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Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population

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Table of contents

1. Background

It is well documented that herbal medicinal products (HMPs) are widely used in the general population and specifically in children even if there are important differences among European countries due to specific historical developments and traditions (1-7).

Probably the most important reason for this general popularity is that parents consider HMPs as safer than the other medicinal products because they are “natural”, used over hundreds of years and may not be considered as “real drugs”.

Nonetheless even if documentation on some of the properties of the herbal medicines is often available, clinical information for properly evaluating indications, posology, length of treatment and safety in children is usually lacking.

HMPs are used in children and adolescents for minor but common problems such as Upper Respiratory Tract Infections (URTIs), gastrointestinal disorders, skin problems, sleep disorders, loss of appetite, urinary tract and gynaecology disorders (8-13). Moreover there are an increasing number of publications (14-29) regarding the HMPs used, often together with other medicinal products, for chronic diseases such as Attention Deficit Hyperactivity Disorder (ADHD), depression, inflammatory bowel disease, cystic fibrosis, rheumatoid arthritis, asthma or cancer. This creates the possibility that a HMP may interact with a standard treatment and highlights the need for more information about the use of such therapies.

Directive 2001/83/EC as amended by Directive 2004/24/EC (30) aims to harmonize the market for HMPs and provides a legal basis to facilitate their authorization/registration in Europe. Important tools in the harmonization process are the Community List of herbal substances, preparations and combinations thereof for use in Traditional Herbal Medicinal Products (THMPs) published by the European Commission and the Community herbal monographs for HMPs having well-established use (WEU) and/or traditional use (TU), established by the Committee on Herbal Medicinal Products (HMPC). Well-established use HMPs (WEU-HMPs) have a recognized efficacy and an acceptable level of safety and have been authorized for more than 10 years in a Member State. THMPs have been in medicinal use for more than 30 years, have been proved to be not harmful in the specified conditions of use and their pharmacological effects or efficacy are plausible on the basis of long-standing use and experience.

Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation (EC) 726/2004 (31) require that in order to obtain a marketing authorization, a Summary of Product Characteristics (SmPC) in accordance with Article 11 of Directive 2001/83/EC must be included in the application. The SmPC guideline (32) provides advice on the principles of presenting information in the SmPC. As far as children are concerned, the age limits should reflect the assessment of the available documentation for which satisfactory efficacy and safety have been shown and the benefit-risk assessment has been performed for each subset of paediatric population. Dose recommendation (e.g. mg, mg/kg, mg /m^2) should be specified per dose interval for each category as appropriate (age/weight/body surface area of subsets of the population). Very often HMPs for children do not completely satisfy the recommendations laid out in the SmPC guideline. This may result in attempts by manufacturers to sell such products as food supplements, in order to avoid the strict pharmaceutical requirements for quality, safety and labelling as an HMP.

It is unethical that children do not have access to properly assessed medications. Regulation(EC) No 1901/2006 as amended (33), the 'Paediatric Regulation', revolutionised the regulatory environment for paediatric medicines in Europe by ensuring that medicines for children are of high quality, ethically researched and authorised appropriately, without subjecting children to unnecessary trials. However, HMPs authorised through the well-established medicinal use procedure and THMPs are exempted from the requirement set out in this legislation to present either studies in the paediatric population in accordance with an agreed Paediatric Investigation Plan or proof of having obtained a waiver or deferral at the time of filing.

It is important to note that, despite such lack of data, a considerable number of European children take HMPs along with or without other medicines, so it is important that they are also studied in this age group.

One of the most important aims of the Paediatric Regulation is to reduce the very frequent off-label use of drugs in children, but the situation of HMPs is similar to the off-label use of medicinal products: they are commonly used but generally have not been adequately studied, they have been on the market for many years via multiple licence-holders, they have no protected intellectual property rights and yet they may be of therapeutic value to children. Moreover performing proper research is very costly and difficult to recoup if there is no incentive.

Taking into account the general priorities of indications of off-label medicinal products compared with those of HMPs, it would be useful to improve the situation to ensure all medicinal products intended for use in children have been properly assessed in that patient population.

2. Purpose

The aim of this document is to highlight the lack of clinical studies on the majority of herbal medicinal products in children and the need for initiatives to stimulate the conduct of clinical studies with HMPs properly designed for children.

3. Discussion

Importance of sound evidence

It is now well accepted that to find the most appropriate treatment for a patient, it is necessary to integrate the best evidence available to the clinician with the wishes of the patient. This is important for all types of medicines including WEU-HMPs and THMPs (34-35).

Considering the ‘best evidence’, the guideline, EMEA/HMPC/104613/2005, on the assessment of clinical safety and efficacy in the preparation of Community herbal monographs (36) refers to the level of evidence and the grading of recommendations used in the WHO General Guidelines for Methodologies on Research and Evaluation of Traditional medicine (37) which considers the strongest evidence is that obtained from meta-analysis of randomised controlled trials, and the weakest that obtained from experts’ opinions.

Considering experts’ opinions, lack of agreement between them has often been reported (38) raising difficulties for the clinician who has to make a decision on the best treatment for the patient. Regarding the need for information based on evidence, it is difficult to find good quality studies especially in children (39-41). For this reason, tools to design good trials for HMPs have been proposed by the CONSORT (Consolidated Standards of Reporting Trials) group (42). However, rigorous research is not limited to randomised clinical trials, which also have disadvantages such as costs (both of time and of

money) and sometimes ethical problems (43) as well as the risk of incorrect conclusions due to badly designed studies (44).

In some situations observational studies can have advantages (45-46), provided that such studies use validated tools such as the Newcastle-Ottawa Quality Assessment Scale (46). Moreover specific post marketing surveillance studies to define the long-term safety of herbal medicines are the most useful ones (47).

HMPC monographs

Eighty-eight monographs on HMPs for 183 indications have been published by September 2011.

There are 155 indications for traditional use and 28 for well established use and only one indication (the traditional use for skin disorders and minor wounds of Avenae fructus) that does not have any age restriction (see Annex Table 1-2).

According to the SmPC guideline (32) a paediatric indication may not be approved if it is not relevant, contraindicated, or because of lack of data or limited/no experience.

Thus, suitable indications for each age group of the tables are considered after excluding those not relevant, or contraindicated. The data show very clearly: the younger the child, the less is the probability of finding indications.

Table 1 shows the situation of WEU by age, where almost all the indications are approved for adolescents, 52.9% for children older than 6 years, 5.9% for children from 2 to 6 years and none for the younger ones.

In the case of TU (Table 2), 58.8 % are approved for adolescents, around 15% for children from 4 to 12 years, 2.8 % from 2 to 4 years and 1% for those <2 years of age. These results are mainly due to lack of efficacy and safety data in these age groups.

4. Conclusions

In spite of frequent use, clinical studies with HMPs in children and adolescents are lacking. For this reason, for the majority of the monographs on HMPs published to date, it was not possible to propose any indication for children.

The HMPC considers that there is a need for initiatives to specifically stimulate research in this field to allow the correct use of HMPs in the paediatric population.

The following approaches are proposed:

1- Identification of herbal substances/herbal preparations for which a therapeutic benefit is expected (HMPC and PDCO should identify appropriate criteria to select them).

2- Provision of guidelines and recommendations for developing appropriate paediatric studies for herbal medicinal products.

3- Promotion of funding to collect more data on monitoring safe use in children and to promote further research.

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6. Annex

Table 1

AGE	Well Established Use					
Years	Not relevant	Contra-indicated	**Total suitable indications per age** (=adults indication –not relevant ind. -contraindicated ind.)	Lacking/ insufficient data	Limited/ no experience	**N° and (%) of indications in HMPC monographs**
18			**28**			
12-18	4		**24**	2	1	**21 (87.5%)**
6-12	5	6	**17**	7	1	**9 (52.9%)**
4-6	6	6	**16**	7	8	**1 (5.9%)**
2-4	6	6	**16**	7	8	**1 (5.9%)**
< 2	6	7	**15**	7	8	**0**

Table 2

AGE	Traditional Use						
Years	Not relevant	Contra indicated	Medical Advise +/- lack of data	**Total suitable indications per age** (=adults indication –not relevant ind. -contraindicated ind.)	Lacking/ insufficient data	Limited/ no experience	**N° and (%) of indications in HMPC monographs**
>18				**155**			
12-18	8	0	**16**	**131**	49	4	**77 (58.8%)**
6-12	16	1	19	**119**	85	16	**18 (15.1%)**
4-6	23	1	19	**112**	83	14	**15 (13.4%)**
2-4	24	3	23	**105**	83	19	**3 (2.8%)**
< 2	24	9	24	**98**	84	13	**1 (1.0%)**