Introduction

The importance of developing safe and effective medicines for children has been recognised now. 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 that are still patent protected drugs 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 are 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 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 EuPFI consortium, highlighting the activities and 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 fulfill 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,

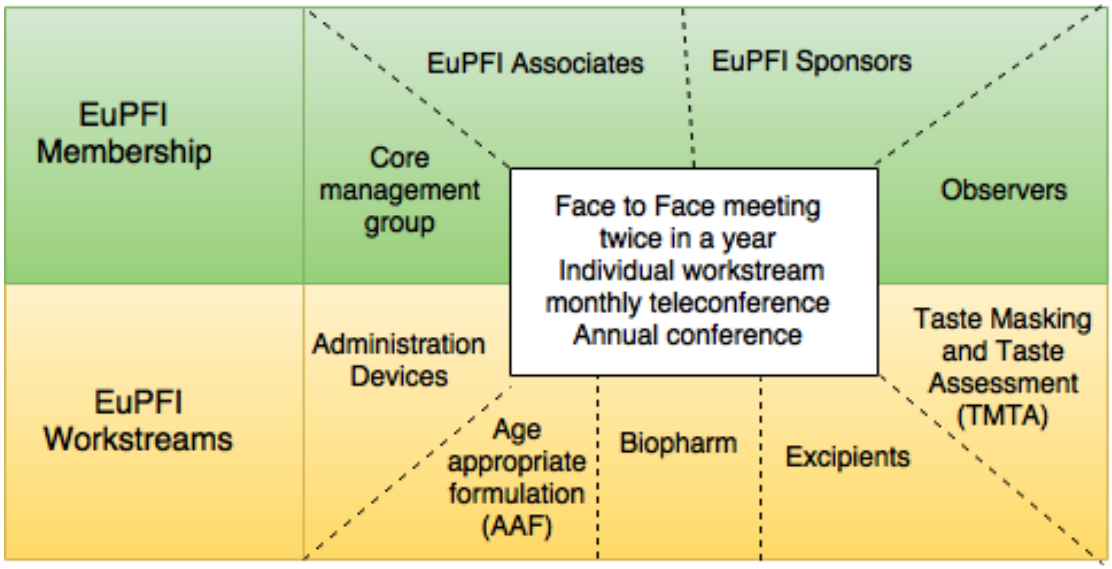
University College London, AstraZeneca, Boeringer Ingelheim and MSD) raised sufficient funds to support the initial development of the EuPFI infrastructure. Since then much has been achieved, aims have evolved and are more refined, more specific and ambitious. Today, EuPFI is a consortium of 10 pharmaceutical companies, 5 universities, 1 hospital and uniquely, the European Medicines Agency (EMA) as an observer. Table 1 provides the goals and objectives of EuPFI consortium.

Table 1: 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, know-how gaps in the paediatric formulation development.
Improve the availability of information of paediatric formulations.

EuPFI Framework

To enhance collaboration and build competencies, several membership options and criteria were defined (Associate, Sponsor and Observer) Figure 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 does 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 recognise the importance of Patient and Public involvement (PPI). EuPFI has five workstreams (Figure 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.

Age Appropriate Formulations Workstream (AAF)

Children require age appropriate formulations that can deliver variable dose with age/weight, are safe 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 authorized for children (3). To overcome age appropriate formulation-related issues, healthcare professionals patients and parents have to resort to pharmaceutical compounding and drug manipulations. These are risky practice and can potentially cause harm, including toxicity or therapeutic failure, without knowing the pharmacokinetic and clinical outcome. The workstream activities are centered around the development and evaluation of medicines for marketing authorisations and guide the use of modifications to the dosage form in practice. The intent is to provide guidance to industry, regulators and academic researchers of the age-appropriateness of different pharmaceutical dosage forms. An initial activity was therefore around the selection of age appropriate

formulations, 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). Recognizing 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 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 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 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 eg for poorly water-soluble drugs is underway in preparation 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 understudied possibly 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 <250mL for newborns and infants and larger volumes from 250-900mL 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) tract in paediatric patients; 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. 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 amongst 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 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 results provided some valuable insights indicating that HCPs are aware of patients and caregivers having difficulty in using these types of devices. The challenge was identifying and contacting the HCPs in each country due to the lack of direct access to HCPs as the group had 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 (diseases 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 United States Paediatric Formulation Initiative (USPFI) and Global Research in Paediatrics (GRiP) to develop the ***S***afety and **T**oxicity of **E**xcipients (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 of excipients for use in children and thus facilitates paediatric drug development (15). STEP launched in October 2014 has now information on 40 excipients with users from industry, academics, hospitals and regulators. It is accessible freely from EuPFI website and perceived as useful and an important addition to 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 & 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. The first inter-laboratory testing of electronic taste sensing systems was led by EuPFI (five participating centers including 3 EuPFI members), each working with the Insent (Insent Inc., Atsugi-Shi, Japan) e-tongue (17). 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 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 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 (18) (19). Current TATM workstream focuses on 1) consolidating "Electronic tongue "user group, 2) 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 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 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. So far the consortium has organized 7 annual conferences with up to 200 participants at a time. The 8th annual conference is scheduled for 21st and 22nd Sept 2016 in Lisbon, Portugal (http://www.eupfi.org/8th-conference/). The proceedings and selected invited publications are published in a special issue in International journal of pharmaceutics following to each conference (20-26). 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. Many challenges came way 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) differ, and sometimes was difficult to reconcile. Maintaining a shared vision is a challenge. Another challenge is keeping it small and manageable. Due to complexity in managing larger organization, the consortium members preferred restricting it to smaller organization with 20- 25 core members. It was also agreed that, at least at first, EuPFI would be limited to Europe. However, later due to large interest from other countries such as India and US, it was decided to accept the members from other countries only if they were able to participate at face-to-face meeting 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 between networks

Considering large number of networks have established since the release of paediatric regulation and currently flourishing globally (Turner) such as GRiP, USPFI, some overlap between their activities is inevitable. Obviously, this might result in duplication of efforts and dissipation of resources. Within EuPFI emphasis is made on establishing links and synergies .The aim is to avoids any duplication of work and indeed encourage harmonization the efforts. In 2014, EuPFI and Pediatric Formulation Working Group of the Innovative and Quality (IQ) Consortium (PFWGIQ) in collaboration conducted a systematic survey of researchers and regulators on current practices in paediatric product development (http://www.grip-network.org/index.php/en/news/item/57). EuPFI members contributed to the paediatric formulation module of the GRiP e-Master of Science in Paediatric Medicines Development and Evaluation. '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. They 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. (27). As both EuPFI and USPFI group 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 of the STEP database. USPFI also contributed to the development of methodologies for data collection, performing the usability study of the STEP database and continues to contribute via performing the searches

on the additional excipients to be included in the database as part of expansion of the database. Additionally, there is 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 (28).

In addition, a first transatlantic workshop on paediatric formulation development is 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 aims 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 pediatric 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 pediatric formulation research area. However, unless stable funding can be secured, sustaining a consortium is truly challenging. The consortium has actively started to explore future options for sustaining the consortium. For example, the excipients workstream has recently launched the “sponsor an excipient” campaign. It will help finance excipients that have not yet been undertaken 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. It depends heavily on the time and commitment of the members with conflicting priorities as they generally work on EuPFI activities in our own time. To date the support from the EuPFI members to

formulating innovative ideas to issues in paediatric formulation development is what has kept the consortium active and on.

Concluding remarks

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