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4 Interim guidance on enhanced safety surveillance for 5 seasonal influenza vaccines in the EU

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Comments should be provided using this template. The completed comments form should be sent to enhanced-surveillance@ema.europa.eu.

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1. Introduction

Seasonal influenza vaccines present several specific challenges for pharmacovigilance. These include mass immunisation in large population cohorts in a relatively short and fixed time period each year, seasonal factors (e.g. differentiating seasonal peaks in background illness from vaccine-induced effects) and multiplicity of seasonal vaccine products on the market with need for product-specific surveillance. There have also been examples when product-specific (or batch-specific) changes in quality specifications, arising from changes to a manufacturing process during the product life-cycle, have led to an unexpected change in reactogenicity or other adverse immune response. Furthermore, recent expansion of national vaccination programmes to include additional target groups (e.g. healthy children and all pregnant women) has created a greater need for information and reassurance on balance of risks and benefits.

Due to these challenges, pharmacovigilance systems for influenza vaccines need capability to rapidly detect and evaluate potential new safety concerns each influenza season. The aim is to mitigate risks before the peak period of seasonal immunisation (i.e. at least within the first month after the start of immunisation).

In accordance with the *Explanatory Note on the withdrawal of the note for guidance on harmonisation of requirements for influenza vaccines*[1], this document focuses on the requirements for annual enhanced safety surveillance to rapidly detect any increased local and systemic reactogenicity, or other unexpected adverse immune response that may arise during the influenza vaccine product life-cycle, e.g. due to changes in the manufacturing process. This guidance also outlines principles to be followed for improved continuous routine surveillance for influenza vaccines. Such surveillance systems need capability to detect, evaluate and act upon new safety signals that may arise during the vaccination campaigns in a near-time manner.

This guidance should be read in parallel with the GVP Product- or Population-Specific Considerations I on vaccines for prophylaxis against infectious diseases[2].

2. Principles, objectives and methods

2.1. Enhanced safety surveillance in the EU

The EU market for seasonal influenza vaccines is very diverse, both in terms of the wide range of vaccine products available and the variety of routes of authorisation, national immunisation policies and operational infrastructure for vaccine administration. In terms of enhanced safety surveillance, no single strategy can fit all situations; plans need to be tailored according to a specific product and where it is used.

Whilst basic routine surveillance should be applied in all Member States where a product is authorised, a strategy for enhanced safety surveillance should be applied in one or few Member States in which the marketing authorisation holder (MAH) can rapidly obtain the best available data to support the objective described in section 2.2. For example, this may be a Member State to which most vaccine has been supplied (and thereby offers a better opportunity to gain exposure and gather data quickly) and/or it may be a Member State that has a suitable data collection system accessible to the MAH, from which relevant data (numerator and denominator) may be extracted more rapidly.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500161022.pdf
[2] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/12/WC500157839.pdf

The main objective of enhanced safety surveillance is to detect and evaluate a potential increase in reactogenicity and allergic events (see section 2.2) that is intrinsic to the product (i.e. not due to a specific batch deviation or local programmatic issue) in near real-time in the earliest vaccinated cohorts. Most of all, any plan for enhanced surveillance must be feasible every year.

The detection of batch-specific safety signals and safety signals due to localised or isolated programmatic errors (e.g. inappropriate handling or breakdown in the cold chain, wrong route or technique of administration, etc.) should be undertaken via routine surveillance. However, to avoid false attribution of such signals to the general, intrinsic safety profile of a product, it is recommended that enhanced safety surveillance should be undertaken in at least two regions, or otherwise involve a region where more than one batch has been marketed during the period of enhanced surveillance.

Relevant product-specific safety data may be available from prior use of the vaccine in the Southern Hemisphere. In such a case, the MAH may justify at the time of the annual strain change procedure the relevance of the data and propose not to perform any of the enhanced safety surveillance activities. This strategy should be discussed with the competent authorities before submitting the annual strain change procedure.

2.2. Objectives of enhanced safety surveillance

The enhanced surveillance should focus on signal detection. The key objective is to rapidly detect a significant increase in the frequency and/or severity of expected reactogenicity (local, systemic or allergic reactions) that may indicate a potential for more serious risks as exposure to the vaccine increases. Examples are the early detection of a marked increase in frequency and/or severity of fever in order to anticipate a risk of febrile convulsion before such cases are observed, or the rapid detection of an unusual pattern of non-serious allergic events to help trigger measures preventing cases of serious allergic events.

Enhanced safety surveillance should continue until such point in time, each year, when a reasonable vaccine exposure and amount of safety data (see section 3.2) have been obtained, in order to have enough power to detect a significant change in reactogenicity (compared to the previous season's product). However, as with any other medicine, the routine pharmacovigilance processes (see section 4) should be continued throughout the life-cycle of the product to ensure detection of any new, unexpected or rare risks.

Given that the individual adverse event reports of interest (AEIs) may be expected and listed in the summary of product characteristics (SmPC), individual case safety reports (ICSR) review alone is not sufficient for early signal detection. Therefore, signal detection should focus on deriving AEI incidence or reporting rates, which should be compared against expected product-specific baseline rates (i.e. rate in the previous season(s)).

2.3. Methodological considerations

The MAHs of seasonal influenza vaccines should consider the options below (see section 2.4) and choose to implement an enhanced pharmacovigilance surveillance system that is able to fulfil the objectives described above.

The enhanced surveillance should be able to quickly generate the results, each season, for submission to the competent authorities within one month after starting the use of the vaccine in the EU. The MAH should design the enhanced surveillance activities to provide timely data each year.

In order to support annual and timely implementation, the MAH should establish an infrastructure/framework for identifying/enrolling vaccinees and gathering follow-up data, or denominator and numerator data. This infrastructure can then be used on a yearly basis. The MAHs should also explore whether existing relevant regional infrastructures/frameworks may already exist and facilitate relevant data capture. This may include, for instance, influenza sentinel surveillance networks or existing research frameworks.

If appropriate infrastructures for surveillance -that would provide the relevant data rapidly and meet the objectives of enhanced surveillance- are already in place and if the above mentioned pharmacovigilance activities are applicable for a new season and already included in the risk management plan (RMP), no further update of the RMP is envisaged (see section 3.1).

2.3.1. Identifying and quantifying rare risks

As any requirement for large sample sizes would likely make a near real-time system of enhanced surveillance prohibitive, it is not a primary objective of the annual enhanced surveillance strategy to identify rare events, nor to quantify the risk of rare events. These events should be detected via routine continuous surveillance (see section 4) and if necessary, evaluated by further investigation through specific measures or *ad hoc* PASS studies (e.g. confirming a risk of febrile seizures; see section 2.4.1).

However, if adequate data are available, quantification of rare risks may be included as a secondary objective of the enhanced surveillance strategy.

2.4. Options for enhanced surveillance

Three options are envisaged for enhanced surveillance:

1. Active surveillance;
2. Passive surveillance;
3. Data mining or other use of electronic health record data.

MAHs should always try to implement active surveillance. If the MAH provides adequate justification for not implementing enhanced active surveillance, then enhanced passive surveillance or data mining by other means should be implemented. Such justifications should be considered adequate and agreed by the competent authorities.

2.4.1. Enhanced active surveillance (post authorisation safety studies (PASS))

For the purpose of regulatory submission and review, the enhanced active surveillance consists of a post authorisation safety study (PASS), which should be included in the Pharmacovigilance Plan in the RMP as a category 3 study (see Module XIII and Module V). The protocols of the PASS should be agreed with the relevant competent authority(ies) in the context of the RMP. The Member State(s) where the study will be performed should also be informed.

The PASS should be designed and put in place with defined cohorts of children and adults actively followed-up (e.g. via web-based reporting and/or diary cards) at 7 days (or up to 14 days for a live attenuated vaccine) after immunisation for a range of reactogenicity endpoints/adverse events of interest (AEIs). It is envisaged that such surveillance would be non-interventional and would seek to identify/enrol vaccinees early through routine clinical practice. As a minimum, the goal should be to

detect a change in the frequency and severity of defined local and general events in at least 100 vaccinees in each defined age groups (e.g. those aged 6 months to 5 years, 6 to 12 years, 13 to 18 years, ≥ 18 years-65 years and > 65 years).

In addition, the sample size should be further justified based on appropriate baseline rates of the relevant local and systemic adverse events.

Depending on the age groups, the PASS should include specific endpoints using standardised case definitions using the following AEIs:

- Fever, including high grade fever;
- Vomiting and nausea;
- Malaise;
- Headache;
- Irritability (for under 5-year-old vaccinees);
- Crying (for under 5-year-old vaccinees);
- Decreased appetite;
- Injection site reactions (e.g. pain, erythema, swelling) including severity and persistence;
- Myalgia/arthralgia;
- Hypersensitivity reactions, including ocular symptoms;
- Use of medicines available without prescription to treat pain and fever;

For live attenuated, intranasal vaccines, endpoints using standardised case definitions should include the following AEIs:

- Nasal congestion/rhinorrhoea;
- Oropharyngeal pain;
- Cough;
- Malaise;
- Headache;
- Decreased appetite;
- Fever;
- Febrile convulsions;
- Myalgia;
- Epistaxis;
- Rash;
- Hypersensitivity reactions, including facial oedema, urticaria and very rare anaphylactic reactions;
- Wheezing (in young children).

In the first year of the implementation of enhanced surveillance activities, the rate of events should be compared against the expected rate based on current product-specific data. In subsequent years, the data obtained through active surveillance in the previous year would become the baseline for signal detection, using identical or equivalent plans for surveillance.

Reports of serious unsolicited events may be discussed in the context of the expected background incidence in the relevant population, to determine the likelihood of case(s) being a chance observation or a possible signal. This is particularly important for serious events that, based on prior experience with the same vaccine, could potentially be related to a change in reactogenicity (e.g. a case of febrile seizures or a serious allergic event). If necessary, consideration should be given to using observed vs. expected methods.

2.4.2. Enhanced passive surveillance

Plans for enhanced passive surveillance should be included in the Pharmacovigilance Plan in the RMP as routine pharmacovigilance activities.

Enhanced passive surveillance should be applied in one (if more than one batch and immunisation centre is subject to surveillance) or more regions where the vaccine is first likely to be used, and where there is likely to be sufficient early vaccine exposure in each of the age groups defined above. The principle of enhanced passive surveillance is to rapidly estimate vaccine usage (number of vaccinees, or doses administered), and to facilitate passive ADR reporting, in order to derive reporting rates as a surrogate of incidence of the type of events described as AEIs in section 2.4.1. Sensitivity analyses should be applied for assumed under-reporting levels to facilitate signal detection. As stated above, the potential to utilise any existing regional frameworks (for instance influenza sentinel surveillance networks) to gather relevant data should be explored.

Denominator

A fundamental requirement is that reliable and near-real time data on actual usage of the vaccine product (rather than sales/distribution data), stratified by the age groups outlined in section 2.4.1 are collected in (a) specified region(s).

This requires the MAH to identify in advance a region(s) in the EU where they know their vaccine is to be used (e.g. when early contracts for supply of vaccine are being placed each year) and in which there is a regional/national policy of immunisation of the relevant adult and paediatric target groups, and to develop a tailored strategy. In such a region(s), MAHs should seek to foster relationships with relevant public health authorities and/or customers that would facilitate exchange of information on actual vaccine usage over time, or to access other sources of exposure data such as electronic health record databases.

The strategy to calculate the exposure should be specified in advance together with an analysis of any limitations of the method.

Numerator

In the same region(s), early plans should be developed to facilitate near real-time vaccine-specific and batch-specific reporting of AEIs (as well as unsolicited serious events), and to minimise under-reporting. This could be supported via facilitated access to reporting forms (either targeted circulation of paper forms or implementation of a web-based interface), including those established by public health and medicines competent authorities in the area, if available. As many of these events may not be medically attended, a focus on vaccinees/carer reporting should be encouraged.

MAHs should engage with the relevant competent authority in the selected region(s) to facilitate data exchange, exploit any opportunities for collaboration and avoid any unnecessary duplication.

In the first year of the strategy, the estimated 'incidence' (reporting rate, subject to assumptions of under-reporting) of AEIs should be compared against the expected rate based on current product-specific data. In subsequent years, the data obtained in previous year of enhanced passive surveillance would become the baseline for comparison, using an identical method for surveillance.

Spontaneous reports of serious ADRs should be discussed in the context of the expected background incidence in the relevant population, to determine the likelihood of case(s) being a chance observation or a possible signal. This is particularly important for serious events that, based on prior experience with vaccines, could potentially be related to a change in reactogenicity (e.g. a case of febrile seizures or a serious allergic event). If necessary, consideration should be given to using observed-vs-expected methods.

2.4.3. Use of electronic health record data and data mining

Whilst the use of electronic health record databases may be informative in evaluating the risk of any serious adverse events arising from increased reactogenicity, such databases are of limited use for enhanced surveillance of these AEIs (see section 2.4.1) given that most will not be medically-attended. However, such databases may be used to obtain data on usage of the vaccines.

If suitable options for use of such databases exist, a PASS using these databases could be proposed, including options for data mining.

3. Data reporting and submission

3.1. Risk management plans and interim surveillance plans

Following pre-submission consultations with the Agency or the relevant national competent authority, the MAHs that have in place an RMP, but no enhanced safety surveillance measures, are required to submit a proposal for enhanced safety surveillance with an update of the Risk Management Plan (RMP). For the 2014-2015 influenza season, such updated RMP should be included in the dossier for the annual strain change procedure, or submitted for review as otherwise agreed with the competent authority.

The MAHs that do not have an approved RMP in place at the time of the annual strain change procedure for the 2014-2015 influenza season should include a stand-alone document (interim surveillance plan) in Module 1.8.2 of the marketing application for the annual strain change variation.

From the 2015-2016 influenza season onwards, all MAHs should put in place RMPs for seasonal influenza vaccines. The format and content of the newly introduced RMPs should be tailored to the scope of introducing the enhanced safety surveillance (e.g. Part I, SVIII of Part II, Part III -limited to the description of the routine activities already in place, and the enhanced surveillance plan-, Part V, Part VI, and annexes as relevant). The submission of a new RMP does not need to coincide with the annual strain change procedure, however plans for safety surveillance should be in place at the time of the annual strain change procedure.

An annual update of the RMP to describe the enhanced surveillance strategy is not necessary if systems are already in place and adequately reflected in the RMP, provided the system is appropriate and applicable for the new season.

3.2. Expedited summary safety report

Regardless of the nature of the enhanced safety surveillance, it is required that adverse reactions reporting data are continuously evaluated, at least weekly during the first month of marketing (see also section 4). A summary safety report should be submitted to the relevant competent authorities within one month of the first doses of the product being used in the EU or as soon as the previously agreed exposure (denominator) and/or extent of safety data have been achieved in the EU. For centrally authorised products (CAPs) results should be submitted to PRAC as a post-authorisation measure (legal obligation).

The report should follow a standardised and simplified format, in order to ensure rapid assessment. It is envisaged that the report constitutes no more than five pages, with the following standard sections:

***a.* Expedited summary safety report section "Executive summary"**

The following should be provided in this section: a short overview of the surveillance method applied, the region(s) to which the surveillance was focused, the time period involved, the total number of doses administered in each age group and the frequency and severity of AEIs observed/reported, a statement on how this compares with the applicable baseline rates/expectation and a conclusion on whether there is any evidence of a significant change in reactogenicity or other apparent safety signal.

***b.* Expedited summary safety report section "Methods"**

The following should be provided in this section: a short description of the method(s) used to collect the data on exposure and AEIs and in which region(s) the surveillance was undertaken. Cross-reference should be made to the relevant part of the RMP which describes the full method(s). It is envisaged that a descriptive analysis of data would be sufficient, but any statistical methods used should be described.

***c.* Expedited summary safety report section "Exposure data"**

The following should be provided in this section: a table summarising the number doses administered to each age group.

***d.* Expedited summary safety report section "Safety data"**

The following should be provided in this section: a table including the number of cases, and frequency or reporting rate for each endpoint/recorded AEI. A different column should be used for the different age groups. Local reactions and fever should be graded.

MAHs should also report tables of the following:

- Adverse events defined as potential risks in the RMP;
- All other unsolicited ADRs;

***e.* Expedited summary safety report section "Discussion"**

The following should be provided in this section: a discussion of the frequency/reporting rate and severity of the reported AEIs and how this compares to the expected rate/severity based on the previous year's data. The previous year's data/report should be included as an annex to the report. The strengths and limitations of the method applied should be discussed.

***f.* Expedited summary safety report section "Conclusion and recommendations"**

The following should be provided in this section: a conclusion on whether there is any evidence of a significant change in reactogenicity or other apparent safety signal, with any recommendations for further action if necessary.

4. Continuous benefit-risk evaluation

The requirements for enhanced safety surveillance should not substitute the routine or additional pharmacovigilance activities considered as required for the product and previously agreed with the competent authorities (e.g. to investigate a specific safety concern). Also all pharmacovigilance requirements as detailed in legislation and all Modules of GVP apply.

Aside from any change in reactogenicity, it is possible that new and rare adverse reactions may be identified, particularly for newer products. As explained in section 2.3.1, such events are unlikely to be detected through enhanced surveillance in small cohorts, therefore routine continuous surveillance and risk-benefit evaluation at EU and global level should be performed (see GVP Modules IX and XII and section 2.3.1 of this document) in addition to enhanced safety surveillance.

Given the challenges of influenza for vaccine pharmacovigilance (see Introduction), signal detection and management should be performed at least monthly throughout the lifecycle of the product and at least weekly during the first month of use. Any potential signals should be communicated to competent authorities without delay.

Any safety concern which may impact on the benefit-risk balance of the vaccine or have implications for public health, and which may require immediate attention by the regulatory authority, should forthwith be notified as an emerging safety issue to the competent authorities of Member States where the product is authorised and to the Agency (at P-PV-emerging-safety-issue@ema.europa.eu). The notification should describe the safety issue and the actions proposed or already taken.

To support the overall aim of strengthening safety surveillance, when preparing their annual plans for enhanced surveillance, the MAHs should review their pharmacovigilance and risk management systems (see GVP Modules I and V) to ensure that they are optimal for an influenza vaccine and compliant with the relevant aspects of Chapter P.I.