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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 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 has grown since its inception in 2007 and continues 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 has 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.
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European Paediatric Formulation Initiative (EuPFI) – Formulating ideas for better medicines for children

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Suggested Running Head:
European Paediatric Formulation Initiative (EuPFI) overview

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 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 has grown since its inception in 2007 and continues 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 has 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.

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 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, 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 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.

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, 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 authorized 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 centered 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 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). 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 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 <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. 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 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 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 (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 and now has 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 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 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). Currently 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 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 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 articles are published in a special issue of International journal of pharmaceutics following 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 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 was 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 organizations, 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 US, it was decided to accept members from other countries, but only if they were able to participate at 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 between networks

Considering the large number of networks that have been established since the implementation of paediatric regulations and which are 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 placed on establishing links and synergies in order to avoid duplication of work and indeed encourage harmonization. In 2014, EuPFI in collaboration with Pediatric Formulation Working Group of the Innovative and Quality (IQ) Consortium (PFWGIQ) 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). '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. (27). 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 continues 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 (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 and future options are being explored. For example, the excipients 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 formulating innovative ideas to issues in paediatric formulation development is what has kept the consortium active.

Concluding remarks

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Response to reviewers (Manuscript No AAPSPT-D-16-00162)
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Salunke S., Liu F., Batchelor H., Walsh J., Turner R., Ju TR, and Tuleu C, on behalf of EuPFI.

Reviewer's comments
This paper is a review of the EuPFI consortium and their work, structure and focus. It gives valuable information on EuPFI and the significant contribution this initiative is making. Being a European initiative, it is important to flag this work worldwide, so also to the readers of AAPS PharmSciTech, in particular considering the significant global focus of EuPFI's work and their collaborative approach.
It is my understanding that the authors have been invited for this manuscript, and as such, the intended focus and scope is likely clearly communicated between the editor/guest editors/journal and the authors.

Reviewer 1

Comment 1:
The structure of the manuscript is built on the historical context, the main focus areas (workstreams), and the way the consortium is working. The paper may give the impression being in a 'report' format, listing aims, tasks and achievements. In this context, some more reflections could have added value. In particular, it would have been interesting to **include some reflections on the challenges** they have experienced during these years of comprehensive work, considering the complexity of this task. Also, **some more specific practical examples** would have shed further light on the importance of their work, concretizing the issues highlighted in the paper.

Author response:
The format/structure of the manuscript is changed so that it does not look like a report. An additional paragraph is added to address the reflections on the challenges the group has experienced during these years of comprehensive work. Also some practical examples are added (see lines 355 to 357).

Revised content:
See additional paragraph on reflections and challenges– lines 427 to 571

Comment 2:
The paper gives a comprehensive review of the tasks of the consortium. However, the language in the paper is rather heavy, several sections with sentences up to 50-60 words. It is this reviewer's opinion that splitting sentences and using fewer words could significantly increase the readability of the paper.

Author response:
The manuscript is revised and simplified. Long sentences are shorten.

Comment 3:
Table 1 should be restructured to not give the impression that the linings group different members. The different stakeholders should be listed consecutively within each category without apparently interlinking them.

Author'response
Table 1 is removed as this information is available on EuPFI website. A reader can access the website to find the details on membership. It has been replaced by general figure on EuPFI framework, which provides the EuPFI composition and working structure.

Comment 4:
References should be numbered in the text and the reference list revised to comply with the format instructions in the guide to authors.

Authors response:
References are cited as per Vancouver style as per the guide to authors. They are numbered consecutively in the order in which they are cited in the text.

Reviewer #2:

Comment 1:
Abstract:
Line 14: five different workstreams are mentioned: age appropriate medicines, biopharmaceutics, administration devices, excipients and taste assessment and taste masking. These workstreams are also mentioned on the EuPFi website, however on the website they are referred to as subgroups.

Authors response:
We have recently renovated our website. All the changes will reflected on updated website soon.

Comment 2:
On the website furthermore different names are used for the workstreams or work goups: Pharmaceutical excipients, taste masking and taste assessment methods, modification of dosage forms required for children (MDFRC), administration devices and age appropriateness of formulations. The use of different names for the workstreams (or work groups or subgroups) is confusing for the reader. I suggest uniformity in the use of the names.

Author response:
We have recently renovated our website. All the changes will reflected on updated website soon. The consistency in the names and terms used will be maintained.

Comment 3:
Introduction:
A word is missing in line 8: off -patent paediatric medicines or formulations?

Author response:
Updated, included the word ‘medicines’

Comment 4:
The main objective of the manuscript can be stated more clearly. I suggest to add a sentence containing the words 'an overview' in the title, abstract and introduction.

Author response
Updated, the term ‘Overview’ is added to title and abstract (line 18)

Comment 4:
Development of EuPFi:
EMA has a role of an observer. Can you explain this in more detail, is EMA only an observer or may have influence on the objectives of EuPFi?

Author reponse:
The role of EMA is elaborated on lines 44 to 47.

Text included :
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.

Comment 5:
Structure of EuPFI:
Figure 1 is blurry

Author response:
Figure 1 is changed to another figure and higher version is provided.

Comment 6:
Age appropriate formulation workstream:
Line 59: A reflection paper on…was published. Can you add more information about the content of this paper?

Author response:
Content added.

Text included:
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

Comment 7:

Line 61- 63: Currently the workstream…acceptability assessment. Can you give some examples? For instance on pharmaceutical products.

Author response:
A systematic literature review is under construction on acceptability assessment methods used in paediatric formulations with the aim to provide an insight on standardising the methodology development.

Comment 8:

Biopharmaceutics:
Line 78: Can you give examples of the in vitro tests used and what amendments are required?

Author response:
Sentence added:
"Specifically research undertaken by the biopharmaceutics workstream 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"

Comment 9:
Line 84: You mention knowledge gaps in current methodologies, can you explain this in more detail?

Sentence added:

“Knowledge gaps identified included: better characterisation of the physiology and anatomy of the 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”.

Comment 10:

Line 95: GI abbreviation. I suggest to use the full word.

Author response:
Agree. Amended the text.

Comment 11:

Administration devices:
The first paragraph is very clear and well written!
Line 113: You mention a survey which was conducted in six European countries. Which European countries were included in the survey? Is the healthcare system in these countries comparable?

Author response:
Sentence added :
“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”.

Comment 12:

Line 116 - 117: caregivers have difficulty in using their devices. Was this applicable for all devices or just specific types of devices, since all devices need a different (tailor made) instruction and some devices are more user-friendly.

Author response:
This phrase relates to the results of the survey so re-phrased to “....caregivers having difficulty in using **these types of** devices.”

Comment 13:

Excipients:
Line 129 -132: Some excipients…still developing. This is dependent on the administration route (differences in e.g., the oral or parenteral route).

Author response:
Amended as suggested.

Revised text:
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.

Comment 14:

Line 145 - 147: STEP database. Is the database updated on a regular basis?

Author response:
Sentence added: Existing data is updated regularly and additional excipients are added quarterly.

Comment 15:
Taste assessment & Taste Masking:
Line 159 - 162: You mention the electronic tongue. Maybe out of the scope of this paper, but can you provide information about the applicability of the e-tongue (suitable for every API? How to interpret the results).

Author response:
Text added :
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.

Comment 16:
Collaboration with other networks:
This paragraph is quite unclear and confusing to me as a reader. Many names and abbreviations are used. I suggest a table (combine with table 1?) with the names and the tasks of the different networks.

Author response:
The paragraph on collaboration with network is deleted and the content in included elsewhere in the text as per the context and connected to the tasks.

Line 178: use the full word in the text and GrIP enclosed by brackets

Author response:
Its abbreviation used by the network and hence is used in the text. Also it is spelled out on line 191 when it was used first time.

Comment 17:
Specific comments and typos:
Line 94: exampler should be corrected to example

Author response :
exampler added.

Comment 17:

Line 236: FDA: why is the abbreviation underlined?

Author response : Typo error, it is corrected.

Table 1: EuPFI Objectives

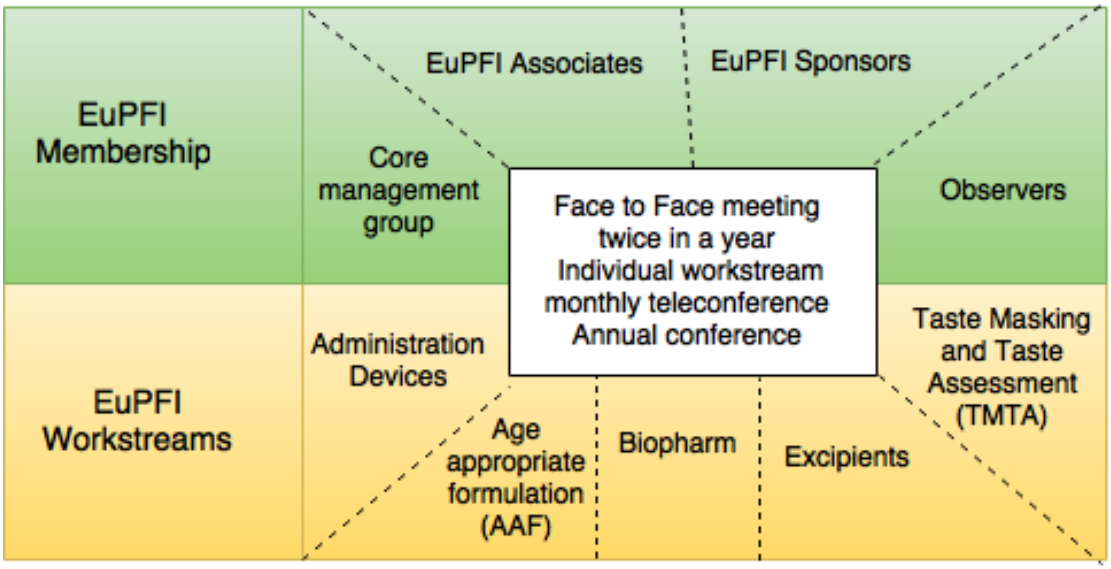
Table 1: EuPFI objectives

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.

Figure 1: EuPFI Framework

Figure

Figure1: EuPFI Framework



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Title: EUROPEAN PAEDIATRIC FORMULATION INITIATIVE (EUPFI) Formulating better ideas for better medicines for children

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