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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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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 them as less dangerous than “conventional” medicinal products because they are “natural”, used over hundreds of years and may not be considered as “real drugs”.

They can usually be bought without consulting a doctor. Even if consulted, the clinician has documentation on some of the properties of the herbal medicines, but very little clinical information for properly evaluating indications, posology, length of treatment and safety in children.

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 gynecology disorders (8-13). Moreover there are an increasing number of publications (14-29) regarding the HMPs used, often together with conventional 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 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 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 have a recognized efficacy and an acceptable level of safety and, usually, 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 and relate to age intervals where a different dosing is recommended and the information given should relate to ages for which satisfactory efficacy and safety have been shown.

Very often HMPs for children do not completely satisfy the above criteria. This may result in attempts by manufacturers to sell such products as food supplements, so as to overcome the requirements to demonstrate their quality, safety and adequate labelling.

It is unethical that children do not have access to properly assessed medications. For conventional drugs Regulation(EC) No 1901/2006 as amended (33), the 'Paediatric Regulation', revolutionized 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, THMPs and HMPs authorised through the well-established medicinal use procedure are not subject to 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 conventional 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: they are commonly used but 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 without any incentives is very costly.

Taking into account the differences between conventional drugs and HMPs it would be useful to improve the situation to ensure 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 studies on herbal medicine 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 conventional, complementary and alternative medicines (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 monograph (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 randomized 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 (39-40) even though many herbal preparations are standardized and can be adequately studied (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 randomized 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).

State of the art of HMPC monographs

Seventy-six monographs on HMPs for 155 indications have been published by November 2010.

There are 128 indications for traditional use and 27 for well established use and only one indication (the traditional use for skin disorders and minor wounds of Avenae fructus) does not have any age restriction.

The tables in the annex report the results of the analysis.

The SmPC guideline (32) says that 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, contraindicated or generally not recommended and the data show very clearly how the younger the child, the less is the probability of finding indications.

Table 1 show the situation of WEU by age where almost all the indications are approved for adolescents, 56.2% for children older than 6 years and none for the younger ones.

In the case of TU (table 2), 55.9% are those approved for adolescents, around 15% for children from 4 to 12 years, 1.7% from 2 to 4 years and 0.9% 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.

The HMPC would welcome information from stakeholders on experiences with studies on the use of HMPs including THMPs in the paediatric population.

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6. ANNEX

Table 1

AGE	Well-Established Use							
Years	Not recommended	Not relevant	Contra indicated	**Total suitable indications**	Medical Advise*	Lack/insufficient data	Limited/no experience	**N° and (%) of indications in the monographs**
>18				**27**				**27 (100%)**
12-18	1	3		**22**	1			**22 (95.6%)**
6-12	1	4	6	**16**	1	6	1	**9 (56.2%)**
4-6	1	4	6	**16**	1	6	9	**0**
2-4	1	4	6	**16**	1	6	9	**0**
< 2	1	4	7	**15**	1	5	9	**0**

**Salicis cortex (medical advise and only in cases other therapies failed, risk of Reye Syndrome*)

Table 2

AGE	Traditional Use							
Years	Not recommended	Not relevant	Contra indicated	**Total suitable indications**	Medical Advise +/- lack of data	Lack/ insufficient data	Limited/no experience	**N° and (%) of indications in the monographs**
>18				**128**				**128**
12-18	2	5	3	**118**	12	37	3	**66 (55.9%)**
6-12	3	6	5	**114**	19	65	12	**18 (15.8%)**
4-6	3	6	5	**114**	20	67	13	**14 (12.3%)**
2-4	3	6	5	**114**	24	67	21	**2 (1.7%)**
< 2	3	6	13	**106**	25	67	13	**1 (0.9%)**