

Consensus Statement on the Outcome of a Workshop on Paediatric Phytotherapy: Rationalising Optimal Dosing for Use in Children by Real-World Data

Authors

Andreas Hensel¹, Rudolf Bauer², Michael Heinrich³, Karin Kraft⁴

Affiliations

- 1 Foundation Plants for Health, Institute of Pharmaceutical Biology and Phytochemistry, University of Münster, Germany
- 2 Foundation Plants for Health; Institute of Pharmaceutical Sciences, Department of Pharmacognosy, University of Graz, Austria
- 3 Society of Medicinal Plant and Natural Products Research, UCL School of Pharmacy, University College London, United Kingdom
- 4 Gesellschaft für Phytotherapie, University Medicine Rostock, Germany

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Correspondence

Andreas Hensel

Foundation Plants for Health, Institute of Pharmaceutical Biology and Phytochemistry, University of Münster
Corrensstraße 48, 48149 Münster, Germany

Phone: + 49 (0) 25 18 33 83 41, Fax: + 49 (0) 25 18 33 33 81
ahensel@uni-muenster.de

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Herbal medicinal products (HMPs) play an important role in paediatric medicine. Based on the strong impact of HMPs in clinical practice, the costs of such products are covered by the statutory health insurance of some European countries. However, the European legal framework of the European Medicines Agency (EMA) for herbal medicine currently does not consider the use of many herbal drugs in children and adolescents because of an obvious lack of data. Many herbal monographs published by the competent scientific committee of the EMA (HMPC) restrict the use of HMPs to ages 12 or even 18 years and up. Thus, in many countries, HMPs lack adequate dosage recommendations for children.

The efforts made so far in assessing bibliographical data to substantiate the use of HMPs in paediatric medicine have had limited success. Collaboration of all stakeholders, therefore, is needed to develop new ideas and possible strategies.

In May 2022, the current situation was analysed in an e-Symposium, attended by more than 300 participants from medicinal and pharmaceutical academia, medicinal professional societies, regulatory authorities, and the pharmaceutical industry. Options to generate evidence for the use of traditional (T)HMPs in children and adolescents were discussed. The symposium concluded that

two approaches are of high interest: the generation of adequate datasets from real-world data (RWD) and real-world evidence (RWE), and extrapolating dosages for children by use of pharmacokinetic and clinical data from adults.

To further evaluate the use of RWD for the regulatory assessment of HMPs in children and for establishing validated dosage regimes for HMPs in paediatric age groups, a workshop titled *Paediatric Phytotherapy: Rationalization of Dosages for Children using Real World Data* took place in Bonn, Germany, on June 19, 2023, which was organised by three professional societies: the Foundation Plants for Health (PfH), Society for Medicinal Plant and Natural Product Research (GA), and the German Society of Phytotherapy (GPT). Experts from clinical practice, academia, the pharmaceutical industry, regulatory health authorities, and a company specialising in collecting RWD to generate RWE assessed possibilities, risks, and practical aspects for the generation, analysis, validation, and use of these data for closing the existing knowledge gap.

Discussions of all participants focused on potential RWD studies, which, in turn, should be the basis not only for child-oriented dosing recommendations for finished herbal products, but also for the respective drug monographs (e.g., HMPC monographs).

Continuous and large-scale data collection on the use of HMPs in Germany and some other countries is already routinely performed using electronic medical records by health information companies such as IQVIA. From such data, information on the use in children and adolescents can be extracted and subsequently analysed and reported/published. On a smaller scale, the

PhytoVIS project of Kooperation Phytopharmaka, Bonn, has also gained valuable RWD data.

Many herbal monographs published by the HMPC restrict the use of HMPs to ages 12 or even 18 years and up due to the lack of adequate data in younger children. This leads to the fundamental question: which data are adequate for HMPs?

In order to obtain valid and scientifically solid data, medical questions have to be precise and testable. A predefined plan of study and analysis is essential prior to the respective study, and data quality must be assessed for correctness, consistency, completeness, and timeliness.

It has been recognised that the EMA considers the evaluation of RWD/RWE for drug development and marketing authorisation. In addition, the HMPC has put the possibilities to use RWD/RWE for complementing treatment of children in its monographs on its work plan 2023 and is supported by the Paediatric Committee (PDCO) of the EMA. However, the fundamental question arises about an adequate database for HMPs.

It has to be kept in mind that the registration of traditional HMPs is based on long-standing and documented safe use in the European Union. Monographs could be expanded for use in adolescents and/or children if valid RWD provides such evidence. This also implies that new data might not necessarily change the (T) HMP monograph status. In contrast, HMPs covered by well-established use are based on clear risk/benefit evaluations based on clinical studies. This implies that new data (e.g., published as peer reviewed publications) could lead to a higher level of knowledge and can thereby be the basis to initiate an unscheduled review of the respective monographs by the HMPC.

Prior to the use of RWD, some problems must be solved, especially concerning the methodology of RWD generation, which is still partially under debate. RWD should be routinely collected data from a variety of different sources. Studies on RWD/RWE for use of HMPs in children should always be performed together with paediatricians. Based on an appropriate methodology for data generation, analysis, and interpretation, RWD/RWE can contribute to the further development of drug registration, especially by providing results in cases where randomised controlled trials (RCTs) are inadequate (e.g., for children due to ethical considerations). Concerning the need for data allowing the rationalisation of adequate dosage regimes for children, it must be discussed whether or not RCTs are suitable for pinpointing dosage regimes for children. In this context, it has to be considered if other study types, e.g., non-interventional studies from the real world, must be taken into account.

RWD/RWE could lead to invalid conclusions by over-interpretation or by inferring causal relationships from associations. Therefore, the challenge is to optimise and validate data quality. It has been pointed out by a representative from the German BfArM that, currently, the uncertainty of RWD/RWE might be too great to make decisions based exclusively on this type of data.

It has been discussed that additional datasets could improve the decision-making process and might be necessary for drug approval. The representative from the BfArM pointed out that RWD/RWE might be useful in a long-term perspective. However, it is currently unlikely that RWD could help to remove certain age groups from “off-label” use. BfArM mentioned that RWD can help

to reduce the number of children needed in RCTs. In this context, it has been discussed whether it is necessary to perform placebo-controlled studies in children if placebo-controlled studies for proof of efficacy have already been performed in adults.

It has been suggested that a pilot project on selected HMPs, for which adequate data based on the requirements of the HMPC monographs already exists (e.g., ivy leaves or marshmallow root), could be initiated to study the generation, analysis, and interpretation of RWD/RWE based on the existing blueprint. If all parties concerned, academia, industry, and regulatory agencies, are involved from the beginning, this could be a learning process for all of them to gain experience with the use of RWD/RWE with respect to the validity and limitations of RWD/RWE. The project could lead to a high impact publication and could be a guide for future applications of this concept. A publication based on such an analysis could also be used as a new data source, initiating an unscheduled monograph review.

In conclusion, the exchange of knowledge between stakeholders from academia, industry, and regulatory authorities was considered to be very useful. It will be essential to assess the more extensive context in European countries in more detail with an even more restricted and controversial use of HMPs. This meeting was intended to be the first step for a regular exchange of experiences, interests, and ideas to advance the issue of RWD/RWE in order to support more extensive use of HMPs in children and adolescents.

The consortium of PfH, GA, and GPT is very open to scientific interactions with the HMPC and industry and would be happy to serve as a joint expert group for helping to push forward HMPC monographs supporting treatment of the paediatric population by use of RWD/RWE.

Participants of the Workshop from June 19, 2023

Dr. Nicole Armbrüster (Bundesverband der Pharmazeutischen Industrie e.V., Germany); **Prof. Dr. Rudolf Bauer**, University of Graz, Austria, Foundation Plants for Health); **Dr. Emiel van Galen**, M.D. Chairman of Herbal Medicinal Product Committee; **Prof. Dr. Michael Heinrich** UCL, London, U.K., Foundation Plants for Health, Society of Medicinal Plants and Natural Products Research; **Prof. Dr. Andreas Hensel**, University of Münster, Germany, Foundation Plants for Health; **Dr. Ulrike Kastner**, Austrian Society for Phytotherapy; **Prof. Dr. Karel Kostev**, IQVIA Inc., Germany; **Prof. Dr. Karin Kraft**, University Medicine Rostock, Germany, Gesellschaft für Phytotherapie; **Dr. Olaf Kelber**, Steigerwald Arzneimittelwerk GmbH, Bayer Consumer Health, Germany; **Silvia Kruppert**, M.Sc., IQVIA Inc., Germany; **Angela Müller**, Dr. Willmar Schwabe, AESGP Committee Herbal Medicinal Products; **Dr. Bernd Roether**, Bionorika SE, Germany, Foundation Plants for Health; **Dr. Mathias Schmidt**, HerbResearch GmbH, Germany, Gesellschaft für Phytotherapie; **Dr. Barbara Steinhoff**, Bundesverband der Arzneimittelhersteller, Germany; **Dr. Nico Symma**, Bundesverband der Arzneimittelhersteller, Germany; **Dr. Jacqueline Wiesner**, Bundesinstitut für Arzneimittel und Medizinprodukte, Germany.