

## **Editorial**

### **Formulating better medicines for children – still too far to walk**

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The objective of European Paediatric Formulation Initiative (EuPFI) is to promote collaboration between industry, academia, clinical and regulatory professionals to facilitate preparation of better and safe dosage forms for children. It provides the platform to discuss contemporaneous issues shared by scientific community in developing paediatric medicines. In order to achieve these objectives, EuPFI conferences have been successfully held for six years. Continuing on its mission, in 2015, EuPFI organised the 7<sup>th</sup> conference on “Formulating better medicines for children” in association with APV (Arbeitsgemeinschaft für Pharmaceutische Verfahrenstechnik). It brought together 140 delegates and keynote speakers from 23 countries on 16-17<sup>th</sup> September 2016 in Antwerp, Belgium to present the current needs and challenges in paediatric drug development. It highlighted in particular the implications from multiple stakeholder perspectives, including regulators, industry representatives academics and clinicians.

The programme aimed to focus on key efforts to expedite the crucial development of paediatric formulations in a global context and to look into both the clinical and regulatory hurdles as well as discuss technological and scientific improvements in paediatric formulation research. Interactive preconference workshops organised just before the main conference offered the opportunity to profit from expertise on two key topics: “Challenges of Administering Medicines to Neonates” and “Constructing & Evaluating Paediatric Investigation Plans (PIPs)”. The administration of drugs to neonates poses significant challenges. Virginia Aguado Lorenzo (Evelina London Children’ Hospital, UK) provided insight into some of these challenges and resolutions that may be encountered with oral and parenteral route of administration in neonatal care. The main focus was on the factors such as excipients, inaccurate doses, dosage form that have an impact on accurate administration

of doses routinely prescribed to neonates and practical considerations when administering small doses to neonates. The enteral and parenteral administration devices were displayed at workstations and the delegates were given a case study on complex method of preparation of infusion. An interactive discussion took place on challenges in using the devices and methods of dilution, risks and accuracy of concentration of final infusion. The second workshop led by Dr Nasir Hussian (MHRA, UK) on constructing & evaluating PIPs provided the insights into the challenges faced during the preparation and evaluation of PIPs. Three PIP case studies relating to different route of administration – oral, injectable and a topical were assigned to three groups. Aspects discussed included paediatric suitability / age-appropriateness of designated PIP case study on quality and biopharmaceutical grounds taking into account the nature of the condition to be treated. Overall, the workshop offered an intimate opportunity for both the naïve and experienced participants to make connections and generate collaborative relationships with colleagues in the field. It served as an introduction to clinical and regulatory challenges in developing age appropriate dosage forms for the participants new to this field. While the moderated interactive sessions and small group work incorporated the experiences of participants from industry, academia, clinical and regulatory.

The main conference was opened with the plenary talk from Dr Marc Lallemand, (Drugs for Neglected Diseases Initiative, Geneva) on refocusing R&D of paediatric HIV formulations on the needs of children in resource poor setting. While overall the pipeline for children looks encouraging, the short- and medium-term requirements of the youngest children in resource-limited settings still badly need to be addressed. Dr Lallemand presented the barriers faced to access to essential medicines due to factors such as price, missing appropriate dosages and formulations or lack of data from pharmacokinetic studies. As to way forward, he highlighted that paediatric HIV treatment is an area where multi-sector efforts are needed to facilitate development of appropriate formulations, to promote manufacturing and supply of paediatric formulations. The second talk by Daniel Schaufelberger (Janssen, US) further emphasized the opportunities and challenges in paediatric drug development and importance of thinking outside the Europe and US when developing medicines for children. He presented the differences in the needs, preferences of dosage forms and regulations in China, Japan, India and Latin America. Harmonizing regulatory approvals across countries and adoption by country programmes were seen as essential steps towards reaching more children and meeting unmet needs. The structural

legacy of siloed pharmaceutical manufacturing and clinical testing organisations is a one of the barrier to innovation and meeting unmet needs in paediatric medicines. It prohibits the rapid and flexible evaluation of drug product formulations in clinical studies. These challenges particularly impact the effective development of paediatric medicines given the need to design and evaluate age-appropriate drug products and have assurances over clinical performance and patient acceptability. Dr Peter Scholes (Clinical Quotient, UK) presented the application of new approach of real-time adaptive manufacturing for the development of patient-centric dosage forms. He shared few case studies to demonstrate how real-time manufacturing enables within-study changes in formulation compositions in response to arising human clinical data. Pertinent to the development of paediatric medicines, formulations can be optimized based on pharmacokinetic, taste and overall acceptability assessments.

Though past decade has seen significant improvement in paediatric formulation research, it still encounters everyday a constant challenge of formulation, biopharmaceutical and other barriers. Focus sessions and case studies were devised around these challenges, which in turn match the EuPFI workstreams on Administration Devices, Age appropriate formulations, Biopharmaceutics, Excipients and Taste Assessment & Taste Masking.

The age appropriate formulation session chaired by Dr Terry Ernest (GSK, UK) included talks by Dr Sandra Klein (University of Greifswald, Germany) and Dr Sara Hanning (UCL School of Pharmacy, UK). Dr Hanning highlighted some practical considerations and challenges with respect to PIP submissions and paediatric clinical trials during the pharmaceutical development phase, using the FP7-funded Clonidine for Sedation of Paediatric Patients in the Intensive Care Unit (CloSed) project as case study paediatric patients. The research paper on this study is published in this issue. Dr Klein presented the update on the ongoing activity within the AAF workstream. She talked through the food characteristics and potential food effects in paediatric patients. To overcome age appropriate formulation-related issues, many people (healthcare practitioners, parents or patients) have to resort to manipulating the dosage form such as, breaking, crumbling or crushing tablets, mixing medicines with food or drink. With case examples on Isoniazid, Phenytoin, Atovaquone and enteric coated pellets, Dr Klein demonstrated the impact of manipulation particularly co-administration of medicines with foods (such as apple sauce, pudding) that are commonly used to facilitate administration and improve compliance. She highlighted that most of these

studies are performed in adults and the limitation is that study design did not always mirror typical dosing conditions in children. There is insufficient evidence to justify extrapolation of existing methods used to predict food effects in adults directly to paediatric populations. The questions that remain to be addressed are what kind of supporting studies should be done to gain information of food effects in children and if there is a need for establishing standardized dosing vehicles?

As part of Excipients session chaired by Dr David Storey (MSD, UK), the update on the European Study for Neonatal Excipient Exposure (ESNEE) research initiative was presented by Dr Mark Turner (University of Liverpool, UK). He provided the insight into the studies performed as part this initiative to address the uncertainties in use of excipients in paediatrics such as what are the circulating concentrations of commonly used excipients, how often are excipients administered to neonates and if we can avoid administering excipients. Continuing on this theme of use and acceptability of excipients in children, Smita Salunke (UCL School of Pharmacy, UK) presented the update on the ongoing work in collaboration with European Medicines Agency (EMA) on compiling the issues, solutions and learnings from the PIP applications on the use of excipients in paediatrics. The aim of this collaborative work with EMA is to assess the information available through PIP submissions, discussions, meeting minutes that are captured in EMA proprietary repository, the Paediatric Records Application database (PedRA). The manuscript in preparation will summarise the questions raised and discussions on PIPs to support the selection and safety of excipients in paediatric. Another aspect in selecting excipients for paediatric medicines is its effect on drug absorption. Dr Abdul Basit (UCL School of Pharmacy, UK) presented few examples (Polyethylene glycol 400, sorbitol, mannitol) on the influence of solubility-enhancing excipients and its dose on drug delivery and bioavailability. He highlighted that certain excipients in high doses can alter small bowel transit and drug absorption in a negative manner while certain excipients in low doses can also increase drug bioavailability. However the effect may vary depending on gender. Sex-based analysis of effect of excipients on drug absorption was presented.

Dr Jenny Walsh (Jenny Walsh Consulting Ltd, UK) chaired the administration devices session, which highlighted the challenges with aerosolized drug delivery in infants and toddlers. Thomas Gallem, (PARI Pharma GmbH, Germany) demonstrated the importance of using the approaches such as Human Factors Engineering (HFE) or Usability Engineering (UE) to

identify the needs of children and understand how they interact with technology, with a case example of a facemask.

The taste masking and taste assessment session chaired by Dr Roy Turner (Novartis, Basel) embraced the talks on taste perception in children and Pediatric Patient-Reported Outcome Instruments for Research to Support Medical Product Labeling. Measuring acceptability in children differs from adult. Children react strongly to sensory properties such as taste, texture and appearance. Similarly, when assessing younger children's health status, it is common to assess the perspective of informants instead of the children themselves. Informant-reported outcome measures may be necessary when children are not able to complete PRO measures reliably on their own because of their developmental stage, illness severity, language ability, or cognitive functioning. Appropriate methods are needed to developing measures and measuring acceptability in children. Judith van der Horst (Wageningen University and Research Centre, Netherlands) highlighted the importance of taste and novel methods such as Facereader, Autonomic nervous system and Articulograph for measuring acceptability. Dr John Chaplin (University of Gothenburg, Sweden) presented the five Good Research Practices for developing measures for children proposed by the ISPOR task force.

Strategies and examples to improve the paediatric drug development through early implementation of physiological based pharmacokinetics modeling and simulation (M&S) was discussed in the Biopharm session chaired by Dr Hannah Batchelor (University of Birmingham, UK). Dr Good (Bristol Myers Squibb, United States) provided critical guidance for the design and conduct of pediatric studies as well as the formulation development. He emphasized that the employment of M&S in the paediatric area will aid in optimisation of drug use and result in minimisation of the number and size of studies needed. Paulien Ravenstijn, (Janssen, Belgium) provided the clinical Pharmacological considerations in the design of studies in children.

The value of innovation was emphasized by 3 presentations in innovative showcase session. Vincenza Pironti, (Adare Pharmaceuticals) provided insight on the increasing role of drug-delivery systems in solving complex drug administration challenges, such as administration of enteric coated multiparticulates through feeding tubes. The company shared the method of administering PERT (Pancreatic Enzyme Replacement Therapy) specifically Zenpep® and Ultresa® via gastrostomy tubes. Skylar Wolfe (Bristol-Myers Squibb, UK) presented

development of an age appropriate, palatable powder for oral suspension (PFOS) using a robust manufacturing process that can be considered as a platform for future pediatric drug development. Eunice Afriye, (University of Birmingham, UK) provided the independent evaluation of different taste masking technologies to enhance the understanding of value of each technology, particularly with respect to industrial application and patient need.

The case studies session provided an opportunity for industries to share their challenges and experiences in developing paediatric formulations. Albertina Arien (Janssen, Belgium) presented the experience of developing a pediatric formulation for a poorly water-soluble compound while Gesine Winzenburg, (Novartis, Switzerland) presented case studies on the application of taste assessment methods for paediatrics.

Recent advances and trends in paediatric drug-delivery systems were highlighted in the selected short talks (soapbox sessions) from submitted abstracts. 60 posters were also presented at the meeting all of which provided opportunities for networking and the initiation of new collaborations. Poster prizes were awarded for the three best posters presented at the meeting. These awards were kindly sponsored by PCCA (Professional Compounding Centers of America) and were presented to Heidi Öblom (Åbo Akademi University, Finland) for her poster on thin substrates manufactured by the means of 3D printing - tailor made drug delivery systems for paediatric use; to Thibault Vallet (ClinSearch) for his poster on preliminary development of a tool assessing the acceptability of medicines for paediatric use and Jessica Soto (UCL School of Pharmacy, UK) for her poster on tasteless solubilizing excipients to be used with the rat BATA (brief-access taste aversion) model to assess the taste of poorly water-soluble drugs. All abstracts are published in this special issue. Additionally three presentations selected for full-length manuscripts are included in this special issue.

1. Towards the development of a paediatric biopharmaceutics classification system: Results of a survey of experts (1)
2. Quality and clinical supply considerations of Paediatric Investigation Plans for IV preparations - A case study with the FP7 CloSed project (2)
3. Pharmacy and formulation support for paediatric clinical trials in England (3)

Dr Catherine Tuleu (UCL School of Pharmacy, UK) closed the conference with the remarks of thanks to the organisers, sponsors and speakers for making it yet another successful

conference. The conference helped build stronger and more effective partnerships at local, national, regional and global levels, to have more integrated, coherent discussions and to share ideas and strategies on addressing issues on developing age appropriate dosage forms for children from all substets. More than the closing of an international conference, it was a celebration of a new enthusiasm and drive to bring innovative products and advanced approaches to improve existing paediatric formulations. To learn about the progress made in development of paediatric formulation join us at the 9th meeting of EuPFI being scheduled for the 20–22nd September 2016 in Lisbon, Portugal. We hope to see you there!

Reference:

1. Batchelor ET, Flanagan T., Klein S., Turner R., Fotaki N., Storey D.,. Towards the development of a paediatric biopharmaceutics classification system: Results of a survey of experts. *International Journal of Pharmaceutics*. 2016 (in press).
2. Hanning SM, Orlu Gul M, Winslade J, Baarslag MA, Neubert A, Tuleu C. Quality and clinical supply considerations of Paediatric Investigation Plans for IV preparations-A case study with the FP7 CloSed project. *Int J Pharm*. 2016 Apr 22. PubMed PMID: 27113865. Epub 2016/04/27. Eng.
3. Wan M, Al Hashimi A, Batchelor H. Pharmacy and formulation support for paediatric clinical trials in England. *Int J Pharm*. 2016 Mar 30. PubMed PMID: 27039151. Epub 2016/04/04. Eng.