



## 'Formulating better medicines for children' – The leap forward



Taking the leap forward towards the awareness and understandings of the paediatric-specific issues in the development of paediatric formulations, the European Paediatric Formulation Initiative (EuPFI) convoked its 5th annual conference in association with the International Association of Pharmaceutical Technology (APV). The conference was held on 18th and 19th September 2013 at the Hotel Porta Fira in Barcelona, Spain. The participation of 162 delegates from industry, academia, regulatory and other organizations from 27 countries with diverse backgrounds and involvement in both formulation development and regulatory submissions, provided a productive setting for the exchange of information and views.

Following feedback received from the previous conference, a new format, including pre-conference workshops and innovative showcase, was introduced. The programme for this 2-day conference was participant driven and touched upon a range of topics for product development with the patient's point of view. In addition, the conference provided the opportunity for practitioners from different disciplines to discuss aspects and issues of formulating paediatric medicines including understanding the research needs for children's medicines, developing new medicines for children or adapting existing medicines so that they could be used safely and effectively in children and improving ways to encourage children to take their medicines.

Two pre-conference workshops led by specialists in each topic area, gave an opportunity for the participants to maximize their learning experience. The first workshop chaired by Prof. Adolf Valls-i-Soler (University of the Basque Country) provided an in-depth review and scientific discussion on how developmental changes may influence the pharmacokinetics and pharmacodynamics of drugs, how pharmacokinetics could be predicted in neonates, infants and children and how it can be linked to pharmacodynamics. The second workshop by Dr. Dirk Mentzer (PDCO, EMA) was an opportunity to learn how the regulatory professionals interpret the paediatric regulation and implement it in practice.<sup>1</sup> In particular, how setting up a paediatric investigation plan links up with the various phases of drug development (designation, protocol assistance, and marketing authorisation).

Long standing problems with potential health risks in children have triggered an international response in the form of the European Union (EU)-funded seventh framework programme FP7/2007–13 under grant agreement n° 261060 GRiP (global research in paediatrics) project. The keynote plenary lecture by Dr. Kalle Hoppu

(Helsinki University) provided insight into this innovative project. The main characteristics of GRiP, infrastructure matrix, expected impact and key areas of work were introduced. The work of GRiP has been divided into nine work packages, each dealing with a fundamental aspect of research and development of medicines for children, the output from which will be the development of a paediatric clinical pharmacology training programme and filling important "gaps" in paediatric medicines research by the validation and harmonization of research tools specific for paediatrics. The additional information is available on GRiP website (<http://www.grip-network.org>).

Development of age-appropriate formulations is an essential part of paediatric drug development and adds additional biopharmaceutical considerations to an already complex problem. Dr. Hannah Batchelor (University of Birmingham) presented the limitations of the biopharmaceutics classification system (BCS) and its use in the development of paediatric medicines. It was highlighted that more research is needed in this area, including potential development of a predictive dissolution testing method, which could correlate *in vitro* data with *in vivo* product performance. In turn having patients as a partner in the process towards innovative medicines would add another helpful dimension in identifying the unmet therapeutic needs considering risks and benefits. Dr. Cor Oosterwijk (the patients network for medical research and health EGAN) reiterated this message in his presentation that the parent/patient organizations have an important role in these developments and interaction between parents and children and the research field will contribute to innovation and quality of treatment and care. Actual European developments in health care policy concerning rare diseases are also of relevance for the research infrastructure in paediatric medicine and paediatric formulations.

While progress has been most notable in the United States (US) and the European (EU) community, there is growing recognition of the need for better medicines for children worldwide. While there are many similarities between US and EU regulatory guidelines, there remain important and critical differences. European legislation involves both the countries and EU specific guidelines. Within Japan the off-license or unlabelled use of drugs in children is as common as in the US and EU, however, there is no paediatric legislation, although there are efforts to develop such legislation. Dr. Hide Nakamura (National Research Institute for Child Health and Development) provided the insight into the current paediatric research situation in Japan. The various aspects related to paediatric formulation and extemporaneous use of medicines in Japan was discussed from different view points, from the view of a clinician, of the pharmaceutical industry and from the government.

<sup>1</sup> PDCO - Paediatric Expert Committee at the European Medicines Agency (EMA).

Another fast-growing area with considerable market interest is the paediatric over the counter (OTC) segment. Dr. Paul Goggin (Pfizer) provided a background to the innovations that are made in over the counter market and outlined the time and costs involved in these activities.

Confirmation of the acceptability is an important aspect in the pharmaceutical development and it constitutes an essential part of a state-of-the-art development programme. The current knowledge about the age-appropriateness of different dosage forms is still fragmented or limited. The regulatory perspectives on acceptability testing were presented by Mr. Piotr Kozarewicz (EMA). The aim was to provide an update on current thinking and understanding of the problem, and discussing issues related to the acceptability testing. The overview just flagged the problem and was meant as the starting block for further discussion on aspects relating to acceptability testing of dosage forms in children's proposition.

The plenary talks were followed by focus sessions centred around EuPFI workstreams. The first focus session on age appropriateness of formulations included a talk by Mr. Simon Bryson (on patient centred administration of friendly dosage form). Mr. Bryson described the studies conducted at Alder Hey Children's Hospital, UK, aiming to determine which factors relating dose form and which organoleptic properties of a medicinal product influence the medication adherence in chronically ill patients aged between 3 and 11 years. The second focus session on modifications of dosage forms required for children (MDFRC) covered a talk on paediatric ad hoc preparation of Tamiflu by Dr. Carsten Timpe (Roche). An overview about extemporaneous preparations for children along with a case study of oseltamivir phosphate (Tamiflu) was presented. He explained the challenges in developing age appropriate formulations for children and modification of dosage forms required for children and discussed how these challenging objectives could be achieved both in Europe and the US against the background of health authority expectations. The development and submission experiences on respiratory product for young children were shared by Dr. Stefan Leiner (Boehringer Ingelheim Pharma GmbH & Co. KG) as part of devices focus session. The final focus session on taste masking and taste testing included an update on inter laboratory testing of e-tongues was given by Dr. Mariam Pein (Heinrich-Heine-University).

As previously, the soapbox sessions provided food for thought and prompted some good discussion. Range of topics were covered related to age appropriateness of formulation, taste masking and taste testing, modification of dosage forms required for children, excipients and administration devices. This year the 'best poster award' was introduced. The overall purpose with the award was to encourage the students to share experiences and results with others through quality poster presentations. The award was kindly sponsored by PCCA (Professional Compounding Centers of America) and was presented to the winners, Ms. Ramona Trastullo, Ms. Eva Julia Laukamp for "Immediate release carbamazepine formulation for individually dosing by the solid dosage pen" and Ms. Sejal Ranmal. Peer reviewed abstracts can be found at [http://eupfi.org/Conference%202013%20/Abstract%20Compilation%20EuPFI%202013\\_final.pdf](http://eupfi.org/Conference%202013%20/Abstract%20Compilation%20EuPFI%202013_final.pdf).

Similarly, the innovative show cases introduced this year provided companies an opportunity to present less traditional yet relevant technologies for children medicines. Different topics covered included:

1. Patient centric medication – elegant dose forms for developing better treatments: Leon Grother (Catalent) presented the Zydys solution to help solve complex taste masking, bioavailability, solubility, and permeability challenges for development of

patient-tailored medication with excellent dispersion time, palatability and mouth feel.

2. Taste masking using an aqueous ethylcellulose film coating: Kevin Hughes (Colorcon) presented the surelease taste masking project evaluating the use of surelease, a barrier membrane coating formulation with paediatric precedence of use, on taste masking of acetaminophen (APAP) immediate release granules.
3. Innovative micropellets for paediatric drug products and orodispersible films: Annette Grave (Glatt) presented the Glatt fluid bed Wurster HS<sup>TM</sup> technology for the development of taste masked micropellets of hydrocortisone.
4. Combining taste masking and convenient application – innovative formulation concepts for children: Dr. Sandra Klein (Losan Pharma GmbH) presented Losan's toolbox (orodispersible granules, taste masking technologies, single unit dosage form: stick pack technology, unique formulation concepts: Liquitab) to address the challenges in formulating better medicines for children.
5. Orodispersible films – a new treatment option especially for children: Dr. Armin Breitenbach (tesa Labtec) presentation was focussed on tesa Labtec oral film technology.

Two industrial case studies were presented with Dr. Gensine Winzerburg (Novartis) highlighting the PIP statistics generated since regulation came into force and presented the challenges and issues related to PIPs (quality/non-quality/clinical), while Dr. Albertina Arien (Janssen and Janssen) shared the experience and learnings on recent PIPs through three case studies: (1) paediatric dosage form for treatment of tuberculosis; (2) age appropriate formulation for intables; and (3) development of combination product.

The "rapid communications" in this IJP special issue resumé the oral presentations that took place over 2 days:

1. Report on workshop 1: neonat/peads pharmacology.
2. Report on workshop 2: introduction to paediatric regulatory framework.
3. Paediatric biopharmaceutics: current status and future decisions.
4. Patient involvement in paediatric medicine development and improving formulations.
5. Patient-centred administration friendly dosage forms – Simon Bryson, Proveca Ltd., Cheshire, United Kingdom.
6. How do Japanese children take their medicines?
7. The place of dosage form innovation and the OTC market: the price to pay.
8. A respiratory product for young children – development and submission experiences.
9. Regulatory perspectives on acceptability testing of dosage form in children.
10. Review of PIPS.

Moreover, presentation on inter laboratory testing of e-tongues was selected for full-length manuscript.

In conclusion, this conference brought together a diverse array of opinion concerning paediatric drug development.

Over the past few years, the responsibility of the scientific community to develop and exploit existing, emerging, and novel technologies to achieve the goal of developing better medicines for children has increased. There have been advances in paediatric drug development and attention to regulatory and ethical issues has progressed so that more paediatric trials are conducted. The gap is shrinking. Despite this progress, much remains to do. There are still on-going issues relating to excipients, appropriateness of the route of administration or pharmaceutical form, dosing accuracy and patient's acceptability. A stronger focus on all these

aspects, considering the target age range, severity of illness and the treatment duration, could streamline the paediatric formulation development process. A part of the path forward was discussed and will continue to be discussed at the upcoming 6th EuPFI conference to be convened in Athens, on 17th and 18th September 2014 in partnership with APV (International Association of Pharmaceutical Technology). There is a real opportunity to share and learn from the lessons of the past for the future implementation of the paediatric regulation and for the benefit of children. More information is available on EuPFI website (<http://www.eupfi.org>).

This special issue is dedicated to the late Prof. Valls-i-Soler. He will be remembered for his spirit and dedication for improving

health care in neonatal infants (<http://www.euroneonet.eu/paginas/publicas/euroneo/euroneonet/Documents/Inmemoriam.pdf>).

Smita Salunke (EuPFI Scientific Manager)\*  
Catherine Tuleu (Chair of EuPFI)

*Department of Pharmaceutics and Centre for Paediatric, Pharmacy Research (CPPR), UCL School of Pharmacy, 29–39 Brunswick Square, London WC1N 1AX, United Kingdom*

\* Corresponding author.

*E-mail addresses:* [s.salunke@ucl.ac.uk](mailto:s.salunke@ucl.ac.uk) (S. Salunke)  
[c.tuleu@ucl.ac.uk](mailto:c.tuleu@ucl.ac.uk) (C. Tuleu).

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