Thieme

Real-World Data to Document the Use of Herbal Medicinal Products in Children – Report of a Workshop in Krakow

Authors
Nico Symma[1], Andreas Hensel[2,5], Bernd Roether[3,5], Barbara Steinhoff[1,5], Rudolf Bauer[4,5]

Affiliations
1 Pharma Deutschland e. V., Bonn, Germany
2 Institute of Pharmaceutical Biology and Phytochemistry, University of Münster, Germany
3 Bionorica SE, Neumarkt, Germany
4 Institute of Pharmaceutical Sciences – Pharmacognosy, University of Graz, Austria
5 Foundation Plant for Health, Neumarkt, Germany

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Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

Correspondence
Em. Univ.-Prof. Dr. DDr.h. c. Rudolf Bauer
Institute of Pharmaceutical Sciences, University of Graz
Beethovenstraße 8, 8010 Graz, Austria
Phone: + 43 31 63 80 87 00
rudolf.bauer@uni-graz.at

ABSTRACT

The workshop "Real-world data to document the use of phytopharmaceuticals in children" was organized by the GA Foundation Plants for Health in collaboration with multiple international scientific societies on July 14, 2024, during the International Congress on Natural Products Research in Kraków, Poland. The event focused on leveraging real-world data and real-world evidence to support the use of herbal medicinal products (syn. phytopharmaceuticals) in pediatric care. The workshop aimed to discuss the current state and future approaches for utilizing real-world data/real-world evidence in expanding the use of herbal medicinal products in children and adolescents. Therefore, the workshop highlighted the unmet needs and challenges in documenting the effectiveness and safety of herbal medicinal products in children and emphasized the coordinated exchange and collaboration among academia, industry, and regulatory authorities. After an e-symposium in May 2022 with more than 300 participants and an in-person workshop on this topic in Bonn in June 2023, this workshop in Krakow was the third event of its kind hosted by the Foundation Plants for Health. Participants concluded that interdisciplinary collaboration is highly needed to establish qualified methods of data collection and assessment of real-world data, e.g., establishing requirements to incorporate nonprescription herbal medicinal products into electronic patient records and registries that can be accessed by all stakeholders.

Rationalizing the Use of (Traditional) Herbal Medicinal Products in Children: Current Situation and New Approaches

Prof. Dr. Andreas Hensel (University of Münster, Germany) provided an overview on the current use of traditional (T)HMPs in children, discussing both existing practices and potential new approaches. The World Health Organization emphasizes that "*children are no small adults*" regarding medicinal treatments, underpinning the EC's pediatric regulation initiative from 2007 aimed at developing child-specific drugs. After 17 years, progress remains moderate due to limitations in pediatric clinical trials [1, 2].

HMPs have been used since ancient times for minor, self-limiting diseases and are still widely used in Europe, including pediatric care. Despite general safety, detailed data on HMP use in children is scarce, especially with respect to dosing studies and effectiveness studies. Although HMPs are an integral part of pediatric treatment, drug registration often relies only on adult data, leading to "*off-label*" use in children. However, children differ from adults in body/organ size, drug metabolism, absorption, and body composition, necessitating tailored dosing.

Review and extraction of existing data could be a solution but possesses limited regulatory utility. High-quality controlled clinical studies (RCTs) have ethical and practical limitations and are very costly. Extrapolation from adult data is standard for many drugs but untested for plant-derived drugs. In contrast, RWD

means using observational data from various sources, e.g., electronic health records, but requires validation for regulatory acceptance.

In the past years, the FDA and the EMA began to consider RWD for drug utilization. Also, the EMA's HMPC has included RWD in its 2023 work plan for pediatric HMPs, with the support of the Pediatric Committee of the EMA. Main challenges for using RWD for HMPs for children are the collection of continuous and large-scale data and the validation of the data quality to meet scientific and regulatory requirements [1,2]. Therefore, there is a need for a concerted action to improve pediatric phytotherapy by leveraging RWD and addressing the unique challenges in dosing for children.

Herbal medicinal products in daily pediatric practice

Pediatrician Univ.-Doz. Mag. pharm. Dr. med. Ulrike Kastner (Austria) discussed the frequent use of HMPs in pediatric practice, emphasizing the challenges and off-label use due to a lack of authorized products for children, especially infants and toddlers.

In pediatric practice, a significant portion of children, around 60%, present with common cold symptoms and feverish illnesses, mostly viral infections affecting children under 6 years old. HMPs play a crucial role in this setting, with 85% of children in Germany receiving at least one HMP annually, and approximately 95% of Austrian pediatricians prescribing HMPs daily.

The primary indications for HMPs include respiratory tract infections, gastrointestinal disorders, skin diseases, and psychovegetative disorders. Commonly used medicinal plants include ivy, primrose, marshmallow, thyme, echinacea, chamomile, peppermint, and valerian.

HMPs offer several advantages in pediatric treatment. They provide mild treatment for frequent mild diseases and are, in general, well tolerated by children of all ages. HMPs are available in various forms like syrups, teas, tablets, and ointments. These treatments are highly accepted by patients and parents, with some countries even offering reimbursement through statutory health insurances. The safety of HMPs is documented through extensive empirical use and routine pharmacovigilance systems.

For respiratory diseases, HMPs exhibit a multimodal mode of action, which includes secretomotoric, secretolytic, anti-congestive, antitussive, antimicrobial, antispasmodic, and anti-inflammatory effects, making them effective in treating and preventing infections and supporting recovery.

Despite these advantages, the use of HMPs in children often occurs outside official marketing authorizations, leading to "*off-label*" use, especially in children under 6 years. This practice is due to the complexity of extrapolating adult data to children, limited data on pediatric use, and the risk of adverse effects falling on prescribing physicians or parents.

Challenges in integrating HMPs into pediatric practice include the lack of Good Clinical Practice documentation, the need for time-consuming and resource-intensive database generation, and a reliance on personal knowledge and interest in medicinal plants.

Future recommendations emphasize the need for official endorsements of HMPs for children based on RCT, RWD, or extrapolated adult data. Without this, pediatricians will continue to prescribe off-label, face inadequate dosage recommendations, and encounter more unverified food supplements or medical devices, risking the loss of an essential treatment option for children.

In conclusion, there is a critical need for proper data collection, validation, and official recognition of HMPs to ensure their safe and effective use in pediatric practice.

Real-world data on herbal medicinal products in children – industry food for thought

Angela Müller (European Self-Care Industry Association, AESGP, Germany) explored the industry's perspective on using RWD to improve the evaluation and safe use of HMPs in children. She emphasized the need for a reflection paper on data requirements for herbal substances used in children and a research project to ensure the safe use of herbals in this age group. The HMPC pilot project includes a study protocol and report focusing on the use of herbals in children, utilizing prescription data from Germany and Belgium. It aims to create a blueprint for similar studies and emphasizes the need for representative pediatric data [3].

Collecting RWD on herbals is difficult, noting that many databases do not contain relevant data on herbal products and that data related to herbal preparations in databases and scientific publications are often lacking a complete description of the herbal preparation [4]. Furthermore, a request by AESGP to the 20 data partners of the DARWIN revealed that only two of them included data on HMPs. Therefore, there is a need for high-quality RWD publications in scientific literature and for a standardized description of herbal substances and preparations in publications and databases. Tackling this, AESGP recently published a white paper to propose clear and consistent descriptions of herbal preparations in publications and databases to better incorporate HMPs in the future [4].

As a further example of collecting RWD, Angela Müller presented a pharmacy-based RWE study approach, highlighting the recruitment and engagement process for pharmacists and consumers. The study aims to generate RWE on the usage and patient-reported outcomes for an herbal product based on Pelargonii radix.

Overall, Angela Müller underscored the important role of RWD in documenting the use of HMPs, particularly in children, and advocates for strategic actions to improve the regulatory framework, data collection, and application of RWE for HMPs. Furthermore, Müller calls to grant access to the EMA databases to the industry.

Unmet need for real-world studies on the effectiveness of herbal medicinal products in children

Prof. Dr. Karel Kostev (IQVIA, Germany) highlighted the urgent need for more RWD to understand the effectiveness of HMPs in pediatric care. There is a growing acceptance of RWE among regulators, physicians, and patients, noting that clinical trials, particularly for children, are lengthy and costly [1,2]. RWD and other studies based on them have gained importance in evaluating the safety and effectiveness of HMPs. However, despite the increased acceptance of RWE, pharmaceutical companies are still hesitant to invest in such studies.

Exemplarily, Prof. Kostev presented the prescription patterns of antibiotics and phytopharmaceuticals for children with respira-

tory tract infections between 2013 and 2022. Respiratory infections are common among children and have a high economic impact. Although these infections are frequently viral, antibiotics are still commonly prescribed, despite their limited effectiveness in shortening symptom duration and the risk of antibiotic resistance. The study indicated that antibiotic prescriptions have decreased over time, while in parallel, the use of HMPs has increased, particularly between 2013 and 2018. This trend suggests a growing awareness among pediatricians on the limitations and risks of antibiotics [5].

Despite the promising trends, the presentation pointed out the lack of scientific literature on the efficacy and tolerance of HMPs in children. More RWD and RWE studies are urgently needed to fill this gap.

Prof. Kostev emphasized the potential of RWE studies, which are significantly cheaper than clinical trials, to provide valuable insights into the effectiveness of HMPs and calls for more comprehensive studies and better data access to fully realize the benefits of HMPs in pediatric care. He highlighted the strengths of the IQVIA Disease Analyzer database, which contains extensive patient data regarding prescribed and reimbursed medicines, making it a valuable resource for conducting epidemiological studies and supporting regulatory decisions.

Capturing use of herbal medicinal products in patient registries and electronic medical records

Dr. Simone Breitkopf (German Society for Pharmaceutical Medicine, DGPharMed, Germany) discussed methods for capturing the use of HMPs through patient registries and electronic medical records, and how these data sources can support research. The presentation provided an in-depth exploration of the methods and significance of integrating HMP data into healthcare databases, emphasizing the potential for enhancing regulatory decision-making through linked RWD as part of the EHDS.

A patient registry, as per the EMA's Patient Registry Initiative, is defined as an organized system that uses observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, followed over time. The primary objective is to leverage existing registries and establish high-quality new ones to provide an adequate source of post-authorization data for regulatory purposes, such as pharmacovigilance.

Dr. Breitkopf discussed the different types of registries, including disease registries, population registries, and product registries. Disease registries focus on specific diagnoses or conditions, population registries cover comprehensive data across entire populations (common in Nordic countries), and product registries collect data on patients exposed to specific medicinal products. Each type of registry collects RWD outside of RCTs.

Registry-based studies, which utilize the infrastructure and patient populations of one or more registries to investigate research questions, were highlighted as essential for analyzing RWD. These studies can be either clinical trials or NISs, as defined in EU regulation 536/2014. The presentation emphasized the suitability of RWD for regulatory purposes, citing examples where NISs using RWD supported regulatory assessments.

DARWIN EU, an EMA initiative within the EHDS, already includes the first projects to make use of routinely collected health data. DARWIN EU collaborates with various sources, including hospitals, registries, and insurance claims, to access comprehensive patient data. This initiative aims to link disease registries with nationwide healthcare administrative databases to enhance the breadth and depth of health data available for research and regulatory purposes.

Dr. Breitkopf also addressed the inclusion of HMPs in electronic medical records and patient registries. She suggested using the Pharmacy Product Number (PPN) or the German pharmaceutical registration number (PZN) to unambiguously identify HMPs in data sources collecting health data routinely. This would enable the tracking of HMP prescriptions, dosages, and usage durations, facilitating more detailed analyses and regulatory evaluations.

Dr. Breitkopf emphasized that combining patient information from healthcare, administrative, and clinical databases could broaden research perspectives and enhance the suitability of data for regulatory purposes and highlighted the role of integrating HMP data into patient registries and electronic medical records, underscoring the value of linked RWD in supporting regulatory decisions and improving patient care outcomes.

Real-world Data and Real-world Evidence to Understand Herbal Medicinal Products in Children

Dr. Tamar Lasky (Senior Advisor on RWE at the FDA's Office of Digital Transformation [retired], USA) provided the information on U.S. accomplishments on using RWD and RWE to enhance the understanding of phytopharmaceuticals in pediatric populations and emphasized the potential of RWD and RWE in regulatory decision-making and drug development.

The FDA's RWE program, initiated in response to the 21st Century Cures Act of 2016, aims to accelerate medical product development. The FDA created a framework in 2018 for evaluating the use of RWE to support the approval of new drug indications and post-approval study requirements. RWD, as defined by the FDA, includes data related to patient health status and healthcare delivery collected from various sources, such as electronic health records (EHRs), medical claims, registries, and patient-generated data. RWE is the clinical evidence derived from the analysis of RWD, providing insights into the usage and potential benefits or risks of medical products [6].

The FDA has several guidances and resources relevant to RWD and RWE, highlight the increasing importance of these data sources in regulatory decisions. Dr. Lasky noted that while RCTs remain the gold standard, observational studies based on RWD are crucial for understanding real-world outcomes and supporting regulatory assessments.

She provided examples of FDA approvals that incorporated RWE, citing a systematic review of publicly available FDA approval documents from January 2019 to June 2021. The review found that RWE played a significant role in 88 approvals, with 65 of these studies influencing the FDA's final decisions and 38 being referenced in product labels. This trend underscores the growing acceptance and utility of RWE in regulatory contexts.

Dr. Lasky also discussed the role of the FDA offices responsible for pediatric drugs, including the Office of Pediatric Therapeutics, the Division of Pediatrics and Maternal Health, and the Clinical Pharmacology Pediatrics Program. These offices ensure that children have access to safe and effective medical products, emphasizing the importance of pediatric-specific research and regulatory oversight.

The presentation highlighted the FDA's approach to botanical drug products, which includes phytopharmaceuticals. Botanical drugs are intended for diagnosing, curing, mitigating, treating, or preventing diseases in humans and consist of vegetable materials such as plant substances, algae, and fungi. The FDA has specific guidance for botanical drug development, requiring substantial evidence of effectiveness, safety, and adequate manufacturing controls.

Dr. Lasky suggested potential steps for advancing the understanding of HMPs in children, such as conducting literature searches, identifying relevant databases (e.g., DARWIN), and defining variables of interest, including safety and effectiveness outcomes. She cited examples of studies utilizing RWD, such as the PhytoVIS study [7], which investigated the use of herbal medicinal products in the pediatric population in Germany.

In conclusion, Dr. Lasky emphasized the great potential of using RWD and RWE to understand the impact of botanical drugs on pediatric health. This area intersects several unique fields, including RWD/RWE, pediatric drug development, and botanical drugs, presenting both challenges and opportunities for future research and regulatory advancements.

Real-world data in the authorization of herbal medicinal products for use in children – the perspective of the German Federal Institute for Drugs and Medical Devices

Dr. Jacqueline Wiesner (German Federal Institute for Drugs and Medical Devices, [BfArM], Germany) presented on the role of RWD in the authorization of HMPs for use in children, providing insights from the perspective of the BfArM.

The EMA has been incorporating RWD into all phases of drug regulation, particularly for post-marketing surveillance, safety studies, drug utilization, and disease epidemiology. Therefore, primary care databases are extensively used [8, 9].

Most studies using RWD are descriptive, focusing on incidence or prevalence rates of clinical outcomes or adverse events, though some comparative analyses also exist. Sometimes RWD studies generate different outcomes. A further problem is that RWD are sometimes heterogeneous, and subject to various biases and measurement errors. Therefore, RWD shall only complement clinical data, but cannot generate clinical evidence by itself. Additionally, RWD should always be product specific. Data on botanical groups or on HMPs with different extracts are not useful for registration of an individual HMP. Despite these challenges, RWD can provide valuable insights, particularly when combined from multiple databases, such as those available through the DARWIN EU project [8].

The monographs of the HMPC provide detailed information on the use of various herbal substances and preparations, including those applicable to pediatric populations. However, some indications and herbal preparations are not recommended for children due to safety concerns or lack of sufficient evidence. Out of the well-established use (WEU) monographs, 8 out of 19 indications (42 %) can be used in children below the age of 12.

Dr. Wiesner provided examples of how RWD can be used to answer specific safety and usage questions for HMPs in children. These questions include usage patterns in different age groups, comedications, duration of use, and appropriateness for self-medication.

Dr. Wiesner emphasized the usefulness of RWD in the development of new HMPs and supporting authorized HMPs and stressed the importance of study design tailored to specific questions and specific herbal products or preparations. Despite the potential of RWD to enhance the understanding and regulation of HMPs in pediatric populations, she acknowledged its limitations, such as data quality, availability, and interpretation challenges and pointed out the need for careful study design.

Prior to starting RWD investigations, discussions with registration authorities should be considered to pinpoint the specific questions to be answered and for optimized design of the study. Dr. Wiesner pointed out that it is essential not to insert to many questions into one RWD study, as this could lead to reduced impact.

Real-world data: What we want to know, need to know, can know and what is nice to know

Dr. Emiel Van Galen (Chair of the HMPC, Netherlands) outlined the different dimensions of RWD, focusing on its potential and limitations in the context of HMPs and discussed the utilization of RWD related to the use of HMPs in children. He focused on the potential and current experiences with RWD, emphasizing what is necessary, possible, and beneficial to know from the perspective of the HMPC.

Dr. Van Galen outlined the relevance of RWD for the HMPC, particularly in establishing EU herbal monographs and list entries. RWD can support the documentation of therapeutic use and safe conditions for well-established and traditional herbal substances and preparations. It can also aid in drafting an EU list of herbal substances.

He discussed the first experiences of the HMPC in 2024 with two pilot Darwin RWD studies. These studies, although not yet complete, are part of an ongoing learning process for the committee.

It is important to have a clear and unequivocal research question when searching for RWD. For example, data on the use of an HMP in different age groups, particularly focusing on children, should be stratified by age categories such as < 3 years, 3–5 years, 6–11 years, 12–17 years, and adults/elderly. Furthermore, it needs a precise description of the herbal substance or preparation as an active substance. This clarity is crucial to avoid irrelevant or missing data, ensuring the output is relevant and accurate. The description should be detailed enough to capture all necessary information but not so restrictive that it excludes significant data.

In the pilot searches, RWD can be obtained for periods up to 10 years, but includes data mostly on prescription medicines. However, the ideal scenario would be to have comprehensive data on the medicinal use of herbal products by patients and consumers,

incorporating the over-the-counter use of nonprescription medicines as well.

RWD searches by DARWIN are quickly advancing, focusing on stratification of indications and large databases. HMPC is interested in RWD in the long-term and broad medicinal use of HMPs, especially in specific age groups. A tailored research question is needed as well as a clear description of the herbal preparation for successful data retrieval.

In summary, RWD has the potential to enhance the understanding and regulation of HMPs, particularly for pediatric use. There are significant opportunities of RWD for improving the evidence base and regulatory framework for HMPs.

Conclusion and Outlook

The workshop underscored the significant potential of RWD and successfully brought together key stakeholders to discuss the use of RWD and RWE to enhance the understanding and regulation of HMPs, particularly for pediatric use. The presentations and discussions highlighted the current challenges, unmet needs, and potential pathways for future research and collaboration and emphasized the importance of integrating RWD into regulatory and clinical practices to ensure the safe and effective use of HMPs in pediatric populations.

The general discussion elucidated the need to produce respective data that can ascertain a safe and evidence-based use of herbal medicinal products in children, an issue that is not easy to solve particularly in the field of nonprescription medicines. Nonetheless, as an option for concrete actions, the conduction of a product-specific pilot study according to priorities to be considered by stakeholders could serve as a first step. Additionally, intensive interdisciplinary collaboration between all stakeholders is needed to establish qualified methods of data collection and assessment of RWD, e.g., establishing requirements to incorporate nonprescription HMPs into electronic patient records and registries that enable access for academia, authorities, health associations, and industry.

List of speakers of the workshop

- Dr. med. Simone Breitkopf, DGPharMed e. V., Germany
- Prof. Dr. Andreas Hensel, University of Münster, Germany
- Univ.-Doz. Mag. pharm. DDr. med. Ulrike Kastner, Pediatrician, Austria
- Prof. Dr. Karel Kostev, Scientific Principal at IQVIA, Germany
- Angela Müller, Dr. Willmar Schwabe, Chair AESGP Committee Herbal Medicinal Products, Germany
- Emiel van Galen M. D., Chairman of the Committee on Herbal Medicinal Products (HMPC) at the European Medicines Agency, The Netherlands
- Dr. Tamar Lasky, PhD, FISPE, Food and Drug Administration (retired), Silver Spring, MD, U. S. A.
- Dr. Jaqueline Wiesner, Head of the Department of Herbal and Traditional Medicines, BfArM, Germany

Organizing and supporting bodies

The event was a joint effort by:

- GA Foundation Plants for Health (PfH)
- Society for Medicinal Plant and Natural Product Research (GA)
- German Society of Phytotherapy (GPT)
- Austrian Society of Phytotherapy (ÖGPhyt)
- Swiss Medical Society of Phytotherapy (SMGP)
- Dutch Society of Phytotherapy (NVF)
- European Scientific Cooperative on Phytotherapy (ESCOP)
- Kooperation Phytopharmaka
- Komitee Forschung Naturmedizin e. V. (KFN)

Contributors' Statement

Organization of the workshop: N. Symma, A. Hensel, B. Roether, B. Steinhoff, R. Bauer; drafting the manuscript: N. Symma; critical revision of the manuscript: A. Hensel, B. Roether, B. Steinhoff, R. Bauer.

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Conflict of Interest

Rudolf Bauer and Andreas Hensel are professors of pharmacognosy and phytotherapy at independent universities. Bernd Roether is working for a pharmaceutical company producing and selling herbal medicinal products. Barbara Steinhoff and Nico Symma are working for Pharma Deutschland, a German pharmaceutical industry association.

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