Session 4: Food effects in paediatric medicines development for products co-administered

Pre-reading for participants

The session objective is to identify best practices /process flow (based on current information) that could be used to de-risk the formulation development strategy; plan appropriate clinical studies and subsequent label claims for paediatric products that are co-administered with food. Gaps where more research or data is required will also be identified.

Foods such as rice pudding, yogurt or apple sauce are commonly used to facilitate administration and improve compliance for pediatric population. These household foods differ in composition and properties from the typical food used in assessing food effect in adult subjects and thus can impart different effect on the bioavailability of the same medicine. The purpose of this session is to address the risk level of household food on bioavailability when it is co-administered with medicines to pediatric patients.

We invite you to reflect on the following two case studies and consider how you would use available *in vitro, in silico* and *in vivo* data to devise a process to follow to risk assess the likelihood of a food effect for a paediatric formulation when dosed with food. Please focus your thinking around the design of PK studies and how to assess a food effect in a paediatric population to support the label.

You will be asked to share your thoughts with others at the session in small groups and to feedback a process within the session.

Some useful references may include:

- Hannah K. Batchelor. Influence of food on paediatric gastrointestinal drug absorption following oral administration: a review. (2015) Children 2(2), 244-271
- Salem, A.H., Chiu, Y.-L., Valdes, J.M., Nilius, A.M., Klein, C.E. A novel ritonavir paediatric powder formulation is bioequivalent to ritonavir oral solution with a similar food effect (2015) Antiviral Therapy, 20 (4), pp. 425-432.

Case study 1:

The API (BCS II, a salt form of a weak base) is known to exhibit a positive food effect in an adult population based on data from a study using a tablet (100mg) and following an FDA breakfast.

The intended paediatric form developed is a sprinkle that patients will have to dose with soft food – what studies would you do to determine how to risk assess potential for a food effect in paediatrics in fasted vs fed states and what data would you need to predict starting paediatric dose?

This product will be designed for use from children aged 2 to 12 years

Existing data available

Study	**Result**
Fed effect study using FDA breakfast Adult PK data	Positive effect (increased bioavailability) – adult formulation dosed with 1(a) food and 1 (b) without food **Cmax increased 3 fold in fed study; AUC increased 2 fold in the fed state compared to fasted** **PK showed typical variability and the drug is <u>not</u> a narrow therapeutic index compound**
Log P Log SR Bile MW	**2.2** **3.6** **362**
API solubility data Aqueous solubility FaSSIF solubility FeSSIF solubility	 **0.04 mg/mL** **0. 4 mg/mL** **1.0 mg/mL**
In vitro disso data	**Rapid and complete dissolution shown in FeSSIF** **Incomplete dissolution observed in FaSSIF** **Rapid and complete dissolution shown in QC method (includes 0.1% SLS, pH 6.5)**
Physchem stability data	
Preclinical *in vivo* data	**Dog study showed 7 fold increase in Cmax and 6 fold increase in AUC in the fed state compared to fasted**

Case study 2:

The API (BCS III, an acidic drug (pKa = 8.3) with a low lipophilicity) is known to exhibit a negative food effect in an adult population based on data from a study using a tablet (300mg) and following an FDA breakfast.

The intended paediatric form developed is a sprinkle that patients will have to dose with soft food – what studies would you do to determine how to risk assess potential for a food effect in paediatrics in fasted vs fed states and what data would you need to predict starting paediatric dose?

This product will be designed for use from children aged 2 to 12 years

Existing data available

Study	**Result**
Fed effect study using FDA breakfast Adult PK data	Negative effect (decreased bioavailability) **Fed study showed ratio of AUC in the fed:fasted state to be 0.31 and the ratio for Cmax to be 0.28** **PK showed typical variability and the drug is <u>not</u> a narrow therapeutic index compound**
Log P MW	**1.01** **662**
API solubility data Aqueous solubility FaSSIF solubility FeSSIF solubility	 **350 mg/mL** **>350 mg/mL** **>350 mg/mL**
In vitro disso data	**Rapid and complete dissolution shown in FeSSIF** **Rapid and complete dissolution observed in FaSSIF** **Rapid and complete dissolution shown in QC method (includes 0.1% SLS, pH 6.5)**
Physchem stability data	
Preclinical in vivo data	**Dog study showed ratio of AUC in the fed:fasted state to be 0.14 and the ratio for Cmax to be 0.08**