Advancing Pediatric Safety Through Systematic Excipient Risk Assessment

Excipient Overview · PERA Framework · Case Study

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INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Shaping the Future of Pediatric Formulation Development, June 24-25, 2026,
University of Maryland, Baltimore School of Pharmacy.

European Paediatric Formulation Initiative

Workshop Agenda

10:00 AM – 11:00 AM

15 min

Excipient Background

10:00 – 10:15

30 min

Case Study Discussion

10:15 – 10:45

10 min

Q&A Session

10:45 – 10:55

5 min

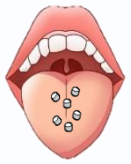
Wrap Up & Summary

10:55 – 11:00

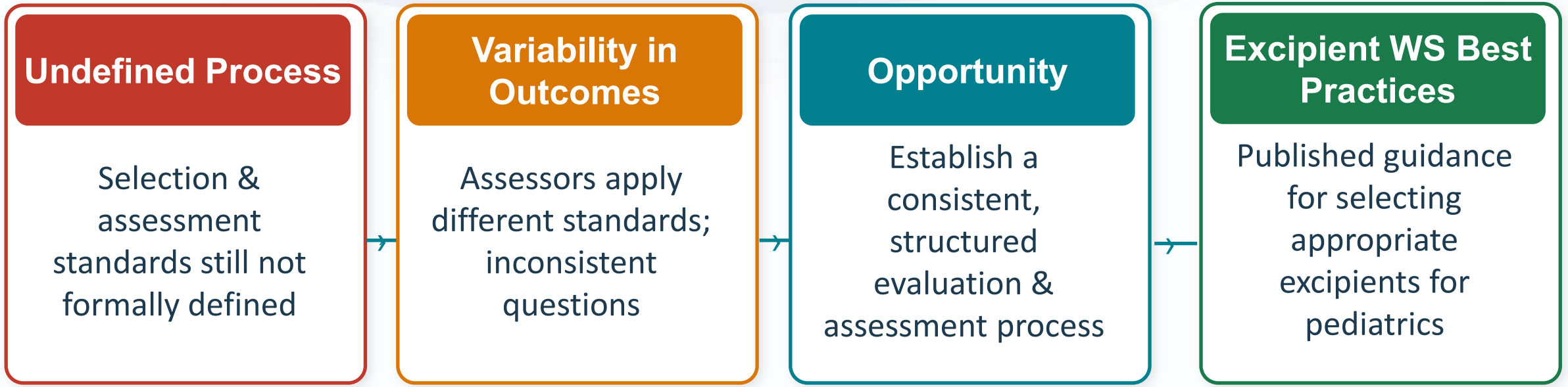
Presentation Topics

01 Understanding the selection landscape and key regulatory concerns

02 Systematic risk assessment methodology and practical implementation

03  Minitablet sprinkles formulation for 2–6 year olds

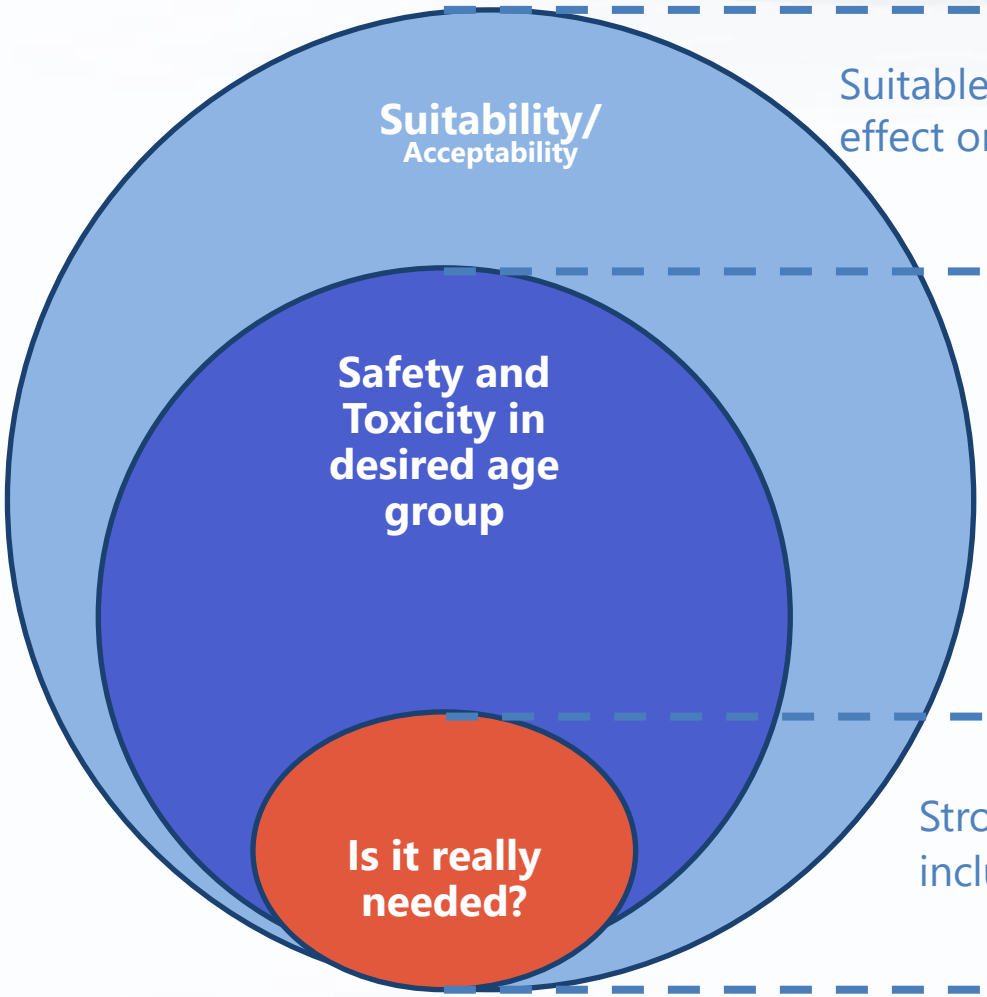
Excipient Selection Process: The Challenge



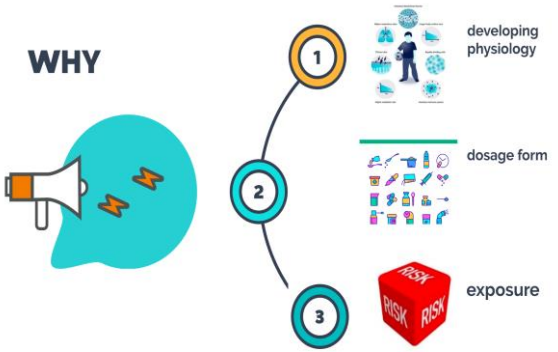
Key Issues: Assessors see different standards of assessment · Variability of assessor questions

Impact:
No general, well-defined principles exist for selecting the most appropriate excipient for pediatric formulations

Excipients Selection Consideration – Pediatrics



Suitable taste, sensitization, trace impurities effect on targeted pediatric age range



- Is Acceptable Daily Intake (ADI) established by FDA, EMA, JPE
- Safety data in juvenile animals and humans
- Impact on ADME of API, impact on children development

Strong rationale needed to include in Pediatric Product

Regulatory Context & Gap

What Exists

- ICH/CHMP Guideline available for certain excipients
- Current CHMP opinions available
- EU Guideline on Pharmaceutical Development for Paediatric Use (2013)
- FDA Guidance: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients
- Linked parameters: age group, route, dose, daily intake, composition

The Gap

- Not everyone agrees on HOW to select excipients or conduct risk assessment for pediatrics
- No general, well-defined principles exist for selecting the most appropriate excipient
- Risk-benefit assessments needed for proposed new excipients
- Existing human data may substitute for certain nonclinical safety data — but methodology is inconsistent

PERA Framework – Addressing the Gap

Goals

- Provide a systematic method for selection and overall risk assessment of pediatric formulations
- Enable rapid screening and prioritisation of excipients

→

Principles

- Creates value
- Integral part of decision-making
- Helps address uncertainty
- Systematic, structured and timely
- Based on best available information
- Transparent and inclusive
- Dynamic, iterative and responsive to change

→

PERA
Paediatric Excipient Risk Assessment

Pediatric Excipient Risk Assessment (PERA) Framework & Tool

IQ Pediatric Excipient Sub-Team: A. Agrawal (Lead), A. Rumondor, K. Thompson, P. Sherratt, B. Enright
EuPFI Excipient Sub-Team: S. Salunke (Lead), J. Walsh, T. Nunn, D. Clapham, K. Hughes, C. Grazia, P. Kuehl

PERA framework development process

01

User Expectations Survey

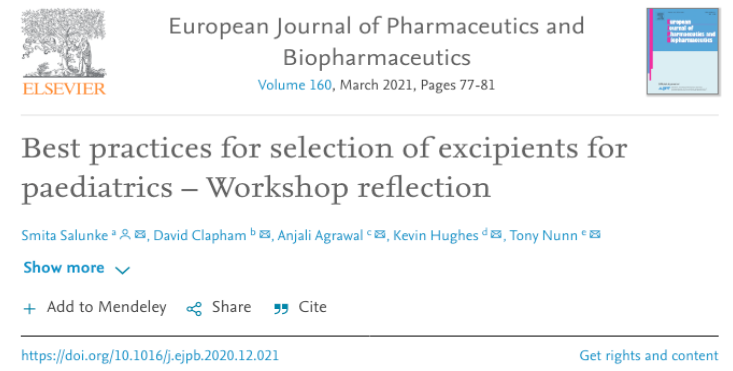
The user expectations (in terms of information required and sources available) and parameters for creation of the framework were obtained through a survey of scientists and regulatory professionals from a group of pharmaceutical companies

02

Compilation of survey response

The survey responses were used to build questions to ask during selection of excipients for paediatric drug development

PERA framework development process



03

Workshop on best practices for selection of excipients for paediatrics

Questions developed through survey and best practices were assessed through a workshop involving formulation scientist and regulators. The list of questions identified through workshop discussion helped to define the elements that are considered essential for the benefits and risks assessment of an excipient. These elements were then transformed into a PERA framework that allowed systematic assessment and documentation

Salunke, S; Clapham, D; Agrawal, A; Hughes, K; Nunn, T; (2021) Best practices for selection of excipients for paediatrics - Workshop reflection. ***European Journal of Pharmaceutics and Biopharmaceutics*** *, 160 pp. 77-81. 10.1016/j.ejpb.2020.12.021.*

Pediatric Excipient Risk Assessment (PERA) Framework

Stage 1: Risk Identification

Patient Attributes

- **Age Range** (pre-term to 18 years)
- **Disease Type & Severity** (e.g. Acute/Chronic)
- **Dosing Regimen** (e.g. Daily, weekly, monthly)
- **Dose Range** (e.g. 1 mg/kg, 0.5 ml/kg)
- **Co-meds and Pre-condition** (e.g. Interaction, Allergies)

Product and Dosing Attributes

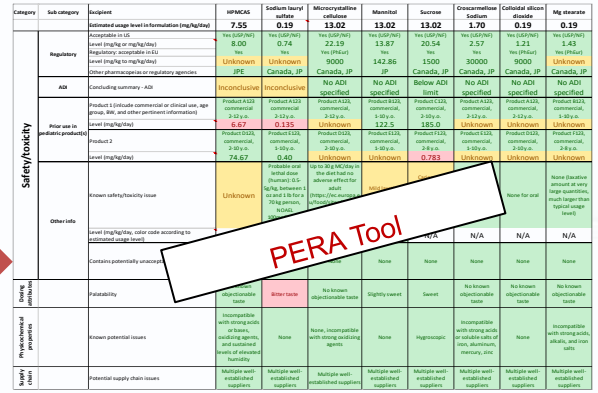
- **Route of Administration** (e.g. Oral, Parenteral,)
- **Dosage Form Type** (e.g. Tablet, Solution,)
- **Single or Multiple Unit**
- **Dosing Approach** (e.g. with drinks or food)
- **Packaging and Delivery Device**
- **Environment of Use** (e.g. Zone I-IV)

Excipient Attributes

- **Level/Amount of Excipient**
- **Acceptable Daily Intake (ADI)** (e.g. FDA, EFSA, JECFA)
- **Global Regulatory Acceptability**
- **Prior use in Pediatric Products**
- **Impurities**
- **Safety and Toxicity** (e.g. STEP, TOXNET, Suppliers)
- **Physicochemical & Biopharmaceutics Properties**
- **Function, Supply Chain, other Attributes**

Stage 2: Risk Analysis

Conduct risk assessment, gap analysis, and create action plan



Stage 3: Risk Management

Outcome: **No Risk/Low Risk**
Action: **Select Excipient** and acceptable level

Outcome: **Medium Risk (Gaps in data)**
Actions: Conduct PK/PD studies in animals, bridging with Human PK data, excipient kinetic study, excipient safety assessments, seek regulatory input, clinical monitoring etc.

Outcome: **High Risk**
Action: **Select alternate excipient or modify formulation approach**

Stage 4: Risk Review

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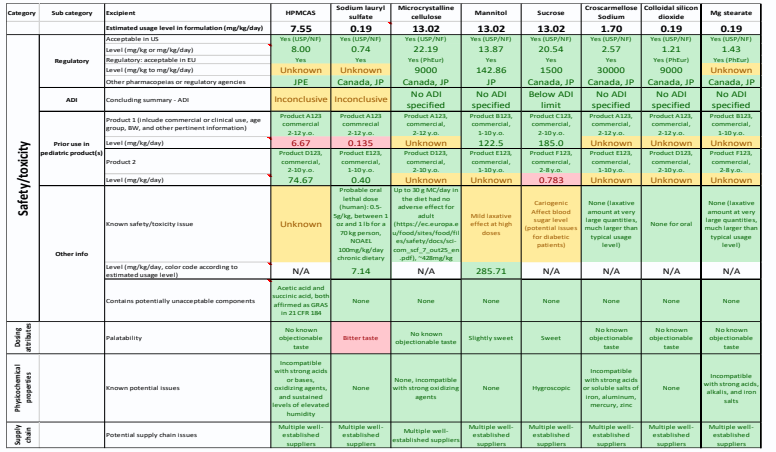
European Paediatric Formulation Initiative

Pediatric Excipient Risk Assessment (PERA) Tool

- **PERA Framework** provides a systematic way to evaluate the fit of a proposed pediatric medication to patients' needs
- **PERA Tool** was developed to address **practical implementation** of the framework — featuring a heat map to assist during Stage 2: Risk Analysis

Is it an appropriate dosage form for intended patients?

Are there any concerns with the type or quantity of excipients used?



Category	Sub category	Excipient	HPMCAS	Sodium lauryl sulfate	Microcrystalline cellulose	Mannitol	Sucrose	Croscarmellose Sodium	Colloidal silicon dioxide	Mg stearate
		Estimated usage level in formulation (mg/kg/day)	7.55	0.19	13.02	13.02	13.02	1.70	0.19	0.19
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
		Regulatory: 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
		Other pharmacopeias or regulatory agencies	JPE	Canada, JP	Canada, JP	JP	Canada, JP	Canada, JP	Canada, JP	Canada, JP
	ADI	Concluding summary - ADI	Inconclusive	Inconclusive	No ADI specified	No ADI specified	Below ADI limit	No ADI specified	No ADI specified	No ADI specified
	Prior use in pediatric product(s)	Product 1 (Include commercial or clinical use, age group, BW, and other pertinent information)	Product A123 commercial 2-12 y.o.	Product A123 commercial 2-12 y.o.	Product A123, commercial, 2-12 y.o.	Product B123, commercial, 1-10 y.o.	Product C123, commercial, 2-10 y.o.	Product A123, commercial, 2-12 y.o.	Product A123, commercial, 2-12 y.o.	Product B123, commercial, 1-10 y.o.
		Level (mg/kg/day)	6.67	0.135	Unknown	122.5	185.0	Unknown	Unknown	Unknown
		Product 2	Product D123, commercial, 2-10 y.o.	Product E123, commercial, 1-10 y.o.	Product D123, commercial, 2-10 y.o.	Product E123, commercial, 1-10 y.o.	Product F123, commercial, 2-8 y.o.	Product E123, commercial, 1-10 y.o.	Product D123, commercial, 2-10 y.o.	Product F123, commercial, 2-8 y.o.
		Level (mg/kg/day)	74.67	0.40	Unknown	Unknown	0.783	Unknown	Unknown	Unknown
	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	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)	N/A	7.14	N/A	285.71	N/A	N/A	N/A	N/A
		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 issues	Incompatible with strong acids or bases, oxidizing agents, and sustained levels of elevated humidity	None	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

Are there alternative formulations or excipients?

Elements of the PERA Tool

Part 1

Safety / Toxicity

Part 2

Dosing Attributes

Part 3

Physicochemical & Biopharmaceutics

Part 4

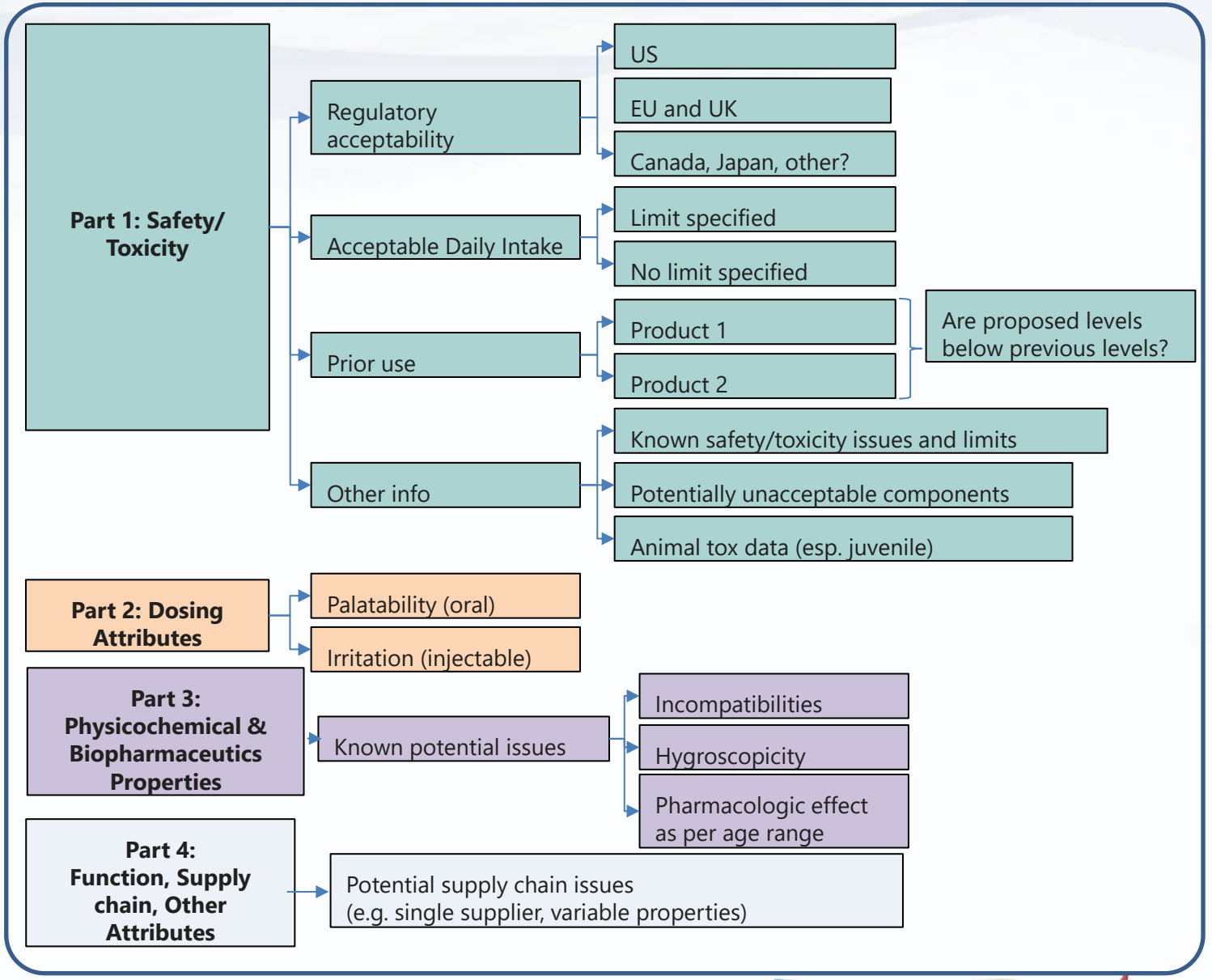
Function, Supply Chain & Other

Elements of PERA Tool

Patient attributes
(age range, disease type, dosing regiment, dose range, co-meds, etc.)

Product and dosing attributes
(route of administration, dosage form type, deliver, pkg, etc.)

Excipient attributes
(function, amount/level, safety/toxicity, physicochemical, biopharmaceutics properties, supply chain, & other attributes)



Case study session

Group A (Moderator : Anjali A)	Group B (Moderator : Smita S)

General Q&A/Discussion topics

Case Study: Minitablet Sprinkles

Scenario Overview

Indication: Chronic dosing for a potentially life-threatening disease

API Challenge: Poorly water-soluble in crystalline form — amorphous solid dispersion (ASD) via spray drying

Adult Form: Film-coated tablets (Phase 3 clinical study); ASD shows dose proportionality in animals and good human PK correlation

Taste Note: API slightly bitter — sweet excipient (mannitol or sucrose) may be needed

Target Age: 2–6 years old

Key Concern: Swallowability → Sprinkle (2mm minitablets) dosage form selected

PERA TOOL - Patient & Dosing Attributes

Age Range	2 – 6 years old
Condition	Chronic / Life-threatening
Regimen	BID (twice daily), 50 mg/dose
Route	Oral
Form	Sprinkle (2mm minitablets)
Administration	Sprinkle onto soft food
Packaging	Sachet packaging
Minimum BW	10.2 kg (5th %ile, 2 y.o. girl); 27.4kg (95%tile 2 y.o. girl)
Environment of use	Zone I-IV

PERA Tool – Excipient Quantities Normalized

Minimum body weight: 10.2 kg | Dosing frequency: 2 × daily (BID) | Dose: 50 mg/dose | Total per sachet: 240 mg

Ingredient	Function	%w/w	mg/sachet	mg/kg/dose	mg/kg/day
Compound X (ASD)	API – amorphous solid dispersion	20.83	50.0	4.90	9.80
HPMCAS	ASD precipitation inhibitor	16.67	40.0	3.92	7.84
Sodium lauryl sulfate	ASD wetting agent	0.42	1.0	0.10	0.20
Microcrystalline cellulose	Binder / compression aid	28.75	69.0	6.76	13.53
Mannitol or Sucrose ✦	Binder / sweet diluent	28.75	69.0	6.76	13.53
Croscarmellose sodium	Disintegrant	3.75	9.0	0.88	1.76
Colloidal SiO_2	Flow aid	0.42	1.0	0.10	0.20
Mg stearate	Lubricant	0.42	1.0	0.10	0.20

✦ *Mannitol or Sucrose highlighted as key binder/diluent choice — subject to palatability and safety considerations*

Minitablet Case Study: PERA Tool – Part 1 (Safety/Toxicity) assessment outcomes

Category	Sub category	Excipient	HPMCAS	Sodium lauryl sulfate	Microcrystalline cellulose	Mannitol	Sucrose	Croscarmellose Sodium	Colloidal silicon dioxide	Mg stearate
		Estimated usage level in formulation (mg/kg/day)	7.84	0.20	13.53	13.53	13.53	1.75	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)
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		Level (mg/kg/day)	6.67	0.135	Unknown	122.5	185.0	Unknown	Unknown	Unknown
		Product 2	Product D123, commercial, 2-10 y.o.	Product E123, commercial, 1-10 y.o.	Product D123, commercial, 2-10 y.o.	Product E123, commercial, 1-10 y.o.	Product F123, commercial, 2-8 y.o.	Product E123, commercial, 1-10 y.o.	Product D123, commercial, 2-10 y.o.	Product F123, commercial, 2-8 y.o.
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	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	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)
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		Contains potentially unacceptable components	Acetic acid and succinic acid, both affirmed as GRAS in 21 CFR 184	None	None	None	None	None	None	None

Minitablet Case Study: PERA Tool – Parts 2, 3, 4 assessment outcomes and conclusion

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Dosing attributes		Palatability	No known objectionable taste	⚠ Bitter	No known objectionable taste	Slightly sweet	Sweet	No known objectionable taste	No known objectionable taste	No known objectionable taste
Physicochemical properties		Known potential issues	Incompatible with strong acids or bases, oxidizing agents, and sustained levels of elevated humidity	None	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

Conclusions based on the PERA tool

- **No significant risk** was identified at the targeted excipient levels for the desired age range.
- Formulations containing **sucrose or mannitol are comparable**.
  - Mannitol: at high levels (higher than levels proposed) may induce laxative effects.
  - Sucrose: may affect blood glucose level and has cariogenic properties.
- One of the excipients proposed (sodium lauryl sulfate) contributes a **bitter taste**.
  - Select a different surfactant that is not bitter (note: changing the wetting agent in the ASD may change PK).
  - Assess the overall palatability of the dosage form; presence of sweet binder/diluent may be enough to overcome bitterness from SLS.

Group Exercise – Case Study Q&A

Group discussion. Use the PERA framework and tool for risk assessment.

1. What PERA attributes need to be considered and how would you evaluate them?
2. Using PERA, list the key excipient attributes for the case study. How do they influence excipient selection or formulation composition?
3. What additional information, if any, is needed to make appropriate excipient selection or risk assessment?
4. What additional studies (if any) would you suggest to generate sufficient data for excipient selection?
5. What are the key challenges in selecting excipients for pediatric formulations, and what solutions could mitigate them?

TIP: Create a flipchart to communicate your findings back to the group

Pediatric Excipient Selection – Wrap Up

Published PERA Framework & Tool

Framework and tool published; workshops conducted to gather industry and regulatory feedback

Digitize PERA Tool

Make tool publicly accessible in digital format for easy use by formulators and assessors

Integrate Excipient Databases

STEPAI

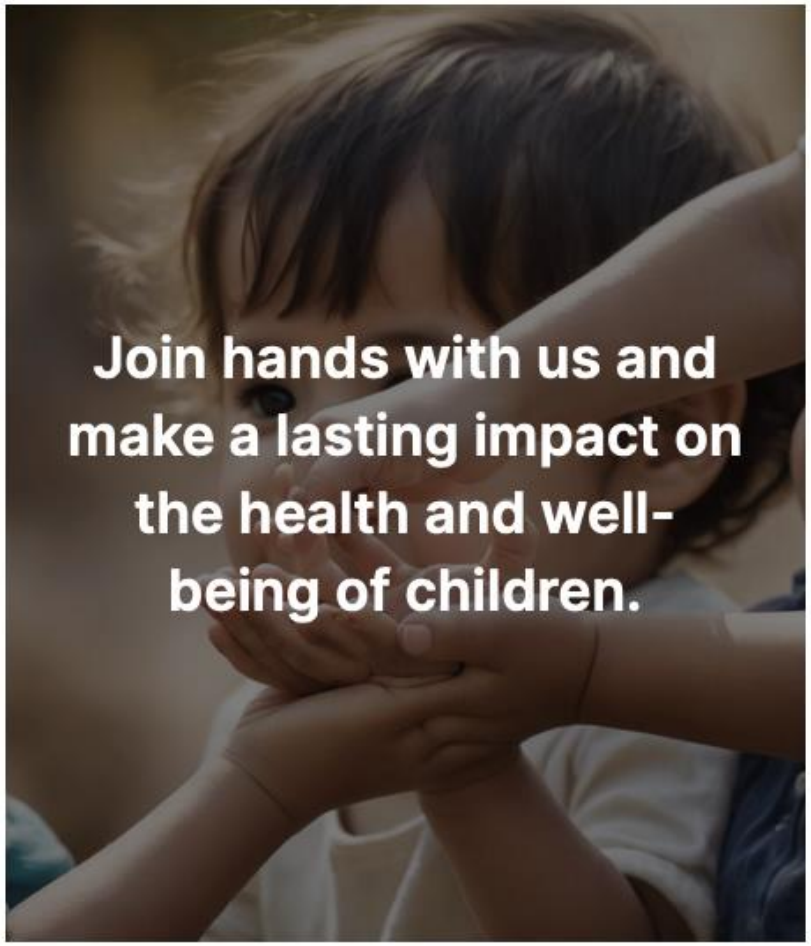
FDA Inactive Ingredient Search for Approved Drug Products

Link STEP database 2.0 and risk assessment into PERA tool for rapid excipient selection for pediatric products

Agrawal A et al. Paediatric excipient risk assessment (PERA) tool and application – Part 2. Eur J Pharm Biopharm. 2024;203:114447.
Salunke S, Agrawal A et al. Selecting appropriate excipients for paediatric dosage form – PERA framework – Part 1. Eur J Pharm Biopharm. 2024;203.

THANK YOU

QUESTIONS



We would love to hear from you…

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