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Human Medicines Development and Evaluation

Report - Workshop on Paediatric Formulations for Assessors in National Regulatory Agencies

31 May 2010, Time: 09:00-16:30

Role	Name
Chair/Vice-chair	Siri Wang / Emilie Desfontaine
Present	Assessors in National Regulatory Agencies: Adela Núñez Velázquez, Agnes Kövari, Anna-Lena Axelson, Audronis Lukosius, Cristina Stanciulica, Daan Debremaeker, Efa Anno, Emma Cassar-Buontempo, Florian Rauchensteiner, Gary Inwards, Giacomina Pugliese, Ilze Bārene, Isabel Ortega Diego, Jens-Uwe Bleich, Jolanta Witkowska-Ozogowska, Konstantinos Ghirtis, Leena Luukkanen, Maaïke van Dartel, Maria Konsap, Marie Mlynarova, Markéta Příhodová, Michael Chetcuti, Ricarda Hühne, Rosann Deegan, Rutger de Vries, Sarah Katherine Branch, Tarja Kankkunen, Tiago Vistulo De Abreu
	PDCO and PDCO Formulation Working Group members: Ann Marie Kaukonen, Hugo Devlieger, Francesca Rocchi, Robert Ancuceanu, Andreas Wilhelm Grummel, Christophe Lahorte, Catherine Tuleu, Diana van Riet-Nales, Sara Arenas-Lopez, Tony Nunn
	EMA: Agnès Saint Raymond, Paolo Tomasi, George Wade, Caroline Le Barbier, Pedro Franco, Piotr Kozarewicz, Caroline Bosc, Emma Sala Soriano, Blanca Quijano Ruiz, Konstantina Makrogianneli, Sophie Olivier, Thomas Girard
	WHO: Henning Gjelstrup Kristensen, Hua Yin, Worku Wondiyfraw
	FDA: Gilbert Burckart by TC

Introduction

This workshop was held at the European Medicines Agency on Monday 31 May 2010 and chaired by Siri Wang, Chairperson of the PDCO Formulation Working Group, and co-chaired by Emilie Desfontaine, EMA Paediatric-coordinator.

Siri Wang welcomed participants from national agencies, FDA, WHO and PDCO.

Participants were asked to confirm they don't have any conflict of interest in relation to all issues planned to be discussed during the meeting.



An introduction on the objectives of the workshop was given by Siri Wang. The adoption of the Paediatric Regulation (EC) No 1901/2006 and the consequent demand for paediatric studies have strengthened the focus on age-appropriate formulations. The workshop intended to provide an overview of the main challenges in assessing paediatric formulations development plans and of the remaining gaps in knowledge (e.g. excipients, palatability). It was also aimed at exchanging experiences and lessons learnt so far.

All participants briefly introduced themselves.

Presentations

1. 'Paediatric regulation: an update on submissions of paediatric investigation plans'

(Speaker: Paolo Tomasi)

Presentation:

The speaker reviewed the objectives of the EU Paediatric regulation, the obligations versus incentives, the PIP procedure, the main quality aspects that should be part of the PIP, the validation and compliance check. Some figures regarding PIP applications and PDCO Opinions were also presented.

Discussion:

Regarding Compliance Check, it was clarified that there is no decision, just opinion.

The increasing number of requests for modification of an agreed PIP can be explained by the fact that a substantial number of PIPs are submitted in the initial phases of the development in adults, as required by the Paediatric regulation.

We do not yet have statistics regarding how many of those requests for modification were related to the quality part.

Generics are excluded from the Paediatric Regulation, but National Assessors should keep in mind the points discussed during this workshop when assessing a generic medicinal product for paediatric use.

2. 'Introduction to the work of the PDCO Formulation Working Group: essentials on the paediatric needs with regard to the formulations; assessing part D.II of paediatric investigation plans; challenges and difficulties'

(Speaker: Siri Wang)

Presentation:

The speaker presented the work of the PDCO Formulation Working Group and the essentials on the paediatric needs regarding formulations that are expected in Part D.II of a PIP. The challenges related to formulations during a PIP process were described.

Discussion:

Clarification of Article 8 definition (authorised medicinal products with Supplementary Protection Certificate or patent) was given by Paolo Tomasi, emphasizing also the fact that the Paediatric Regulation does not apply to generics and that if a product is authorised and off patent, there is no obligation for a PIP (according to the Global Marketing Authorisation concept).

There was a discussion regarding off label use of medicinal products in the paediatric population. One of the risks of this practice is the inaccuracy of dosing and the increase of drug adverse reactions. The first challenge is to have better knowledge about this off-label use. Some of the PDCO members were able to share their experiences as practicing medical doctors. A specific survey is also going on. However, it is very difficult to interpret data from off-label use in paediatrics.

3. 'Collaboration with other groups and committees such as WHO, FDA and EuPFI'

(Speakers: Agnès Saint-Raymond, Piotr Kozarewicz and Caroline Le Barbier)

Presentation:

Paediatric sector and Quality sectors are working together on paediatric formulation issues. They are also collaborating internally and externally with various groups.

Internal collaboration: various committees (PDCO, CHMP...) and working parties (QWP, BWP...).

External collaboration: FDA (mainly through monthly teleconferences), NIH, EuPFI (European Paediatric Formulation Initiative), WHO (global campaign 'Make medicines child size', PmRN-Paediatric Medicines Regulators' Network).

Discussion:

EuPFI and USPFI are working together on the common project to build a database gathering safety data on excipients used in paediatric formulations.

WHO is developing a guideline on the development of paediatric formulations, which is currently in draft. WHO is also proposing trainings on formulations to manufacturers in India and Africa. The work done in developing countries is also applicable to Europe and US (e.g. work on fixed-dose combinations for antiretroviral for children). There is a need to collaborate and communicate to be sure that medicines are available everywhere.

Next meeting of the PmRN (Paediatric medicines Regulators' Network) will be in December in Singapore.

4. 'New pharmaceutical form: definition'

(Speaker: Thomas Girard)

Presentation:

Clarification on the definition of a new pharmaceutical form was presented in order to better understand which case triggers an Article 8 and which does not.

Discussion:

This general guidance will be published soon on the public EMA website.

5. 'Presentation on preliminary data from paediatric investigation plans submitted to the PDCO Formulation Working Group for assessment: types of requests to and advice from the PDCO Formulation Working Group and PDCO based on proposals and arguments from the applicants'

(Speakers: Blanca Quijano Ruiz and Caroline Bosc)

Presentation:

Statistics on PIP applications assessed by the PDCO Formulation Working Group were presented. The different issues identified by the PDCO FWG during their assessment were described (main issues depending on the pharmaceutical form, the route of administration or the composition).

6. 'Clinical paediatric issues with dosage forms, e.g. acceptability/palatability of formulations, size, administration of IV formulations and through feeding tubes, etc'

(Speakers: Sara Arenas-Lopez and Tony Nunn)

Presentation:

The main challenges related to the clinical administration of paediatric formulations were described. For example: acceptability of tablets and capsules depending on the size and the age, palatability of oral formulations, dosage forms needing manipulations, specific paediatrics challenges related to intravenous use.

Discussion:

In PIP Opinions, companies are sometimes asked to assess palatability of their oral liquid formulations in the paediatric population. There are some age-appropriate tools that can be used during clinical trials (e.g. scales to be included in clinical trials, electronic tongue and taste panel), although they are not simple and present many bias (e.g. cultural differences). It was mentioned that the possibility of having a standard tool regarding the above issue would be very useful. It could be part of the future guideline on development of paediatric formulations. However, having a unique simple tool is not possible.

7. 'Excipients: safe or not safe; what do we know?'

Presentations:

- **'Preservatives'**

(Speaker: Piotr Kozarewicz)

The current problematic situation in relation to the safety of preservatives was pointed out during the presentation. The current approach is that: preservative free formulations should be considered whenever possible; when preservatives are required, the concentration should be at the minimum level and a thorough justification for the choice of the preservative should be provided.

- **'Antioxidants, colouring agents, taste masking agents and co-solvents'**

(Speakers: Caroline Le Barbier and Pedro Franco)

Speakers gave an overview of the issues related to excipients encountered during the assessment of the PIPs; furthermore some specific cases were presented. The conclusion was that there is a need for further research on excipients in paediatric formulations. In addition, further guidance must be developed.

- **'Poorly water soluble substances: challenges, options and limitations for children'**

(Speaker: Ann Marie Kaukonen)

An increasing number of poorly soluble compounds decrease the number of options remaining for paediatric formulations. The different formulations approaches for parenteral and oral products poorly soluble were reviewed. The examples of some problematic co-solvents were given (ethanol, propylene glycol). Lipid formulations options and cyclodextrins as solubilisers of lipophilic compounds were presented.

Discussion:

Exposure to excipients is different in food and in medicinal products. How applicable is the food legislation to medicines? Taking the example of the colorants: in general, when the colorants are considered acceptable for food, can they be acceptable as well for use in medicinal products? It seems the most important point to take into consideration is whether or not chronic studies have been performed in children.

8. 'Formulations for clinical trials in children: possibilities and pitfalls?'

(Speaker: Robert Ancuceanu)

Presentation:

Formulation refers either to the process in which different components are combined or the dosage form. The speaker reviewed the available data regarding paediatric formulations in clinical trials. When it is different from the to-be-marketed formulation, challenges related to the use of the adult formulation or to the use of extemporaneous formulations in clinical trials were discussed. Finally, challenges related to blinding were exposed.

Discussion:

An important lack of information is found regarding formulations in clinical trials. National assessors explained that the level of information given depends on the phase of development: there is a remarkable lack of information regarding the formulation process during phase I and II.

The main problem is that there is a restricted legal basis to request more information from the applicant. In this regard, the future guideline could help.

9. 'Existing guidelines (i.e. regarding quality, formulation and excipients): what do we have; are they relevant for paediatrics?'

(Speaker: George Wade)

Presentation:

The main guidelines currently available as well as other possible sources of information were listed.

10. 'Draft Guideline on the Pharmaceutical Development of Medicines for Paediatric Use'

(Speaker: Diana Van Riet-Nales)

Presentation:

The current content of the draft guideline was presented.

Discussion:

There is a need to set up communication ways between EMA, PDCO FWG and National Competent Authorities to improve consistency in general and to share information on safety of excipients in particular. The example of MHRA not aware of PDCO FWG recommendations on the ethanol content of one product involved in a PIP procedure highlighted the need for a common platform for scientific exchanges (e.g. blog accessible from the different parties?). Most importantly, the future guideline could be the common tool that is currently lacking. The participants were in agreement of adding an annex in the guideline (updated on a regular basis) listing the excipients with the available information on their safety. One of the main challenges of this guideline is to define the level of details that should be provided.

Agnes Saint Raymond stressed the fact that an important connection exists between Paediatric Investigation Plan and Marketing Authorization as the Paediatric Investigation Plan is a requirement for a Marketing Authorization.

11. 'Completion of the development of a formulation: requirements for compliance check versus requirements for marketing authorisation'

(Speakers: Caroline Le Barbier and Pedro Franco)

Presentation:

Compliance check procedure was reminded. Requirements from a quality view point were exposed through several examples.

Discussion:

It appeared that no participant from the National Agencies had already been involved in the compliance check of a PIP so far.

12. 'Assessment of a marketing authorisation application (Awareness of the paediatric investigation plan recommendation from a quality point of view; Issue in relation to generic)'

(Speaker: Pedro Franco)

Presentation:

The importance of the awareness of the PIP recommendations from a quality point of view when assessing a MAA was highlighted through several examples (e.g. impurities, breakability). Generics are excluded from the Paediatric Regulation therefore no Paediatric Investigation Plan is needed, but the same kind of quality recommendations should be kept in mind during MAA assessment.

Discussion:

The ways to find out if a specific product has a PIP and the corresponding recommendations are:

- The EMA paediatric database that is accessible to the PDCO members and NCA members of the Clinical Trials Authorization Units.
- PIP Opinions published on EMA public website.

Conclusion

There is limited experience on paediatric formulations development given the relatively "young" EU Paediatric Regulation.

All the different parties involved are on a learning curve, but to improve this situation a closer collaboration between PDCO, PDCO FWG and National Agencies is required. NCA were encouraged to "use" their PDCO National delegate as a national contact point. They can also contact the PDCO FWG on a case-by-case basis or become part of the national experts in the PDCO FWG.

Scientific research is also needed to fill the gaps in knowledge, e.g. safety of excipients in the paediatric population.

The need for an EMA Guideline on development of paediatric formulations was reinforced during this workshop. It would help in sharing awareness of the issues and challenges and in harmonizing assessment of both PIP and MAA.