

Editorial

Formulating better medicines for children – collaborate to innovate

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Continuing on its mission and conference series to raise awareness and understand paediatric-specific issues in the development of age appropriate dosage forms, the European Paediatric Formulation Initiative (EuPFI) convoked its 8th annual conference with the International Association of Pharmaceutical Technology (APV) on 21st and 22nd September 2016 at the Hotel Novotel in Lisbon, Portugal. The participation of 158 delegates from Industry, Academia, Regulatory and other organisations from 26 countries with diverse backgrounds and involvement in both formulation development and regulatory submissions provided a productive setting for the exchange of information and views.

The two pre-conference workshops provided much needed focus and interactive session to both the experienced and participants who were new to the area. One on “Benefit risk approach to dosage form design for paediatrics” orchestrated by Dr. Jenny Walsh and team helped participants to identify the key components of the Quality Target Product Profile that influence the selection of a paediatric dosage form. The workshop illustrated how it may be necessary to make compromises to certain elements of the design to ensure a product with acceptable ease of use, safety and patient access can be developed. The participants were asked to utilise information provided on a fictional antibiotic to propose and justify an age appropriate product, taking into account the relative benefits and risks of potential dosage form options. In the second one Dr. Nassir Hussian introduced the regulatory framework/quality section of PIPs and the data package that comes into licensing division when the product has reached the market authorisation submission stage.

The programme included a variety of thought-provoking and discussion-stimulating topics tailored specifically to paediatric product development with the patient’s point of view in mind. A shift has occurred in the culture of drug development with industry and regulatory agencies showing more interest in incorporating the perspectives of patients and innovative approaches in paediatric medicine development. In that respect, the conference opened with the plenary session by Simon Stones, the youngest presenter of the conference who gave the view of a young person on effectively engaging young patients people in the prioritisation and early clinical trial design stages to help the delivery of relevant research that addresses the unmet needs of young people and their families.

There is a lot of effort going into developing medicines for children that are acceptable in

terms of taste but also provide the relevant dose and exposure required for such patients. Dr Alastair Coupe shared how UK pharmaceutical companies, academia and technology suppliers are working collaboratively and innovatively to generate a structured approach to designing age-appropriate medicines for children and technology for predicting their quality and performance. He introduced the project SPaeDD-UK: *Smart Paediatric Drug Development - UK Accelerating paediatric formulation development through smart design and predictive science* which aims to provide a smarter route to developing children's medicines to reduce costs and time of development by determination of the most appropriate testing strategies that drive formulation design (http://www.paediatricscienceuk.com/store/c1/Featured_Products.html).

Paediatric Investigation Plans (PIPs) are regulator's main tool to ensure that previously unmet therapeutic needs in children are researched and that appropriate medicines are developed. All PIPs should address the need for specific forms suited to the targeted age group(s), and provide qualitative and quantitative information on the formulation proposed, with a thorough justification of its appropriateness. Dr. Brian Alyward shed the light on how to improve the quality and consistency of data submitted on paediatric pharmaceutical development in PIPs.

The plenary talks were followed by thematic focus sessions addressing common current challenges (Excipients, Taste assessment and Taste Masking, Administration devices, Age appropriateness of formulations, and Biopharmaceutics) in paediatric product development.

Age appropriate session chaired by Dr. Fang Liu (University of Hertfordshire, UK) covered two talks one on Paediatric development for poorly water soluble drugs (PWSDs) and other on Medicine Acceptability in Children: An Original Tool for Standardized Evaluation. The landscape of how to deliver PWSDs for children is quite complex due to limitations in excipients (amounts), different physiology of the GI tract for paediatric populations and different drug delivery technologies. EuPFI Age Appropriate Workstream members are writing a position paper about paediatric approaches/strategies for PWSDs to get a better overview about the drug delivery landscape for these challenging molecules with regards to their administration in children. Dr. Carsten Timpe (F. Hoffmann-La Roche, Switzerland) introduced this paper and highlighted technical challenges and constraints in selecting the appropriate enhancing PWSD technology for a paediatric formulation such as short in-use times in case of solid dispersions, administration devices, safety of excipients, human factor (caregivers) with examples from marketed drug products.

The concept of age-appropriateness is not limited to the selecting suitable technologies and development of age appropriate dosage forms but also needs to take into account patient acceptability to optimize patient adherence. Mr. Fabrice Ruiz presented an original standardised tool assessing the medicine's acceptability irrespective of their characteristics and the patient features¹. The model is based on mapping and clustering processes providing relevant standardized acceptability assessments and comparison among medicines. Any medicine may be positioned on the acceptability map and defined by an acceptability profile using the barycentre of their evaluations.

Dr. Gesine Winzenburg (Novartis, Switzerland) chaired the taste masking and taste assessment session. Unacceptable sensory properties such as bitterness of drug molecules present a major problem of compliance for children. Recognition of sensory issues in early stages of clinical development can help in selection of appropriate compounds and/or salt versions of compounds for further development. Two talks in this session presented different approaches for efficient prediction of compounds' bitterness in the initial stages of drug discovery. Marco Cocorocchio presented a novel non-animal model to investigate taste-related responses i.e the amoeba *Dictyostelium discoideum* and particularly identification of compounds with a bitter taste liability. Exposing *Dictyostelium* to substances that evoke the five basic tastes in humans showed that it was only affected by the bitter tastants. Dr. Masha Niv presented computational in-silico approach towards bitterness prediction. She introduced the BitterDB ([Wiener et al., 2012](#)), a freely accessible repository of compounds that were reported to be bitter for humans or to activate bitter taste receptors (Tas2Rs) in cell-based functional assays.

The excipient's focus session was chaired by Dr Floriane Sequier (AstraZeneca, UK). Dr Dave Schonecker (Colorcon, IPEC America, US) provided the update on interactions between FDA, IPEC and IQ on the Inactive ingredient database (IID) and paediatric formulations. He highlighted some of the key issues with the IID identified by IPEC Americas that still needs to be addressed. These include updating the database, unclear requirements for how families of materials is handled and what data is needed to support safe use levels in Abbreviated New Drug Applications (ANDA). It is not possible to identify the maximum daily intake (MDI) of ingredients required for ANDAs. The IPEC Americas IID team has coordinated meetings to accelerate progress on these issues. Many changes have been made to the IID and FDA is still working on IID clean up process and is expected to make additional changes. He informed that FDA is developing a new database for inactive ingredients that will include information on MDI levels and there have also been discussions about possible benefits of including MDI levels for paediatrics.

Dr. Massimo Montalto, (Università Cattolica del Sacro Cuore, Italy) addressed several issues regarding use of lactose in medicines including lactose intolerance prevalence, health outcomes in association with lactose intake, genetic predisposition, lactose malabsorption and intolerance, and amount of lactose likely to be tolerable. The usefulness of different approaches to address these issues such as exogenous β -galactosidase, yogurt and probiotics for their bacterial lactase activity, pharmacological and non-pharmacological strategies were presented. Therapeutic strategies for managing lactose-intolerant individuals to ensure that they ingest calcium, vitamin D, and other nutrients found in dairy products were proposed. The suggestion was to gradually re-introduce dairy products considering the individual threshold dose and in order to raise the threshold dose, some non-pharmacological and pharmacological strategies should be considered².

Dr Jenny Walsh (Jenny Walsh Consulting Ltd, UK) chaired the administration devices session, which included talks on The Combination Product Development Roadmap by Dr Esmerald Hermans (Janssen Research & Development, Belgium) and Kinderleicht- Usability Testing with Kids by Torsten Gruchmann (Use-Lab GmbH, Steinfurt, Germany). Patient engagement and behaviour are becoming as critical to achieving successful health outcomes as safety and

efficacy. This is probably even more important in paediatric medicines where both patients and care givers are involved with the administration process and often both play an active role. Dr Hermans unfolded the question on how do we design combination products for paediatric patients that help engage both caregivers and patients and enable ease of use, adherence and persistency? She presented the combination product development roadmap and illustrated with some examples on how to use the roadmap in the development process considering both the FDA and EMA requirements for dosing devices. Through the examples various concerns of the health authorities were discussed. Whereas, Mr Gruchmann shed the light on Human Factors (Usability) Engineering. He presented different methods that can be applied on Usability test design, testing environment and user groups. He further provided the detailed process and points to consider while performing the usability testing in children.

The biopharmaceutics session chaired by Dr. Hannah Batchelor covered the issues with the strategies such as mixing medicine with food and drinks used to address the problem of administration of medicines to children due to the lack of age-appropriate oral formulations. Mixing medicine with food and drinks can affect medicine efficacy, dosing accuracy and bioavailability. Case study on managing food effects for paediatric was presented by Dr. David Harris (Merck & Co Inc., US). He illustrated the use of preclinical studies for evaluating paediatric formulations. Through case studies, general considerations on clinical tools for evaluating bioequivalence of paediatric formulations, food and vehicle effects were discussed. He also presented applications of modelling and simulation in paediatric drug development with a case study on use of Physiological Based Pharmacokinetic (PBPK) modelling to describe a formulation intended to be dosed with food in paediatrics. He concluded that preclinical in vivo studies provide a tool for screening formulations, food effects, and vehicle effects prior for improving clinical trial design. While clinical studies help characterize effects of formulation, food, and dosing vehicle in healthy adult subjects. The data from healthy adult subjects forms the basis of modelling and simulation studies to provide recommendations for paediatric PK and Phase III studies. Continuing on theme of using biopharmaceutical tools for evaluating paediatric formulations, Dr Nikoletta Fotaki gave a talk on predicting performance in paediatric populations with PBPK modelling and biorelevant in vitro data. She provided the overview on modelling of paediatric clinical data and matching to in vitro data. Ann Marie Kaukonen (Fimea Finnish Medicines Agency, Finland) provided the feedback from EuPFI – IQ / M-CERSI workshop session on risk mitigation of food effects in paediatric medicines development for products co-administered with food. This workshop on 'Challenges and Strategies to Facilitate Paediatric Drug Development' took place in Baltimore US in June 2016. Dr. Trupti Dixit (Takeda Development Center Americas, US) presented the snapshot of this workshop. A short paper summarising the key take away points and next steps from MCERSI/IQ/EuPFI workshop is published in this special issue. Additionally, in depth discussions and case study outcomes from each session of workshop is captured in three manuscripts published as part of this special issue.

The innovation shows case session was presented on "Novel Solutions for Pediatrics towards Better Compliance and Performance" by Edurado Jule from Capsugel and on "Chemistry Manufacturing and Controls Considerations in Pediatric Drug Formulation Development for Low Resource Setting Applications" by Stephen Gerrard from Bill Melinda Gates Foundation.

The soapbox session, one of the popular sessions of the conference saw researchers presenting new ideas, innovative technologies and products in development. Attendees greatly enjoyed the fast pace of the Soapbox Sessions, along with the opportunity to meet one-on-one with those presenting. Due to high quality poster and oral presentations, the Professional Compounding Centers of America (PCCA) sponsored and announced an additional oral presentation award this year making it up to 4 awards in total.

The three poster awards were presented to:

- Stefanie Keser, Development And Evaluation of Taste-Masked Pediatric Minitablet Formulations With Bitter Model Drugs.
- Danielle Andrews, A Novel Approach To Assess And Improve Palatability Of An Inhaled Asset Using The Rat Brief Access Taste Aversion Assay And An In Silico Model Of Salivary Flow.
- Frank Karkossa, Simulating Different Dosing Scenarios For A Paediatric Valproic Acid ER Formulation In A New Paediatric Multistage Dissolution Model.

and Oral presentation award was given to:

- Felipe Lopez, Palatability and acceptability of multiparticulate formulations: adults vs. children comparison.

The engaging and varied agenda was punctuated with social breaks and the guided Lisbon city tour allowing maximal interactions between participants.

Once again this was a very successful meeting and hope has incentivized the participants to collaborate and work together towards formulating better medicines for children. We would like to thank our speakers, delegates, exhibitors and sponsors for their active contribution to the discussions in this meeting. The presentations, conference proceedings and picture gallery is posted on our website and is available at <http://www.eupfi.org/past-conferences/8th-eupfi-conference/>. This special issue includes publications of selected presentations from the conference and accepted abstracts.

What we all have to keep in mind is that collaboration among a broad range of disciplines and fostering a knowledge-sharing environment that places the patient's needs at the centre of paediatric drug development, consistent with science and risk-based approach, are the key gears of the path forward. Make sure you attend the next upcoming **9th EuPFI** conference as continuation of collaborative efforts and to mark the 10th anniversary of the Paediatric Regulation and foundation of the EuPFI consortium. The conference will be held on **19th to 21st September 2017 in Warsaw, Poland**. A gritty city that knows how to surprise you!

Reference :

1. Ruiz, F., Vallet, T., Pensé-Lhéritier, A.-M. and Aoussat, A. (2017), Standardized method to assess medicines' acceptability: focus on paediatric population. *J Pharm Pharmacol*, 69: 406–416. doi:10.1111/jphp.12547

2. Montalto, M., Curigliano, V., Santoro, L., Vastola, M., Cammarota, G., Manna, R., ... Gasbarrini, G. (2006). Management and treatment of lactose malabsorption. *World Journal of Gastroenterology : WJG*, 12(2), 187–191. <http://doi.org/10.3748/wjg.v12.i2.187>