

Formulating better medicines for children-reflections

Batchelor, Hannah; Salunke, Smita; Tuleu, Catherine

DOI:

[10.1016/j.ijpharm.2015.05.017](https://doi.org/10.1016/j.ijpharm.2015.05.017)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Batchelor, H, Salunke, S & Tuleu, C 2015, 'Formulating better medicines for children-reflections', *International Journal of Pharmaceutics*. <https://doi.org/10.1016/j.ijpharm.2015.05.017>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

NOTICE: this is the author's version of a work that was accepted for publication in International Journal of Pharmaceutics. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in International Journal of Pharmaceutics, DOI: 10.1016/j.ijpharm.2015.05.017.

After an embargo period this article is subject to a Creative Commons Non-Commercial No-Derivatives license.

Eligibility for repository checked June 2015

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Accepted Manuscript

Title: Formulating better medicines for children—reflections

Author: Hannah Batchelor

PII: S0378-5173(15)00427-5
DOI: <http://dx.doi.org/doi:10.1016/j.ijpharm.2015.05.017>
Reference: IJP 14887

To appear in: *International Journal of Pharmaceutics*

Author: Smita Salunke Catherine Tuleu

PII: S0378-5173(15)00427-5
DOI: <http://dx.doi.org/doi:10.1016/j.ijpharm.2015.05.017>
Reference: IJP 14887

To appear in: *International Journal of Pharmaceutics*

Please cite this article as: Salunke, Smita, Tuleu, Catherine, Formulating better medicines for children—reflections. *International Journal of Pharmaceutics* <http://dx.doi.org/10.1016/j.ijpharm.2015.05.017>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Formulating better medicines for children – reflections

Hannah Batchelor^{1, a,}, Smita Salunke^{1, b*}, Catherine Tuleu^{1, b,}

¹ On behalf of the European Paediatric Formulation Initiative (EuPFI).

^aPharmacy, Pharmacology and Therapeutics Section, School of Clinical and Experimental Medicine, College of Medical and Dental Sciences (CMDS), Medical School Building, University of Birmingham, Edgbaston B15 2TT

^bDepartment of Pharmaceutics, UCL School of Pharmacy, 29–39 Brunswick Square, London WC1N 1AX, United Kingdom

•Corresponding author contact details: Department of Pharmaceutics, UCL School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom Tel.: +44 2077535846; fax: +44 2077535942. E-mail address: s.salunke@ucl.ac.uk

The European Paediatric Formulation Initiative (EuPFI, www.eupfi.org) with the APV (Arbeitsgemeinschaft für Pharmaceutische Verfahrenstechnik) hosted its 6th conference on “Formulating better medicines for children” on the 17-18th September 2014 in Athens, Greece. This meeting attracted 119 delegates with good representation from industry, regulatory agencies, academic and clinical settings.

This meeting is now in its 6th year and offers a unique opportunity for paediatric formulation specialists to exchange and present recent accomplishments as well as discuss remaining challenges for the future with a vision of better medicines for children. Although this is a European meeting, collaborations with the US have always been integral to the success of improving formulating paediatric medicines and bridging the adult-child medicines gap. This meeting was no exception to this with a great presentation by Trupti Dixit on the United States of America based Innovation and Quality (IQ) Consortium survey. The survey focused on understanding the current status of pediatric formulation development in the US including common approaches used, limitations of those approaches, current regulatory expectations and unmet needs. Dr Jenny Walsh presented the European survey on paediatric medicine administration devices: experiences and opinions of healthcare professionals.

Although this meeting is well established on the calendar of those interested in paediatric formulation there was an opportunity for those attending who are new to the area to get up to speed by attending the two pre-conference workshops. The workshops are held to provide much needed focus on paediatric clinical pharmacology and to introduce the regulatory framework/quality section of PIPs. These sessions were presented by Dr Janko Samardzic (University of Belgrade, Belgrade, Serbia) and Dr Siri Wang (Norwegian Medicines Agency, Oslo, Norway) respectively and allowed attendees to ask questions to build up knowledge and dialogue in these areas. Dr Janko Samardzic talked through the fundamental differences that mean that children are not just small adults and reflected on clinical knowledge in this area. Dr Wang highlighted many interesting aspects from PIPs submitted to date and reflected on the low numbers of PUMAs since the regulations were

introduced in 2007. She noted that PUMA reflect product development funded through a series of projects where potentially a different source funds is required at each step and therefore it may be anticipated that these will be slower compared to PIPs to reach the market. As a smaller, more engaged and focused conference, the pre-conference workshops offered an opportune setting to meet and connect with many friends and colleagues working in this field, and provided an effective learning platform given the wide array of presentations on offer.

The programme for the EuPFI meeting is participant driven and is typically designed around the challenges faced in developing paediatric medicines, which in turn are also the workstreams that comprise the EuPFI activity (<http://www.eupfi.org/gpage2.html>)

- Pharmaceutical Excipients
- Taste masking and taste assessment methods
- Administration devices
- Age appropriate formulations
- Modification of Dosage Forms Required for Children
- Biopharmaceutics (NEW)

Talks were related to these workstreams or presented as the result of ongoing activity lead from within the workstreams. As with previous years any feedback is included into future programmes to ensure that the meeting meets the needs and expectations of the attendees.

A main emphasis of the meeting was reflecting on the updated EMA Guideline on pharmaceutical development of medicines for paediatric use, which came into effect in February 2014. It was acknowledged by all parties that although these guidelines are required, the evidence base is not sufficiently robust and further work is required to underpin aspects of this guidance. However, it was recognised that paediatric formulation development is leading the way for other special populations and this year the alignment of formulation development for paediatric and geriatric populations was the subject of two stimulating presentations (industry and academia).

Both Europe and the United States of America have dedicated networks that collaborate to improve medicines for children, however, this issue is global. It is essential that age-appropriate medicines are available for all children who require them. Sonja Skopp (Merck KGaA, Darmstadt, Germany) presented a paediatric schistosomiasis treatment; an innovation to play a more direct role in the fight against the second-most severe tropical disease in Africa. The current gold standard treatment of schistosomiasis employs annual single oral dose of the drug praziquantel (PZQ) 600 mg tablets. The available formulation of praziquantel (PZQ) is not suitable for paediatric use and cannot be readily administered to children especially to preschool-age children and infants. In order to tackle this important public health problem, a consortium was formed in July 2012 under the leadership of Merck KGaA with the goal of developing a suitable paediatric praziquantel formulation appropriate for children from the age of 3 months to 6 years and register its use in schistosomiasis.

Norbert Poellinger (Glatt GmbH, Germany) presented the TAIN project, treatment of adrenal insufficiency in neonates and infants (www.tain-project.org/). The off-patent drug hydrocortisone is a glucocorticoid hormone that has been used as a replacement therapy for the treatment of Adrenal Insufficiency across Europe for many years. However, effective hydrocortisone replacement is particularly acute among young patients (neonates and infants) for whom no licensed therapy exists.

The aim of TAIN is to develop a new formulation of hydrocortisone – Infacort® - that can be used from birth and specifically in the age range 0 – 2 years. It also aims to raise awareness of the unmet needs in paediatric adrenal insufficiency patients.

Shorts talks (soapbox sessions) from submitted abstracts, innovation showcases and 50 posters were also presented at the meeting all of which provided opportunities for networking and the initiation of new collaborations.

The soapbox sessions included a wide range of topics and highlighted the diversity of research within the umbrella of paediatric formulations. Particular highlights included a talk from Jennifer Bellis (Alder Hey Children's NHS Foundation Trust, Liverpool, UK) on the frequency and type of unlicensed medicines implicated in adverse drug reactions (ADRs) in paediatric inpatients; the results showed that unlicensed medicines were more than twice as likely to be implicated in an ADR as authorised medicines. Ramona Trastullo (University of Bologna, Bologna, Italy) presented on the development of fast dissolving granules containing praziquantel as a formulation that is likely to improve acceptability compared to the current tablets used in children. A continuous manufacturing process that produces double-layer orodispersible films as a paediatric formulation was described by Yasmin Thabat (Heinrich-Heine-University, Dusseldorf, Germany); this formulation has advantages in the manufacture of combination therapeutics. Annette Grave (Glatt GmbH, Germany) shared results where the extremely bitter drug, hydrocortisone was successfully taste masked within a micropellet whilst maintaining an immediate release dissolution profile. This production of taste-masked micropellets was also successfully scaled up to the production scale providing a product that allows a flexible capsule filling over a wide range of a range of strengths for adaptive dosing

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 Jessica Soto from UCL School of Pharmacy for the presentation "Assessing the taste of medicines with rodents: the in vivo rat brief-access taste aversion (BATA) model"; Jonas Buck for "Development and characterization of dispersible tablets employing novel characterization methods" and joint award to Saskia Blank and Elizabeth Kersten from University of Greifswald, Germany for "Monitoring food and fluid intake as a basis for establishing biorelevant dissolution methods for children in the age of 1 – 6 years" Conference proceedings are available at <http://eupfi.org/Conference%202014/default.htm>

The innovation showcase provided an opportunity for businesses working in paediatric formulations to raise the profile of their technology and share potential applications. The X-Straw dose sipping technology was presented by Elke Sternberger-Rützel (DS Technology, Harro Höfliger, Germany) this is a prefilled straw with an exact dose that is delivered upon drinking. Mauro Serratoni (Aptalis Pharma, Italy) highlighted patient centered paediatric drug formulation options using MicroCAPS® taste masking technology in combination with AdvaTab® to create an immediate release orally disintegrating tablet of a bitter tasting drug. The RauDose™ technology was introduced by Gero Eichelkraut (Raumedic AG, Germany); this device provides a means of measuring precise and safe doses of liquid medicines.

The "rapid communications" summarizing the oral presentations that took place over the 2 days are presented in this special issue

1. Workshop 1: Introduction to developmental pharmacology
2. Workshop 2: Introduction to regulatory framework / quality section of PIPs
3. Drug dosage forms and food mixing
4. Milk as a medium for paediatric formulations: experimental findings and regulatory aspects
5. Quality considerations of PIPs for monoclonal antibodies: a regulatory perspective
6. Formulation factors affecting acceptability of medicines in children and older adults

In addition, 2 presentations were selected for full length manuscripts:

1. European survey on paediatric medicine administration devices: experiences and opinions of healthcare professionals
2. Usability testing – STEP database through end-users eyes

The other presentations that are not part of the IJP issue include cell-based assays for taste prediction by Dr Afzal Mohamed. The data about cell lines that respond to taste stimuli and are likely to have value in the in vitro assessment of the taste of paediatric medicines was shared. A spinout workstream of age appropriateness of formulation has been introduced this year and Prof Sandra Klein (University of Greifswald, Germany) presented on the biopharmaceutical evaluation of developmental paediatric products. An overview on the limitations of existing methodologies in this field and how researchers are addressing this to better predict the in vivo performance of paediatric oral medicines was presented.

This meeting was a success that embodied the EuPFI's mission to share expertise and interactive discussion between industry, academia, clinical and regulatory professionals to promote and facilitate preparation of better & safe medicines for children. The participant list demonstrated that this topic was of interest to people with a wide range of background and questions or expectations, creating stimulating and rich discussions among attendees. This diversity is reflected by the articles published in this special issue of the International Journal of Pharmaceutics Sciences written by invited speakers.

The issues and challenges associated with development of paediatric formulation were identified together with collaborative approaches to solving these issues as a result of the networking aspect of the meeting. This makes this the premier meeting on paediatric formulation. The willingness of participants to meet again resulted in the 8th meeting of EuPFI being scheduled for the 16-17th September 2015 in Antwerp, Belgium. We hope to see you there!