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**Food Effects in Paediatric Medicines Development for Products Co-administered with Food**

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†This workshop was organized by an independent planning committee whose role was limited to the identification of topics and speakers. This workshop summary was prepared as a factual summary of the presentations and discussions that took place at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, are not necessarily endorsed or verified by the US Food and Drug Administration.

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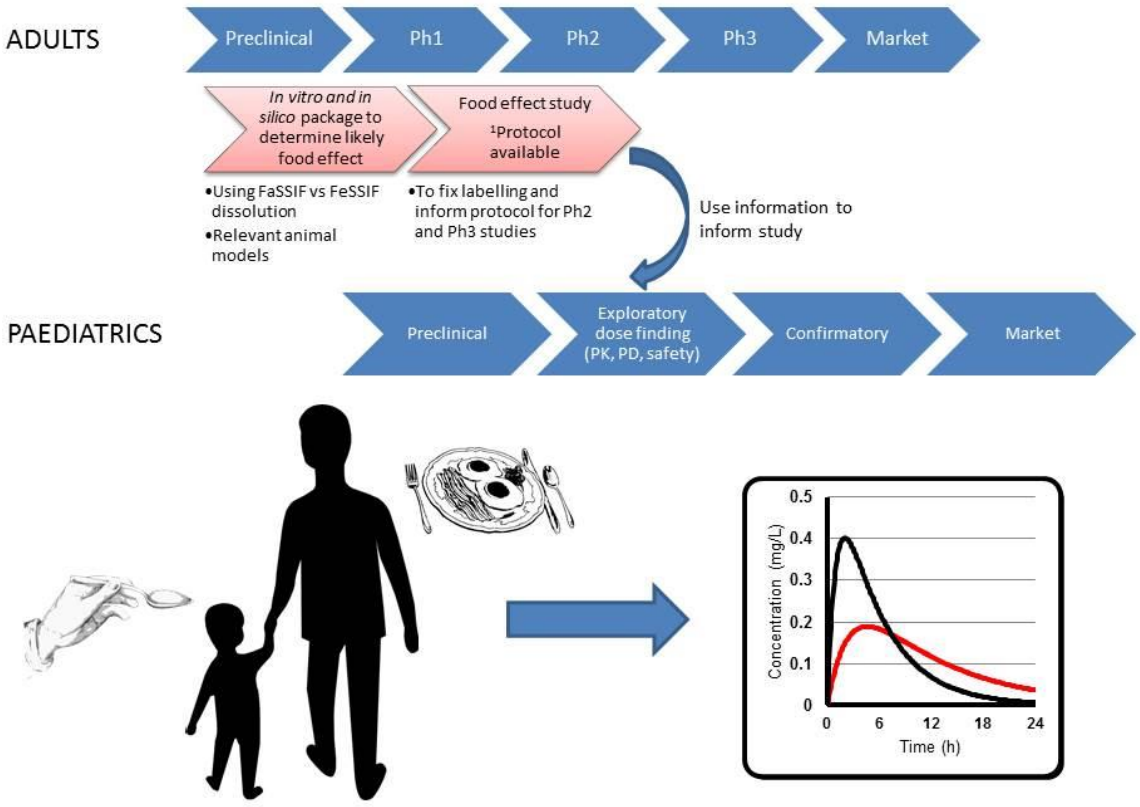
**Graphical abstract**




**Abstract**

A small amount of food is commonly used to aid administration of medicines to children to improve palatability and/or swallowability. However the impact of this co-administered food on the

absorption and subsequent pharmacokinetic profile of the drug is unknown. Existing information on food effects is limited to standard protocols used to evaluate the impact of a high fat meal in an adult population using the adult medication. In the absence of a substantial body of data, there are no specific guidelines available during development of paediatric products relating to low volumes of potentially low calorie food.

This paper brings together expertise to consider how the impact of co-administered food can be risk assessed during the development of a paediatric medicine. Two case studies were used to facilitate discussions and seek out commonalities in risk assessing paediatric products; these case studies used model drugs that differed in their solubility, a poorly soluble drug that demonstrated a positive food effect in adults and a highly soluble drug where a negative food effect was observed. For poorly soluble drugs risk assessments are centred upon understanding the impact of food on the *in vivo* solubility of the drug which requires knowledge of the composition of the food and the volumes present within the paediatric gastrointestinal tract. Further work is required to develop age appropriate *in vitro* and *in silico* models that are representative of paediatric populations.

For soluble drugs it is more important to understand the mechanisms that may lead to a food effect, this may include interactions with transporters or the impact of the food composition on gastro-intestinal transit or even altered gastric motility. *In silico* models have the most promise for highly soluble drug products although it is essential that these models reflect the relevant mechanisms involved in potential food effects.

The development of appropriate *in vitro* and *in silico* tools is limited by the lack of available clinical data that is critical to validate any tool. Further work is required to identify globally acceptable and available vehicles that should be the first option for co-administration with medicines to enable rapid and relevant risk assessment.

Keywords: paediatric; biopharmaceutics; fed-effect

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## 1. Introduction

Food is often used as an aid in the administration of medicines to children and differences in physiology, anatomy and the composition of food consumed within a paediatric population can lead

to food-drug interactions that cannot be predicted based on adult studies [1]. Foods and vehicles such as pudding or apple juice are commonly used to facilitate administration and improve compliance in the paediatric population. These household foods differ from food used in assessing food effect in adult subjects, and thus can impart different food effect on the bioavailability of the same medicine. Information on the impact of co-administration of a small amount of food to aid palatability/administration of a medicine upon drug efficacy and how this can be risk-assessed during product development is lacking. Existing methods to predict food effects in adults cannot be directly extrapolated to allow predictions within paediatric populations due to the differences in food volume and composition as well as patient populations. It is acknowledged that often a paediatric product is administered with the relevant food to an adult population to determine the impact of this co-administration. This manuscript describes the output from a meeting of experts to provide current perspectives on de-risking the impact of co-administered food using *in vitro* and *in silico* methods during product development. The experts included representatives from industry, academia and regulatory agencies working in paediatric drug development.

Two case studies were used to facilitate discussions as a means to provide current perspectives on de-risking the impact of co-administered food using *in vitro* and *in silico* methods during product development. Co-administration with food was defined as, “the use of small amounts of food to aid administration” rather than “dosing with a meal”. The two case studies were selected based on the properties of the model drug where one represented a poorly soluble compound that demonstrated a (positive) food effect in adults and a highly soluble drug where a negative food effect was observed. Knowledge about the *in vitro* de-risking for drug products based on existing physico-chemical properties is known to be compound specific and the two case studies were designed to explore alternative de-risking approaches. The anticipated output was to capture best practices/process flow currently used to enable planning of appropriate clinical studies. Areas where more research or data are required were also identified. The meeting benefitted from the diverse backgrounds of the participants.

## 2. Background

### 2.1. Current limitations of existing *in vitro* methods used to risk assess paediatric products during development

Prof Sandra Klein (University of Greifswald, Germany) presented on, “*In vitro* tools to Risk Assess the Likelihood of a Food/Vehicle Effect in Paediatric Populations”. The following information is based on this presentation.

The use of *in vitro* tools, specifically dissolution to risk assess co-administration with food, must consider the physiology and anatomy of the paediatric population in designing and undertaking these tests. The need to develop new *in vitro* methods that are relevant to paediatric populations has been highlighted previously [2, 3], although this activity is currently limited due to the lack of clinical data that is essential to verify such methods. Specific issues to be considered in the design of *in vitro* tests include the different gastrointestinal volumes related to the age of the child [4] as well as the relative amount of food that may be considered appropriate for co-administration. There is limited evidence on volumes of food used as administration aids although there is a weight related relationship within FDA (United States Food and Drug Administration (FDA)) guidance on co-administration of tablets with food that suggests a range from half a teaspoon for a child of 2 months (12 lbs) up to 3.5 teaspoons for a child of 12 years (76-88 lbs) [5].

The impact of food composition on the physical/chemical stability of the drug/formulation and the huge variability in properties of food used for co-administration globally has been highlighted previously as an issue [6].

### 2.2. Current limitations of preclinical models used to risk assess paediatric products during development

Barbara Davit (Merck & Co., USA) presented on, "Preclinical *in vivo*, Clinical pharmacokinetic, pharmacokinetic/pharmacodynamic (PK/PD) Tools to Assess Food and Vehicle Effects". The following information is based on this presentation.

Within the pharmaceutical industry, typically a clinically meaningful food effect observed in adults consuming a meal may trigger consideration and evaluation of the impact of food on the paediatric product. Dogs and piglets are useful for pre-clinical screening of the likelihood of a food effect for paediatric formulations [7]. A food effect study for the paediatric product is typically conducted in adults using the paediatric product with an appropriate dosing vehicle as well as using a meal [1]. Physiologically based pharmacokinetic (PBPK) modelling is used to predict food effects although it is acknowledged that these models are much more predictive of adult populations compared to children [8]. Preclinical development efforts for drug development are likely to include *in vitro* screening of transporter substrate activity and metabolic profiling to identify potential food effects as part of the standard development pathway. For example, substrates of peptide transporters such as PepT1 could have reduced absorption when given with a milky meal; substrates of organic anion or cation transporters might have interactions with e.g. apple or orange components; food components could affect intestinal metabolism (CYP3A4) [9].

The difference in risk assessment (according to the approach described here) for a food effect during development pathways for adult and paediatric products is shown in Figure 1.

There is no guidance on how to assess the risk of using food to aid administration of drug products, either by design or manipulation for either an adult or a paediatric product, yet there is clear guidance on assessment of a food effect (co-administration with a meal) for adult products [10].

Well-established regulatory guidance on clinical protocols is available to address the impact of food on the pharmacokinetics on the drug in order to underpin labelling claims regarding dosing with (fed) or without a meal (fasted) [10, 11]. There are well-defined *in vitro* tools for estimating the effects of food, such as the use of biorelevant dissolution media, to probe the potential increased solubilisation by fed state bile salt levels [12]. However, as noted above, these assessments are focused on risks associated with dosing with regard to meals, as opposed to using small amounts of food to aid administration and does not take into account differences in composition of the meals and differences in feeding patterns that include a wide spectrum across the age range of the paediatric patients. There have been recent efforts to manufacture paediatric simulated intestinal fluids that represent the fed and fasted state and these are of value in the risk assessment of potential food effects [13, 14].

Regulatory agencies and associated guidance documents acknowledge issues associated with co-administration of food in dosing to children and the influence of food on pharmacokinetics/pharmacodynamics (PK/PD) of medicines, and state that these should be considered by those developing the product [15-18]. This situation results in increased variability in how medicines are developed and increased barriers to those developing paediatric medicines. The use of relevant *in vitro* and *in silico* tools can support the design and optimisation of clinical trials and even recommendations on dosing and labelling medicines in specific populations. These tools can also aid in the prediction of variability or the suggestion of any foods/drinks that should be avoided for specific medicines and/or populations.

A recent literature review highlighted the issues at hand namely that food effects in adults are not always seen in children, while sometimes food effects seen in children are not evident in adults [1]. The potential consequence of food effects apparent in children that were not apparent in adults is a significant risk as these may not be exposed until after development when the medicine is being

used in a clinical population [19, 20]. These factors result in children being at risk of sub-optimal therapy when medicines are co-administered with food.

The challenge for pharmaceutical industry, regulators and academic researchers is to design lean efficient processes to adequately risk assess the impact of co-administration with food in paediatric populations and ensure safe and effective age-appropriate medicines. It is essential that the likelihood of a food effect by co-administration with food is appropriately addressed in addition to a traditional food effect assessment, where the medicine is administered with a meal.

## 3. Best practice/process flow to risk assess co-administration with food during paediatric product development

Knowledge on *in vitro* and *in silico* tools is currently fragmented due to the relatively new initiatives to develop paediatric medicines, therefore two anonymised case studies were used to allow industrial and regulatory experts to share typical processes that are currently in use to understand what still needs to be done in this area to de-risk the development of paediatric medicines. The case studies provided brief information about the drug substance and product and data on the adult food-effect study.

## 4. Case Study 1: BCS II with clinically relevant food effect in adults

The active pharmaceutical ingredient (API), a Biopharmaceutics classification system (BCS) II, salt form of a weak base is known to exhibit a positive, **clinically relevant** food effect (FE) in an adult population based on data from a fed vs fasted pharmacokinetic study using a tablet (100mg) and a ”standard FDA breakfast”[10], together with PK/PD modelling. The intended paediatric formulation to be developed is a sprinkle that patients will have to dose with soft food.
This product is designed for use in children aged 2 to 12 years.

### 4.1. Discussion of Case Study 1.

As this is a poorly soluble drug (BCS II), the positive food effect may be attributed to a change in solubility of the drug due to the presence of food. The major focus of discussion was around the solubility and dissolution data that could be generated to understand the increased exposure observed in adults and whether this would translate into a paediatric population. There was debate

around the choice of co-administration vehicle to better understand the solubilising potential of a typical vehicle and debate around what a typical vehicle should be. This is further complicated by the fact that the typical vehicle is likely to be different for different age sub-sets, particularly if the product had been developed to include neonates and small infants, as well as considering global differences in food availability and preferences.

The direct extrapolation of BCS classification from adult to child was also queried as it was noted that the dose number (defined as the dose taken divided by the volume of water taken with the medicine (250 mL) and solubility of drug) should be considered, although it was acknowledged that the volume of water consumed is an unknown quantity for children.

The dog model was considered to be a useful model to predict a food effect in adults therefore it may be useful to use this model to evaluate the paediatric formulation with a range of relevant vehicles. However, the absence of any paediatric clinical data limits its usefulness for the target population. The use of a dog model was also queried relating to the higher levels of bile salts in dogs compared to adults and the lack of knowledge on bile salt concentration in paediatric populations. Meal components and lower bile salt concentrations may affect drug absorption in neonates and young infants, who were not of relevance in this case study (as product was designed for use in those aged 2-12 years) were still considered in discussions [21]. Questions of potential benefits of using juvenile animal models, including the pig, were raised.

There was considerable debate on the quantity and composition of food that is required to generate a food effect in children. It was noted that children have less predictable eating habits in terms of volume and frequency compared to adults and that this is subject to huge global variation. In particular for neonates and infants, there may not exist a true fasted state due to frequent feedings and as a child gets older, due to differences in eating and snacking habits. Additionally, a true fed state may not exist for neonates and very young infants due to the low bile salt concentrations in the small intestine. It was noted that the specific disease state of the child may also impact on their diet and appetite which, together with concomitant treatments, could further complicate the risk assessment.

The use of physiologically based models was discussed where typically adult fed/fasted data are modelled to better understand how well the models predict adult data; where the fit is good the model is likely to be extrapolated for use in children although the gaps in knowledge were again highlighted.

The need to assess the stability of the drug substance/product in the co-administration vehicle was mentioned although this was excluded from further discussion as the emphasis was on the biopharmaceutics aspects of risk assessment. In general, it was discussed that not all potential vehicles can be tested, and it could be most important to identify which type of vehicles should **not** be used from a stability perspective.

There was no clear process for the risk assessment of co-administration of food with this case study that arose from discussions. The main commonalities were:

1. Solubility screening over a physiologically relevant pH range and in some biorelevant media is helpful to estimate the impact of "fed-state" micellar composition on solubility of the drug substance. Currently the recognised adult FaSSIF and FeSSIF are most commonly used as biorelevant media for paediatric risk assessment.
2. Dissolution testing is undertaken to compare performance of the paediatric product to the adult product. Typically standard USP apparatus is used which does not account for paediatric intestinal volumes; standard buffers and FaSSIF/FeSSIF are the typical media used; in some cases two-step methods (stomach→ small intestine) are used; and although some more advanced and biorelevant dissolution apparatus and the use of lower volumes was discussed their use was not widespread. Information is lacking on the predictability of *in vitro* methods used during the formulation development process/when choosing between formulations to be taken forward.
3. The impact of food on the systemic exposure in paediatric populations can be age-dependent as well as formulation and dose-dependent for BCS II and IV drugs.
4. Mechanism-based absorption model may be used: When using modelling software the food effect should be maximised in the adult population to seek out potential food effect in the paediatric absorption model. Specific software such as GastroPlus™ Advanced Compartmental and Transit (ACAT) Model or Advanced Dissolution, Absorption and Metabolism (ADAM) in Simcyp®, among others are available although there may be a need to develop a bespoke simulator tailored to paediatric needs using MATLAB® (Simulink) or another simulation platform.
5. If a PBPK model was available that showed good correlation with modelled data to adult clinical data, linear pharmacokinetics and a known metabolic pathway then this would be used as the most reliable predictor of *in vivo* performance in children. This assumes that the paediatric formulation leads to the same rate of *in vivo* dissolution in paediatric patients as the adult formulation does in adults, and also assumes that a similar

composition/formulation technology does not carry risk for differences in excipient related effects e.g. on transit time, transporter activity or intestinal metabolism.

## 5. Case Study 2: BCS III with clinically relevant food effect in adults

The API (BCS III, an acidic drug (pKa = 8.3) with a low lipophilicity) is known to exhibit a negative, **clinically relevant** food effect in an adult population based on data from a fed vs fasted pharmacokinetic study using a tablet (300mg) and a ”standard FDA breakfast”, together with PK/PD modelling.

The intended paediatric formulation is a sprinkle that patients will have to dose with soft food.

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

### 5.1. Discussion of Case Study 2.

The focus of discussions on case study 2 were on the mechanisms behind the observed food effect as this is a highly soluble drug (BCS III) and therefore the reduction in exposure does not have a clear cause. The food effect was considered likely to be an interaction between food and drug uptake transporters, bile salt micelle entrapment or a physiological response where the presence of food alters the gastrointestinal transit which in turn influences the pharmacokinetic profile.

Preclinical and adult data are likely to be available to understand the uptake pathway(s) therefore this can be risk-assessed provided the ontogeny of the paediatric pathways is well understood. However, it was noted that there is limited evidence on the ontogeny of many transporters (absorptive as well as efflux) and/or part of the metabolic pathways in paediatric populations. The use of PKPB models was discussed although their utility is limited unless both the mechanism behind the food effect is known and the ontogeny of that mechanism is well-understood and included within the model.

There was debate around the choice of co-administration vehicle to better understand the potential of a typical vehicle to induce a food effect and the composition of a typical vehicle. Most studies start by evaluating a single variant of soft food; apple sauce was the most common vehicle; with a view to considering a range of products if required at a later stage in development. There is very limited knowledge on the calorific content of soft foods and the volume required to induce a food effect; the most relevant volume of soft food to use in an adult study was debated in terms of matching the volume relative to gastric size of adults versus children or using the same volume likely to be used by children. The composition of an ideal soft food was debated with most participants

agreeing that a low volume/low calorie product is likely to be least likely to induce a food effect. Some food items contain components that are also used as excipients, which have been recognised to induce shortened transit times and thereby lower bioavailability. For example, poorly absorbed carbohydrates such as fructose or sorbitol are present in fruit derived products such as apples, pears, plums which may be used as co-administration aids. There is very limited information on the amounts of food components/excipients that would have an effect on bioavailability and this is probably very compound specific. Further work is required to better understand this area. In addition to transit time effects and bile salts micellar entrapment, food components could have transporter related effects.

As the drug is highly soluble, discussions on solubility and dissolution were limited to using confirmatory testing only to detect any changes compared to the adult formulation.

There was no clear process for the risk assessment of co-administration of food with this scenario that arose from the breakout discussions. The main commonalities were:

1. Understanding the mechanism behind the food effect was paramount to managing the risk assessment for co-administration with food for a highly soluble drug.
2. Dissolution testing is undertaken purely to confirm that the paediatric product behaves as the adult product in standardised dissolution tests (typically in United States pharmacopoeial (USP) apparatus, USP II).
3. PBPK models that accurately reflect the relevant mechanisms underpinning the food effect for a BCS III drug are likely to be of most value; however, these do not yet exist in many cases. If a PBPK model was available that showed good correlation of modelled data to adult clinical data, linear pharmacokinetic exposure with dose, and a known metabolic and/or transporter-mediated elimination pathway, then this would be used as the most reliable predictor of *in vivo* performance in children.

## 6. Overall discussions/conclusions

The complexity of food-drug interactions should not be underestimated; there are no simple pathways/processes to follow to predict the likelihood of a food effect for a paediatric product co-administered with food. The strongest evidence used in risk assessment is the adult fed versus fasted bioavailability study, yet it is known that this generally represents a worst case scenario in adults and may be very different from the situation where drugs are co-administered with a low-volume low-calorie vehicle (e.g. apple sauce). However, food effects in children, especially for

neonates and small infants, cannot be fully ruled out in cases where adult studies show no or little food effect. This is likely due to many factors including differences in the relative gastric volumes, gastro-intestinal physiology and potential food items that could be used. The definition of low volume needs to be clearly defined as even small volumes of food used as a co-administration aid in neonates and small infants represents a substantial percentage of the gastric volume. This fact in combination with uncertainties in transporter expression leaves the youngest paediatric patients at risk of inadequate dosing. There was consensus by the workshop participants that insufficient experience and knowledge are available to develop a best practice/process flow to de-risk the impact of co-administered food for paediatric formulation development. However, gaps where more research or data are required were identified as an output from this meeting.

More work is required to gain information on the composition and volume of food that triggers a physiological response to food in children in order to better understand the consequences of co-administration of medicines with food. A standardised protocol, to mirror the FDA breakfast, which could be used to mimic co-administration with food would be a huge benefit to those developing medicines for children. The use of common vehicles which are globally accepted and globally available, for co-administration would move understanding forwards in this area.

There is a need for more clinical data to be published showing food effects in children and supported by mechanistic understanding of the potential interactions, in order to verify biorelevant *in vitro* and *in silico* method development against relevant data.

There is scope for Government / Pharma / Academic pre-competitive collaboration in this area to address the many unmet needs in risk assessing the pharmacokinetic impact of co-administration of paediatric medicines with food. This workshop was designed to be the starting point for these discussions and it is anticipated that these discussions will evolve over time into collaborations that address some of the many unmet needs in this area.

**References**

1. Batchelor H. Influence of Food on Paediatric Gastrointestinal Drug Absorption Following Oral Administration: A Review. Children. 2015;2(2):244.

2. Batchelor HK, Fotaki N, Klein S. Paediatric oral biopharmaceutics: key considerations and current challenges. Advanced drug delivery reviews. 2014;73:102-26. doi:10.1016/j.addr.2013.10.006.

3. Batchelor HK, Kendall R, Desset-Brethes S, Alex R, Ernest TB. Application of in vitro biopharmaceutical methods in development of immediate release oral dosage forms intended for paediatric patients. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2013;85(3 Pt B):833-42. doi:10.1016/j.ejpb.2013.04.015.

4. Shawahna R. Pediatric Biopharmaceutical Classification System: Using Age-Appropriate Initial Gastric Volume. The AAPS Journal. 2016;18(3):728-36. doi:10.1208/s12248-016-9885-2.

5. FDA. In an Emergency: How to Prepare Doxycycline for Children and Adults Who Cannot Swallow Pills.
http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM131006.pdf2008.

6. Kersten E, Barry A, Klein S. Physicochemical characterisation of fluids and soft foods frequently mixed with oral drug formulations prior to administration to children. Die Pharmazie - An International Journal of Pharmaceutical Sciences. 2016;71(3):122-7. doi:10.1691/ph.2016.5145.

7. Gasthuys E, Vandecasteele T, De Bruyne P, Vande Walle J, De Backer P, Cornillie P et al. The potential use of piglets as human pediatric surrogate for preclinical pharmacokinetic and pharmacodynamic drug testing. Current Pharmaceutical Design. 2016;22(26):4069-85. doi:10.2174/1381612822666160303111031.

8. Michelet R, Dossche L, De Bruyne P, Colin P, Boussery K, Vande Walle J et al. Effects of Food and Pharmaceutical Formulation on Desmopressin Pharmacokinetics in Children. Clinical Pharmacokinetics. 2016;55(9):1159-70. doi:10.1007/s40262-016-0393-4.

9. Won CS, Oberlies NH, Paine MF. Mechanisms underlying food-drug interactions: inhibition of intestinal metabolism and transport. Pharmacology & therapeutics. 2012;136(2):186-201. doi:10.1016/j.pharmthera.2012.08.001.

10. FDA. Guidance for Industry. Food-Effect Bioavailability and Fed Bioequivalence Studies. 2002.

11. EMA. Guideline on the investigation of drug interactions. http://wwwemaeuropaeu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606pdf. 2013;Accessed Febraury 2017.

12. Klein S. The Use of Biorelevant Dissolution Media to Forecast the In Vivo Performance of a Drug. The AAPS Journal. 2010;12(3):397-406. doi:10.1208/s12248-010-9203-3.

13. Maharaj AR, Edginton AN, Fotaki N. Assessment of Age-Related Changes in Pediatric Gastrointestinal Solubility. Pharmaceutical Research. 2016;33(1):52-71. doi:10.1007/s11095-015-1762-7.

14. Gandhi SV, Rodriguez W, Khan M, Polli JE. Considerations for a Pediatric Biopharmaceutics Classification System (BCS): Application to Five Drugs. AAPS PharmSciTech. 2014;15(3):601-11. doi:10.1208/s12249-014-0084-0.

15. WHO. Paediatric clinical trials guidance for assessors. http://wwwwhoint/childmedicines/CTguidancepdf. 2011;Accessed July 2016.

16. FDA. DRAFT GUIDANCE. General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. http://wwwfdagov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885pdf. 2014;Accessed July 2016.

17. EMA. Guideline on pharmaceutical development of medicines for paediatric use. http://wwwemaeuropaeu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002pdf. 2014;Accessed July 2016.

18. EMEA. ICH Topic E 11. Clinical Investigation of Medicinal Products in the Paediatric Population http://wwwemaeuropaeu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926pdf. 2001;Accessed July 2016.

19. Fernandez E, Perez R, Hernandez A, Tejada P, Arteta M, Ramos JT. Factors and Mechanisms for Pharmacokinetic Differences between Pediatric Population and Adults. Pharmaceutics. 2011;3(1):53-72. doi:10.3390/pharmaceutics3010053.

20. Singh BN, Malhotra BK. Effects of food on the clinical pharmacokinetics of anticancer agents: Underlying mechanisms and implications for oral chemotherapy. Clinical Pharmacokinetics. 2004;43(15):1127-56. doi:10.2165/00003088-200443150-00005.

21. Murphy GM, Signer E. Bile acid metabolism in infants and children. Gut. 1974;15(2):151-63.

**Figure 1.** Schematic representation of the parallel development of adult and paediatric products to highlight the risk of co-administration with food

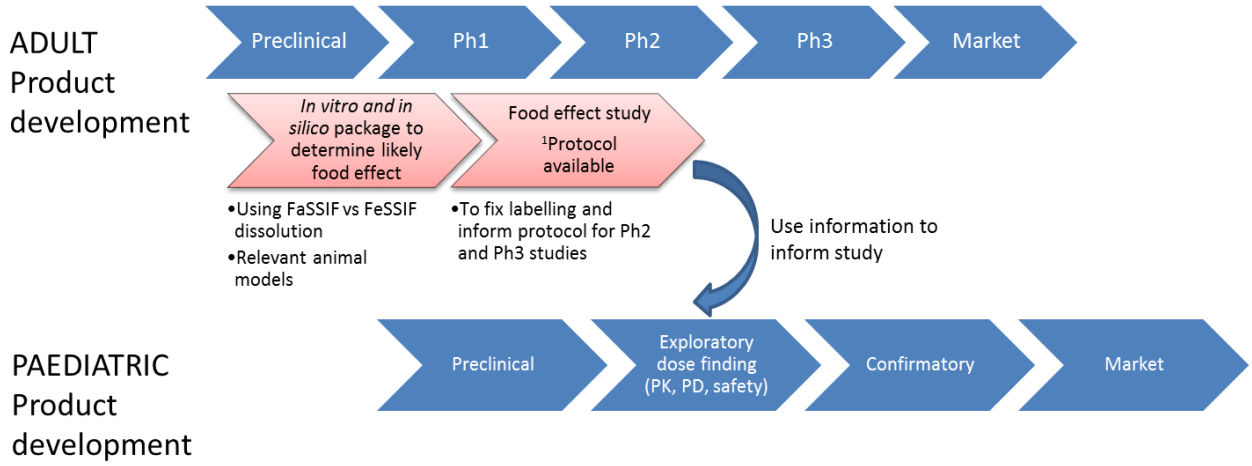

**Table 1. Existing data available regarding the API in Case Study 1**

| Data available | Result/Comments |
|---|---|
| Fed effect study using FDA breakfast on adult formulation in healthy adult population | $C_{max}$ increased 3 fold in fed study; AUC increased 2 fold in the fed state compared to fasted<br>Pharmacokinetic profile showed typical variability and the drug is not a narrow therapeutic index compound |
| Log P<br>Log SR Bile<br>Molecular Weight | 2.2<br>3.6<br>362 |
| API solubility data<br>• Aqueous solubility<br>• FaSSIF solubility<br>• FeSSIF solubility | <br>0.04 mg/mL<br>0. 4 mg/mL<br>1.0 mg/mL |
| *In vitro* dissolution data | Rapid and complete dissolution shown in FeSSIF<br>Incomplete dissolution observed in FaSSIF<br>Rapid and complete dissolution shown in QC method (includes 0.1% SLS, pH 6.5) |
| Preclinical data<br>*In vivo* dog data | Dog study showed 7 fold increase in $C_{max}$ and 6 fold increase in AUC in the fed state compared to fasted |

$C_{max}$: Maximum plasma concentration following oral administration
AUC: Area under the curve of the plasma concentration vs time; this value represents the overall exposure of the drug
Log SR Bile: SR is the ratio of the solubilisation capacity of the bile salt to the solubilisation capacity of water for the drug
FaSSIF: Fasted state simulated intestinal fluid
FeSSIF: Fed state simulated intestinal fluid

**Table 2. Existing data available regarding the drug in Case Study 2**

| Study | Result |
|---|---|
| Fed effect study using FDA breakfast on adult formulation in healthy adult population | Negative effect (decreased bioavailability)<br>Fed study showed ratio of AUC in the fed:fasted state to be 0.31 and the ratio for $C_{max}$ to be 0.28<br>PK showed typical variability and the drug is not a narrow therapeutic index compound |
| Log P<br>Molecular weight | 1.01<br>662 |
| API solubility data<br>• Aqueous solubility<br>• FaSSIF solubility<br>• FeSSIF solubility | <br>350 mg/mL<br>>350 mg/mL<br>>350 mg/mL |
| *In vitro* dissolution data | Rapid and complete dissolution shown in FeSSIF<br>Rapid and complete dissolution observed in FaSSIF<br>Rapid and complete dissolution shown in QC method |
| Preclinical data<br>*In vivo* dog data | Dog study showed ratio of AUC in the fed:fasted state to be 0.14 and the ratio for $C_{max}$ to be 0.08 |

$C_{max}$: Maximum plasma concentration following oral administration
AUC: Area under the curve of the plasma concentration vs time; this value represents the overall exposure of the drug
FaSSIF: Fasted state simulated intestinal fluid
FeSSIF: Fed state simulated intestinal fluid
QC: Quality Contol