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EVDAS – Signal Detection, Year One. The challenges so far and future steps.

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Did you know…

In the late 1960s, Dr. Ed Napke set up Canada's system for ADR reporting. "*Although the reporting system was computerized, Napke developed a system of "pigeon holes" into which reports were filed. Coloured tabs were attached to reports of severe or unusual reactions as they were filed. When clusters of coloured tabs began to emerge, Napke and his small team had a visual cue that something might be wrong*." [1]

A lot of progress has been made since then. There have been various computerized approaches for signal detection. EVDAS is of the most sophisticated methods of analysis used so far.

Regulatory aspects

Regulatory guidance for the detection and reporting of signals from EudraVigilance is provided within the Good Pharmacovigilance Practices Module IX and its addendum.

In order to support the MAHs, EMA has released a number of guidance documents, e-Learning modules and training initiatives.

Some important statistics to be considered, which reflect the significant contribution of Eudravigilance to drug safety monitoring, can be found in the *'Annual Report on EudraVigilance for 2017'* [8]:

- 1.4 million new suspected adverse drug reaction reports were added to the database;
- the Agency reviewed 2,062 potential signals for CAPs. Approximately 82% originated from the analysis of ADR reports received in the EudraVigilance database;
- the Pharmacovigilance Risk Assessment Committee (PRAC) assessed 82 signals of new or changing safety issues and about two thirds of these were detected in full or part from EudraVigilance.

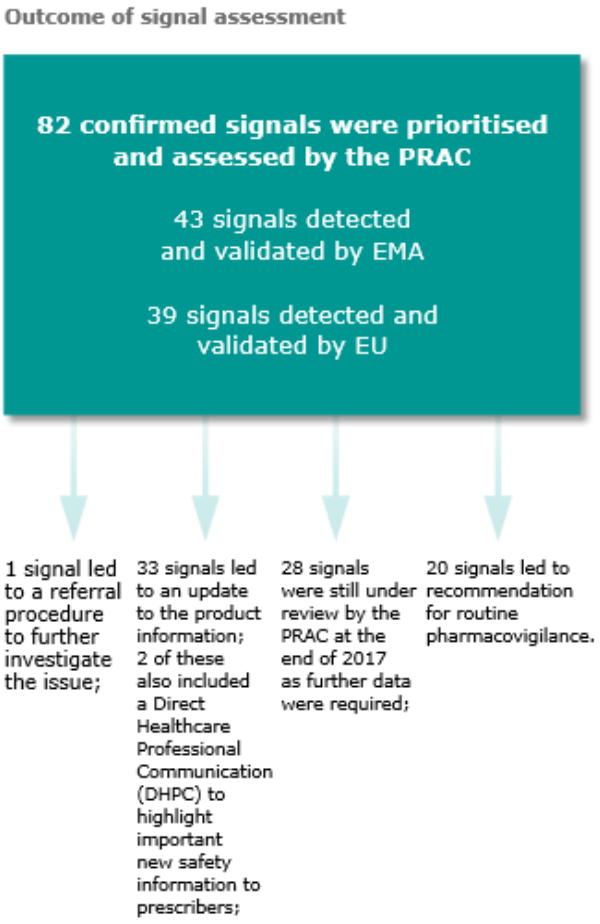

Figure 1.

Figure taken from 2017 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission.

EVDAS access provided to MAHs since 22 Nov 2017, gives the opportunity to retrieve electronic Reaction Monitoring Reports (eRMRs) for any active substance and allows for comparison and statistical analysis of products within the same pharmacological class[2]. It enables users to analyze safety data collected in EudraVigilance so that better-informed decisions can be made about the medicinal products' safety profile[2].
The universal data access allows for direct actions improving the ability to detect emerging issues and protect public health, however, there is no ready-made solution for managing and analyzing the extensive dataset efficiently.

What are the challenges and how cost effective is the detection of true signals in EVDAS, especially for MAHs of generic products and SMEs?

One of MAHs' main challenges is to outline an approach, a method in order to be able to analyze the data and detect signals from EVDAS. This method should itself depend on the specific product's safety profile, be duly justified and in line with the legislative obligations.
Some important questions to be answered are the following: on which DECs will the MAH focus, which criteria, filters and their combinations will the MAH select in order for no true signals to be missed? How will the MAH decide which DECs shall be further analyzed and validated?

The eRMR output provides only the rough picture of the DECs that might demand further attention. As clearly depicted in the guidance documents "*MAHs should exercise scientific rationale when deciding which DECs from the eRMR deserve further analysis*[3]" suggesting that alternative approaches can be applied in different cases but always in line with the legislative obligations.

One of the most important values present within the eRMR output, is the signal of disproportionate reporting (SDR). The SDR is a combination of fulfilled statistical criteria that may reflect a causal relationship between the exposure to a product and the occurrence of an adverse event[7]. That said, to begin further investigating the DECs filtered by "YES" in the column of SDR is a good place to start.

What needs to be decided afterwards, is which DECs shall be further analyzed and validated. A few of the many aspects mentioned within the guidance documents, to be considered are[4,5]:

- Is the event reflected in the SmPC or the Innovator SmPC of the active substance?
- Does the event reflect a new aspect of a known association?
- Has the association previously been addressed in a regulatory procedure?
- Do you have similar cases in your database that support an association?

Even after the completion of the steps described above, the picture remains far from being complete. As well-depicted in [3], "*An SDR is not the same as a validated signal and on the other hand there could be real safety signals that do not show as SDRs at a certain point in time*[3]". The SDR alone does not usually constitute a signal in the pharmacovigilance context[7].

So what about all the other DECs?
How will the MAHs single out those DECs that do require further analysis but do not meet the criteria for SDRs from this extensive dataset?

A recommendation is to focus on and filter by predefined events such as events that are not

SDRs but are likely to have a high public health impact such as events on IME and DME lists or fatal ones[5,7].

Additional efforts should be put not only on focusing the screening on events of specific MedDRA terms groupings, but also on the subgroups of paediatric and geriatric populations, thus making the methodology that needs to be developed rather complex.

Based on the knowledge of product's safety profile including but not limited to risk minimization, exposure, patient population, previous assessments[3], the MAH is responsible to design a methodology that is specially tailored to each product.

Many argue that MAHs' participation in the EVDAS analysis together with the NCAs and the Agency leads to duplication of efforts. However, an important lesson to be taught from the pilot phase might be that alternative approaches to analysis may lead to different outcomes.

What are the next steps?

The extension of the pilot period beyond the 22nd of February 2019 has been already announced. As described in [6], EMA aims for the finalization of a report that will reflect the first year of experience by September 2019. By the end of December 2019, a decision on the next implementation phase is expected to be communicated to stakeholders.

The waiting period soon comes to an end with MAHs steadily rooting for an approach which will somehow avoid duplication of efforts between NCAs, MAHs and the Agency.

Table of Abbreviations:

ADR	Adverse Drug Reaction
CAP	Centrally Authorised Product
DEC	Drug-Event Combination
DME	Designated Medical Events
EMA	European Medicines Agency
eRMR	electronic Reaction Monitoring Report
EVDAS	EudraVigilance Data Analysis System
IME	Important Medical Events
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
PRAC	Pharmacovigilance Risk Assessment Committee
SDR	Signal of Disproportionate Reporting
SMEs	Small Medium Enterprises
SmPC	Summary of Product Characteristics

References:

1. www.cbc.ca/news2/adr/, CBC News Online; 17Feb2004
2. GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions, EMA/209012/2015; 09Oct2017
3. EVDAS User Manual v.1.2, EMA/167839/2016; 14May2018
4. GVP Module IX – Signal management (Rev. 1), EMA/827661/2011; 09Oct2017
5. Work Package 5 – Signal Management - Best Practice Guide, SCOPE; Jun2016
6. Update on the pilot of signal detection in EudraVigilance by marketing authorisation holders, EMA/MB/493254/2018; 04Oct2018
7. Screening for adverse reactions in EudraVigilance, EMA/849944/2016; 19Dec2016
8. 2017 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission, Reporting period: 1 January to 31 December 2017, EMA/7552/2018; 15Mar2018 (including Annual Report 2017, the European Medicines Agency's contribution to science, medicines and health in 2017)