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Mini-Review

Theme: Pediatric Drug Development and Dosage Form Design
Guest Editors: Maren Preis and Jörg Breitkreutz

European Paediatric Formulation Initiative (EuPFI)—Formulating Ideas for Better Medicines for Children

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Abstract. The European Paediatric Formulation Initiative (EuPFI), founded in 2007, aims to promote and facilitate the preparation of better and safe medicines for children through linking research and information dissemination. It brings together the capabilities of the industry, academics, hospitals, and regulators within a common platform in order to scope the solid understanding of the major issues, which will underpin the progress towards the future of paediatric medicines we want.The EuPFI was formed in parallel to the adoption of regulations within the EU and USA and has served as a community that drives research and dissemination through publications and the organisation of annual conferences. The membership and reach of this group have grown since its inception in 2007 and continue to develop and evolve to meet the continuing needs and ambitions of research into and development of age appropriate medicines. Five diverse workstreams (age-appropriate medicines, Biopharmaceutics, Administration Devices, Excipients and Taste Assessment & Taste Masking (TATM)) direct specific workpackages on behalf of the EuPFI. Furthermore, EuPFI interacts with multiple diverse professional groups across the globe to ensure efficient working in the area of paediatric medicines. Strong commitment and active involvement of all EuPFI stakeholders have proved to be vital to effectively address knowledge gaps related to paediatric medicines, discuss potential areas for further research and identify issues that need more attention and analysis in the future.

KEY WORDS: administration devices; age appropriate; biopharm; EuPFI; excipients; formulation; paediatric; taste assessment; taste masking.

INTRODUCTION

The importance of developing safe and effective medicines for children has now been recognised. It has resulted in a paradigm shift in the profile of and the expectations for research with paediatric populations including policy changes in the global medicines environment. Regulations in both Europe and the USA mandate the development of paediatric medicines for new products of drugs that are still patent protected, and incentives are in place for the development of off-patent paediatric medicines (1,2). The formulation of paediatric medicines can be challenging since it is necessary to consider the diversity of this patient population in terms of age with associated compliance challenges such as acceptable palatability and potential safety concerns associated with excipients. Considering the issues in paediatric product development is shared among the stakeholders (governments, regulatory authorities, research institutions, pharmaceutical industry and healthcare professionals), an integrated and co-coordinated approach is needed to address the issues and knowledge gaps. In 2007, the European Paediatric Formulation Initiative (EuPFI) was launched with the objective of identifying the issues and challenges in paediatric drug formulation development. This article provides an overview of the EuPFI consortium, highlighting the activities and

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efforts invested by EuPFI members. It also presents the challenges faced by the group members to advance and promote development of better medicines for the paediatric population.

EUPFI BACKGROUND

Creation of the EuPFI consortium has been a major achievement in itself. EuPFI was created informally in 2007 based on the genuine willingness of formulation scientists' aspiration to work together to in a non-competitive environment to understand better and learn how formulation research and development could better fulfil the needs of sick children. It evolved quickly into a structured established consortium with a mission to promote and facilitate the development of better and safe medicines for children through linking research and information dissemination. Seven founding members (GlaxoSmithKline, Novartis, Roche, University College London, AstraZeneca, Boeringer Ingelheim and MSD) raised sufficient funds to support the initial development of the EuPFI infrastructure. Since then, much has been achieved; aims have evolved and are more refined, more specific and ambitious. Today, EuPFI is a consortium of 10 pharmaceutical companies, 5 universities, 1 hospital and uniquely, the European Medicines Agency (EMA) as an observer. Table I provides the goals and objectives of EuPFI consortium.

EUPFI FRAMEWORK

To enhance collaboration and build competencies, several membership options and criteria were defined (associate, sponsor and observer) (Fig. 1). EMA acts as an observer to the group to observe proceedings/discussions in a passive way. They contribute to the exchange of comments and understanding of any recommendations raised by group members but do not influence the objectives of the EuPFI. The consortium members meet regularly (usually twice a year face to face and then over teleconferences as required). From time to time, other stakeholders are invited to attend the face-to-face meetings and present their work to the group. For example, EuPATI (European Patients' Academy on Therapeutic Innovation) expressed interest in being part of EuPFI and was invited to provide an overview to explore how to set up a two-way collaboration as EuPFI recognises the importance of patient and public involvement (PPI). EuPFI has five workstreams (Fig. 1) each addressing a fundamental aspect of the development of medicines for children. Information on the work of each workstream including key deliverables for the near future are listed below.

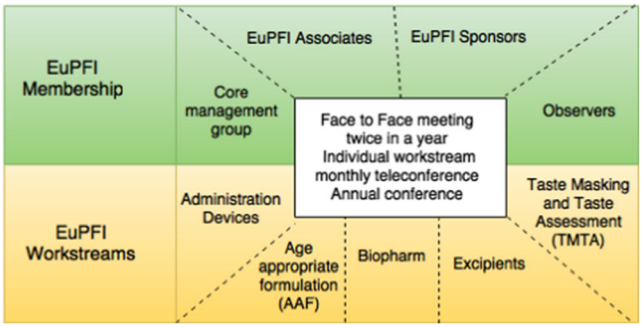

Fig. 1. EuPFI framework

Age-Appropriate Formulations Workstream (AAF)

Children require age-appropriate formulations that can deliver variable dose with age/weight, have acceptable safety and are adapted to their development and ability to take medicines. However, there is limited knowledge about the age appropriateness of different dosage forms and limited availability of appropriate dosage forms even when the medicine is authorised for children (3). To overcome age-appropriate formulation-related issues, healthcare professionals, patients and parents often have to resort to pharmaceutical compounding and drug manipulations. These are risky practices that can potentially cause harm, including toxicity or therapeutic failure, with the pharmacokinetic and clinical outcome of the medication not being fully known. The workstream activities are centred around the development and evaluation of medicines for marketing authorisation and guide the use of modifications to the dosage form in practice. The intent is to provide guidance to the industry, regulators and academic researchers of the age appropriateness of different pharmaceutical dosage forms. An initial activity was therefore to consider a means by which age-appropriate formulations could be selected, which requires a risk/benefit analysis on a case-by-case basis. The group proposed a structured integrated approach for assessing the risk and benefits of different pharmaceutical design options against pre-determined criteria relating to different routes of administration and formulation options including the safety of excipients, efficacy, usability, manufacturability, cost and patient access (4). Recognising that there is confusion about the types of paediatric pharmaceutical preparation that are available for approval by medicines regulators, a reflection paper on "Preparation of medicines for children—a hierarchy of definition" was published by AAF workstream members (5). The paper explores compounding and manipulation of medicines in relation to

Table I. EuPFI Objectives

Identify the issues and challenges associated with development of paediatric formulation and consider ways towards better medications and clinically relevant dosage forms for children
Promote early pharmaceutical consideration for development of paediatric medicines
Identify potential information, knowledge and know-how gaps in the paediatric formulation development
Improve the availability of information of paediatric formulations.

approval by medicines regulators to fulfil the needs of the individual patient. The team has proposed standardised definitions and terminology to clarify the types of paediatric pharmaceutical preparation. It aims to simplify strategies in product development to ensure quality and bioavailability. Another key aspect in the development of age-appropriate formulation is patient acceptability. Children and older adults differ in many aspects from the other age subsets of population and require particular considerations in medication acceptability. AAF workstream published a review highlighting the similarities and differences in the two age groups in relation to factors affecting acceptability of medicines (6) and a paper highlighting how formulation factors affect the acceptability of different oral medicines in children (7). Currently, the workstream is examining the acceptability of pharmaceutical products for children, evaluating formulation attributes, methodology development and criteria for acceptability assessments. Moreover, addressing manufacturing challenges in developing paediatric formulations and proposing novel solutions, e.g., for poorly water-soluble drugs, is underway through publications. Future tasks include considering industrial perspectives in harmonising formulation development for adults and children and collaborating with regulatory bodies on issues of age-appropriateness of paediatric formulations. Another task would be to review the use of modified release formulations and different routes of administration in children to shift the emphasis to alternative routes which are potentially understudied and bridge the evidence gap.

Biopharmaceutics

Improving the understanding of biopharmaceutical assessment of paediatric pharmaceutical products enables more efficient development of medicines designed for children due to availability of appropriate *in vitro* tests that de-risk clinical assessment. The workstream has reviewed *in vitro* tests used in adult populations to determine what amendments are required to ensure they are relevant for a paediatric population (8). Specifically, research undertaken by the biopharmaceutics workstream was to identify the relevant volume to classify a dose as highly soluble; values increased with age from a volume of 25 mL being proposed for neonates compared to the adult volume of 250 mL. Dissolution conditions also suggested reduced volumes for younger children with <250 mL for newborns and infants and larger volumes from 250 to 900 mL for older children and adolescents. In addition, the applicability of the Biopharmaceutical Classification System (BCS) to paediatric populations was reviewed both using the literature (9) and from the results of a cross industry survey (10). The results of these reviews highlight several knowledge gaps in current methodologies in paediatric biopharmaceutics that are being addressed by the group. This includes better characterisation of the physiology and anatomy of the gastrointestinal tract (GI) in paediatric patients and characterisation of age-specific changes in drug permeation across the intestinal membrane and the development of biorelevant media and testing conditions for dissolution.

In collaboration with AAF, the current priority for the workstream is to understand the impact of co-administration of paediatric medicines with foods (such as apple sauce, pudding) that are commonly used to facilitate administration and improve compliance. There is no guidance on how the impact of manipulations is risk assessed from the laboratory to the patient. Non-standardised development approach for paediatric products increases the relative cost and timelines to support labelling claims. The Biopharm group aims to address the risk level of co-administration of food with medicine on bioavailability based on a literature search and a discussion among experts. The group will also explore the biopharmaceutics tools used to predict food effects and evaluate how bridging may be achieved for *in vitro* prediction of *in vivo* performance in children. Future priority is to extend the understanding the biopharmaceutics of excipients, for exampler identifying how excipients can affect the absorption of drugs and GI physiology in children.

Administration Devices

It is undeniable that the need for and the type of paediatric administration device should be considered as an integral part of the paediatric product development process. The device should not only be technically capable of measuring the required/correct doses but also be easily accessible and sufficiently user-friendly so as to facilitate compliance. To address these issues, the devices workstream aims to identify and highlight current paediatric medicine administration devices practices and issues, with the ultimate aim of informing and facilitating the development and access to easy-to-use devices.

The workstream has reviewed currently available paediatric administration devices (oral, pulmonary, parenteral, nasal and ocular routes) together with challenges associated with their use and recent developments (11,12). In addition, as both the understanding and the usage of medical devices for oral and respiratory drug administration are heterogeneous among patients and caregivers, the workstream conducted a survey in hospital-based healthcare professionals (HCPs) (doctors, pharmacists and nurses) in six European countries to gain an understanding of HCP experiences of and opinions on oral and pulmonary paediatric administration devices (13). The countries selected (UK, Italy, Spain, France, Hungary and Germany) were considered to represent the geographical and cultural diversity of Europe. The survey results provided some valuable insights indicating that HCPs are aware of patients and caregivers having difficulty in using these types of devices. The challenge for this activity was identifying and contacting potential participants in each country since group members had no direct access to HCPs and no formal links to any hospitals or patient groups. To build upon these findings, the workstream is planning to conduct a similar survey in patients and their caregivers (parents, non-HCPs) to help identify areas for improvement. Long-term activities of the workstream include the development of guidance for conducting user handling studies and an investigation into industry knowledge gaps for the development of administration devices and combination products, including regulatory requirements.

Excipients

One critical element in the development of paediatric formulations is the selection and use of excipients, as their safety in paediatric subpopulations is often unknown.

There are many issues (disease specific, idiosyncratic reactions, physiological limitation) that have to be considered in the excipients selection process. Some excipients (e.g., propylene glycol, benzyl alcohol) are known to be less well tolerated by children depending upon the administration route, especially neonates and young children whose physiological system are still developing. Since excipients may be toxic, focused and detailed research is urgently needed to identify and support the use of excipients in different subsets of the paediatric population. Even though the demand for paediatric data on the safety of excipients has grown considerably, there is very limited paediatric excipient safety data in the public domain, and it is distributed throughout many sources. In an effort to address these availability and accessibility issues, the excipients workstream has worked in collaboration with other networks such as the United States Paediatric Formulation Initiative (USPFI) and Global Research in Paediatrics (GRiP) to develop the Safety and Toxicity of Excipients (STEP) database (14). This user-designed resource compiles the clinical, non-clinical, *in vitro* review and regulatory information of excipients into one freely accessible source. The database assists in screening and selecting excipients for use in children and thus facilitates paediatric drug development (15). STEP was launched in October 2014 and now has information on 40 excipients with users from the industry, academics, hospitals and regulators. It is accessible freely from EuPFI website and perceived as useful and an important addition to the current resources (16). Existing data is updated regularly, and additional excipients are added quarterly. It is important to focus on the future by moving forward with the addition of excipients and enriching the existing content for the continuation of the use of the STEP database. Hence, "Sponsor an Excipient" scheme has been introduced. The scheme allows end-users to include the excipients of their choice in the STEP database at minimal costs.

Taste Assessment and Taste Masking (TATM)

Improving the understanding of taste assessment tools and methodology used during the development of pharmaceutical products designed for paediatric populations is a must in parallel with better understanding of taste masking strategies that lead to the development of paediatric pharmaceutical products that have an acceptable taste (17). The first inter-laboratory testing of electronic taste sensing systems was led by EuPFI (five participating centres including three EuPFI members), each working with the Insent (Insent Inc., Atsugi-Shi, Japan) e-tongue (18). Most of the published data reported good correlation between the human taste panel test and the electronic taste sensing systems. However, in most of these studies, methods followed for bitterness prediction and constructing the correlation with human taste data were not always fully described. Electronic sensors give a relative taste statement and should be validated with human taste panel tests. Ideally, electronic tongues could be used for early screening of taste of pure APIs and optimisation of taste masked preclinical formulations in the industry.

However, until it is demonstrated that electronic tongues can reliably predict bitterness intensity of the compounds, which were not used for developing calibration model, the use of this technology is still limited. A review paper to provide an overview of different approaches to taste masking APIs in paediatric oral dosage forms, with a focus on the tolerability of excipients used, was also published (19, 20). Currently, TATM workstream focuses on consolidating "Electronic tongue" user group, the application of non-human *in vivo*, *in silico* and cell-based taste assessment tools in pharmaceutical taste assessment.

REFLECTION AND CHALLENGES

Nine years after its initiation, EuPFI is a well-established collaboration of academia, industry, hospital and regulatory authorities, formed to harness the energies of these stakeholder groups for their common purpose and most importantly to provide the drive for finding solutions to issues in paediatric drug development. One of the strengths of the consortium has been its association with EMA, as an observer on the group. The EMA representative participates in the consortium meetings, and the group works together to update the research, identify gaps and discuss the regulatory needs and implications for paediatric product development. EuPFI members are invited to represent the group at several external meetings including EMA workshops. The annual conferences organised by EuPFI offers the opportunity for paediatric formulation specialists to exchange ideas and present recent accomplishments as well as discuss remaining challenges for the future with a vision of better medicines for children. So far, the consortium has organised seven annual conferences with up to 200 participants at a time. The 8th annual conference is scheduled for the 21st and 22nd of Sept. 2016 in Lisbon, Portugal (http://www.eupfi.org/8th-conference/). The proceedings and selected invited articles are published in a special issue of the International Journal of Pharmaceutics following each conference (21–28). The collaborative effort has resulted in significant progress to date and the identification of new challenges to be met. However, the process has not been a smooth journey, and success has been achieved through developing partnerships and collaboration.

Shared Vision and Consortium Management

Given the diversity of approaches to the development of paediatric formulations, consortium members worked to develop a shared vision. This is a long-term and evolving process. As new members joined the consortium, the agenda of various stakeholders (patients, academia, clinicians, industry and policy makers) differed and were sometimes difficult to reconcile. Maintaining a shared vision is a challenge as is keeping the group small and manageable. Due to the complexity of managing larger organisations, the consortium members preferred to restrict EuPFI to 20–25 core members. It was also agreed that, at least initially, EuPFI would be limited to Europe. However, later due to large interest from other countries such as India and the USA, it was decided to

accept members from other countries, but only if they were able to participate in face-to-face meetings held twice in a year. The success of the consortium has been to achieve a balance between the shared vision of the consortium, added value of each member and the specific aims of each workstream.

Potential Overlap Betweeen Networks

Considering the large number of networks that has been established since the implementation of paediatric regulations and which are currently flourishing globally (Turner) such as GRiP and USPFI, some overlap between their activities is inevitable. Obviously, this might result in duplication of efforts and dissipation of resources. Within EuPFI, emphasis is placed on establishing links and synergies in order to avoid duplication of work and indeed encourage harmonisation. In 2014, EuPFI in collaboration with Paediatric Formulation Working Group of the Innovative and Quality (IQ) Consortium (PFWGIQ) conducted a systematic survey of researchers and regulators on the current practices in paediatric product development (http://www.grip-network.org/index.php/en/news/item/57). "GRiP" is an initiative funded by the European Union Seventh Framework Programme (FP7/2007-2013) to stimulate and facilitate the development and safe use of medicines in children through development of a comprehensive training programme and integrated use of existing research capacity. EuPFI members contributed to the paediatric formulation module of the GRiP e-Master of Science in Paediatric Medicines Development and Evaluation and were also actively involved in delivering "Meet the Expert in Paediatric Formulations" webinars series (http://www.grip-network.org/index.php/cms/en/Webinars - top). GRiP has partially funded the development, quality control and validation of the STEP database, which is developed in collaboration with USPFI. The USPFI was formed as a project of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) in 2005 to identify the issues and challenges in developing formulations for children (29). As both EuPFI and USPFI groups were working on similar issues, it was decided to join the forces in the development of the STEP database. The EuPFI excipients workstream worked with USPFI in collecting the information needs of the potential users and evaluating the need for the STEP database. USPFI also contributed to the development of methodologies for data collection, performing the usability study of the STEP database and continuing to contribute *via* performing the searches on the additional excipients to be included in the database as part of the database expansion. Additionally, there is some overlap between EuPFI membership and the SPaeDD-UK project (Smart Paediatric Drug Development—UK, accelerating paediatric formulation development http://www.paediatricscienceuk.com), funded by Innovate UK which aims to generate a structured approach to designing age-appropriate medicines for children and technology for predicting their quality and performance (30).

In addition, a first transatlantic workshop on paediatric formulation development was organised through M-CERSI (University of Maryland's Center of Excellence in Regulatory Science and Innovation funded by the *FDA as* a collaborative partnership between University of Maryland and FDA) and held in US in June 2016. It aimed to provide an opportunity for experts to share their experiences and move towards consensus regarding best practices for developing age-appropriate drug products, which meet the needs of paediatric patients aligned with the requirements of regulatory agencies.

Sustainability of the consortium

There is the clear commitment of all partners to work together, to combine their expertise and strength, and to create a critical mass that is well integrated in the European paediatric formulation research area. However, unless stable funding can be secured, sustaining a consortium is truly challenging and future options are being explored. For example, the excipient workstream has recently launched the "sponsor an excipient" campaign. It will help finance excipients that have not yet been reviewed under the STEP database project and will help expedite the data curation process and maintain the database.

Member's Commitment

Maintaining a balance between the interests of members and their day-to-day responsibilities is another challenge. The consortium depends heavily on the time and commitment of the members who often have conflicting priorities and hence generally work on EuPFI activities in their own time. To date, the support from the EuPFI members to formulate innovative ideas to issues in paediatric formulation development is what has kept the consortium active.

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