European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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CHMP Recommendations for the Core Risk Management Plan for Influenza Vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context

Adopted by CHMP in January 2008

1. Introduction

In January 2007, the CHMP adopted the *Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context* (EMEA/CHMP/VWP/263449/2006). This guideline includes a chapter related to post-approval commitments and risk management planning. It recommends that the following information should be provided in the Risk Management Plan (RMP) at the time of authorisation or in updates to the RMP:

- plans to assess antibody persistence, cross-reactivity and cross-protection to new circulating strains
- plans for assessment of response to booster doses in cohorts of vaccinees from each age and risk group for which an indication has been granted
- plans to collect information, whenever the opportunity arises
  - from observational studies to expand the safety and the immunogenicity database
  - on breakthrough cases if there is exposure of vaccinees to circulating influenza strains with a potential to cause a pandemic
  - in populations which have been studied to a lesser extent in the pre-authorisation clinical trials
- plans to compare immunogenicity and effectiveness of the pandemic vaccine between any previously vaccinated and unvaccinated cohorts, in countries where the strategy has been to prime with pre-pandemic vaccine(s) and to administer a dose of the pandemic vaccine as soon as it becomes available (provided the pandemic vaccine can be given early enough to potentially impact on infection rates, complication rates and/or death rates).

It is acknowledged that monitoring the effectiveness and safety of the chosen strategy needs careful planning in conjunction with public health authorities.

This document aims to provide further guidance on post-marketing studies and risk management planning for these vaccines. These recommendations have been developed following discussions between representatives and experts from CHMP, the Vaccine Working Party (VWP), the Pharmacovigilance Working Party (PhVWP), EMEA, ECDC, DGSANCO and the European Vaccine Manufacturers association (EVM). They provide the elements of a "core Risk Management Plan" to be included in the authorisation application of all avian influenza vaccines. Additional activities may be proposed by applicants in agreement with the (co-)Rapporteurs and the CHMP.

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2. Legal framework

The Guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005) provides guidance on how Marketing Authorisation Applicants (MAAs) should meet the requirements for a description of a risk management system that they will introduce for a new medicinal product.

The Guideline on Influenza Vaccines Prepared from Viruses with the potential to cause a pandemic and intended for use outside of the Core Dossier Context (Doc. Ref. EMEA/CHMP/VWP/263499/2006) provides guidance on post-approval commitments, risk management plans an other post-authorisation activities related to these vaccines.

According to Article 24(3) of Regulation (EC) No 726/2004, the timing/periodicity of submission of periodic safety update reports (PSURs) may be specified as a condition of the marketing authorisation, and may deviate from the periodicity specified in that article. The format of the PSUR can also be specified in the conditions of the marketing authorisation. These conditions should be laid down in Annex II of the Opinion and justified in public health terms.

The content of the Individual Case Safety Reports is described in the draft Volume 9A of the Rules Governing Medicinal Products in the European Union. Section I.4.1. (Requirements for Expedited Reporting of Individual Case Safety Reports) requires that all available clinical information relevant to the evaluation of the reaction should be provided.

3. General recommendations

The EU Risk Management Plan (EU-RMP) should differentiate between activities proposed to be carried out when the vaccine is used before a pandemic and activities proposed to be carried out if the vaccine is used after the announcement of a pandemic.

If an activity proposed in the EU-RMP is used in order to collect data on several different outcomes, like a prospective cohort study, it should be described in the EU-RMP and an overview of the study protocol should be presented in Table 2.4 of the EU-RMP Template, with a specification of all outcomes to be studied.

The EU-RMP is an evolving document. It should be updated whenever new significant information arises, e.g. a change in the profile of adverse events of interest, results of studies or change in benefit-risk profile. Updates should be provided in Periodic Safety Update reports and as per the milestones presented in the EU-RMP.

4. Immunogenicity

The above-mentioned guideline on influenza vaccines for use outside of the core dossier context identifies the following aspects to be followed after initial authorisation: assessment of antibody persistence (study of antibody kinetics), induction of immunity to other influenza strains (cross-reactivity and cross-protection studies) and investigations in special populations.

The following points need to be taken into consideration when studying antibody kinetics:

- The RMP should propose the frequency for testing and a selection of tests to be performed at specific timepoints. It may not be necessary to perform a full characterisation of immune response each time. However, Hemagglutination Inhibition (HI) titres should be measured at each timepoint for each vaccine formulation. As no international validated and harmonised assays exist, MAHs should use the assay with which they are familiar.
  In the pre-pandemic situation, testing of cell-mediated immunity and microneutralisation assays should also be performed on a subset of the sera. The level of cell-mediated immunity and microneutralisation testing should be included in the RMP. The importance of using standardised methods is stressed.

- The frequency of testing is likely to be higher at the time of initial use of the vaccine. It is also linked to the company's assessment of the need to change the vaccine strain in their pre-pandemic vaccine.
- Retained serum samples should be kept under appropriate storage conditions allowing for testing with novel methods.

The RMP should provide a strategy to investigate cross-reactivity of the pre-pandemic vaccine when a new drift variant is announced. The applicant should identify what and when new variants will be tested. The MAHs should also consider the possibility of cross-protection testing in animals. As soon as the pandemic strain is available to the manufacturer, the company is expected to rapidly evaluate the cross-reactivity between the vaccine strain and the pandemic strain, in order to guide the decisions of the public health authorities on the widespread use of the (stockpiled) vaccines. This investigation might be based on a limited dataset, using the assays with which the company is most familiar.

Ability to boost should also be addressed in the RMP. It is important that the latest timepoint for boosting with the homologous strain vaccine is identified. The RMP should also describe a protocol to investigate the priming effect of the vaccine to a heterologous strain if this becomes available. The latter is especially important if the manufacturers are or become aware of public health authorities' intentions to perform priming with a pre-pandemic vaccine and boosting with a pandemic vaccine when this becomes available.

5. Effectiveness

Protocols to study effectiveness will be product-specific and depend on the intended use of the vaccine by the Public Health Authorities. Some Public Health Authorities may develop and conduct effectiveness studies for vaccines used in their country. Collaboration should therefore be in place in order to avoid duplication of efforts and agree to exchange data needed for public health actions. The setting up of vaccine registries and/or analysis for specified endpoints should be discussed by manufacturers and public health authorities, e.g. as part of any advanced purchase or purchase contracts. The potential for incorporating efficacy endpoints in the planned safety cohort studies should be explored and discussed.

In the pre-pandemic phase, vaccinees that come in contact with an avian influenza virus (e.g. poultry workers, cullers, veterinarians) could be followed-up, and a list of symptoms to be investigated should be predefined. Seroconversion should be tested in these population groups. As it will be difficult to know if seroconversion was from vaccine or from exposure, pre-exposure titres should also be considered if available.

The true effectiveness of the vaccine can only be studied during exposure of the population to the pandemic virus (i.e during the influenza pandemic). The method(s) to be used will depend on the vaccination strategy used by countries. If for example a fraction of the population is vaccinated, non-exposed comparison groups will be available for cohort studies.

The protocols of effectiveness studies, when developed and agreed with public health authorities, should be included in the RMP updates. If national authorities have established plans to monitor vaccine effectiveness for specific pandemic vaccines, those plans, if publicly available, should also be incorporated in the RMP.

6. Safety

6.1. General principles

Prepandemic period

- In contrast to the mock-up pandemic influenza vaccines, the safety database for avian influenza vaccines at the time of authorisation will be important, as minimum requirements for the safety database at the time of authorisation are 3,000 adults from 18 to 60 years, 30 to 300 for specified

age groups (e.g. infants, adults, adolescents, adults over 60 years of age, and 300 for specified risk groups (e.g. immune compromised individuals, chronically ill patients). Additional data will need to be collected on groups of subjects not studied or inadequately studied before authorisation. In addition, some of the vaccines will use new adjuvants, and this may also have safety implications. The prepandemic period will therefore provide the opportunity to proactively investigate the vaccine's safety profile.

- Routine pharmacovigilance activities should be performed. Adverse events of special interest (AESI) notified through the spontaneous reporting system should be closely followed and discussed in Periodic Safety Update Reports (see sections 6.2 and 6.4). In the prepandemic period, there should be time to collect and report additional safety information relevant to population groups not studied or inadequately studied in pre-authorisation studies, and to investigate signals detected through the spontaneous reporting system or other means (section 6.5).

- The immunisation strategy during this period will be defined by national competent authorities (NCAs) and may vary across Europe, e.g. population coverage or choice of target groups for immunization such as poultry workers or health care workers. It is therefore important that vaccine manufacturers contact the relevant health authorities in each Member State in order to identify how the vaccine will be used, as this pattern of use will influence how pharmacovigilance should be performed. Collaborations should be established at an early stage to ensure adequate identification and follow-up of subjects first immunised and/or to obtain access to data collected by national authorities in the context of their vaccination programmes. In countries where whole population coverage is decided, it is possible that a large number of adverse events will be reported to the MAH within a short period of time. Specific pharmacovigilance activities are recommended for this situation.

- In order to avoid duplication of efforts (provided an adequate sample size is achieved and adequate collaboration is obtained), vaccine manufacturers will not be requested to repeat the same studies (including those initiated by NCAs) in all countries where their vaccine is marketed. Similarly, vaccine manufacturers should collaborate with international institutions (e.g. ECDC) to establish an inventory of specific activities evaluating the post-marketing safety of avian influenza vaccines.

- At the time of authorisation, the Applicants should include the following in the EU-RMP:
  - Published information or plans regarding the vaccination strategy in countries where the vaccine is likely to be administered; this information is to be revised in subsequent updates of the EU-RMP
  - Contacts made with Competent Authorities for the surveillance of vaccine safety and sharing of information, and/or plans for such discussions.

Pandemic period

During the pandemic period, the same conditions as those described in the document on CHMP recommendations for pandemic influenza vaccines will apply,[1] i.e. probable disruption of the routine pharmacovigilance system and need to concentrate resources on timely and effective monitoring of the safety profile of influenza vaccines. In principle, the same recommendations as for the surveillance of the pandemic influenza vaccines will therefore apply, and protocols for additional pharmacovigilance activities should be presented in the EU-RMP. Any deviation from the pandemic influenza vaccines core pharmacovigilance plan should be presented in the EU-RMP and agreed by the CHMP.

6.2. Spontaneous reporting system

Prepandemic period

Procedures described in the routine pharmacovigilance system should be applied. In addition, the following adverse events of special interest (AESI) notified by health care professionals are considered important and should be specially monitored: neuritis, convulsions, severe allergic

[1] http://www.emea.europa.eu/pdfs/human/pandemicinfluenza/3270607en.pdf

reactions, (myelo)encephalitis, thrombocytopenia, vasculitis, Guillain-Barré Syndrome, Bell's palsy, and other autoimmune disease (e.g. multiple sclerosis, optic neuritis, diabetes mellitus). For each of these adverse events, standard case definitions from Brighton Collaboration should be used if available (http://brightoncollaboration.org/internet/en/index/definition_guidelines/document_download.html). If such a definition does not exist, the definition that is used should be provided. These AESI, as well as specific safety aspects of adjuvents should be presented and discussed as identified, risks, potential risks or elements of missing information in the Safety Specification (according to the information available).
Background data for these AESI are important for the interpretation of incidence rates and should normally be presented in the epidemiology section of the Safety Specification. Only relevant data in terms of scientific evidence and relevance to the populations concerned should be selected and presented.

Cases of syncope should be evaluated to distinguish severe adverse reactions from other immediate events such as vaso-vagal syncope.

In the case of priming of a large fraction of the population with the avian influenza vaccine, it is recommended that NCA(s) and MAH(s) collaborate to actively encourage health care professionals to prioritise the reporting of the following adverse events:

- Fatal or life-threatening adverse reactions
- Serious unexpected adverse reactions
- The AESI listed above.

It is also recommended that health care professionals are encouraged to include in their reports a minimum set of criteria which are needed to properly evaluate the suspected adverse events/reports (see Annex 1). The elements of the reporting form proposed in Annex 1 should be used for that purpose. Pending agreement between the NCA(s) and MAH(s), an ad-hoc reporting system (e.g. electronic reporting) should be put in place for the duration of the vaccination campaign, and the MAH reporting of fatal and life-threatening reactions and of AESI could be expedited by the MAH to NCA(s) should be expedited preferably within 7 days. Any such arrangements agreed by the NCA and MAH prior to authorisation should be presented in the submitted RMP.

Pandemic period

i) General principle

The probable disruption of the postal system and limited time available to health care professionals require the development or strengthening of alternative reporting channels by health care professionals, such as fax, telephone or electronic transmission.Postal reporting should be discouraged in order to avoid loss of data at a critical time due to postal back-logs.

Consideration should be given to national systems already in place for reporting adverse drug reactions to vaccines. Discussions with regulatory authorities should be initiated if additional channels are developed, in order to ensure compatibility of reporting systems.Functioning of these additional reporting channels should be tested before the pandemic period.

MAHs should be prepared to use an alternative system of ADR reporting in case of disruption of the main system.

ii) Spontaneous reporting from health care professionals

It is recommended that MAHs and National Competent Authorities actively encourage health care professionals to include in their reports a minimum set of criteria in order that a proper evaluation of the suspected adverse events/reactions may be carried out. A standardised reporting form is proposed (see Annex 1). Preferably, each MAH should develop an electronic format of the report form. In order to minimise data entry errors, consideration should be given to pre-fill the form with the tradename of the product authorised and marketed in the EU.

It is recommended that MAHs and NCAs actively encourage health care professionals to prioritise reports of fatal or life-threatening adverse reactions, serious unexpected adverse reactions and the following AESI: neuritis, convulsion, severe allergic reactions, encephalitis, thrombocytopenia, vasculitis, Guillain-Barré syndrome and Bell's palsy.

For each of these AESI, the MAH and NCAs should use standard case definitions from Brighton Collaboration if available. Where such a definition does not exist, the definition that is used should be provided.

iii) Spontaneous reporting from patients

In the pandemic situation, patients' reports should be accepted and followed-up, as appropriate, as they may be a source of a large amount of information. However, experience regarding their usefulness is limited, especially for influenza vaccines.

Only medically confirmed patients' reports should be expedited by MAHs to regulatory authorities. These reports should be compiled for aggregated data summaries and signal detection. Reports from patients should be analysed and reported separately to regulatory authorities.

iv) Expedited reporting from MAHs to regulatory authorities

Expedited reporting should follow the timelines defined in the Volume 9A of the Rules Governing Medicinal Products in the European Union, but it is recommended that reporting of fatal, life-threatening reactions and AESI should take place as soon as possible, preferably within 7 days.

6.3. Signal detection

It is likely that potential safety issues will emerge when avian influenza vaccines are used in a large population, and it is important for MAHs to identify them. The method(s) used for the detection of new safety signals should be described in the pharmacovigilance plan.

In case of widespread use of the avian influenza vaccine, it is expected that a large number of spontaneous reports will be received by MAHs; it is important that focus is directed on important new safety signals based on a comparative quantitative method.

The following aspects should be considered for signal detection applied to avian influenza vaccines:

- In order to facilitate implementation of data queries, vaccines should be coded (and recoded if needed) by product name if they have been reported by substance.

- In databases of spontaneous reports (where incidence rates cannot be computed), the method of choice for signal detection is a measure of disproportionality or its 95% confidence interval, such as the PRR, the IC or the EBGM. In a pandemic situation where large numbers of report are expected in a relatively short period of time, no difference between these three measures is expected, and the MAHs should use the method with which they are familiar. If none of these methods are used, an alternative procedure should be discussed.
- Insofar as reporting of a limited number of AESI is prioritised, the interpretation of disproportionality analyses may be difficult, and care will need to be taken in perhaps modifying the expected counts to take the prioritization into account. Adapting the background profile by exclusion of some events will be difficult; such exclusion should be decided and programmed in advance although the profile of adverse events reported during a pandemic will be difficult to predict. Observed to expected analyses might therefore require access to datasets in order to estimate the expected number of predefined AESIs.

- Stratification is an important element of signal detection for vaccines. Stratification by age is required in order to differentiate between children and adults and between young adults and elderly; age strata should be aligned with those proposed for the reporting of aggregated data

(section 5.4). Stratification by country/region may be needed in a second-step analysis in order to take account of clustering of reports in one country or different uses of vaccines across countries/regions. Stratification by seriousness is also recommended if possible, seriousness being defined not only by classical criteria (hospitalisation or prolongation of hospitalisation, fatality, life-threatening condition, etc…) but also, whenever this is possible, by medical relevance.
Irrespective of the stratification variables being used, it is essential to look at the data in each stratum to explore how signals behave across categories.

- It is recommended that comparisons are made with all vaccine-related reports available in the database together with a stratification by age in order to avoid detecting age-related reactions. There is currently no evidence that a comparison with seasonal influenza vaccines only would provide additional information. A comparison with all medicinal products may also be performed but may result in the detection of mild and expected reactions linked to the vaccination (e.g. local reactions).
- Background rates are necessary for the interpretation of signals detected for potentially important and rare events. They are also useful for putting results of observational studies into context and can be used in observed to expected analyses. It is a prerequisite to identify relevant background rates as early as possible (and regularly update this information) in order to perform such analyses without delay when a signal is detected.

- Spontaneous reports of lack of efficacy should be included in the routine monitoring.

6.4. Periodic Safety Update Reports

Prepandemic period
The normal PSUR periodicity and format will be maintained, with a specific review of AESI and possible adverse events related to adjuvants.
In case of vaccination of the whole population, or a large fraction of the population, there may be a need for rapid, ad-hoc additional safety reports. The need, format and periodicity of such additional safety reports should be discussed with the (co-)Rapporteurs and EMEA on the basis of emerging information on national strategies.

Pandemic period
During a pandemic situation, resources must be concentrated on a timely and effective monitoring of the safety profile of the influenza vaccines used during the pandemic. Moreover, a 6-monthly cycle may be too long to permit assessment of the safety of a vaccine for which high levels of exposure are expected within a short period of time. Therefore, 6-monthly or annual PSURs falling within the pandemic period should be replaced by bi-weekly "simplified PSURs" accompanied by a summary of vaccine distribution. The preparation and submission of these safety reports should follow the requirements included in the terms of the marketing authorisation. These requirements are described below:

i) Objectives of the simplified PSUR

- To notify regulatory authorities of the ADRs that have been received within a pre-specified time period and that may have the greatest implications for risk-benefit balance in a pandemic.
- To flag any preliminary safety concerns and prioritise them for further evaluation within the appropriate timeframe.

ii) Frequency of submission

- The clock should start from the first Monday after the date of announcement of the influenza pandemic (Phase 6 of the WHO Preparedness Plan) (Day 0)
- First data-lock point is 14 days later.
- Report submission is no later than day 22 (i.e. the following Monday).
- Reporting to be fortnightly for the first 3 months of the pandemic.
- Periodicity should be reviewed by the MAH and the (Co-)Rapporteur at 3 monthly intervals.

After the end of the pandemic, a full PSUR covering the period since the data lock point of the last pre-pandemic PSUR should be submitted.

iii) Format of the simplified PSUR

The report should include the following tables of aggregate data (using the pre-defined templates attached in Annex 2):

1. Fatal and/or life-threatening reactions – for each Preferred Term (PT), including the proportion of fatal reports[2]
2. Adverse Events of Special Interest (PTs)
3. Serious unexpected reactions (PTs)
4. All events occurring in the following age groups: 6-23 months, 2-7 years, 8-17 years, 18-60 years, >60 years, and all events occurring in pregnant women
5. All events reported by patients that have been entered into the database by data-lock point
6. A cumulative overview of all events reported during the period, stratified according to type of reporter (patient or health care professional), seriousness, expectedness, and whether spontaneous or solicited.

The following principles should be followed when compiling the data:

- Serious expected reactions will be reviewed by the MAH as part of their signal detection procedures and will only form part of the report if an issue of concern arises.
- All tables will be based on number of events (presented on PT level, sorted by System Organ Class [SOC]) and not number of cases.
- Tables 1 to 4 will be based on events reported from healthcare professionals.
- In Tables 1 to 5, numbers will be provided for events received during the reporting period and cumulatively.
- All tables will be based on generic and not product-specific data[3]. Product-specific data can be evaluated during signal work-up.
- A measure of relative reporting rate of signals for each reported PT should be provided if possible (e.g. Proportional reporting ratio [PRR], Information Component [IC)] or the Empirical Bayesian Geometric Mean [EBMG])
- No line listings are required – these can be provided in signal evaluation reports as necessary.

A short summary should also be provided in which any areas of concern should be highlighted, signal work-up prioritised (if the event of multiple signals) and appropriate timelines for submission of a full signal evaluation report provided. All signal evaluation reports should be provided, including those that were subsequently not identified as being signals.
The format of the simplified report will need to be tested and amended as necessary.

iv) Ad hoc safety reports

If, at any time a serious safety concern arises in between reporting periods, this will be reported on an expedited basis.

v) Vaccine distribution report

To put the safety report into context, a summary of vaccine distribution should be included and should provide details of the number of doses of vaccine distributed in

[2] This should include all PTs that were specifically recorded as causing or contributing to death or of being life-threatening. In cases where the death cannot be attributed to a single ADR, all serious ADRs should be considered as having contributed to the death, and all the serious PTs for these cases should be included. Any comments that may be necessary can be provided in the summary.

[3] Based on the assumption that product name will not be provided in a significant proportion of cases.

i) EU member states for the reporting period by batch number,
ii) EU member states cumulatively and
iii) Rest of the world.

6.5. Additional pharmacovigilance activities

Additional pharmacovigilance activities should have three objectives in order to expand the safety database. It is considered that a single approach will not adequately address these objectives.

Objectives

i) To expand the safety database in populations studied in clinical trials, such as young health adults and the elderly
ii) To collect information in populations not studied in clinical trials, mainly pregnant women, immunocompromised subjects and children, should these populations be vaccinated.
iii) To collect and compile data on rare adverse events of special interests such as Guillain-Barré syndrome, autoimmune disease (eg. multiple sclerosis, optic neuritis, type I diabetes mellitus), severe allergic reactions, thrombocytopenia, vasculitis and Bell's palsy.

Methods

i) Observational studies

Expansion of the safety database and collection of information in populations not studied in clinical trials should be performed as soon as the vaccines are used in large populations, i.e. in Phases 4 to 6. Therefore, once a MAH has identified countries where its vaccine is likely to be used, it should develop a study protocol that could be implemented in one or several countries as soon as vaccination begins. Any study that has been agreed with public national authorities should be specified in the EU-RMP. As it is not possible to predict at this stage how pre-pandemic vaccines will be used in different countries, a single approach cannot be recommended. Vaccine manufacturers should liaise in advance with competent authorities of the countries where their vaccine(s) will be marketed in order to discuss how these target groups could be identified and followed for collecting data on safety. The time where contracts are made may provide a good opportunity for such discussion.
Several studies may need to be performed in different countries in order to collect data on different populations and obtain an adequate sample size. Vaccine manufacturers are encouraged to develop study protocols in countries outside Europe in order to increase the sample size, especially if the vaccine is to be used earlier in such countries. Studies do not need to be carried out in all countries where a vaccine is marketed. A well-structured study in 1 or 2 countries may be sufficient if an adequate sample size is obtained.

Appropriate sample size calculations should be included in the protocol for each study, with the possibility of providing different estimates for different outcomes.

The database should be designed in such a way that it encompasses a signalling system and allows a rapid analysis of data as soon as a signal has been detected from the database or from another source. Protocols should include a plan to ensure rapid sharing of information among interested parties, including EMEA and EU Member States.

ii) Other methods

Prospective observational studies are unlikely to provide adequate information on rare adverse events of special interest and other methods will need to be identified in countries where the vaccine will be used. If there is widespread population exposure to the prepandemic vaccine, the possibility and usefulness of using linked databases such a GPRD or using cohort, case-control or case series methodology should be explored.
Different AESI might require different methods, for example through specialist networks or web-based notification systems. The methods to be used should be discussed and agreed with the competent authorities. In addition, it is essential that background rates for each AESI are estimated

for the country in order to put the number of cases detected into context. This information could act as the basis for observed-to-expected analyses.

iii) Other data

In order to provide background information, vaccine exposure data compiled by public health authorities should also be provided if available to the manufacturer.

Information to be included in the risk management plan
At the time of authorisation, the Risk Management Plan should include the following information:

i) Clinical trials
- a list of clinical trials to be performed after authorisation and the safety data to be collected

ii) Observational studies
- outline(s) of protocol(s) for observational studies to be conducted when the product is to be used in phases 4 to 5/6, including endpoints and study populations to be included
- a list of countries where observational studies are to be performed (with endpoints and study populations), if this information is available; this information should be updated in each PSUR, along with a presentation of the progress made for the design and conduct of prospective observational study(-ies)
- a commitment to provide study protocol(s) as soon as concrete proposals can be made
- a plan to ensure rapid communication of any safety data to the concerned parties, including EMEA and Member States.

iii) Other methods
- a commitment for collecting data on AESI and for providing an update at least with each PSUR
- possible approaches for collecting data on AESI in countries where the vaccine may be used; this information should be updated in each PSUR, along with a presentation of the progress made for the implementation of methods of data collection.

Available data on exposure should be provided in updates of the risk management plan.

Annex 1

Proposed adverse event reporting form

ADVERSE EVENT FOLLOWING FLU IMMUNISATION REPORTING FORM

Please forward completed form to……by fax :……or mail :……or Email : ……@……

Date of report: |__|__|__|__|__|__|__|__| (D D M M Y Y Y Y) Country : _____

Source : ❒ Physician ❒ Pharmacist ❒ Nurse ❒ Patient ❒ RA ❒ Other

VACCINEE DETAILS

Name: |__|__| (Initials) Date of birth : |__|__|__|__|__|__|__|__| (D D M M Y Y Y Y) or Age : …….. Sex : ❒ M ❒ F

Pregnanc : ❒ YES ❒ NO ❒ Unknown *If YES, specify gestational age at the time of immunization* :……..

Pre-existing conditions/Relevant medical history : ❒ YES ❒ NO ❒ Unknown *If YES, specify* :……

……

Ongoing treatment: ❒ YES ❒ NO ❒ Unknown *If YES, specify;*……..

……

FLU VACCINES ADMINISTERED

	Vaccine (*Name*)	Manufacturer	Batch number	N°Doses	Date given	Route of administration
1.	_____	_____	_____	❒ 1st dose ❒ 2nd dose ❒ Unknown	|__|__|__|__|__|__|__|__|	❒ IM ❒ SC ❒ Unknown
2.	_____	_____	_____	❒ 1st dose ❒ 2nd dose ❒ Unknown	|__|__|__|__|__|__|__|__|	❒ IM ❒ SC ❒ Unknown
3.	_____	_____	_____	❒ 1st dose ❒ 2nd dose ❒ Unknown	|__|__|__|__|__|__|__|__|	❒ IM ❒ SC ❒ Unknown

DETAILED ADVERSE EVENT INFORMATION

Adverse event	Start date	Stop date	Description of Adverse event (clinical examinations, lab tests) and treatment, if any

Seriousness : ❒ YES ❒ NO ❒ Unknown

If YES : ❒ Life-threatening ❒ Hospitalization ❒ Resulted in permanent disability/incapacity ❒ Congenital anomaly ❒ Other (e.g. medically significant)

Outcome : ❒ Recovered ❒ Improving ❒ Not yet recovered

❒ Sequelae : ❒ YES ❒ NO, *If YES, Describe* :

……

❒ Fatal : Autopsy ❒ YES ❒ NO Cause of death :

……

CONCOMITANT VACCINES AND MEDICATIONS

Medicinal product	Start date	Stop date	Indication

REPORTER (HEALTH PROFESSIONAL OR CONSUMER)

Name : _____ Postcode : _____ Profession (only health professional) : _____

Phone number : _____ Fax number : _____ Email : _____@_____

Address :

_____

Signature : .....

Annex 2

Templates of tables for bi-weekly safety update reports

Table 1 - Fatal and life-threatening - number of events

Preferred term	No in reporting period	% fatal	Cumulative number	% fatal
Total no of events				
Total no of cases				

Table 2 - Adverse events of special interest

Generic term of special interest	No in reporting period	Cumulative number	Strength of signal[4]
Total no of events			
Total no of cases			

Table 3 - Serious unexpected adverse reactions

Preferred term	No in reporting period	Cumulative number	Strength of signal
Total no of events			
Total no of cases			

Table 4. Special populations (separate tables)

Preferred term	No in reporting period	Cumulative number	Expectedness
Total no of events			
Total no of cases			

[4] PRR/EBGM/other if possible

Table 5. Patients' reports

Preferred term	No in reporting period	Cumulative number	Expectedness
Total no of events			
Total no of cases			

*Only those reports that have been entered onto the database at data-lock. X patient reports remain outstanding.

Table 6 - Cumulative overview - number of reports

	Health care professionals				Patients*			
	Serious		Non-serious		Serious		Non-serious	
	Expected	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected	Unexpected
Spontaneous								
Solicited								

*Only those reports that have been entered onto the database at data-lock. X patient reports remain outstanding.