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Reflection paper on particulars for safety signals for (traditional) herbal medicinal products

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1. Scope

The 'Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management' (EMA/827661/2011)[1] provides general guidance and requirements on scientific and quality aspects of signal management. The addendum to this Module, the GVP Module IX Addendum I (EMA/209012/2015)[2], describes methodological aspects of signal detection from spontaneous reports of suspected adverse reactions. In addition, the EMA scientific guidance on 'Screening for adverse reactions in EudraVigilance' (EMA/849944/2016) serves as a basis for the guidance on methods of routine signal detection as used in EudraVigilance database together with the elements for their interpretation and their potential advantages and limitations in the frame of pharmacovigilance. There are no particular considerations mentioned regarding herbal medicinal products or traditional herbal medicinal products in these EU guidelines. Therefore, this reflection paper discusses particular aspects to be considered for safety signals for herbal medicinal products, including traditional herbal medicinal products, in addition to established EMA guidance documents. It should be read in conjunction with Directive 2001/83/EC, Regulation (EC) No 726/2004 and Commission Implementing Regulation (EU) No 520/2012, as well as relevant guidelines on GVP. The guidance published as GVP is the principal guidance supporting implementation of, and compliance with, legal requirements.

2. Introduction

A safety signal is information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action (IR 520/2012 Art 19(1))[3]. Thus, safety signals are generated from several sources, such as spontaneous reports, clinical studies and the scientific literature.

Signal detection is the process of looking for and/or identifying signals using data from any source (based on CIOMS VIII[4]). Signal detection should follow a methodology which takes into account the nature of data and the characteristics (e.g., time on market, patient exposure, target population) as well as the type of medicinal product concerned. Herbal substances[5] and herbal preparations[6] as active substance of (traditional) herbal medicinal products are complex mixtures of constituents and assessment of their safety and/or efficacy relies on adequate pharmaceutical documentation. The quality dossier of a (traditional) herbal medicinal product includes quality control data from the starting material to finished product to ensure consistent quality for products of herbal origin which is correlated to the safety of the product. For example, the starting materials should be defined in a rigorous and detailed manner in the dossier, particularly the specific botanical identification of the plant material used. Agricultural treatment(s) of the plant material during growth with for example pesticides, and inadequate drying and storage conditions could also translate into safety issues. Generally, herbal substances must be tested for microbiological quality, mycotoxins, residues of pesticides and fumigation agents, heavy metals and likely contaminants (including potentially toxic

[1] Guideline on good pharmacovigilance practices (GVP): Module IX – Signal management (EMA/827661/2011 Rev.1)
[2] Guideline on good pharmacovigilance practices (GVP): Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions (EMA/209012/2015)
[3] Commission implementing regulation (EU) No 520/2012, Article 19(1)
[4] Council for International Organizations of Medical Sciences (CIOMS). Practical aspects of signal detection in pharmacovigilance (report of CIOMS Working Group VIII). Genève: CIOMS; 2010
[5] Definition in Directive 2001/83/EC: All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author)
[6] Definition in Directive 2001/83/EC: Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

contaminants from extraneous sources or specific conditions of processing). For some herbal substances/preparations the quality requirements in the European Pharmacopoeia monograph include limits for constituents of toxicological concerns. Medicinal products need to comply with these requirements.

Like for all medicinal products, the risks for (traditional) herbal medicinal products are assessed before approval. Most herbal substances/preparations in medicinal products have been in medicinal use in the EU for many years, in particular herbal substances/preparations in traditional herbal medicinal products, where the requirements include safe use for more than 30 years before approval. Nevertheless, monitoring the safety of a medicinal product once it is on the market (i.e., the post-authorisation stage of the product lifecycle) is the cornerstone of pharmacovigilance. It is the European Medicines Agency (EMA), together with the National Competent Authorities (NCAs) in the Member States and marketing authorisation holders that are responsible for detecting and managing safety signals. The Pharmacovigilance Risk Assessment Committee (PRAC) is the EMA committee responsible for assessing and monitoring the safety of human medicinal products in the EU, including (traditional) herbal medicinal products.

To support EU Member States and the harmonisation of the European market for (traditional) herbal medicinal products, one of the main tasks of the Committee on Herbal Medicinal Products (HMPC) is to establish EU herbal monographs and EU list entries[7]. An EU herbal monograph contains the HMPC's scientific opinion on safety and efficacy data of a herbal substance and its preparations, intended for medicinal use. Monographs form the basis for the required individual medicinal product information such as the summary of product characteristics (SmPC) and the package leaflet (PL). These are published together with other documents, including an assessment report containing a review of all available data relevant for the medicinal use of the herbal substance or preparations. The monographs and list entries give applicants and NCAs a clear reference point when preparing or assessing an application for marketing authorisation or registration of (traditional) herbal medicinal products in Member States. In order to prevent EU herbal monographs from becoming outdated, there is an established process for the periodic review and, if necessary, the subsequent revision processes[8]. A revision of an EU herbal monograph could be triggered by, for example, a PRAC recommendation on a herbal substance/preparation.

3. Discussion

Common sources for safety signals include spontaneous reporting systems, clinical studies and scientific literature. The EudraVigilance database is an important source of information on suspected adverse reactions[9], frequently used for signal detection. However, underreporting of suspected adverse reactions is a general problem for medicinal products. For (traditional) herbal medicinal products this could be even more challenging due to for example misconception in the society that herbal products are safe due to their natural origin. In addition, most herbal medicinal products are over-the-counter (OTC) products and, consequently, patients might not report their use to their doctor or when they are admitted to hospital. As for all medicinal products, few reports could still be the basis for a relevant signal if well documented.

Importantly, the presence of a safety signal does not directly mean that a medicinal product has caused the reported adverse event, and additional aspects should be considered when assessing

[7] Procedure for the preparation of European Union herbal monographs and European Union list entries and appointment of HMPC rapporteurs and peer-reviewers (EMA/HMPC/887331/2022)
[8] Procedure for the review and revision of European Union herbal monographs and European Union list entries (EMA/HMPC/124695/2011 Rev.3)
[9] Adverse reaction; synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect: A response to a medicinal product which is noxious and unintended [Directive 2001/83/EC Art 1(11)].

potential causality. The composition of herbal substances/preparations as active substance of (traditional) herbal medicinal products presents a challenge. Herbal substances/preparations are complex mixtures of constituents and in most of cases, not all constituents in the medicinal product are known. In addition, herbal combination products are frequent, i.e., multiple herbal preparations of different origin in the same medicinal product.

In some herbal substances or preparations a few major constituents can be easily detected and characterised; minor constituents can be of significance for the safety of a medicinal product. Overall, it is the whole mixture of constituents that is relevant for the safety of the medicinal product. Moreover, different plant parts such as flowers, leaves or roots contain different constituents and a safety issue detected for one plant part may not be relevant for a medicinal product containing another part of the same plant. Furthermore, herbal preparations can be produced by steps that exceed comminution such as extraction, distillation, expression, fractionation, purification, concentration or fermentation that leads to herbal preparations as extracts, tinctures, essential oils, expressed juices and processed exudates. Herbal preparations from the same part of the plant but produced by different extraction solvents of diverse polarity, could have different safety profiles. For example, depending on the extracts and posologies of medicinal products with St. John's wort, some could cause interactions with other medicinal products. Adding to that, in most case reports a description of the herbal preparation is missing, and the plant names used may include a wide variety of synonyms in different languages.

Another important aspect to be considered for safety signals for (traditional) herbal medicinal products is that the EU herbal substances/preparations are also found in other product categories such as food supplements, cosmetics or medical devices. This aspect is not exclusive to herbal medicinal products and traditional herbal medicinal products as it is also the situation for other substances found in medicinal products in EU, for example vitamins. Importantly, herbal substances/preparations found in other product categories (i.e. not medicinal products) have different quality and safety requirements.

4. Summary and conclusion

In conjunction with Directive 2001/83/EC, Regulation (EC) No 726/2004 and Commission Implementing Regulation (EU) No 520/2012, as well as relevant GVPs, the following aspects should be taken into consideration for safety signals for (traditional) herbal medicinal products:

- The underreporting of suspected adverse reactions for (traditional) herbal medicinal products;
- There is generally very limited information on the herbal medicinal product involved in a suspected adverse reaction;
- The quality of products of herbal origin, including the botanical identification and phytochemical characteristics of herbal substances/preparations, is correlated to the safety of the medicinal product;
- Herbal substances/preparations are complex mixtures of constituents and adding to that, herbal combination products, i.e., multiple herbal substances/preparations of different origin in the same medicinal product, are frequent;
- Herbal substances/preparations are found in other product categories (i.e. not medicinal products) with different quality requirements.