

RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA Submission ID: 125419/0 Office: OVRR

Product:

Influenza A (H5N1) Virus Monovalent Vaccine

Applicant:

ID Biomedical Corporation of Quebec (dba GlaxoSmithKline Biologicals)

Telecon Date/Time: 29-Jun-2012 12:00 PM Initiated by FDA? Yes

Telephone Number:

Communication Category(ies):

1. Advice

Author: KIRK PRUTZMAN

Telecon Summary:

Clarification of Item 36 from the April 30, 2012 IR

FDA Participants: KIRK PRUTZMAN, JEREMY WALLY, ELIZABETH SUTKOWSKI, ANDREA JAMES, LEW SCHRAGER, WEI HUA, YANDONG QIANG

Non-FDA Participants: KATI ABRAHAM, MIKE SCHWARTZ, BOB BROBST, ALLISON KING, CATHERINE COHET, HARRY SEIFERT, WENJUN JIANG

Telecon Body:

CBER met with GSK to clarify Item 36 to the April 30, 2012 IR. At the beginning of the meeting CBER stated that the meeting was for clarification purposes only and the no regulatory decision would be made.

Item 36: *"In the Pharmacovigilance Plan (m1.16), you proposed to conduct post-authorization active safety surveillance using a Pandemic Cohort (section 3.1.3.1.1.). The objectives were stated. Please clarify the study design and population, outcomes of interest, ascertainment of outcome, ascertainment of exposure, statistical analysis, and sample size and power calculation, in order to achieve those objectives."*

GSK explained to CBER that they had difficulty responding to CBER's request because they need to coordinate safety surveillance studies with European countries under the regulation of the EMA and the specific countries in Europe. GSK referenced the EMA Guidance "CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a

Pandemic Influenza Vaccine” (Doc. Ref: EMEA/359381/2009). GSK explained that they cannot be sure of which variables in a post-marketing safety surveillance study will be accepted (including which countries in the EU will participate, which AE’s will be collected, inclusion/exclusion criteria). CBER understood and told GSK to submit the guidance to the BLA as well as any information that could elucidate how they would attempt to conduct a post marketing safety study.

CBER agreed that GSK could submit the EMA guidance and any other information related to safety surveillance as a response to the April 30, 2012 IR. CBER indicated that we may have additional questions after GSK’s response is submitted. CBER told GSK that they did not need update the Pharmacovigilance Plan in the BLA with the current update.

Call ended.

Post meeting update: GSK emailed EMA Guidance “ CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine” (Doc. Ref: EMEA/359381/2009). to Kirk, Jeremy, and Carmen immediately after the meeting. It is attached below.

*****The next 5 pages can be found at
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500051739.pdf

Consider removing the 15 pages and adding link?*****



CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine

Adopted by CHMP in November 2006
Revision 1.0 adopted by CHMP on 25 June 2009

Revision 1.1 adopted by CHMP on 24 September 2009

1. INTRODUCTION

The CHMP Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (CPMP/VEG/4717/03) specifies that, as part of the post-approval commitments, Marketing Authorisation Holders (MAHs) should have protocols in place at the time of authorisation of the mock-up vaccine to ensure that immunogenicity, effectiveness and safety of the final pandemic vaccine are adequately documented during use in the field (i.e. during the pandemic), since there will be only limited immunogenicity and safety data and no efficacy data at the time of licensing. Marketing Authorisation Holders may seek scientific advice from European competent authorities, and should collaborate with European health authorities to assure adequate performance of post-marketing surveillance. In 2005, all European influenza vaccine manufacturers agreed to collaborate in the preparation of a common core risk management to be submitted with the Marketing Authorisation Application for a pandemic influenza vaccine.

This document provides recommendations on how routine and additional pharmacovigilance activities should be conducted during the pandemic period, as well as the preparatory activities to be undertaken in the pre-pandemic period to achieve a high level of preparedness. These recommendations have been drafted following discussions between representatives from the Pharmacovigilance Working Party (PhVWP), the Vaccine Working Party (VWP), the European Vaccine Manufacturers association (EVM), the CHMP, EMEA and ECDC.

Revision 1.0 has been prepared by EMEA in collaboration with the PhVWP, EVM and individual vaccine manufacturers in the context of the influenza A/H1N1 pandemic. The A/H1N1 influenza pandemic and the likelihood of a mass vaccination with A/H1N1 pandemic influenza vaccines have highlighted the need to revise this document taking into account differences between the situation in 2009 and the one foreseen in 2006. The following elements have been taken into account:

- the influenza pandemic has already been declared;
- the epidemiological characteristics of the A/H1N1 pandemic may differ from those foreseen for the H5N1 pandemic, with a lower case-fatality rate; in benefit-risk assessment, greater attention may therefore be given to less severe adverse reactions;
- the pilot testing of the simplified PSUR (S-PSUR) showed there was a need to revise its content and format.

Revision 1.1. includes changes mainly related to:

- the simplified PSUR, following the re-testing of the revised version
- the definition of vaccination failure to include a documented laboratory confirmation.

2. SCOPE

This document applies to the pharmacovigilance plan as part of the risk management plan introduced with the authorisation application of mock-up pandemic influenza vaccines according to the CHMP Guideline on dossier structure and content of pandemic influenza vaccine marketing authorisation application (CPMP/VEG/17/17/03). It also applies to the pharmacovigilance plan of vaccines authorised outside the context of the mock-up dossier and to be used during an influenza pandemic.

This document specifies additional pharmacovigilance activities to be carried out during an influenza pandemic, as soon as the pandemic has been announced by WHO (Phase 6 of the WHO global Influenza preparedness plan) or by the European Commission in the framework of Decision 2119/98/EC. The pandemic influenza pharmacovigilance plan will terminate when it has been agreed with national competent authorities that it is no more necessary.

In addition to these activities, Applicants may propose further measures considered appropriate for the evaluation of the efficacy and safety of their product. These measures should be discussed and agreed with national competent authorities. This document does not address the safety specification, the need for additional risk minimisation measures and the risk minimisation plan itself.

The risk management plan for pandemic influenza vaccines will be an evolving document. It should be amended 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 balance.

3. LEGAL FRAMEWORK

The Guideline on risk management systems for medicinal products for human use (EMA/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.

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.

4. RECOMMENDATIONS FOR THE PANDEMIC INFLUENZA PHARMACOVIGILANCE PLAN

4.1. Content of the pharmacovigilance plan

In the Pharmacovigilance plan, the Applicant should describe:

- specific activities performed during a pandemic in relation to the collection, collation, assessment and reporting of spontaneous reports of adverse reactions (see section 4.2);
- the format and content of the simplified PSUR (see section 4.3);
- specific activities performed for signal detection (see section 4.4);
- the post-authorisation safety study (see section 4.5) ; the protocol of the prospective cohort study should be presented in Annex 5 of the Risk Management Plan
- additional activities related to the:
 - detection of cases of Guillain-Barré syndrome

- the monitoring of immunocompromised subjects exposed to the vaccine
- the monitoring of pregnant women exposed to the vaccine.

4.2. Spontaneous reporting

4.2.1. General principles

The possible disruption of the postal system and limited time available to health care professionals may require the development or strengthening of alternative channels of reporting suspected adverse reactions by health care professionals, such as fax, telephone or electronic transmission (e.g. web-based system). Depending on the circumstances, postal reporting may need to 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.

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

4.2.2. Spontaneous reporting from health care professionals

- i) It is recommended that MAHs and National Competent Authorities actively encourage health care professionals to report at least a minimum set of criteria needed for a proper evaluation of the suspected adverse events/reactions. An optional standardised reporting form is proposed in Annex 1 as an example of the elements to be reported. Each MAH should preferably 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 vaccine authorised and marketed in the EU.
- ii) It is recommended that MAHs and National Competent Authorities (NCAs) actively encourage health care professionals to report the following adverse reactions:
 - Fatal or life-threatening adverse reactions
 - Serious unexpected adverse reactions
 - Adverse events of special interest (AESI): neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's palsy, demyelinating disorders, laboratory-confirmed vaccination failure.

Standard case definitions should be used for the classification of cases of AESIs, as they will need to be reported in the simplified PSUR.

- For anaphylaxis, convulsion, Guillain-Barré syndrome and encephalitis, the MAH and NCAs should use standard case definitions from Brighton Collaboration: http://www.brightoncollaboration.org/internet/en/index/definition__guidelines/document_download.html
- For Bell's palsy, a Brighton Collaboration case definition is being developed.
- For neuritis, vasculitis and demyelination, for which Brighton Collaboration definitions do not exist, an operational definition should be proposed by the Applicant in the Risk Management Plan. The narrow MedDRA SMQs for demyelination and vasculitis may be used to classify cases in these two categories.
- For laboratory-confirmed vaccination failure, Applicants should propose a definition taking into account the Concept Paper on Vaccination Failure developed by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance (<http://www.cioms.ch>). Vaccination failure would qualify as an AESI only if there is a documented laboratory confirmation. A narrative

documenting the laboratory confirmation should be included in all ADR reports of laboratory-confirmed vaccination failure.

- iii) The list of AESIs and the Risk Management Plan may be updated if a signal of severe safety issue is observed in pre-authorisation studies or from post-authorisation surveillance.
- iv) The basis for the assessment of an association between A/H1N1 influenza vaccines and severe adverse events should be Observed-to-Expected analyses. For this purpose, data will be needed on vaccine exposure and the expected number of cases. It is therefore crucial that background incidence rates on AESIs are collected as early as possible, before the vaccine is introduced on the market. Vaccine manufacturers should actively liaise with public health and regulatory authorities in countries where its vaccine(s) will be used in order to explore the availability of such data. Use of large electronic databases could be used if available. If data are not available, they could be extrapolated from other countries. Background incidence rates should be provided with any specific signal evaluation.
- v) In the context of the A/H1N1 influenza, specific attention should be given to the active detection and investigation of cases of Guillain-Barre syndrome (GBS). Vaccine manufacturers should actively liaise with public health and regulatory authorities in countries where their vaccine(s) will be used in order to identify sources of information such as networks of specialists or other programmes that may help identify early cases of GBS. Applicants should also propose methodologies to further investigate the incidence of GBS following vaccine administration in other sources of information such as large computerised databases (see section 4.6).

4.2.3. Spontaneous reporting from patients

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

Only medically confirmed reports should be expedited by MAHs to regulatory authorities. Non-medically confirmed reports should be compiled for signal detection. They should be analysed and reported separately to regulatory authorities (section 4.3.3).

4.2.4. Expedited reporting from MAHs to regulatory authorities

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

4.3. Periodic Safety Update Reports

During a pandemic situation, the 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 allow 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 will be replaced by monthly simplified PSURs (S-PSUR) accompanied by a summary of vaccine distribution.

4.3.1. Objectives of the simplified PSUR

- To notify regulatory authorities of 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.

4.3.2. Frequency of submission

- The clock should start from the first Monday after shipment of the first batch of vaccine.
- First data-lock point is 28 days later and Day 0 of S-PSUR submission is 14 days later.

- Day 0: S-PSUR submission to the Rapporteur and CHMP members.
- Day 5: Preliminary Rapporteur's assessment report is circulated to CHMP members.
- Day 7: Deadline for comments on the preliminary assessment report
- Day 9: Written procedure for agreement of the final assessment report
- Day 10: Final assessment report approved
- Day 11: The MAH receives the final assessment report.

- Reporting to be monthly for the first 6 months.
- Periodicity should be reviewed by the MAH and the (Co-)Rapporteur at 6 monthly intervals.

When it has been agreed by the CHMP that the S-PSUR is no longer necessary, a full PSUR covering the period since the data lock point of the last routine PSUR will be submitted within a time frame to be agreed with the Rapporteur.

4.3.3. Format of the simplified PSUR

Only spontaneously reported data should be included in the PSUR. The report should include the following Tables of aggregate data (using the pre-defined templates attached in Annex 2).

1. An overview for all spontaneous reports 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.
2. An overview for 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. MAHs should explore ways to present such cases without double counting if SMQs include overlapping terms.
3. Adverse Events of Special Interest stratified according to type of report (medically confirmed or non-medically confirmed). AESIs will be defined as follows:
 - Neuritis: PT "Neuritis"
 - Convulsion: narrow SMQ "Convulsions"
 - Anaphylaxis: narrow SMQ "Anaphylactic reaction" and narrow SMQ "Angioedema"
 - Encephalitis: narrow SMQ "Non-infectious encephalitis"
 - Vasculitis: narrow SMQ "Vasculitis"
 - Guillain-Barré syndrome: narrow SMQ "Guillain-Barré syndrome"
 - Demyelination: narrow SMQ "Demyelination" (as GBS is also included in this SMQ, there will be an overlap in the number of cases for these two categories).
 - Bell's palsy: PT "Facial palsy"
 - Laboratory-confirmed vaccination failure: PT "Vaccination failure" (a report should be classified as medically confirmed based on a narrative documenting the laboratory confirmation).
4. Serious unlisted adverse reactions (SOC, HLT, PTs) stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.
5. All spontaneous adverse reactions by age group, per SOC, HLT and PT, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by

the report and cumulatively. The following age groups will be used: < 2 years, 2-8 years, ≥ 9 years.

6. All spontaneous adverse reactions (SOC, HLT, PT) occurring in pregnant women, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

The following principles should be followed when compiling the data:

- Table 1 will be based on the number of reports, while all other tables will be based on number of reactions (presented on PT level, sorted by System Organ Class [SOC] and High Level Term [HLT]).
- All tables will be based on generic and not product-specific data¹. Product-specific data can be evaluated during signal work-up.
- “Cumulatively” means all adverse reactions since the use of the vaccine..
- All non-medically confirmed events are those that have been entered into the database by the data-lock point. Those which have not yet been entered should be reported in the following S-PSUR.
- “Serious” refers to the seriousness using regulatory criteria based on outcomes. This definition should be used consistently in all tables.
- Narratives of fatal cases and cases of Guillain-Barré syndrome will be provided in Annex.

A short summary should be provided in which the total number of new ADRs since the last S-PSUR is outlined and validated signals and areas of concern are highlighted, taking into account information arising from the prospective cohort study described in 4.5. In the event of multiple signals, signal work-up may be prioritised and appropriate timelines for submission of a full signal evaluation report should be provided.

Signals occurring in pregnant women should be described in terms of gestational age at time of vaccination, gestational age at time of occurrence of adverse event, adverse event, outcome.

4.3.4. 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

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

4.3.5. Testing of the production of the S-PSUR

The S-PSUR should be used as soon as the vaccine is used post-authorisation. It is therefore important to test the production and evaluation of the S-PSUR before the authorisation. The testing can be performed on a single S-PSUR based on another vaccine product. The Applicant should liaise with the EMEA Product Team Leader for practical aspects of the testing.

4.4. Signal detection

It is likely that potential safety issues will emerge when pandemic influenza vaccines are used in a large population. It is important for MAHs to identify them and this activity should be performed at least on a weekly basis. Identified signals should be validated and assessed using an Observed to Expected analysis as recommended in the Draft Guideline on the Conduct of Pharmacovigilance for

¹ Based on the assumption that product name will not be provided in a significant proportion of cases.

Vaccines for Pre- and Post-Exposure Prophylaxis against Infectious Diseases
(<http://www.emea.europa.eu/pdfs/human/phvwp/50344907en.pdf>).

Newly identified signals should be highlighted in the S-PSUR. Furthermore, any signal leading to a change in the balance of risks and benefits of the vaccine should be immediately notified to the competent authorities.

The method(s) used for the detection and investigation of new safety signals should be presented in the description of the pharmacovigilance system and summarised in the pharmacovigilance plan, especially if specific activities are established for the pandemic vaccine.

Whenever a prioritisation of the evaluation is needed, the choice of the events to be considered for primary review should be guided by their potential impact on Public Health. If prioritisation is required, it is proposed to use the following criteria:

- seriousness of the adverse event
- incidence of the adverse event.

If further prioritisation is needed, the following MedDRA SOC should be examined in a first stage:

- Nervous system disorders
- Vascular disorders
- Immune system disorders
- Blood and lymphatic system disorders.

4.5. Post-Authorisation Safety Study

Very limited knowledge on safety will be available from A/H1N1 influenza vaccines before use. Additional pharmacovigilance activities for the vaccines used during pandemic are therefore needed to assess safety. Given differences in the vaccination policy between member states in terms of type of vaccine used, target population prioritised for vaccination, setting of vaccination and surveillance systems already in place, it is considered that a single method cannot be proposed.

A minimum requirement is that each MAH puts in place a prospective cohort study for each vaccine, for which specifications are described below. The design of the prospective cohort study of exposed subjects and of other additional pharmacovigilance activities should be presented in the risk management plan.

i) General principles

The following principles should be included in proposals for additional pharmacovigilance activities by Applicants:

- rapid generation and communication of data (e.g. through a web-based system) is essential as a basis for operational decisions
- proposals should be detailed enough to show that they are feasible and may be started as soon as vaccination begins
- the work plan for preparation and implementation should be described in the risk management plan
- adequate human resources should be secured in order to maintain and access the database during the pandemic period
- additional pharmacovigilance activities will not be requested in all Member States where the vaccine is used, provided the required sample size is obtained
- wherever possible, e.g. in countries where different vaccines will be used, it is desirable that the concerned MAHs agree on a common protocol or perform a common study.

ii) Objectives

A prospective non-interventional cohort study will be conducted for all vaccines in at least one European Member State and started as soon as the vaccine is used post-authorisation. Concurrent cohorts of non-exposed patients are not required given the conditions of a pandemic situation.

The primary objective of the study will be to investigate the incidence of adverse events in different age groups following an active surveillance of all vaccinated subjects. Primary endpoints and solicited events should be proposed in the study protocol and agreed with the competent authorities. Secondary objectives will include the collection of data on any AESIs and unexpected severe adverse events occurring in the study.

Effectiveness endpoints could also be included in the PASS provided they do not delay its implementation. The feasibility of their inclusion should be assessed and balanced with the advantages of conducting a specific effectiveness study (see section 5.1).

Immunological endpoints (except results of the investigation of cases of laboratory-confirmed vaccination failure reported in the study) should be included only if they do not delay the study implementation and do not impact on the speed of recruitment and availability of safety data. If needed, immunological data should be collected in specific studies (see section 5.2).

iii) Setting

The prospective cohort study will not need to be carried out in all Member States where the vaccine will be used. In selecting the setting(s) where the study will be initiated, Applicants should pay attention to feasibility criteria, such as the recruitment of an adequate number of high-risk subjects (e.g. health care workers), and the collection of data in a short period of time. MAHs should seek agreement from Ethics Committees in the pre-pandemic period according to national requirements. The countries and settings where the study is to be performed should be presented in the pharmacovigilance plan.

In Member States where Applicants will concomitantly market a number of vaccines, they are encouraged to perform common studies.

Cohorts to be included in prospective cohort studies should be identified early. National pandemic plans should be investigated in the countries where the vaccine is likely to be used, in order to identify groups of subjects prioritised for vaccination with the pandemic influenza vaccines and for consideration for recruitment into the study as soon as vaccination begins. Subjects may also be recruited in centres with at risk patients.

Systems used for the surveillance of seasonal influenza vaccination should also be investigated in order to evaluate their potential as a source of subjects for a prospective cohort study of the pandemic influenza vaccine.

iv) Target population and sample size

The recruitment procedure should ensure that an adequate number of subjects are included in each age category. The following numbers of subjects to be studied are considered a minimum sample size:

- 2 - 23 months: 500
- 2 - 8 years: 500
- 9 - 17 years: 3,000
- 18 - 44 years: 1,500
- 45 - 60 years: 1,500
- >60 years: 2,000.

For practical reasons, flexibility in the age categories is allowed if specific child groups with different age categories are targeted by national immunisation programmes.

The total sample size of 9,000 subjects would be able to rule out events occurring with a frequency of 1 per 3,000 if no event is observed (provided the event may occur in all age categories).

For all subjects, medical information should be obtained at the time of entry in order to allow stratified analysis of incidence rate. Medical information to be collected includes at least: asthma in children,

chronic obstructive pulmonary disease (COPD) in elderly patients, whether immunocompromised, cardiovascular disorders, diabetes, chronic neurological diseases.

Pregnancy information should be collected at baseline and during the course of the study. MAHs should also consider studying the safety of their pandemic influenza vaccine in women vaccinated during pregnancy using specific sources of data (section 4.4.3.).

Subjects already vaccinated with another pandemic vaccine should be excluded from the study population. However, subjects who were primed in the pre-pandemic period may be included.

v) Duration of follow-up

Subjects enrolled in the cohort should be follow-up for at least 6 months after the last dose of the vaccine.

vi) Analysis and reporting

Procedures should be put in place to allow rapid communication of data to the MAH, taking into account potential difficulties occurring during the pandemic. Web-based or other automated procedures for active follow-up of subjects and data collection are encouraged.

The database should be dynamic, allowing an analysis of available data in real time when a signal is detected from the spontaneous system, in order to give a preliminary estimate of incidence.

Analyses should include an estimation of the proportion of subjects (95% CI) presenting the primary endpoint, SAEs and/or AESI after the first and second vaccinations. For new safety concerns, Observed-to-Expected analyses should be performed (in different age categories if relevant). It is therefore important that background rates in countries where the vaccine will be used are collected as early as possible before the vaccine is introduced on the market.

Analyses should take into account the time period between different doses.

Milestones for interim and final reports should be presented in the study protocols and agreed with competent authorities. New signals should be highlighted in the S-PSUR. Serious adverse reactions arising from such studies should also be reported on an expedited basis according to the same criteria and timelines as adverse reactions reported spontaneously by healthcare professionals.

4.6. Other activities

- i) For rare events such as Guillain-Barré syndrome, MAHs should investigate the possibility of constituting case series through the participation of specialist centres or clinics. Aggregated analyses could be performed to investigate potential risk factors; such series could also be a source of cases for further investigations (such as case-control analyses) performed after the pandemic. During the pandemic, the choice of the study design should take into account the time needed to obtain results.
- ii) Safety monitoring of vaccinated immunocompromised subjects (either due to an underlying disease or due to treatment with immunosuppressants) should be considered; such patients could be recruited in specialised settings like dialysis or transplant centres.
- iii) In order to document the safety of vaccines in pregnant women, the company should investigate whether a national pregnancy registry or another source of information exist in the countries where its vaccine will be used, in order to identify pregnancies exposed to the A/H1N1 vaccine and determine their outcome. Pregnancies occurring during the prospective cohort study should also be followed up. Activities undertaken to identify and access these sources of data should be reported in the pharmacovigilance plan in order to facilitate the coordination of efforts.

5. OTHER ACTIVITIES TO BE PRESENTED IN THE RISK MANAGEMENT PLAN

- 5.1. Effectiveness of the pandemic influenza vaccine should be studied in collaboration with regulatory authorities, in particular to have access to laboratory data and for laboratory confirmation. Applicants should actively liaise with public health and regulatory authorities in countries where its vaccine(s) will be used in order to agree on activities to be performed to assess effectiveness. Possible options are the inclusion of effectiveness outcomes in the prospective observational safety study, use of other sources of data such as local networks or sentinel physicians, or specific studies. Recommendations from ECDC for effectiveness studies should be consulted. Concerted efforts by vaccine manufacturers could facilitate the surveillance of the effectiveness of different vaccines in a same country. Effectiveness studies proposed to be carried-out post-authorisation should be described in the risk management plan.

- 5.2. A specific immunological study may be conducted to collect serum samples in a subset of vaccinated subjects to be tested for cross-reactivity against potential drifted variants of the A/H1N1 virus. Sera might also be used for cross-protection experiments in non-clinical models. Vaccine immunogenicity in a subset of immunosuppressed subjects may help evaluate whether alternate vaccination schedules should be applied, including more than 2 doses (or higher HA antigen content in the vaccines). Immunological studies proposed to be carried-out post-authorisation should be described in the risk management plan.

ANNEX I

Optional 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	Y	Y

 Country : _____

Source : Physician Pharmacist Nurse Patient RA Other

VACCINEE DETAILS

Name:

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 Date of birth:

D	D	M	M	Y	Y	Y	Y	Y	Y

 or Age : Sex :
 M F
Initials

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 Route of (Name) administration	Manufacturer	Batch number	N°Doses	Date given
1. _____ IM <input type="checkbox"/> SC <input type="checkbox"/> Unknown	_____	_____	<input type="checkbox"/> 1 st dose <input type="checkbox"/> 2 nd dose <input type="checkbox"/> Unknown	_ _ _ _ _ _ _ _ _
2. _____ IM <input type="checkbox"/> SC <input type="checkbox"/> Unknown	_____	_____	<input type="checkbox"/> 1 st dose <input type="checkbox"/> 2 nd dose <input type="checkbox"/> Unknown	_ _ _ _ _ _ _ _ _
3. _____ IM <input type="checkbox"/> SC <input type="checkbox"/> Unknown	_____	_____	<input type="checkbox"/> 1 st dose <input type="checkbox"/> 2 nd dose <input type="checkbox"/> Unknown	_ _ _ _ _ _ _ _ _

DETAILED ADVERSE EVENT INFORMATION

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

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 :

.....

REPORTER (Health professional or consumer)

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

TEL Phone number : _____ ? Fax number : _____ Q Email :
_____ @ _____

} Address :

Signature :

ANNEX 2. Format and content of the simplified PSUR

Table 1 – All spontaneous reports per country

Country	Medically confirmed				Non-medically confirmed*			
	Serious		Non-serious		Serious		Non-serious	
	No in reporting period	Cumulative number	No in reporting period	Cumulative number	No in reporting period	Cumulative number	No in reporting period	Cumulative number

Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Table 2 – All spontaneous adverse reactions

SOC HLT PT	Medically confirmed				Non-medically confirmed*			
	No in reporting period		Cumulative number		No in reporting period		Cumulative number	
	All	Fatal	All	Fatal	All	Fatal	All	Fatal
<i>Total</i>								

Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Table 3 – Adverse Events of Special Interest

Term (SMQ or PT)	Medically confirmed		Non-medically confirmed*	
	No in reporting period	Cumulative number	No in reporting period	Cumulative number
<i>Total</i>				

Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Table 4 – All serious unlisted adverse reactions

SOC	Medically confirmed	Non-medically confirmed*

HLT PT				
	No in reporting period	Cumulative number	No in reporting period	Cumulative number
<i>Total</i>				

Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Table 5a, 5b, and 5c– All spontaneous adverse reactions per age category

SOC HLT PT	Medically confirmed		Non-medically confirmed*	
	No in reporting period	Cumulative number	No in reporting period	Cumulative number
<i>Total</i>				

Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Table 6 – All spontaneous adverse reactions in pregnant women

SOC HLT PT	Medically confirmed		Non-medically confirmed*	
	No in reporting period	Cumulative number	No in reporting period	Cumulative number
<i>Total</i>				

Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Annex 1: Narratives of fatal cases.

Annex 2: Narratives of cases of Guillain-Barré syndrome.