European Paediatric Formulation Initiative (EuPFI) successfully navigating the road to formulating better medicines for children

Smita Salunke
European Paediatric Formulation Initiative, UCL School of Pharmacy, 29–39 Brunswick Square, London WC1N 1AX, UK

The field of paediatric drug development has progressed significantly in the last ten years, following the implementation of several paediatric policies both in Europe and the USA. Consequently, the number of medicines developed for children increased during this period and demand for greater consideration of medicines for children has strengthened. Industry has gained expertise under these regulations and have started to also apply their knowledge to investigational products designed to address diseases primarily observed in paediatric populations. Novel pathways for research, development, funding, and collaboration have been created, setting new standards and best practices for innovation in the future. It also has revealed specific challenges in developing medicines for diseases that only affect children or diseases with different manifestations in adults and children. Maintaining global incentives for research and development of new medicines has become even more essential for the continued innovation of treatments that help improve the health and lives of patients all over the world.

EuPFI (European Paediatric Formulation Initiative) annual conferences are an intellectual feast bringing together senior and pioneering scientists from academia and the pharmaceutical industry together with young researchers, students and regulators to share information about current research and to discuss the latest advancements and challenges facing the evolving field of paediatric medicines. Delegates have come from all corners of Europe and elsewhere in the world. The 2-day program includes an interesting line-up of close to 30 talks, spread across five major themes of EuPFI; Age-appropriate formulations, Administration devices, Biopharmaceutics, Excipients and Taste Masking and Taste Assessment. These ideas, woven together, represent the core principles of formulating medicines for children, i.e., how different elements of appropriateness of a formulation are adapted in response to the specific needs of children. As EuPFI has demonstrated since its formation, incorporating these principles is essential for complete understanding of paediatric formulation development. Running throughout the conference are presentations on how recent advances in paediatric formulations have inspired the development of new tools and methodologies that could help accelerate appropriately designed research studies and therein lies the promise of age-appropriate formulations– the central theme of this scientific meeting.

In addition to the formal conference sessions most conferences also included pre-conference workshops which gave the opportunity for attendees new to the field to gain some background on particular areas or for more experienced attendees to discuss a particular area of paeadiatric development in some depth[1].

This special issue is dedicated to the proceedings from the 2018 -2020 EUPFI conferences[2]. It includes the abstracts accepted for 2018 – 2020 conference and research articles on the key presentations made at the conference. In addition, it includes papers summarising the discussion and action plans emerging from the workshops

The EuPFI's 10th Anniversary Conference was held at the British Medical Association (BMA) House on 11-13 September 2018 to commemorate EuPFI's achievements and successes over the past decade, and to set out new goals and research directions for the coming years. Over 200 delegates joined not only in a celebration, but also to reflect and to ask where we should be in another ten

years' time. It reflected on the decade-long journey of EuPFI as a consortium to scope issues in paediatric formulations and its contributions towards its mission to resolve them as well as in the innovation of new tools (e.g., STEP database) and technologies. The EuPFI's 10th Anniversary Conference was hugely successful in driving scientific discussions, advancing the current understanding of this highly promising, interdisciplinary science, and generating collaborative ideas that could become seeds of innovation in the future.

A decade is a significant milestone to have passed, but as paediatric medicine continues to develop, more areas of need and their solutions will be found. The 11th Annual Conference held in Malmo, Sweden in September 2019, discussed the latest advances and challenges facing the evolving field of paediatric medicines. In total more than 150 participants attend the conference, with approximately one-third of the attendees travelling from overseas. Experts in each of these specific areas spoke in detail on the latest findings from their labs and its implications in the wider field. The ideas discussed under various themes ranged from transdermal and topical delivery in paediatrics; breastfeeding mediated therapeutic delivery; in vitro models to estimate oral drug solubilization in the young paediatric population; design of a precision medication dispenser; update on evolving Titanium Dioxide situation in Europe and its potential impact; excipients in neonatal medicinal products; the discovery and use of bitter taste receptor antagonists to alleviate off-tastes; sensory strategies and technologies to improve the palatability of medicines; and harmonisation of biopharmaceutics risk assessment. The other talks focused on real life case studies on the device development for paediatric and antimalarial product development.

The scientific talks were followed by an hour-long panel discussion that was aimed at bringing out the various contributing factors towards challenges in developing medicines for children in low resource settings. The panellists got into a highly engaging and stimulating discussion on various aspects covering the topic, including but not limited to, the technical challenges in making child-friendly formulations; the need to investigate safety and dosing across the paediatric spectrum of ages; regulatory incentives and requirements for paediatric development plans; individual country regulatory approvals; supply chain management strategies; and the need/effort of cross-sectoral collaboration to develop and articulate solutions to meet with the needs of children in resource-limited settings.

The Pre-Conference workshops at the 10th and 11th conferences provided in-depth insights into topics such as best practices for selection of excipients, strategies to choose for paediatric formulation development, and development of multiparticulates and minitablets. It included a mix of lecture content and group exercises designed to help attendees who are not familiar with formulations for children to understand the considerations involved in designing and choosing appropriate dosage forms for this important demographic. The workshop on multiparticulates and minitablets however was targeted more to the experts and those familiar with the area and designed to advance the field. It reviewed the current state of knowledge around development of multiparticulate and minitablet dosage forms for children and highlighted the areas that remain challenging. The papers on these workshops outputs and future action plans are published in this issue.

The take home message for these conferences was that a global perspective in identifying paediatric medical needs and determining regulatory requirements is very important. Global paediatric drug development is poised to meet a series of new challenges that will drive the outlook for next few years and beyond. Neonates, paediatric oncology, and orphan diseases are the new frontiers in paediatric medicine, and the revolution in global paediatric drug development will continue. This became the foundation for the EuPFI 2020, i.e 12th Annual conference that was turned into a virtual conference due to the unprecedented circumstances of the COVID 19 pandemic. The event was a

booming success with over 230 participants from 23 countries. It was very well received particularly with positive feedback on the content showcasing leading edge science and personal touches with live zoom and chat rooms. The virtual conference allowed participation from far-far away and thus extended the global reach offering a chance to engage with researchers who might not be able to attend the in-person meetings.

The shared experience is what has always driven EuPFI conferences and was a key theme of the plenary presentations. It covered talks on the development of a child appropriate formulation of 13-Cis Retinoic Acid (isotretinoin) for the treatment of high-risk neuroblastoma (My-CRA) and the paediatric development for SARS CoV-2 therapy, addressing challenges in designing a strategy for Remdesevir (RDV) and dosing of RDV in children. The other two plenaries shared the ongoing efforts on global paediatric drug development with a focus on the emerging role of non-governmental organizations (NGOs) in global drug development: CHAI and the Global Accelerator for Paediatric Formulations (GAP-f) as collaborators are facilitating paediatric product development and affordable access to low and middle-income countries. Paediatric Medicine and Healthcare Initiative (PMHI) a newly formed initiative in India (a companion organisation to EuPFI) aims to strengthen and expand international networking in paediatric formulation research to accelerate the pace of global progress in child health and drug regulatory reforms in low resource settings.

Furthermore, the conference covered a broad range of talks under five major themes of EuPFI. This included regulatory perspectives for oral syringes (appropriate size for required dose volume, graduations in mL) and enteral tubes (investigation of worst-case scenarios for blocking and dose recovery, provision of information on use for patients/caregivers); using facial recognition software to capture taste responses objectively; development of chocolate-based taste-masked tablets for children; development of a new paediatric medical device to measure whole gut transit time using Magnetic Resonance Imaging (MRI) which will help to better tailor drug formulations to the needs of paediatric patients; and how to approach excipients choice and risk assessment for paediatric formulations.

Between the plenary and focus session talks, more scientific discussions flowed into the soap box sessions presented mainly by students and early career scientists. These included interesting topics such as dissolution testing and PBPK modelling to assess effect of age on PK; taste strips for kids taste panels; dosing multiparticulates: how to do it accurately; what do children think about tablets manufactured using different 3D printing methods?; feasibility of amoxicillin suppositories and characterization of chloroquine ion-exchange resinates in the solid-state and in vitro taste masking.

To maximise the virtual experience, discussion forum session were introduced which generated much discussion and lent deeper insights into the various aspects of paediatric formulation development: from what are preferred age-appropriate formulation for children under 11yrs to generics acceptability. Of particular interest was how to assess the taste and pros and cons of different taste assessment tools. Taste is important but measuring it is difficult in children. Understanding the potential ways or tools to capture taste responses objectively is vital. Facial recognition software offers recording facial expressions to assess taste in children and teenagers. However, the high levels of inter and intra subject variability can make it hard to get fully reliable data especially in younger children.

In addition to stimulating discussions stemming from various presentations, virtual exhibition booths and a networking area, the conference also introduced the participants to new ideas and findings through posters presented by postdoctoral and graduates. Dedicated virtual poster showcase sessions, along with lightning (5min) presentations to introduce the central theme of their posters, ensured adequate time and opportunity for the poster participants to present their research to the

audience. Out of the 55 posters on display, three were awarded best poster prizes based on content and presentation. Thus, the 2 days of talks, posters and social events successfully propelled meaningful discussions on the various aspects of paediatric drug development and advanced the current understanding of this emerging field.

In its journey of successfully navigating the road to developing and delivering paediatric products, #EuPFI 2021 (virtual) will provide a further unique opportunity to advance knowledge and understanding in the areas where the needs of adult and paediatric patients overlap, where they differ and also area of diseases that occur mainly in children. A dialogue on the respective therapeutic landscapes, identifying most promising drug developments and defining success criteria and milestones in the development processes is of great importance and will be theme of #EuPFI 2021.

References:

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[2] EuPFI, European Paediatric Formulation Initiative website available at www.eupfi.org, (2021).