, the incidence of miscarriage among pregnancies is estimated between 12 and 15% (even more when including early pregnancy losses).

Therefore, whatever the considered rate, the 14 cases of intrauterine death and the 10 cases of miscarriage reported are very small numbers. In conclusion, it is reasonable to affirm that there is not a sign of intrauterine death or miscarriage associated with the use of Focetria.

The overall B/R of Focetria in pregnant women is, at present, considered positive.

However the MAH is committed to continuously monitor the AEs in pregnant women.

Overall, the data available did not reveal any specific concern regarding the safety profile of Focetria (H1N1)v which was found similar to that of seasonal vaccines. Furthermore, the current content of the safety database for this product has been largely substantiated with data from routine use and clinical studies.

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 latest evaluated RMP version (1.6) can be considered adequate. An updated version (1.7) of the RMP is currently under evaluation. This version includes an update of the RMP linked to FUM 29, FUM 30 and FUM 31. This latest version submitted will require an update in the PSUR cycle.

III.3 Product Information

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

The current SPC and PL are appended in the Appendix to this report. These versions reflect completion of all the clinical variations listed in III.1 and in the Appendix.

Further changes are anticipated during the completion of variations II/0019.

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). Focetria 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 Focetria 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 FOCETRIA has been administered to 7 million 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 > 60 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 variation(s), such provision is therefore considered adequately fulfilled and the exceptional and temporary nature of the variations to the terms of the Marketing Authorisation for Focetria 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 during the coming year. The addition to section 4.4 is intended to underline the difference between Focetria and the forthcoming trivalent seasonal vaccines.

Updates to other sections

It is proposed that several other sections of the FOCETRIA SmPC should be updated during this procedure so that the emphasis is now placed on the substantial data obtained with Focetria, 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. 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 Focetria.
- 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 11.1 (dated 05 January 2010) 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.

PSUR submission

The marketing Authorisation holder 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 RMP 1.6 (dated 29 January 2010) 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 (FUMs)

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the continuous reassessment of the benefit/risk profile.

Area	**Description**	**Due Date**
Clinical FUM 28	Study V111_03: The MAH commits to provide the final report	End August 2011
Clinical FUM 29	The MAH commits to provide the results of the clinical effectiveness study	Results of study to be provided within two weeks of availability. Interim report on effectiveness by August 2010 Final report on effectiveness: nine months after the end of the pandemic declared by WHO.

Pharmacovigilance FUM 30	The MAH will submit the results of a 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 study report by end August 2010:
Pharmacovigilance FUM 31	The MAH commits to report the results of a study in a pregnancy registry.	Upon issuance of Commission Decision
Pharmacovigilance FUM 37	The next updated RMP	By 21 November 2010
Clinical FUM 36.1	Clinical trials timelines – The MAH commits to report the results	V111_02 and V111_03: Interim and final results will be submitted in accordance with the protocol. Final study report for V111_02 by end July 2011 and final study report for V111_03 by August 2011
Clinical FUM 40.1	The MAH commits to provide additional data as listed in the AR for FUM 40 at the time of the submission of the clinical data for the annual update variation of seasonal influenza vaccines 2010-11.	By September 2010
Quality FUM 43	The applicant should provide all stability data	By end July 2010
Pharmacovigilance	The MAH commit to submit on a monthly basis safety report including: - 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 - 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. - a line listing of Adverse events of special interest (as defined in the CHMP Recommendations [EMEA/359381/2009])	Submission to continue on a monthly basis until otherwise informed by the CHMP.

	reported from countries of the European Economic Area. Furthermore, the MAH commits to submit 6 monthly PSURs for the medicinal product authorised by this decision until further review by CHMP.	 Next PSUR submission date: 21 November 2010

A number of FUMS have been submitted since the revision of the opinion of the switch of MA status. Annexe II is updated to reflect the FUMs that are still pending. FUMS submitted since the revision of the opinion include: First monthly pharmacovigilance report on 21 May 2010; RMP update on 7 May 2010; Clinical FUM 35 (final study report) on 30 April 2010; pharmacovigilance FUM 31 3rd interim report on 30/04/2010, fourth interim report on 29/05/2010; Pharmacovigilance FUM 30, Interim and final results submitted in accordance with the protocol by end May 2010.

IV OVERALL CONCLUSIONS AND BENEFIT/RISK ASSESSMENT IN THE CONTEXT OF THE NEW INDICATION AND CHANGE TO FULL MARKETING AUTHORISATION

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

The CHMP considered that from a quality perspective there are no outstanding concerns regarding conversion to a full MA.

The non-clinical data package provided by the applicant at the time of the initial application for a marketing authorization for the mock-up vaccine and data provided afterwards are considered to be satisfactory to support the conversion to a full MA for Focetria (H1N1)v. There are no outstanding concerns from a non-clinical point of view.

Since the approval of the strain change variation, the clinical data package for Focetria has been substantiated with data coming from post-approval studies and marketing experience.

Benefit profile

Data coming from post-approval studies support the use of a single dose of the adjuvanted H1N1 vaccine in subjects from 9 to 60 years regardless of their serostatus at baseline and seasonal influenza vaccination history. The analyses restricted to the immune response developed by subjects seronegative at the baseline showed that the CHMP criteria were not met in the elderly and therefore the use of a second dose was recommended. These data are currently reflected in the relevant posology section of the SmPC

In children aged 3-8 years all CHMP criteria were met after a single dose of the adjuvanted vaccine. It is the CHMP opinion that overall data on immunogenicity support the use of a single dose of the adjuvanted vaccine in the age-stratum 3-8 years, in line with the current posology recommended for influenza seasonal vaccines. The relevant SmPC sections has been updated to reflect the CHMP opinion (please refer to the above section on variation II/19)

In the 12 to 35 months age stratum immunogenicity results for the adjuvanted vaccine met all three CHMP criteria as early as 3 weeks after the first vaccination, achieving the HI seroprotection threshold of 1:40. Final data related to the effect of the second dose in the age group 12 to 35 months have been recently assessed as well as overall immunogenicity data in children aged 6-11 months. Immunogenicity provided by one full dose of Focetria has been shown to induce a satisfactory immune response, achieving the HI seroprotection threshold of 1:40. A further dose has been shown to

augment the immune response. This information will be mentioned in the relative sections of the SmPC (please refer to the above section on variation II/19).

Risk profile

All the available data on safety from clinical studies and routine use suggested that there was no undue risk associated with use of Focetria. Following more than four months of marketing experience with Focetria (H1N1), reflected in the latest reviewed sPSUR, the overall safety data indicated that the safety profile was acceptable. The majority of ADRs reported related to the signs and symptoms of the listed and expected side effects. Focetria safety profile could be considered similar to the adjuvanted seasonal influenza vaccine. Via the comprehensive RMP the CHMP will continue to closely review safety of Focetria including Guillain-Barre syndrome (GBS), safety in pregnant women, and response in immunocompromised subjects.

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 Focetria in the current Community epidemiological situation.

The CHMP consider 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.

In addition 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 FOCETRIA 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), 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 Focetria (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 should read as follows: Prophylaxis of influenza caused by A(H1N1) 2009 virus (see section 4.4 of SmPC). Focetria 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).