Pediatric Excipient Risk Assessment (PERA) Framework

Stage 1: Risk Identification

Patient Attributes

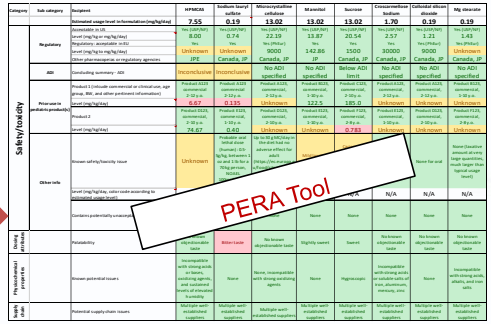
- **Age Range** (pre-term to 18 years)
- **Disease Type & Severity** (e.g. Acute/Chronic)
- **Dosing Regimen** (e.g. Daily, weekly, monthly)
- **Dose Range** (e.g. 1 mg/kg, 0.5 ml/kg)
- **Co-meds and Pre-condition** (e.g. Interaction, Allergies)

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

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

European Paediatric Formulation Initiative

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)
		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 (inlcude commercial or clinical use, age group, BW, and other pertinent information)	Product A123 commercial 2-12 y.o.	Product A123 commrecial 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

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

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
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 excipient selection process and tools do you currently use? What is the regulatory acceptability experience?
2. Will PERA framework and tool be suitable to harmonize excipient selection process based on systematic benefit-risk assessment?
3. What additional information, if any, is needed to make appropriate excipient selection or risk assessment?
4. What is regulatory feedback on use of PERA framework and tool to guide 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