European Journal of Pharmaceutics and Biopharmaceutics 203 (2024) 114447

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Paediatric excipient risk assessment (PERA) tool and application for selecting appropriate excipients for paediatric dosage forms – Part 2

Anjali Agrawal [a], Smita Salunke [b,*], Alfred Rumondor [c], Karen Thompson [d], Grazia Caivano [e], Jennifer Walsh [f], Brian Enright [g], Philip Sherratt [h], Kevin Hughes [i], David Clapham [j], Peter Kuehl [k], on behalf of the International Consortium (IQ) for Innovation and Quality in Pharmaceutical Development and European Paediatric Formulation Initiative (EuPFI)

[a] Novo Nordisk Inc., 300 North Beacon Street, Suite 501, Watertown, MA 02472, USA
[b] European Paediatric Formulation Initiative (EUPFI), University College London School of Pharmacy, London WC1N 1AX, UK
[c] Bristol Myers Squibb, One Squibb Drive, New Brunswick, NJ 08901, USA
[d] Merck & Co., Inc., 126 E Lincoln Ave, Rahway, NJ 07065, USA
[e] Chiesi Farmaceutici S.p.A. Largo Francesco Belloli 11/A—43122 Parma, Italy
[f] Jenny Walsh Consulting Ltd., Nottingham, UK
[g] Abbvie Inc. 1 N Waukegan Road, North Chicago, IL, 60064, USA
[h] Bristol Myers Squibb, 556 Morris Avenue, Summit, NJ 07901, USA
[i] IPEC Europe (International Pharmaceutical Excipients Council) and Colorcon Ltd, Dartford, UK
[j] Independent Pharmaceutical Consultant, Bishops Stortford, UK
[k] F. Hoffmann La Roche AG, Grenzacher Str. 124, CH-4070 Basel, Switzerland

ARTICLE INFO

Keywords:
Paediatric
Age-appropriate
Formulation
Excipients
Inactive ingredients
Risk assessment

ABSTRACT

It is necessary to use a scientifically sound process for excipient risk evaluation, selection, and management in order to develop paediatric medicinal products that are both safe and effective. The "Paediatric Excipient Risk Assessment (PERA)" framework, which proposes a comprehensive approach by considering all relevant factors related to patient, dosage form, and excipient attributes, was developed and published as part 1 of this paper series, to enable the rational selection of excipients for paediatric medicinal products.

This article is Part 2 of the series and presents the PERA tool that allows easy adoption of the PERA framework. Using a straightforward heat map scoring approach (Red, Yellow, and Green category) for risk evaluation, the PERA tool can be used to compare and choose excipients. The PERA tool will help users identify potential gaps in excipients information that will help with risk-based mitigation planning. Several case studies covering frequently used and novel excipients for oral, as well as the choice of excipient for parenteral products for neonatal administration, serve to illustrate the PERA tool's usefulness.

1. Introduction

Age-appropriate formulations are required to deliver pharmaceutical actives safely and efficaciously to patients aged < 18 years of age. This has been reinforced in both the United States (US) and European Union (EU) via guidelines that require consideration of the formulation in the paediatric study plan (PSP) and paediatric investigation plan (PIP), respectively [1–5]. Pharmaceutical excipients are required to enable suitable, acceptable, and stable dosage forms to be formulated [6]. Whilst a scientifically sound process for excipient selection is required for any formulation, additional factors need to be considered when selecting appropriate excipients for paediatric formulations. Accordingly, a systematic risk–benefit assessment process called the "Paediatric Excipient Risk Assessment (PERA)" framework was developed as reported in Part 1 of this series of papers (Fig. 1). The PERA Framework enhances the objectivity and transparency of the decision-making

* Corresponding author.
E-mail addresses: vagr@novonordisk.com (A. Agrawal), s.salunke@ucl.ac.uk (S. Salunke), Alfred.Rumondor@bms.com (A. Rumondor), karen_thompson@merck.com (K. Thompson), g.caivano@chiesi.com (G. Caivano), jenny@jennywalshconsulting.com (J. Walsh), Brian.Enright@abbvie.com (B. Enright), Philip.Sherratt@bms.com (P. Sherratt), KHughes@colorcon.com (K. Hughes), david.clapham@ntlworld.com (D. Clapham), peter.kuehl@roche.com (P. Kuehl).

https://doi.org/10.1016/j.ejpb.2024.114447
Received 14 May 2024; Received in revised form 31 July 2024; Accepted 6 August 2024
Available online 8 August 2024

process by providing a structured and systematic risk–benefit assessment approach that could be adopted by both companies and regulatory agencies. Part 1 of the publication also highlights current resources available on excipients for paediatric products, common practices used in the industry, regulatory guidance and knowledge gaps.

The current paper (Part 2 of the publication) presents a risk–benefit analysis tool developed using the PERA framework to systematically document the analysis for a particular excipient or multiple excipient options with similar functionality to enable decision-making using the PERA principles. Several case studies are presented to demonstrate the use of the PERA framework and tool to facilitate adoption of the tool by users.

2. Paediatric excipient risk assessment (PERA) tool

The PERA tool has been created to facilitate the comparison and selection of excipients based on the considerations outlined in the PERA framework and is presented in the following section. It is a spreadsheet tool that prompts the user to systematically capture required information about the patient, treatment regimen, dosage form, and potential excipients. This tool can be adopted to compare prototype formulations containing different excipients and identify potential gaps.

2.1. PERA tool structure to conduct excipient risk–benefit analysis

The first section of PERA tool captures attributes of the patients for the proposed treatment, including patient age range, disease type and severity, proposed dosing regimen, and dose ranges, as well as any potential co-medications or patient associated conditions. An example of how this information may be captured is presented in Table 1. When capturing Body Weight (BW) values, it is recommended that a wide range of population is considered by incorporating the lowest and highest body weight values for the most vulnerable gender in targeted markets. It is especially important to ensure the lowest body weight value is captured, since this value will result in the highest numerical exposure for each excipient when calculated on mg/kg basis.

Once attributes related to the patients and proposed treatment have been recorded, it is recommended to capture attributes related to the proposed paediatric product, including route of administration, proposed dosage form, geographical area of use, as well as proposed packaging and any medicine delivery device(s). An example of how this information may be captured is presented in Table 2.

Table 1
An example of the first section of a PERA tool used to capture patient attributes for the proposed treatment.

Patient Attributes	
Patient age range	2 – 6 years old children
Body weight range (kg)	10.2 kg (5th percentile for 2-year-old girls) to 27.4 kg (95th percentile for 6-year-old girls) – (https://www.cdc.gov/growthcharts/index.htm)[4]
Disease type and severity	Chronic treatment for a potentially life-threatening condition
Dosing regimen	Twice a day (BID), 50 mg/dose
Conditions and co-medication	None

After patient, product, and dosing attributes have been captured, the proposed excipient attributes should be recorded (see Fig. 2). These include the functions of the excipient, proposed level or quantity, information on acceptable intake quantities (e.g. Acceptable daily intake – ADI), acceptability in the targeted age range (if information is available), regulatory acceptability, prior use in other marketed paediatric products (specifically in similar disease settings such as acute versus chronic use and paediatric age range), safety, toxicity, function, supply aspects, as well as physicochemical properties.

It is proposed that the excipient attributes are separated into four major parts/categories: safety/toxicity, dosing attributes, physicochemical properties, function, supply chain, and other attributes (see Fig. 2). Each category can be further organized into sub-parts accordingly. As much detail as possible should be included when capturing the

Table 2
An example of the second section of a PERA tool used to capture proposed product and dosing attributes.

Product and Dosing Attributes	
Route of administration	Oral
Proposed dosage form	Sprinkle (minitablets)
Administration approach	Sprinkle onto soft food
Geographical area of use	Zone I – IV
Packaging and delivery device	Sachet

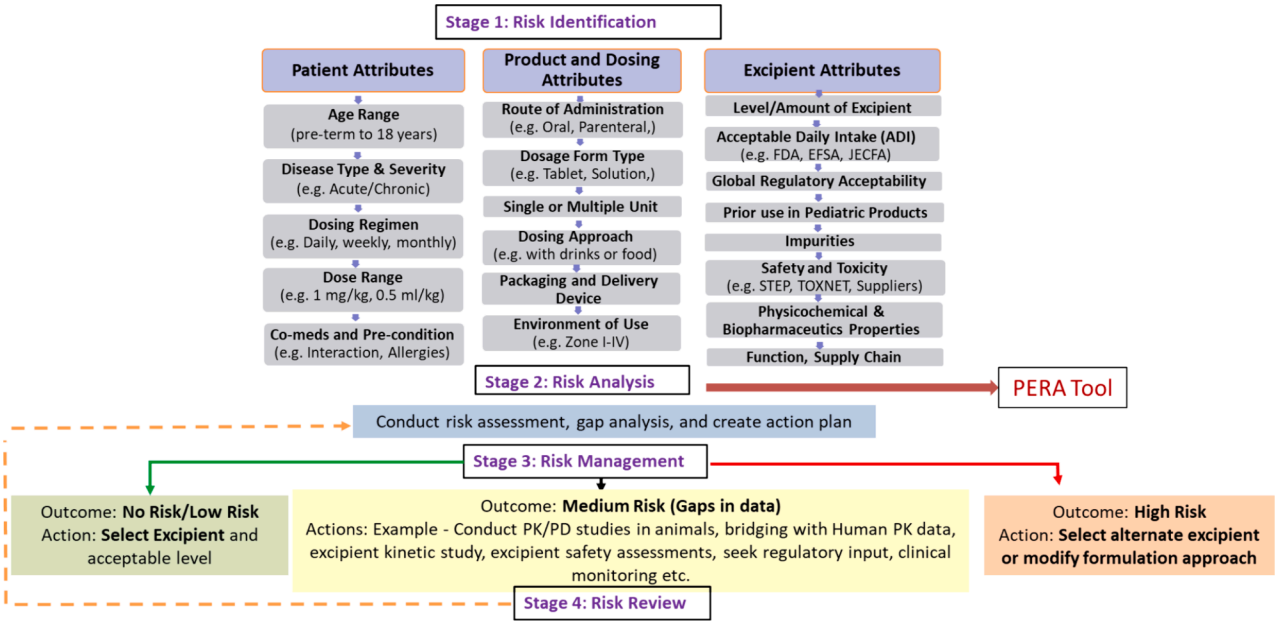

Fig. 1. Paediatric Excipient Risk Assessment (PERA) Framework.

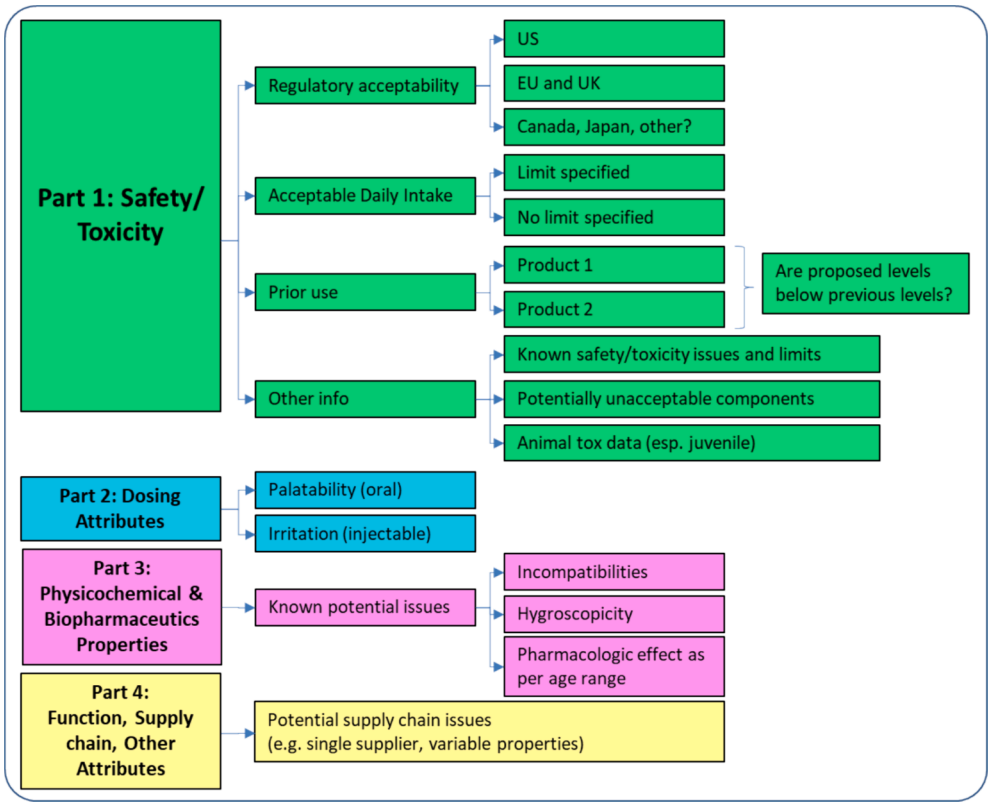

Fig. 2. Schematic diagram of the third section of a PERA tool used to capture excipient attributes.

excipient attributes to enable a thorough risk–benefit assessment.

The proposed formulation composition should be captured in the product attribute section. In addition to the percentage and mass per unit listing of each ingredient, the normalized quantity for each ingredient should be calculated. To determine the normalized quantity of a proposed excipient, the targeted quantity of an excipient in the dosage form should be divided by the minimum body weight for the youngest age group (representing the most vulnerable population from a safety perspective) to get the theoretical exposure level in mg/kg. Depending upon the dosing regimen, the exposure level in mg/kg/day can then be calculated. By expressing the quantity of excipient dosed in the same units as ADI (e.g. mg/kg/day, see Table 3 and case study 1 in section 3.1), direct comparisons between theoretical exposure versus reported acceptable intakes can be made.

Table 3
Preliminary formulations for the oral minitablet sprinkle dosage form for case study 1.

Ingredient	Function	% w/w	mg/sachet	mg/kg/dose for minimum BW	mg/kg/day for minimum BW
Compound X	API	20.8	50.0	4.90	9.80
Hypromellose acetate succinate	Stabilizer	16.7	40.0	3.92	7.84
Sodium lauryl sulfate	Wetting agent	0.4	1.0	0.10	0.20
Microcrystalline cellulose	Binder/filler	28.7	69.0	6.765	13.53
Mannitol or Sucrose	Sweet diluent	28.7	69.0	6.765	13.53
Croscarmellose sodium	Disintegrant	3.7	9.0	0.88	1.76
Colloidal silicon dioxide	Flow aid	0.4	1.0	0.10	0.20
Magnesium stearate	Lubricant	0.4	1.0	0.10	0.20
TOTAL		**100.0**	**500.0**		

For paediatric products, the safety/toxicity profile of the excipients is arguably the most important consideration in formulation composition, and therefore it is listed as the first part in the excipient attribute section. Under safety/toxicity, there can be multiple sub-parts, such as regulatory acceptability, ADI, prior use in marketed paediatric products, and other information. For the sub-part on regulatory acceptability, considerations from different geographical regions, regulatory agencies, or pharmacopeial standards can be captured depending on the intended markets of the proposed paediatric product. If allowable quantities for an excipient are different depending on the regulations in different jurisdictions, it may be prudent to ensure that the most conservative limit is met for a global clinical study or commercial product.

Different scenarios can arise when considering the ADI, which can be summarized in the second sub-part. For many common excipients, the ADI limit is “not specified” because based on available safety and toxicity data, the excipient is considered not to be a safety concern at reported levels of use, for example in the case of powdered cellulose in oral formulations [7,8]. For other excipients, an ADI limit may be established, for example in the case of saccharin [9,10]. Still for others, no specific ADI is listed, but a recommended intake amount or daily value may be listed, for example in the case of added sucrose [11]. All this information can be summarized along with the source link in this sub-part of the tool to further establish the safety of the excipient. A thorough review of various resources (e.g. World Health Organization (WHO), Joint FAO/WHO Expert Committee on Food Additives (JECFA), European Food Safety Authority (EFSA), Inactive Ingredient Database (IID), Safety and Toxicity of Excipients for Paediatrics (STEP) database) is needed to assess if other, more restrictive acceptable limits may be applied to the targeted age range of the paediatric population [12]. If the acceptable limit is not established in very young age groups such as neonates or infants, then additional juvenile toxicity studies in animals

may be required to assess the safety of the proposed excipient.

Evidence of an excipient's prior use in other paediatric products can also be considered during assessment of its potential safety/toxicity. Justification through prior use can be more conclusive when the comparison is made for the same route of administration, dosing regimen, and age range as the intended product. It is also more beneficial to select recently approved paediatric products for this purpose since products approved before the publication of US and European paediatric development guidance may contain unacceptable type or level of excipients based on current knowledge.

Finally, additional information should be included in the last subpart for safety/toxicity to capture potential toxicity for specific patient populations (e.g. sources of phenylalanine for phenylketonuria patients). It can also be used to capture usage limit information (e.g. based on published no-observed adverse effect level (NOAEL) limits), the potential for the presence of unacceptable components (e.g. processing aids or residual impurities from production of the excipients) etc. Ultimately, it is imperative to consider any potential adverse effects in the context of benefit versus risk for the specific disease, proposed treatment, and intended age groups.

In the next part of the excipient attribute section of the PERA tool, dosing attributes of the proposed excipient can be evaluated. For example, palatability would be an important consideration when designing an oral formulation. If an excipient has the potential for undesirable organoleptic attributes, particularly taste, it can be noted here, so that during development, efforts to assess and potentially improve overall palatability/acceptability can be taken into consideration. It should be noted, however, that palatability of all oral paediatric products should be evaluated regardless of excipients. In contrast, for an injectable formulation, irritation may be a more appropriate dosing attribute to evaluate, and if an excipient has a potential to cause injection site irritation, it can be noted here.

The third and fourth part of the PERA tool focuses on excipient attributes that are related to the technical aspect of a pediatric product. An assessment of technical risks together with patient related aspects is beneficial to obtain a holistic understanding of the overall risk of using a certain excipient for the targeted product profile. The third part of the excipient attribute section of the PERA tool comprises physicochemical properties considerations. In this part, any potential physical or chemical instability of the excipient can be listed, as well as any potential impact on the quality attributes of the final dosage form. During preformulation studies, compatibility of excipients and preliminary stability in accelerated/stressed conditions are usually conducted to select chemically compatible excipients. The PERA tool can be used to capture any potential incompatibility among excipients or in-use condition to ensure a holistic capture of all available information on the excipient as the paediatric drug product development progresses.

The last part of the excipient attribute section is related to supply chain as well as other potential issues. For pharmaceutical products, many excipients can be sourced from multiple vendors with established supply chains. However, if there are any potential concerns for supply-related issues, e.g. a single-supplier ingredient, or if the quality of the excipient can be impacted by natural variations as commonly observed with natural-based excipients, these considerations can be captured and highlighted in this part of the PERA tool. Any additional information on the excipient related to functionality and biopharmaceutic properties can be captured in the additional attributes section as needed by the users. It is important to note that the PERA tool is a "living document" and needs to be reviewed and if necessary, updated from time to time in the light of emerging information, at least at every clinical milestone.

2.2. Heat map scoring to conduct excipient risk–benefit analysis

Once detailed information on each attribute has been collected, a risk assessment can be performed for each proposed excipient through the simple heat map scoring of red-yellow-green approach. The green color scoring is used to represent no concerns for the use of an excipient at the proposed level in the paediatric formulation based on the information collected, while yellow color scoring may indicate potential gaps or concerns. The red color scoring may indicate significant gaps or concerns that need to be addressed through additional studies (see gap mitigation studies examples in Part 1 of publication and PERA framework in Fig. 1), or the need to consider the use of an alternative excipient. Once gaps are identified the project team can come up with an appropriate risk mitigation strategy or action plan for the generation of additional data on the proposed excipients. Upon availability of any additional data, the PERA tool can be updated and based on a new risk–benefit analysis, a decision could be reached about the proposed excipient.

The application of the color scheme can be adapted for the different categories in the tool. For example, where the proposed normalized quantity for a specific excipient in the formulation is under the published or derived ADI limit for the desired age range, then the cell can be colored as green. If the proposed normalized quantity is above the ADI limit specified, then the cell can be colored as red but specific details related to how high above the ADI limit and for which age group can be mentioned in the cell to assist in the risk–benefit analysis discussion later with the team. If the ADI value is not known, or there are other potential concerns, then the cell can be colored as yellow along with specific details, and subsequently recolored into green or red as more information becomes available.

For precedence of an excipient's use in other products, it is proposed that the cell is colored as green if an excipient has been used in other recent products under similar or lower dose and/or dosing regimen for similar patient age range, and the risk–benefit consideration justifies it. If the excipient has been approved in a product used in a different context (e.g. chronic indication or significantly different patient population), then the cell can be colored as yellow, to indicate that there is precedence for use in humans but there are gaps that need to be addressed. If there is no precedence of human administration or other robust safety data, then the cell should be colored red.

Based on the information summarized and the color scheme-based assignment, a heat map can be constructed, which would highlight potential gaps in knowledge (See Table 4 below as an example of a heat map). If more than one excipient is considered for a functional category (e.g. sweetener or bulking agent), then the heat map can be used to highlight which excipient presents the greatest potential risks.

While interpreting the PERA tool heat map, it is important to note that just because an excipient contains cells that are colored as red or yellow, it does not mean that the excipient cannot be used at the levels proposed. Instead, it may indicate there are gaps and/or concerns that need to be addressed. If there is a concern that the gaps in the risk profile of an excipient are insurmountable, then the use of an alternative ingredient to achieve the same functionality should be considered (see gap mitigation examples in Fig. 1).

If the proposed excipients in a particular functional category present concern in the targeted patient age group or there are gaps in knowledge that cannot be addressed, then the selection of an alternative dosage form or dosing strategy should be considered. For example, if the use of the proposed surfactant or co-solvents in a paediatric liquid oral formulation presents concerns, then other formulation approaches such as a fast-dissolving solid dosage form could be explored. However, cross-functional discussions are required to ensure safety, stability, manufacturability, dose flexibility, product palatability/acceptability, and business risks are considered to select the most suitable option.

Table 4
Application of the PERA Tool to case study 1 to design the heat-map for the proposed paediatric sprinkle minitablet formulation shown in Table 3.

Category	Sub category	Excipient	Hypromellose acetate succinate	Sodium lauryl sulfate	Microcrystalline cellulose	Mannitol	Sucrose	Croscarmellose sodium	Colloidal silicon dioxide	Mg stearate
		Usage level in proposed formulation (mg/kg/day)	7.84	0.20	13.53	13.53	13.53	1.76	0.20	0.20
Safety/toxicity	Regulatory	Acceptable in US	Yes (USP/NF)	Yes (USP/NF)	Yes (USP/NF)	Yes (USP/NF)	Yes (USP/NF)	Yes (USP/NF)	Yes (USP/NF)	Yes (USP/NF)
		Level (mg/kg or mg/kg/day)	8.00	0.74	22.19	13.87	20.54	2.57	1.21	1.43
		Source/assumption/reference	FDA IIG, 560mg for adult tablet, assume 70kg BW	FDA IIG, 51.69mg for adult tablet (IIG), assume 70kg BW	FDA IIG, 1553mg for adult tablet, assuming 70kg BW	FDA IIG, 971mg for adult ODT, assuming 70kg BW	FDA IIG, 1438mg for adult tablet, assuming 70kg BW	FDA IIG, 180mg for adult tablet, assuming 70kg BW	FDA IIG, 85mg for adult tablet, assuming 70kg BW	FDA IIG, 100mg for adult tablet, assuming 70kg BW
		Acceptable in EU	Yes	Yes	Yes (PhEur)	Yes	Yes	Yes	Yes (PhEur)	Yes (PhEur)
		Level (mg/kg to mg/kg/day)	Unknown	Unknown	9000	142.86	1500	30000	9000	Unknown
		Source/assumption/reference	Listed in Ph Eur	Listed in Ph Eur	NOAEL, https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out68_en.pdf	E421, 10g oral threshold, https://www.ema.europa.eu/en/documents/scientific-guideline/annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human_en.pdf, assume 70kg BW	Ph. Eur, for 1-3yo EFSA Journal 2016;14(1):4361 NOEL 1500mg/kg BW/day, https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out68_en.pdf	Listed in PhEur 30g/kg in oral dietary supplements is acceptable, https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out02_en.pdf	Listed in Ph.Eur No adverse effects detected to 9g/kg/day, https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2018.5088	No safety concern at the reported uses and use levels as food additive, https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5180
		Other pharmacopeias or regulatory agencies	JPE	Canada, JP	Canada, JP	JP	Canada, JP	Canada, JP	Canada, JP	Canada, JP
	ADI or other daily limits		Inconclusive	Inconclusive	No ADI specified	No ADI specified	Below recommended daily intake limit	No ADI specified	No ADI specified	No ADI specified
	Prior use in pediatric product(s)	Product 1 (Inlcude commercial or clinical use, age group, BW, and other pertinent information)	Incivek	Incivek	Felbamate/Felbatol® oral suspension	Tenofovir disoproxil fumarate/Viread® oral granules	Zithromax (azithromycin) poweder for oral suspension	Eslicarbazepine acetate tablets	Carglumic acid/ Carbaglu	Eslicarbazepine acetate tablets
		Level (mg/kg/day)	6.67	0.135	Unknown	122.5	185.0	Unknown	Unknown	Unknown
		Source, assumptions, references	3-17 yo, 15-90kg BW, 100, 250, or 375mg tablet, (100mg for 3yo), 49.5:49.5 weight ratio excipient to API per WO2013116339A1	3-17 yo, 15-90kg BW, 100, 250, or 375mg tablet,, 0.134mg/kg SLS (100mg for 3yo), 1:49.5 weight ratio excipient to API per WO2013116339A1	Dose unknown	622mg mannitol per g granules (Viread SmPC, https://www.medicines.org.uk/emc/product/2912), 2-12yo, 1225mg/10kg or 122.5mg/kg/day	Each 5mL prepared suspension contains 200mg azythromycin and 3.87g sucrose (Zithromax SmPC, https://www.medicines.org.uk/emc/product/3006/smpc#gref). Dose is 10mg/kg/day azithromycin			
		Product 2	Zelboraf	Orkambi oral granules	Levetiracetam/Desitin® minitablet	Tivicay® (dolutegravir sodium)	Isentress/raltegravir powder for oral suspension	Orkambi tablets	Levetiracetam/Desitin® minitablet	Orkambi tablets
		Level (mg/kg/day)	74.67	0.40	Unknown	Unknown	0.783	Unknown	Unknown	Unknown
		Source, assumptions, references	12-17 yo, 720mg API BID for patients >45 kg, 3:7 ratio of API to HPMCAS per WO2010114928A2	2-5yo, 12.5kg BW for 2 yo per CDC, 2.52mg SLS (1:49.5 ratio SLS to active ingredient ivacaftor)	Dose unknown	Dose unknown, 6yo and above	4.7mg sucrose per sachet containing 100mg raltegravir (Isentress SmPC, https://www.medicines.org.uk/emc/product/6904); dose for 3kg BW is 25mg raltegravir BID			
	Other info	Known safety/toxicity issue	Unknown	Probable oral lethal dose (human): 0.5-5g/kg, between 1 oz and 1 lb for a 70 kg person, NOAEL 100mg/kg/day chronic dietary	Up to 30 g MC/day in the diet had no adverse effect for adult (https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_7_out25_en.pdf), ~428mg/kg	Mild laxative effect at high doses (>10 g, Ellis FW, Krantz JC (1941) J. Biol. Chem. 141: 147–154. doi:10.1016/S0021-9258(18)72829-9), assume 70kg BW	Cariogenic Affect blood sugar level (potential issues for diabetic patients)	None (laxative amount at very large quantities, much larger than typical usage level)	None for oral	None (laxative amount at very large quantities, much larger than typical usage level)
		Level (mg/kg/day, color code according to estimated usage level)	Not available	7.14	Not available	142.86	Not available	Not available	Not available	Not available
		Contains potentially unacceptable components	Acetic acid and succinic acid, both affirmed as GRAS in 21 CFR 184	None	None	None	None	None	None	None
Dosing attributes		Palatability	No known objectionable taste	Bitter taste	No known objectionable taste	Slightly sweet	Sweet	No known objectionable taste	No known objectionable taste	No known objectionable taste
Physicochemical properties		Known potential physicochemical issues	Incompatible with strong acids or bases, oxidizing agents, and sustained levels of elevated humidity	Oral mucosa irritant - dose dependent	None, incompatible with strong oxidizing agents	None	Hygroscopic	Incompatible with strong acids or soluble salts of iron, aluminum, mercury, zinc	None	Incompatible with strong acids, alkalis, and iron salts
Supply chain		Potential supply chain issues	Multiple well-established suppliers	Multiple well-established suppliers	Multiple well-established suppliers	Multiple well-established suppliers	Multiple well-established suppliers	Multiple well-established suppliers	Multiple well-established suppliers	Multiple well-established suppliers
Function and other Attributes		Function	Polymer	Surfactant	Filler	Bulk sweetner	Bulk sweetner	Disintegrant	Glidant	Lubricant

3. Implementation of PERA tool to select excipient for paediatric products

3.1. Case study 1: Selecting the sweetener for a minitablet sprinkle paediatric dosage form

The first case study illustrates how the tool described above can be used to help determine the acceptability of excipients in an oral paediatric dosage formulation. In this case study, a paediatric dosage form was being developed for a BCS class II poorly water-soluble compound for a chronic but potentially life-threatening condition for 2 years and above age group. The adult formulation was designed as an amorphous solid dispersion to ensure adequate exposure, where the active substance was intimately mixed with two excipients (Hypromellose acetate succinate and sodium lauryl sulfate) as a spray dried dispersion (SDD). The SDD was compressed into swallowable tablets and film coated. Pharmacokinetic (PK) data collected throughout the development of the adult formulation exhibited dose proportionality in animal models, and good correlation with human PK data.

An age-appropriate and acceptable dosage form for children ages 2–6 years old was required. A decision was made to use the same amorphous solid dispersion formulation technology for the paediatric formulation as the adult formulation to leverage the dose–response linearity observed in adult clinical studies. A sprinkle minitablet dosage form was selected, which would allow mixing the dosage form with soft food during administration to aid swallowability and improve patient compliance.

During development of the adult dosage form, feedback was received from the clinical sites that the SDD had a weak bitter taste. There were several potential options to overcome this issue and improve its palatability. First, the final dosage form (i.e. tablets or minitablets) or the SDD could be coated using appropriate taste masking coating materials. Second, ingredients that can overcome the bitterness of the active substance (e.g. high-intensity sweeteners or bulk sweet diluents) could be incorporated into the formulation. It was decided to prioritize the second approach to minimize the potential of altering the compound's release profile from the dosage form. Since the SDD displayed only weak bitter taste the formulation team chose to evaluate bulk sweet diluents first instead of high intensity sweeteners. Among bulk sweet diluents, mannitol and sucrose were considered for further evaluation as they are commonly used excipients for oral solid dosage forms. Preliminary formulations were proposed using either of these excipients as shown in Table 3, and the PERA tool was used to compare the risks between the two bulk sweet diluents. In addition, the PERA tool was used for all other excipients to check their suitability of use in the targeted children age range of 2–6-year-old. The resulting heat map for excipients in the proposed formulations is shown in Table 4. As shown in Table 3, the normalized quantity was determined for each ingredient. In this case study the targeted age range is 2–6-year-old and the body weight range as per CDC growth chart is 10.2–27.4 kg (https://www.cdc.gov/grow

thcharts/clinical_charts.html)[4] (Refer to Tables 1 and 2 for additional patient and product attribute details). To calculate mg/kg/dose for the minimum body weight, the quantity of each excipient per sachet was divided by 10.2 kg (minimum body weight of 2-year-old girl). Since the dosing was twice a day, mg/kg/day for minimum body weight was determined by doubling the mg/kg/dose quantity for each excipient as shown in Table 3.

In assigning the color coding for the heat map, risks are considered acceptable (colored green) if the proposed usage levels are lower than the maximum levels or lower than the levels found in other products. Conversely, risks are considered elevated (colored red) if the proposed usage levels are higher than the maximum levels or higher than the levels found in other products. The heat map shows that the two excipients in the SDD, namely Hypromellose acetate succinate and sodium lauryl sulfate, are acceptable to be used at the levels proposed in the targeted age range of 2–6 years old from safety and toxicity considerations. They have also been used in commercial paediatric products [13,14] for similar age range in chronic disease dosing at similar or higher than the proposed levels, although no specific information was found for their ADI values. The toxicity data on both excipients including juvenile toxicity data provides justification for use in targeted age range. In terms of other attributes, for sodium lauryl sulfate, a bitter taste was noted, which may have contributed to the reported bitter taste of the SDD in the adult dosage form. In addition SLS can have an irritant effect on oral mucosa [15] depending upon the dosage form and level used in the formulation; therefore it was listed in the PERA table and coded red so that the team can review the information holistically and discuss an irritation assessment approach with the desired dosage form.

While populating the PERA tool, the references and contexts for other paediatric product information should be captured. In general, trying to find excipient level information in products is not straightforward and requires a thorough search of the literature. Sources such as IID, STEP database [16] PharmaCircle database, Summary of Product Characteristics (SmPC) monograph [17], product prescribing information, and product patents can be leveraged. If specific information for an excipient cannot be found after thorough search, then it should be captured in the tool and colored coded as yellow so that the team can discuss potential gap mitigation studies or alternate options.

All other proposed excipients, namely microcrystalline cellulose, mannitol, sucrose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate, were also acceptable to be used in the US, EU, and Japan at the levels proposed. Except for mannitol, information was found on the acceptability of these excipients in Canada. Prior use information of these excipients in other commercial paediatric products were also found, although information on the exact levels was not available for many of them.

Close examination of mannitol and sucrose shows that both bulk sweeteners were equally acceptable for use from regulatory, quality, ADI, and prior use perspectives. Both excipients impart sweet flavor, which can overcome the mild bitterness reported with the SDD. However, both excipients have potential safety/toxicity concerns, and were thus colored “yellow” in the heat map. The color-coding of the heat map in the PERA tool assists in the identification of excipients which require additional considerations. Mannitol may have a laxative effect; however this effect is observed at levels of $>$ 142 mg/kg/day, much higher than the proposed usage level of 13.5 mg/kg/day, and thus the color green (acceptable) was assigned to this risk. In contrast, sucrose is commonly understood to be potentially cariogenic [18] and can affect blood sugar levels which is undesirable for diabetic patients. It was decided that the development of the proposed formulation containing mannitol as the bulk sweetener would be prioritized over the formulation containing sucrose. Although both excipients have potential safety concerns, the potential concern for mannitol is lower than sucrose based on the proposed usage levels [19].

3.2. Case study 2 – Novel excipient for paediatric use (e.g. Stevia sweetener)

The second case study illustrates the considerations related to the use of a novel excipient compared to a commonly used excipient in a paediatric formulation. The complexities of this approach are illustrated with stevia, steviol glycosides containing a mixture of stevioside, rebaudioside A and rebaudioside C. This excipient is approximately 200–350 times sweeter than sucrose and has the potential to be used as a palatability enhancer in paediatric formulations [20,21]. Within the PERA framework as depicted in Fig. 1, the use of this excipient should first consider patient attributes, including age range (>2–18 years old), disease type (chronic), dosing duration (once a day), and dose range (1 mg). In terms of product characteristics, the goal was to develop oral powder for reconstitution for global distribution (climatic zone I –IV) and supplied in bottles. The risk assessment for stevia was performed using PERA tool as shown in Table 5. A risk–benefit assessment of this excipient versus other known sweeteners such as aspartame (which exhibited chemical instability so not selected) and sucrose was conducted.

As a food additive, stevia can be found in food products and beverages such as soft drinks, juices, dairy products, canned fruits, syrups and condiments marketed to adults and children alike [21]. Owing to its high relative sweetness when compared against sucrose, stevia can be a good choice when trying to select a palatability enhancer for solid or liquid oral dosage forms, although the authors are not aware of any marketed paediatric medication that uses stevia as an ingredient to date. The amount proposed in the formulation is much lower than the established ADI limit of 4 mg/kg BW/day [22]. In addition, stevia is known to be heat stable, pH stable, and does not ferment. The leaf extract is Generally Recognized as Safe (GRAS) by the FDA, but whole leaf and raw extracts are not [23]. As some of the steviol glycosides can have a bitter aftertaste, one desire has been to glycosylate the steviol glycosides, but the converted material has not been approved by the European Food Safety Authority (EFSA).

In March 2018, an applicant asked for an amendment to the existing European Union (EU) specifications for steviol glycosides to allow for the inclusion of all steviol glycosides identified in Stevia rebaudiana Bertoni leaves, including both ‘major’ and ‘minor’ glycosides, that may comprise the assay value of not less than 95 % total steviol glycosides [22]. However, the EFSA panel concluded that the submitted data was insufficient to assess the safety of proposed amendment to the specifications of the food additive steviol glycosides (E960). Similarly, in March 2022, the EFSA Panel considered that separate specifications would be needed for enzymatically produced steviol glycosides (E 960c) with respect to the inclusion of rebaudioside D produced via enzyme-catalysed bioconversion of purified stevia leaf extract [24]. The Panel concluded that there is no toxicological concern but based on the available data, there is the possibility that some residual amount of DNA coding for the kanamycin resistance gene could remain in the final product. The potential of gene propagation in microbiota due to the presence of recombinant DNA in the final product would be of concern. Therefore, the Panel concluded that “the safety of Rebaudioside D produced via this enzymatic bioconversion was not sufficiently demonstrated with the available data given that the absence of recombinant DNA was not shown”.

If one plans to continue with this specific ingredient, further controls on the supply and method of manufacture would be needed to confirm that the specific grade of steviol glycoside used matches the material approved by health authorities. A risk–benefit assessment of this excipient versus sucrose was conducted. Based on the source variability and potentially unacceptable impurities concern stevia could not be selected. Sucrose did not present any concern except the cariogenic effect, which was considered a minimal risk considering the level of sucrose targeted in the formulation and dosing regimen; hence it was selected for further evaluation in paediatric product development.

Table 5
Application of the PERA Tool to design the heat-map for the proposed stevia excipient in paediatric formulation for case study 2.

Category	Sub category	Excipient	Stevia	Sucrose
		Usage level in proposed formulation (mg/kg/day)	**0.15**	**0.60**
Safety/toxicity	Regulatory	Acceptable in US	Yes, Leaf extract is GRAS	Yes (USP/NF)
		Level (mg/kg or mg/kg/day)	4.0	20.54
		Source/assumption/reference	https://www.fda.gov/food/food-additives-petitions/high-intensity-sweeteners	FDA IIG, 1438mg for adult tablet, assuming 70kg BW
		Acceptable in EU	Yes	Yes
		Level (mg/kg to mg/kg/day)	4.0	1500
		Source/assumption/reference	Safety evaluation of glucosylated steviol glycosides as a food additive in different food categories - - 2022 - EFSA Journal - Wiley Online Library	Ph. Eur, for 1-3yo EFSA Journal 2016;14(1):4361 NOEL 1500mg/kg BW/day, https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out68_en.pdf
		Other pharmacopeias or regulatory agencies	Canada, JP, WHO, > 60 countries	Canada, JP
	ADI or other daily limits		Below recommended daily intake limit	Below recommended daily intake limit
	Prior use in pediatric product(s)	Product 1 (inlcude commercial or clinical use, age group, BW, and other pertinent information)	No Information	Zithromax (azithromycin) poweder for oral suspension
		Level (mg/kg/day)	Not available	185.0
		Source, assumptions, references	Not applicable	Each 5mL prepared suspension contains 200mg azythromycin and 3.87g sucrose (Zithromax SmPC, https://www.medicines.org.uk/emc/product/3006/smpc#gref). Dose is 10mg/kg/day azithromycin
		Product 2	No Information	Isentress/raltegravir powder for oral suspension
		Level (mg/kg/day)	Not available	0.783
		Source, assumptions, references	Not applicable	4.7mg sucrose per sachet containing 100mg raltegravir (Isentress SmPC, https://www.medicines.org.uk/emc/product/6904); dose for 3kg BW is 25mg raltegravir BID
	Other info	Known safety/toxicity issue	None	Cariogenic Affect blood sugar level (potential issues for diabetic patients)
		Level (mg/kg/day, color code according to estimated usage level)	Not available	Not available
		Contains potentially unacceptable components	Remnant recombinant DNA (https://www.efsa.europa.eu/en/efsajournal/pub/7291)	None
Dosing attributes		Palatability	Sweet	Sweet
Physicochemical properties		Known potential physicochemical issues	Hygroscopic	Hygroscopic
Supply chain		Potential supply chain issues	Source variability need to be monitored	Multiple well-established suppliers
Function and other Attributes		Function	Sweetner	Sweetner

This case study illustrates that even if a particular excipient can be selected due to superior chemical stability, and in general has GRAS status, the specific grade and supply selected may fall outside of established limits, which compels further evaluation before the ingredient can be used in a paediatric product formulation.

3.3. Case study 3 – Excipient for neonatal delivery by parenteral route of administration

The third case study describes how the tool can be applied to evaluate the safety of a specific excipient that was proposed to be used in a sterile solution formulation for intravenous administration to neonates (Table 6).

Since neonates have immature organs and systems, the safety of excipients in this age group is of key importance. An additional challenge in the neonatal patient population is that fluid intake volumes are carefully controlled and may be low, especially in hospitalized patients admitted to neonatal intensive care (NICU) with low weights, resulting in the need for parenteral formulations to be of an appropriate concentration to enable accuracy of dosing without exceeding fluid limits

Table 6
An example of the first and second sections of PERA tool used to capture patient, product, and dosing attributes for case study 3.

Patient Attributes	
Patient age range	Neonates (0–28 days)
Body weight range (kg)	2.4 kg (3rd percentile for neonate girl at birth) to 5.3 kg (97th percentile for 4-week old neonate girl)[20] (WHO growth chart)
Disease type and severity	Acute treatment for a potentially life-threatening condition
Dosing regimen	30 mg/kg/day
Co-medications and pre-conditions	None
Product and Dosing Attributes	
Route of administration	Intravenous
Proposed dosage form	Sterile liquid formulation for intravenous administration
Dosing approach	Ready to use injection
Environment of use	Zone I – IV, administration in hospitals
Packaging and delivery device	Glass vials or ampoule

[25].

The compound under clinical development is a crystalline powder with poor solubility over physiological pH and hence requires solubility enhancement to enable the formulation of a solution for IV administration of an appropriate concentration. Based on experience with the adult drug product development program, the proposed neonatal formulation was a simple aqueous solution containing a cyclodextrin as the solubilizing agent. Cyclodextrins are cyclic oligosaccharides with cup-like structures and are well known for their ability to form non-covalent inclusion complexes with many types of compounds, enhancing their solubility and stability [26].

During development studies, two different beta (ß) cyclodextrin derivatives were evaluated; sulfobutylether (SBE) ß cyclodextrin and hydroxypropyl (HP) ß cyclodextrin. These modified ß cyclodextrins have superior renal safety compared to the parent molecule (ß cyclodextrin) when administered intravenously and hence are permitted for parenteral use. For example, HP-ß cyclodextrin is used in Itraconazole and Mitomycin intravenous solutions and SBE-ß cyclodextrin is used in Voriconazole, Posaconazole and Carfilzomib intravenous solutions [27-29]. Indeed, based on literature evidence, overall, SBE-ß cyclodextrin and HP-ß cyclodextrin are considered safe in relatively high doses, and it has been reported that approximately 250 mg/kg/day of HP-ß cyclodextrin and SBE-ß administered for 21 days and 6 months respectively are safe for humans above the age of 2 years. It is recognized that renal function in neonates and infants is pre-mature compared to older children and they may therefore be more vulnerable to the effects of cyclodextrins [28]. However, juvenile toxicology studies in rats do not appear to have shown worse effects than in adult rats and there are reports of cases where intravenous products containing high doses of HP-β-CD and SBE-βCD were given to neonates and young children and showed no signs of toxicity [27,30–32].

Any potential harmful effects of cyclodextrins are not expected when used at doses below 20 mg/kg/day [27]. However, given the limited availability of robust safety information on cyclodextrin use in neonates and children below 2 years, their use in this patient population needs to be carefully considered and justified regarding the risk–benefit to the patient.

Based on physicochemical properties of the compound to be solubilized, chemical stability and the inclusion constant stability of cyclodextrins, the SBE-βCD was considered as a better choice compared to HP-β-CD. An additional reason for the choice of SBE-β-CD was its stability to terminal sterilization that allows the development of a sterile solution for IV administration [33].

The PERA tool was used to collect information and evaluate the risks of using a certain amount of SBE-β-CD in a formulation for IV administration in neonates as shown in Table 7. While conducting the risk assessment, the weight range of neonates, the dosage and the amount of cyclodextrins in the formulation were considered. Information regarding prior administration in neonates, known or reported safety issues, dosing attributes and physicochemical attributes were also captured, as shown in Table 7. Although dosing attributes, physicochemical properties, supply chain and function attributes were well defined and therefore easily evaluated with the tool due to previous experience acquired during the development of the adult product, a key challenge regarding the application of the tool in this example was the limited availability of safety and toxicity data on the use of and effects of SBE-β-CD in neonates and infants. The PERA tool clearly highlighted the lack of robust information on the safety of this excipient in this fragile patient population and enabled methodical assessment of potential risks to patient safety. The process allowed choices to be defined to control and reduce potential patient safety risks to an acceptable level. For this specific case the outcome was to run an additional study to mitigate the safety/potential alert related to the ADI value considering the target concentration of the compound to be dissolved and the potentially high concentration of cyclodextrin required in order to achieve complete solubilization in a limited fluid volume to be administered in neonates. The resulting heat map for the SBE-β-CD in the proposed formulation is shown in Table 7 below, where key safety and toxicity risks are highlighted in red.

The main outcome from this risk assessment heat map is that there are concerns of exceeding reported ADI values. Considering the lack of sufficient information regarding the presence of this excipient in paediatric/neonatal formulations, additional safety studies are needed prior to using this excipient for neonatal delivery or the formulation approach might need to be altered. Mitigation approaches might include juvenile animal toxicity studies and a risk management study plan during clinical studies which focuses on potential harm from the excipient.

4. Future work

The PERA framework and tool presented in parts 1 and 2 of this manuscript aim to guide users to systematically conduct risk–benefit assessments and facilitate the selection and justification of excipients for paediatric dosage forms for targeted age groups. One key limitation is the PERA tool's dependency on the availability of information from various sources. To address this, integrating the tool with the STEP database would be beneficial. This integration would enable seamless use of the tool, facilitating more efficient decision-making. By ensuring compatibility with a wide range of data inputs and enhancing the tool's ability to aggregate and analyze information from the STEP database, the PERA tools functionality and user experience can be significantly improved. As a next step, the ability to automatically populate the attributes in the PERA tool from the STEP database using artificial intelligence would be assessed. Additionally, the tool is currently in Excel format, which may limit its usability. Developing it as an application or digital platform would significantly enhance its accessibility, user experience, and functionality. This evolution would allow for more sophisticated features, better data integration, and a more intuitive interface, ultimately ensuring the tool remains relevant and effective in various contexts. As a next step, the authors plan to further disseminate the tool, for example through conference workshops and collect input from users and regulators on the usability of the tool. Based on the feedback received the tool might be enhanced further as needed and an update will be communicated, to ensure the tool remains relevant, effective, and continuously improved to meet users' needs.

5. Conclusions

In Part 1 of this series of articles, the "Paediatric Excipient Risk Assessment (PERA)" framework—a method for risk and benefit-based assessment, was introduced. It enables the systematic selection of excipients for paediatric medical products. The PERA framework improves

Table 7
Excipient risk assessment heat map for proposed SBE-β-CD using PERA tool for parenteral product in neonates for case study 3.

Category	Sub category	Excipient	SBE-β-CD
		Usage level in proposed formulation (mg/kg/day)	**250**
Safety/toxicity	Regulatory	Acceptable in US	Yes (USP/NF)
		Level (mg/kg or mg/kg/day)	200
		Source, assumptions, references	cited in the FDA's list of inactive Pharmaceutical Ingredients. FDA approved prescription drugs (e.g. Vfend©, Nexterone©, Abilirfy©, Kyprolis©, Geodon©)
		Acceptable in EU	Yes
		Level (mg/kg to mg/kg/day)	200
		Source, assumptions, references	(EMA/CHMP/495747/2013) Listed in Ph Eur
		Other pharmacopeias or regulatory agencies	JPE
	ADI or other daily limits		Above ADI limit
	Prior use in pediatric product(s)	Product 1 (inlcude commercial or clinical use, age group, BW, and other pertinent information)	The only product for neonatal IV use containing 10% solution
		Level (mg/kg/day)	Not available
		Product 2	No Information
		Level (mg/kg/day)	Not Applicable
	Other info	Known safety/toxicity issue	Unknown
		Level (mg/kg/day, color code according to estimated usage level)	Not available
		Contains potentially unacceptable components	No
Dosing attributes		Injection irratability	No known issue
Physicochemical properties		Known potential issues	Stable to acid, base, heat & light, no particulates
Supply chain		Potential supply chain issues	Single supplier worldwide
Function and other Attributes		Function	Solubilizer

the objectivity and transparency of the decision-making process by adopting a comprehensive approach and considering all pertinent factors related to patient, dosage form, and excipient attributes. It also offers a structured and systematic approach that companies and regulatory agencies can use. This study (Part 2) suggests a heat map-based tool that can be used to quickly analyse, compare, and choose possible excipients based on the principles described in the PERA framework in order to enable proper utilization of the PERA framework. This PERA tool can be used to analyse potential formulations comprising various excipients as well as to evaluate proposed excipients for use in the specific product. The PERA tool makes it easier to spot any informational gaps for potential excipients, which will assist users choose the best excipient option and/or create an appropriate mitigation study or action plan for the selected excipient. Once new data is generated on the excipient the risk assessment should be conducted again using the PERA tool to update the heat map and ensure correct decisions are being made in terms of selection of the desired excipient. The tool's usefulness has been illustrated by several case studies in part 2 paper, which cover both conventional and novel excipients. The development and implementation of the PERA tool will represent a significant advancement in paediatric product development activities. By providing a streamlined, efficient method for data analysis and decision-making, the tool has the

potential to revolutionize current excipients selection or benefit risk assessment practices. Widespread adoption of this tool is expected to lead to more informed and accurate decisions, ultimately accelerating development timelines, reducing costs, and improving the overall success rate of new paediatric products. Furthermore, by integrating diverse information sources and evolving into a digital platform, the tool's usability and impact will be further enhanced. The anticipated benefits underscore the importance of this tool, making it an essential asset for professionals involved in overall drug and product development. The PERA framework and tool will play a crucial role in advancing best practices in selection and risk–benefit assessment of excipients for paediatric products.

CRediT authorship contribution statement

Anjali Agrawal: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Smita Salunke:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **Alfred Rumondor:** Writing – review & editing. **Karen Thompson:** Writing – review & editing. **Grazia Caivano:** Writing – review & editing, Writing – original draft. **Jennifer Walsh:** Writing – review & editing, Writing – original draft. **Brian Enright:** Writing – review & editing. **Philip Sherratt:** Writing – review & editing. **Kevin Hughes:** Writing – review & editing. **David Clapham:** Writing – review & editing, Writing – original draft. **Peter Kuehl:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

This manuscript was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org) and EuPFI excipients workstream members. IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community. EuPFI is an international paediatric formulation consortium and the EuPFI excipients workstream focuses on safety/toxicity issues and acceptability of excipients in paediatric formulation.

The authors acknowledge the EuPFI excipients workstream members and especially Anthony Nunn from University of Liverpool, Department of Women's and Children's Health, Liverpool Women's NHS Foundation Trust for thorough review and insightful comments that enhanced the quality and consistency of this manuscript.

References

[1] EMA. European Medicines Agency, Guideline on Pharmaceutical Development of Medicines for Paediatric Use. EMA; London, UK: 2013. [(accessed on 2 February 2022)]. Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf. 2013.

[2] FDA. Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Available at https://www.fda.gov/media/168201/download. 2023.

[3] FDA. Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry.U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Available at https://www.fda.gov/media/86340/download. 2020.

[4] FDA. E11 Clinical Investigation of Medicinal Products in the Pediatric Population. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Available at https://www.fda.gov/media/71355/download. 2000.

[5] EC. Regulation (EC) no 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use. 2006.

[6] K. Rouaz, B. Chiclana-Rodríguez, A. Nardi-Ricart, M. Suñé-Pou, D. Mercadé-Frutos, J.M. Suñé-Negre, et al., Excipients in the Paediatric Population, A Review. Pharmaceutics. 13 (3) (2021).

[7] Additives EPanel oF, Food NSat, Younes M, Aggett P, Aguilar F, Crebelli R, et al. Re-evaluation of celluloses E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468 and E 469 as food additives. EFSA Journal. 2018;16(1):e05047.

[8] JECFA. Powdered Cellulose. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Available at https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/251. 1976.

[9] JECFA. Saccharin. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Available at: https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/3164. 1990.

[10] EuPFI. Saccharin. Safety and Toxicity of Excipients in Paediatrics (STEP) database. Available at https://step-db.ucl.ac.uk/. 2012.

[11] FDA. Added Sugars on the New Nutrition Facts Label. Available at : https://www.fda.gov/food/new-nutrition-facts-label/added-sugars-new-nutrition-facts-label. 2022.

[12] EC. Opinion of the Scientific Committee on Food on the applicability of the ADI (Acceptable Daily Intake) for food additives to infants (expressed on 17/09/1998). Available at: https://food.ec.europa.eu/system/files/2020-12/sci-com_scf_out13_en.pdf. 2020.

[13] Dokou E, Brodeur GG, Tauber M, Sanghvi T, Knezic D, Pesha Y, et al. High potency formulations of vx-950. WO2013116339A. Available at : https://patents.google.com/patent/WO2013116339A1. 2013.

[14] Desai D, Diodone R, Go Z, N. P, Raman I, Iyer M, et al. Compositions and uses thereof. WO2010114928A2. Available at: https://patents.google.com/patent/WO2010114928A2/en. 2010.

[15] I. Rantanen, I. Nicander, K. Jutila, S. Ollmar, J. Tenovuo, E. Söderling, Betaine reduces the irritating effect of sodium lauryl sulfate on human oral mucosa in vivo, Acta Odontol. Scand. 60 (5) (2002) 306–310.

[16] S. Salunke, B. Brandys, G. Giacoia, C. Tuleu, The STEP (Safety and Toxicity of Excipients for Paediatrics) database: part 2 - the pilot version, Int J Pharm. 457 (1) (2013) 310–322.

[17] Electronic medicines compendium. Available at: https://www.medicines.org.uk/emc#gref. 2023.

[18] L. Bigeard, The role of medication and sugars in pediatric dental patients, Dent Clin North Am. 44 (3) (2000) 443–456.

[19] EMA. European Medicines Agency, Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668).EMA/CHMP/302620/2017 Rev. 2*. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/annex-european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human_en-1.pdf. 2017.

[20] J. Sepúlveda, R. Pinto, R. Garcés, J. Antileo, C. Gómez, D. Muñoz, et al., Use of Stevia rebaudiana purified extract as a sweetener on pediatric oral formulations, Int. J. Pharm. 536 (2) (2018) 518–519.

[21] insight F. Everything You Need to Know About Stevia Sweeteners. Food Insight Available at: https://foodinsightorg/everything-you-need-to-know-about-stevia-sweeteners/. 2021.

[22] Additives EPoF, Flavourings, Younes M, Aquilina G, Engel K-H, J Fowler P, et al. Safety evaluation of glucosylated steviol glycosides as a food additive in different food categories. EFSA Journal. 2022;20(2):e07066.

[23] FDA. Aspartame and Other Sweeteners in Food. Available at: https://www.fda.gov/food/food-additives-petitions/aspartame-and-other-sweeteners-food. 2023.

[24] Panel EF, M. Younes, G. Aquilina, K.-H. Engel, P.J. Fowler, M.J. Frutos Fernandez, et al., Safety of the proposed amendment of the specifications for enzymatically produced steviol glycosides (E 960c): Rebaudioside D produced via enzymatic bioconversion of purified stevia leaf extract, EFSA J. 20 (5) (2022) e07291.

[25] EMA. European Medicines Agency, Committee for Medicinal Products for Human Use. Reflection paper: formulations of choice for the paediatric population, 2006; EMEA/CHMP/PEG/194810/2005. Available at : https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-paediatric-population_en.pdf. 2006.

[26] M.E. Brewster, T. Loftsson, Cyclodextrins as pharmaceutical solubilizers, Adv Drug Deliv Rev. 59 (7) (2007) 645–666.

[27] EMA. Cyclodextrins used as excipients. Report published in support of the 'Questions and answers on cyclodextrins used as excipients in medicinal products for human use'. EMA/CHMP/333892/2013. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-cyclodextrins-used-excipients-medicinal-products-human-use_en.pdf. 2017.

[28] EMA. Background review for cyclodextrins used as excipients. EMA/CHMP/333892/2013. Available at: https://www.ema.europa.eu/en/documents/report/background-review-cyclodextrins-used-excipients-context-revision-guideline-excipients-label-package_en.pdf. 2014.
[29] V.J. Stella, R.A. Rajewski, Sulfobutylether-β-cyclodextrin, Int J Pharm. 583 (2020) 119396.
[30] S. Gould, R.C. Scott, 2-Hydroxypropyl-β-cyclodextrin (HP-β-CD): A toxicology review, Food Chem. Toxicol. 43 (10) (2005) 1451–1459.
[31] S.M. Abdel-Rahman, R.F. Jacobs, J. Massarella, R.E. Kauffman, J.S. Bradley, H. C. Kimko, et al., Single-dose pharmacokinetics of intravenous itraconazole and hydroxypropyl-beta-cyclodextrin in infants, children, and adolescents, Antimicrob Agents Chemother. 51 (8) (2007) 2668–2673.
[32] V.J. Stella, Q. He, Cyclodextrins, Toxicol Pathol. 36 (1) (2008) 30–42.
[33] L. Ferreira, J. Campos, F. Veiga, C. Cardoso, A.C. Paiva-Santos, Cyclodextrin-based delivery systems in parenteral formulations: A critical update review, Eur. J. Pharm. Biopharm. 178 (2022) 35–52.