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Pharmacovigilance Risk Assessment Committee (PRAC)

Explanatory note on the withdrawal of the Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU - Scientific guideline

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This note replaces ' Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU - Scientific guideline ' (EMA/PRAC/222346/2014)

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction (background)

In April 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU.

At that time, seasonal influenza vaccines presented several specific challenges for pharmacovigilance. These included 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, led to an unexpected change in reactogenicity or other systemic adverse drug reaction. Furthermore, the expansion of national vaccination programmes to include additional target groups (e.g. healthy children and pregnant women) created a greater need for information and reassurance on balance of risks and benefits.

Whilst routine standard surveillance has been applied for seasonal influenza products, as for any other medicinal product authorised, a strategy for annual enhanced safety surveillance (ESS) was agreed.

The interim guidance focused on the requirements for annual enhanced safety surveillance (ESS) to rapidly detect any increased local and systemic reactogenicity that may arise during the influenza vaccine product life cycle, e.g. due to significant changes in the manufacturing process. This guidance also outlined principles to be followed for improved continuous routine surveillance for influenza vaccines. Such surveillance systems needed capability to detect, evaluate and act upon new safety signals that may arise during the vaccination campaigns in a near-time manner, so that this experience could be considered in the next variant vaccine update.

The guidance envisaged three options for enhanced surveillance: 1. Active surveillance; 2. Passive surveillance; 3. Data mining or other use of electronic health record data, though active surveillance was encouraged as it was considered the most reliable estimate of the frequency and severity of the AESIs to meet the objectives. The corresponding enhanced surveillance system agreed between the Applicant and the EMA was included in the Risk Management Plan.

2. Problem statement

The PRAC has gathered more than 10 years of experience assessing the agreed ESS of different marketing authorisation holders (MAH) for seasonal flu vaccines and identified the following challenges:

- Proportionality: the usefulness of the safety information gathered in the different ESS evaluated was not proportionate to the MAHs and EU network's efforts on conducting and assessing this surveillance system. Changes in the frequency of occurrence of adverse events (AEs) could not be assessed as it was not possible to ascertain the number of people who were exposed to the vaccine(s). In addition, the quality of the individual case reports was overall weak and lower than of case reports received via routine pharmacovigilance. Finally, there was no option to follow-up the cases to further characterise the case reports.
- Relevance: the proposed methodology is not suited to detect rare or unexpected events as most of the information collected related to common and expected adverse drug reactions (ADRs). In addition, data interpretation was difficult as the AEs reported were in large majority unspecific

and could be impacted by other respiratory viruses circulating at the time of the vaccination campaigns. Furthermore, the system has not proved to be useful to detect batch related issues.

- Timeliness: the possibility to detect changes in reactogenicity or unexpected AEs in a timely manner (before manufacturing process for the next season) did not materialise.

3. Future safety monitoring of seasonal influenza vaccine

The EU has a comprehensive safety monitoring and risk management (pharmacovigilance) system, which ensure measures are in place for detecting any potential new risks, conducting rigorous scientific assessments of all safety data and introducing any necessary mitigating actions early on. The safety of all EU medicines is monitored according to guidance set out by European Medicines Agency (EMA) and National Competent Authorities (NCAs) in the good pharmacovigilance practices (GVP).

Since the publication of the interim guidance, the methodologies, technologies, systems and pharmacovigilance tools have evolved significantly. Importantly, the COVID-19 pandemic has significantly enhanced the development of tools and methods to manage the unprecedented volume of safety data generated for the COVID-19 vaccines. The European Union (EU) safety monitoring and risk management system was strengthened to collect and monitor the high volume of data from the vaccination campaigns. This allowed the Network to promptly identify, assess and manage safety issues. The pandemic demonstrated that the system is robust and fit for purpose, as it allowed to identify rare adverse drug reactions following use in vaccination campaigns.

The PRAC is of the opinion that the system in place is robust to monitor the safety of seasonal influenza vaccines and the Network is leveraging the existing and additional methodologies and tools developed during the COVID-19 pandemic, as follows:

- The MAHs in the EU have the general obligation to keep their product information up to date throughout the product's lifecycle by regulatory applications. Additionally, MAHs are obliged to provide regular evaluation of the risk-benefit balance of their products via periodic safety update reports, by presenting comprehensive safety information in these reports, which are assessed by the regulatory agencies.

- Furthermore, the MAHs have the obligation to continuously monitor the safety of their medicinal products by conducting signal detection activities considering all available sources. MAHs should inform the authorities of any new information that might have an impact on the marketing authorisation, including emerging safety issue (safety issues with a major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health which may require prompt regulatory action and communication to patients and healthcare professionals).

- The EU regulatory Network and the national competent authorities (NCAs) are also responsible for monitoring the EudraVigilance database and all other relevant sources such as the literature and conduct signal management for active substances contained in at least one centrally authorised product, as well as active substances contained in nationally authorised products. Signal management is a set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as if any related recommendations, decisions, communications and tracking are needed.

- In terms of post-authorisation safety monitoring, the selection of vaccine adverse events of special interest (AESI) is a key preparedness activity. Case definitions and background incidence

rates for selected AESIs after vaccination are available and updated when necessary (Brighton collaboration, ACCESS, DARWIN-EU, etc). At the time of authorisation, the MAH should agree with the authorities the list of AESI to be monitored and keep the list updated throughout the life cycle of the product.

- Other preparedness activities include assessing the feasibility of using real-world data (RWD) sources available in the network to monitor the safety and effectiveness of vaccines. This includes EMA's real-world evidence (RWE) generation pathways that support RWD studies under the EU Vaccines Monitoring Platform, including DARWIN EU.

4. Conclusion

Since 2014, when the interim guidance came into effect, MAHs for seasonal influenza vaccines have applied ESS measures in addition to the EU standard pharmacovigilance activities.

The current EU pharmacovigilance system with the standard pharmacovigilance activities is robust, fit for purpose and demonstrated to be efficient in promptly identifying and dealing with emerging issues during the COVID-19 pandemic. The Network is currently leveraging tools and methods originated during the pandemic. It is also noteworthy that EMA has initiated the revision of the Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious disease.

It is therefore considered that the EU pharmacovigilance system fulfils the goals set out by the Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU.

Thus, the PRAC agreed that the Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU - Scientific guidance (EMA/PRAC/222346/2014) is considered obsolete.

Should the 'interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU - Scientific guideline' have been applied for other influenza vaccines, such as zoonotic or pandemic influenza preparedness, the above considerations would also apply for these vaccines.

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COVID-19 lessons learned (europa.eu)

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Data Analysis and Real World Interrogation Network (DARWIN EU) | European Medicines Agency (EMA) (europa.eu)

Vaccine Monitoring Platform | European Medicines Agency (EMA) (europa.eu)

Homepage | HMA-EMA Catalogues of real-world data sources and studies (europa.eu)

Case Definitions Table View - Brighton Collaboration