Basic Requirements and Framework Conditions of Real-World Data (RWD) on Herbal Medicinal Products

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ABSTRACT

Real-world data (RWD) is becoming increasingly relevant for evaluating safety and effectiveness of medicinal products, including non-prescription medicines and herbal medicinal products in particular. In order to use real-world data for regulatory decision-making in the field of herbal medicinal products, it is crucial to have an accurate description the herbal substances and preparations, as herbal medicinal products, in contrast to chemically defined medicinal products, contain a complex mixture of natural compounds. However, it remains challenging to get standardised information on herbal products from current literature. This publication gives a brief overview of necessary information of herbal medicinal products in scientific literature and data sources to ensure high-quality real-world data.

Introduction

Real-world data (RWD) is gaining in importance in the medical and pharmaceutical fields. When using the terms real-world data or real-world evidence (RWE), it is necessary to clarify their meanings, as they have different definitions and are often incorrectly used interchangeably. RWD in this paper is defined as "data used for decision making that are not collected in [...] randomized controlled trials" [1]. In the EU, "Real-world evidence (RWE) is then defined as the information derived from analysis of RWD" [2]. While RWD is applied for prescription and nonprescription drugs, this paper focuses on herbal medicinal products that are often authorised as nonprescription medicines, also called over-the-counter (OTC) medicines and describes basic requirements and framework conditions for the quality of RWD on herbal medicinal products.

As RWD is becoming more and more relevant in the present time due to the "increased adoption of the internet, social-media, wearable devices, e-health services, and other technology-driven services in medicine and healthcare" [3], authorities reviewing herbal medicinal product applications might start integrating RWD into their assessment of both safety and effectiveness. The availability of databases with standardised data (e.g., ICD-11, MedDRA, SNOMED, IMPD, etc.), as well as the possibility of evaluating large amounts of data, promote this development. The "Data Analysis and Real World Interrogation Network" (DARWIN EU) was established in 2022 by the European Medicines Agency (EMA) to deliver RWE from across Europe on diseases, popula-

tions, and the uses and performance of medicines [4]. With help of DARWIN, EMA's Committee on Herbal Medicinal Products (HMPC) is looking for new data sources such as RWD on the use of herbal substances and preparations in the paediatric population according to their 2024 work plan. The objective is to improve the HMPC's WEU and TU assessments for children in order to harmonise practice for EU herbal monographs [5]. While regulatory authorities are currently taking a closer look at RWD, opportunities for the use of RWD have gained increasing attention, first from the prescription-only medicines and more recently from the self-care sector. The article "How can real-world evidence aid decision making during the life cycle of non-prescription medicines?" [6] reviewed the existing and potential applications of RWE for nonprescription medicines and established the specificities of non-prescription medicines in terms of RWD uses and sourcing of data.

Description of Herbal Substances/Preparations

Even though there is an immense amount of literature on the use of herbals, a literature search and subsequent assessment of published reviews revealed various difficulties. The main challenge is insufficient information on the category and quality of the herbal ingredient, which makes a robust analysis and conclusion very difficult. Since there is no official guidance how herbal preparations and herbal medicinal products should be described in publications, registries, and databases, this often is an important limitation of RWD publications. Thus, RWD on herbal medicinal products requires an appropriate description of the herbal active ingredient in accordance with EU guidance related to the description of herbal medicinal products. This is a prerequisite to draw regulatory conclusions. A good example is St. John's wort, as its efficacy and safety is strongly dependent on the herbal active ingredient and its components [7]. This shows that an exact description of the herbal substance or preparation is needed, as quality is key, impacting efficacy and safety.

WHAT NEEDS TO BE MENTIONED WHEN DESCRIBING HERBAL SUBSTANCES/PREPARATIONS IN SCIENTIFIC LITERATURE.

The following parameters should be specified to enable an appropriate description of herbal substances/preparations:

1. Name of the used herbal substance in Latin and, optionally, English.
2. Type of herbal preparation (e.g., dry extract, tincture).
3. Quantity of the (genuine) herbal preparation.
4. Drug extract ratio (DER genuine) or equivalent quantity of the herbal substance (as a range), if applicable.
5. Name and composition of extraction solvent(s), if applicable.

Herbal substances and herbal preparations are to be distinguished. According to the guidelines on the declaration of herbal substances and herbal preparations in herbal medicinal products "a declaration for a herbal substance should cover the name and the quantity of the herbal substance. The name of the herbal substance is the scientific Latin name of the plant species according to the binomial system (genus, species, variety and author) with the Latin term of the plant part" [8], whereas the herbal preparation is a "simply processed, comminuted plant material to complex processed preparations such as refined extracts" and "should cover the name of the herbal substance and the definition of the herbal preparation including the physical state, ratio of herbal substance to genuine herbal preparation (DER genuine, also named native DER), and extraction solvent(s) if appropriate" [8]. Both definitions demonstrate important and essential information on the quality of herbals, which should always be named; scientific Latin name of the plant species according to the binomial system (e.g., *Hypericum perforatum* L.), Latin term of the plant part (e.g., folium, radix, or fructus), physical state (e.g., dried or fresh plant), native DER (DER 3–7 : 1), and the extraction solvents (methanol, ethanol, etc.) [8].

Beyond the accurate description of the herbal preparation, it is important, if feasible, to provide a correct description of the finished product with its dosage form, posology, and indication in RWD publications, e.g., Hyperici herba dry extract (DER 3–7 : 1, methanol 80 % V/V) as film-coated tablets, 2–3 times 300 mg a day for the treatment of mild to moderate depressive episodes [7]. Further, distinction between the regulatory categories (herbal medicinal products, food supplements, medical devices, cosmetics, non-registered products) may be of potential relevance and should be indicated where possible. If known and existing, the brand name can be given. Depending on the scientific question of the RWD publication, the regulatory pathway of herbal medicinal products might be of potential relevance (full market authorisation, well-established use marketing authorisation, traditional use registration) [9].

Furthermore, consideration should be made not to confuse RWD on botanicals, i.e., food supplements with herbal ingredients under EU legislation or dietary supplements in the U. S. where another legal framework applies. In Europe as well, herbals can be medicinal products, food supplements, general food, medical devices, or even unregistered products. Therefore, distinguishing the different regulatory category of the products containing is key, as they may fall under different legislations with different requirements, notably on quality.

Conclusion

RWD is becoming increasingly important as a source for regulatory activities for herbal medicinal products. Nevertheless, there are still challenges limiting the potential of RWD in the regulatory field. An adequate description of the herbal ingredient and herbal medicinal product is essential, making it possible to draw clear and correct conclusions. As a recommendation, global recommendations or guidelines on the correct description of herbals in articles, publications, databases, and registries are needed, although it is acknowledged that when it comes to databases (and registries), it is a challenge to meet this high level of expectations, as detailed in 4 and 5 of the box, as this might not be available to doctors, pharmacists, or patients and, hence, not filled in. Thus, expectations should be balanced in relation to the

research question. But still, ensuring data on herbal products are of sufficient quality and contain minimal information would be a game changer for regulatory activities, academia, healthcare professionals and industry, and would ensure that the opportunities of RWE can be unleashed ultimately for the benefit of the patient.

Contributors' Statement

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Conflict of Interest

Salome Sophie Hölzle, Thorsten Reineke, Stefan Hoch, Bernd Roether and Matthew Francis are working for pharmaceutical companies producing and selling herbal medicinal products. Christelle Anquez-Traxler is working for AESGP and Nico Symma is working for Pharma Deutschland, both are pharmaceutical industry associations. The authors are members of the AESGP working group focusing on real-world data on herbal medicinal products.

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