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Human Medicines Development and Evaluation

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

08 November 2011, Time: 09:00-16:30

Role	Name
Chair/Vice-chair	Siri Wang / Ann Marie Kaukonen
Present	Assessors in National Regulatory Agencies: Agnes Kövari, Isabelle Delneuve, Antoniya Purcheva-Georgieva, Boyka Vaseva, Radka Hostašová, Birgitte Corydon-Petersen, Maria Konsap, Niina Makkonen, Saira Antila, Elisabeth Ricchi, Christel Raffournier, Maria Orfanon, Beata Szabady, Mirza Catibusic, Maria Di Marzo, Danila Renzo, Hali Nur Herzi Aden, Dace Peiseniece, Emma Cassar Buontempo, Fokaline Vroom, Rutger de Vries, Maja Walentynowicz, Marie Mlynarova, Nevenka Tršinar, Carmen Mónica Beteta Robles, María García-Vaquero Soriano, Anna-Lena Axelson, David Deutsch, Morag Bratby, Efua Anno, Godwill Iheagwaram, Delphine Ammar, Øyvind Holte, Gunnar Þór Gunnarsson
	QWP members: Cornelia Nopitsch-Mai
	PDCO and PDCO Formulation Working Group members: Daniel Brasseur, Jacqueline Carleer, Catherine Tuleu, Anne Paavola, Badis Bensaad, Andreas Grummel, Lida Kalantzi, Francesca Rocchi, Herbert Lenicker, Jolanta Witkowska-Ożogowska, Nela Vilceanu, Nigel Fox
	EMA: Emilie Desfontaine, Piotr Kozarewicz, Caroline Le Barbier, Pedro Franco
	EDQM: Julia Maier
	Health Canada: via Adobe Connect Barbara Nije

Introduction

This workshop was chaired by Dr Siri Wang, Chairperson of the PDCO Formulation Working Group, and co-chaired by Ann Marie Kaukonen, EMA Paediatric co-ordinator.

Siri Wang welcomed participants from National Agencies, EDQM and the PDCO.

Participants were asked to confirm that they did not have any conflict of interest in relation to any issue planned to be discussed during the meeting.



An introduction to the scope and the objectives of the workshop was given by Siri Wang. The Paediatric Regulation (EC) No 1901/2006 has raised the awareness about the need for development of paediatric formulations and forms. New regulatory guidance is being developed on paediatric specific issues: the draft guideline on pharmaceutical development of medicines for paediatric use is presently under consultation until 31 December 2011. In view of the feed-back received after the first workshop on paediatric formulations, held on 31 May 2011, and the still emerging regulatory framework on paediatric formulations, the general scope of the current workshop was to share the experiences gained at the PDCO and the present approach in reviewing the appropriateness of paediatric formulations as part of the paediatric investigation plans (PIP).

Presentations

1. PIP assessment procedure

(Speaker: Emilie Desfontaine)

Presentation: A short overview of the paediatric regulation and its objectives were provided. The review procedure of paediatric investigation plans (PIP) by the paediatric committee (PDCO) was clarified, including the steps for review of paediatric formulations and the involvement of the PDCO Formulation Working Group (FWG) and the Quality of Medicines sector at the EMA.

The Paediatric Committee's Formulation Working Group was established in February 2008. The FWG is currently composed of 15 formulation experts. Experts are from the PDCO, the Quality Working Party and Medicines Regulatory Authorities in European Union Member States, as well as from hospitals or academia. The group is chaired by a member of the PDCO.

The FWG reviews the proposed paediatric formulations of a PIP for the first time before the Day 30 PDCO discussion and can suggest modifications to the PDCO. In reviewing the proposed formulations, the approach of the FWG is to evaluate any paediatric specific issues and/or the development strategy; this differs from the review of a quality file of a Marketing Authorisation Application (MAA). The PIP Summary Report documents the review of the PIP including comments from the FWG and outcomes of the PDCO discussions. The sections on Quality (D.I.c, D.II) contain the main information relating to the planned paediatric formulation(s), although information on the proposed dosing may be found in the clinical sections.

As the paediatric development must be in compliance with measures and timelines agreed in the PIP Decision, a positive compliance check is compulsory for validation of a MAA (a copy of the PIP Decision is provided in Module 1.10).

Discussion: The PDCO FWG was established to answer the need to complement the expertise of the members in the PDCO with respect to formulations and dosage forms.

It was further clarified that PIPs are not exclusively linked to medicinal products seeking marketing authorisation via the centralised procedure, also national applications or applications submitted via decentralised or mutual recognition procedures may have a PIP.

For off-patent medicines, PIPs are not mandatory, but incentives are in place in case a medicinal product is developed specifically for the paediatric population (paediatric use marketing authorisation; PUMA). A PIP is needed for a PUMA.

2. Regulatory update on guidelines relevant to paediatric formulations

(Speaker: Piotr Kozarewicz)

Presentation: The presentation summarised current guidelines and other documents, which are relevant to the development of paediatric formulations.

Guidelines constitute an important tool in medicines development as their purpose is to set out principles and general requirements to be followed. The armamentarium of regulatory guidelines dedicated to paediatric topics is still very limited and further development in this area is needed. To address the need, either new guidelines are being prepared, e.g. Guideline on Pharmaceutical Development of Medicines for Paediatric Use, or existing guidelines will be reviewed to include paediatric specific information e.g. Guideline on excipients in the label and package leaflet of medicinal products for human use.

Some non-EU guidelines are emerging and these can also be consulted, e.g. the WHO Guideline: Development of paediatric medicines: Points to consider in pharmaceutical development. Also the food legislation can be a source of information on some aspects (e.g. excipients).

Discussion: Many concepts expressed in guidelines (for adult medicines) on pharmaceutical development are relevant as the general principles may well be applicable to paediatric formulations including e.g.: Excipients in the dossier for application for marketing authorisation of a medicinal product, ICH Q8: Note for guidance on pharmaceutical development. However, it should be acknowledged that guidelines are not legally binding and deviations from the guidelines are acceptable providing they are adequately justified.

3. Draft guideline on pharmaceutical development of medicines for paediatric use

(Speaker: Cornelia Nopitsch-Mai)

Presentation: An overview on the draft guideline was presented and the audience was reminded that it should be read in conjunction to the Directive 2001/83/EC and the (paediatric) Regulation (EC) No 1901/2006, and other guidelines relevant to pharmaceutical development. The new guideline is intended to introduce additional, paediatric specific aspects only. The scope of the guideline covers paediatric medicines as part of marketing authorisation applications or any variations related to the paediatric population. The principles of the guideline are to be applied in PIPs. Pharmaceutical problems and challenges related to administration of paediatric medicines are discussed as background for the guideline. The main principles of the guideline on aspects related to oral, nasal, ocular, cutaneous, and parenteral administration were presented. The basis for the choice and justification of excipients was reviewed, with the need for an overall risk-benefit evaluation in case excipients with potential safety concerns cannot be avoided.

Discussion: Although generic products do not require a PIP for the validation of the MAA, the same considerations as in PIPs should apply with respect to dosage forms for paediatric use. The problematic situation of palatability testing was further discussed for generic products where no clinical trials are conducted and the possibility to collect palatability testing during post-marketing was raised.

The principles of the guideline should similarly be applied also to formulations used in clinical trials, although specific considerations may apply in view of the stage of development.

The subdivision of tablets was discussed and the FWG informed that content uniformity of tablet parts has been requested in PIPs in cases where dosing has been seen as critical, and only a part of the tablet used to provide a lower dose. It was concluded that assessors can require content uniformity beyond the pharmacopoeial requirements for breakability where needed (e.g. for tablets with low content of active substance).

4. Age appropriate formulations - paediatric needs

(Speaker: Catherine Tuleu, on behalf of Tony Nunn)

Presentation: The main considerations on the choice of dosage form and route of administration in relation to age group and dosing needs were presented.

A major question on oral dosage forms is 'at what age can children take tablets or capsules'? There is little published evidence linking the size of tablet/capsule and the acceptability at different ages. Mini-tablets may be acceptable from 2-3 years of age, but in fact only half of 9-11 year olds will accept tablets, all depending on the tablet/mini-tablet size and the clinical condition of the children. PIP applicants proposing to use tablets for children under 12 years should be expected to demonstrate acceptability during clinical studies and to propose alternative administration strategies where tablets are found not acceptable.

For any alternative administration strategies, e.g. administering the dosage form with food or liquid and especially where the dosage form is manipulated by crushing, there is the risk of modifying the bioavailability and pharmacokinetic profile, which can affect efficacy and safety of the product. In cases where alternative strategies need to be considered, the consequences of the proposed strategy must be verified to assure consistent and reproducible quality and bioavailability confirmed clinically.

A major issue with injections is drug concentration and the need to ensure that dose volumes can be measured accurately and infusion rates can be delivered accurately. The injection vial size should assist in preventing medication errors through miscalculation. Compatibility with common injections and infusions should be investigated.

The need for accurate and precise dosing will greatly affect the choice of dosage form, the choice of strength/concentration and the requirements for the measuring device. For example, for oral liquids, the measuring device should be part of the presentation and the graduation (in volume units) shown to provide accurate and reproducible dosing across the full dosing range.

Discussion: For chronic conditions, the importance of the choice of the dosage form and its acceptability to the child is heightened. In practice, carers of patients with chronic conditions are likely to use any means possible to deliver the medicine. The importance of including any available information on incompatibility with food or beverage described in the product information was acknowledged.

Further to the discussion of risks involved in dosing practices, it was recognised that spreading of information both to healthcare personnel, carers, parents and children could be an important aspect of improving medication/treatment of children and reducing risks of medication/dosing errors.

5. Excipients – general approach

(Speaker: Caroline Le Barbier and Pedro Franco)

Presentation: While reviewing the PIPs, it was found that one of the major issues relates to excipients. European guidelines on excipients, the reflection paper on paediatric formulations and the

upcoming guideline on pharmaceutical development for paediatric formulations, opinions of the CHMP, opinions of the European Food Safety Agency (EFSA) and literature are consulted during the assessment. The presentation was illustrated with issues on the following excipients (non-exhaustive): colourants, preservatives, flavouring agents and sweeteners. The main uncertainties lie within the safety and the need for further data informing on doses that could be considered safe. Four case studies were presented focusing on the main issues encountered in PIPs, i.e. justification for excipients with known adverse effects, excipients chosen and their potential toxicity, justification of preservatives and their level.

Discussion: The possibility and usefulness of a 'negative' or 'positive' list of excipients was discussed. As the safety of excipients is linked to dose, length of treatment, route of administration and target age subsets, and as data to establish safe levels are often lacking even for excipients with identified risks, such lists were not seen as feasible. There is a need to provide information on the excipients where concerns exist and to identify where additional data are needed. The ongoing EuPFI project to compile published information on excipients and to make this available in a publicly accessible database was seen as very encouraging.

6. Development of paediatric formulations - points to consider

(Speaker: Ann Marie Kaukonen)

Presentation: The presentation contained considerations on paediatric formulations in view of the properties of active substances in relation to dosing needs and potential risks associated with the use of different formulation approaches during the development, and/or across age groups. The PIP should provide a formulation development strategy with a justification that reviews the active substance properties (solubility, lipophilicity, solid state properties, stability, permeability, absorption mechanism, intestinal first pass) as a rationale for the development in relation to the proposed dosing and the targeted age range and condition to be treated. The potential hurdles and risks associated in achieving the targeted product properties and alternative strategies should be discussed.

The use of a different formulation strategy in paediatric compared to adult formulations may generate significant differences in exposure for compounds having solubility-limited oral absorption, especially if combined with permeability limitations and/or significant intestinal first-pass. Considerations on excipient effects on e.g. intestinal transit times or transporter function should be discussed as part of the formulation strategy. as this may have an impact on bioavailability.

Discussion: Dosing needs for clinical trials was raised as an issue often requiring clarifications during the assessment of clinical trial applications. The need for accurate and precise dosing (e.g. weight or surface area normalised) may be even higher in clinical trials than for the final marketed product, as the results provide the relationship between exposure and efficacy and safety, hence, the dose. The possibility to use dose banding is one of the potential outcomes of a clinical trial and may then affect the choice of the appropriate dosage form.

Administration through feeding tubes represents an additional source of inaccuracy of dosing and needs to be considered. Dose recovery after extrusion through the feeding tube using flush volumes relevant to the age group is requested to demonstrate feasibility of approach. The particle size (active or dosage form), viscosity, volume and active substance (and excipient) properties will contribute to the feasibility of accurate dosing and to the risks of incompatibility.

7. Experience of paediatric formulations in marketing authorisation applications

(Speaker: Elisabeth Ricchi)

Presentation: Some examples were presented on paediatric formulations recently submitted as part of marketing authorisation applications or variations. Issues related to the choice of preservative system, the lack of palatability studies, the concentration of preservative(s), the appropriateness of the measuring device and reconstitution method/instructions were discussed. For clinical trial applications, issues on the suitability of the excipients, accuracy of dosing and acceptability of the preparation for administration (.e.g. via nasogastric feeding tube) had been identified.

Discussion: The examples highlighted the need for a guideline addressing paediatric specific aspects of pharmaceutical development. The need for collaboration between clinical and pre-clinical assessors is central to address the appropriateness of paediatric formulations, also in view of aspects related to acceptability and palatability. The lack of palatability studies was discussed as an important issue affecting potentially the clinical outcome.

8. Acceptability and palatability - methods available for assessment

(Speaker: Catherine Tuleu)

Presentation: Acceptable palatability [overall taste and acceptability of dosage form (size, shape)] is essential, though a major and complex challenge. Formal studies examining role of palatability and formulation factors involved in medication compliance, adherence, and concordance relationship are lacking. Many taste-masking strategies are available and should be chosen and assessed concomitantly to the dosage form (age appropriateness, safety of excipients, mixing with food, ease of administration etc). Taste should be evaluated as early as possible during development, but validated pre-clinical taste assessment methods are lacking. So human palatability assessment is inevitable and the methodology is important especially when children are involved. Special considerations (physical, emotional and cognitive levels of development) should be made to develop tasks that are understandable to children, with adapted modes to communicate their opinions or perceptions e.g. appropriate scales and measures. Parents and carers can be involved if the child is too young for verbal evaluation. There is a strong need for a concept paper for a guideline on the demonstration of 'palatability' of paediatric medicinal products to support assessment of PIPs in respect to palatability.

Discussion: As discussed already in connection to previous presentations, acceptability and palatability were seen as an important point to address during development of paediatric medicines. It was agreed that further work in this field is needed.

9. Case studies from paediatric investigation plans

The participants gained some practical experience of the variable scenarios that are encountered during the assessment of the paediatric formulations in the PIPs. The afternoon was dedicated to review and discussion of the case-studies in smaller groups, followed by discussion in plenary.

Conclusion

Compared to the previous workshop, the lively exchange demonstrated a leap forward in the awareness and understanding of paediatric-specific issues in the development of paediatric formulations. The participation of 43 assessors from the national agencies from 25 countries with diverse backgrounds and involvement in both MAA and clinical trial applications provided a productive setting for the exchange of information and views and was very encouraging.

The need for follow-up workshops was agreed, considering especially emerging guidelines and evolving research in several aspects relating to the palatability, age appropriateness of dosage forms and routes of administration of medicines intended for children of all ages.