Regulatory Applications and Research of Absorption Modeling for Pediatric Products

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New drug products: pediatric formulation development	Generic drug products with pediatric indication
Relative bioavailability studies (RBA) • Pediatric vs adult formulation • Clinical trial formulation vs commercial formulation • Certain post-approval changes (SUPAC) • 505(b)(2) applications for drug products with pediatric indication	**Bioequivalence (BE)** • Reference vs generic formulations • Abbreviated new drug applications (ANDAs)
• Potentially greater changes in formulation and BE limits does not necessarily have to be demonstrated (allowing different dosage in pediatrics) • RBA studies are generally followed by studies determining the PK, safety and potentially efficacy in children	• Approval frequently supported by BE studies with AUC and Cmax as PK endpoints in adults • PK BE data are not collected in children

SUPAC: Scale-Up and Post-Approval Changes; PK: Pharmacokinetics; BCS: Biopharmaceutics Classification System
IR: Immediate-Release

Guidance Recommendations on RBA

Relative bioavailability (rBA) studies
(bridge adult to pediatric formulation)

- **ICH E11** Relative bioavailability comparisons of pediatric formulations with the adult oral formulation **typically should be done in adults**.
- **FDA** The bioavailability of any formulation used in pediatric studies should be characterized in relation to the adult formulation. If needed, a relative bioavailability study comparing the age-appropriate formulation to the approved drug should be **conducted in adults**.
- **EMA** Bioequivalence studies for bridging pediatric clinical documentation between two formulations should **preferably be performed in adults**, **but the applicant should justify that the study results can be extrapolated to the pediatric population**.

Approved Generic Products are Considered Therapeutic Equivalent in Pediatrics

- Therapeutic equivalent
  - Pharmaceutical equivalent
  - Bioequivalent (BE)
- Substitutable for all labeled uses
  - All indications
  - All patient populations (including pediatric population)
- BE results from approved generic products showed small drug exposure difference in healthy subjects (N = 2070 BE studies)
  - The average difference in Cmax and AUC between generic and innovator products was 4.35% and 3.56%, respectively (*The Annals of Pharmacotherapy, 2009 October, Volume 43, 1583).*

Establish BE for Pediatric Generics

- In general, the FDA recommends that BE studies be conducted in healthy adult subjects (HS) and the BE conclusions in HS can be extrapolated to pediatric population
  - consistent with ICH E11 Guideline entitled “Clinical Investigation of Medicinal Product in the Pediatric Population”
  - HS are considered the most sensitive population to detect formulation differences as they are more homogenous and have relatively lower variability
  - BE conclusions in HS have been used to support drug use in all populations (such as patients with renal or hepatic impairment). The same reasoning can also be applied to pediatric population unless there is a concern of impact of age on drug availability due to different formulations.

Guidance Recommendations on BE

Bioequivalence studies (generic drug products)

FDA guidance (2021 BE guidance for ANDAs)

- Subjects recruited for in vivo BE studies should be **18 years of age or older**
- In vivo BE study subjects should be **representative of the general population**, taking into account **age, sex, and race**.
- In general, a BE assessment in adults between two products can be used to support a BE assessment in pediatric patients. If the drug product is predominantly intended for use in **pediatric patients younger than 6 years**, the applicant should justify that the BE study results obtained from adult subjects are relevant to the pediatric population. FDA recommends that this justification include information supporting that the inactive ingredients in the proposed products are appropriate for use in the pediatric population.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioequivalence-studies-pharmacokinetic-endpoints-drugs-submitted-under-abbreviated-new-drug

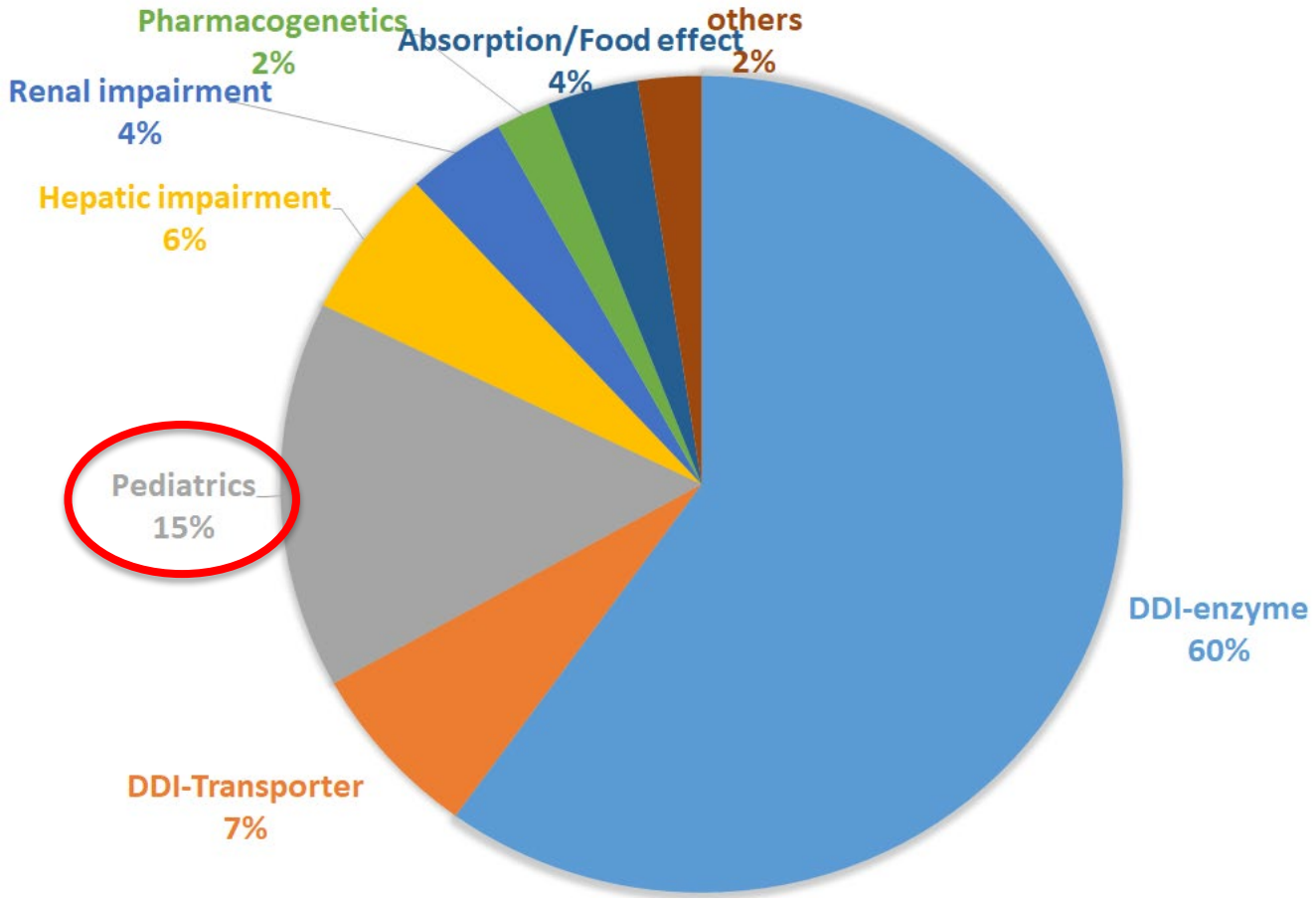
Considerations

- What is our degree of certainty that differences in absorption of different formulations in pediatric patients are adequately detected in adult volunteers?

- How do we identify drug products where we should be cautious?

- What would be our approach if high risk products are identified?

PBPK to Address Pediatric Clinical Pharmacology Issues in Recent Submissions



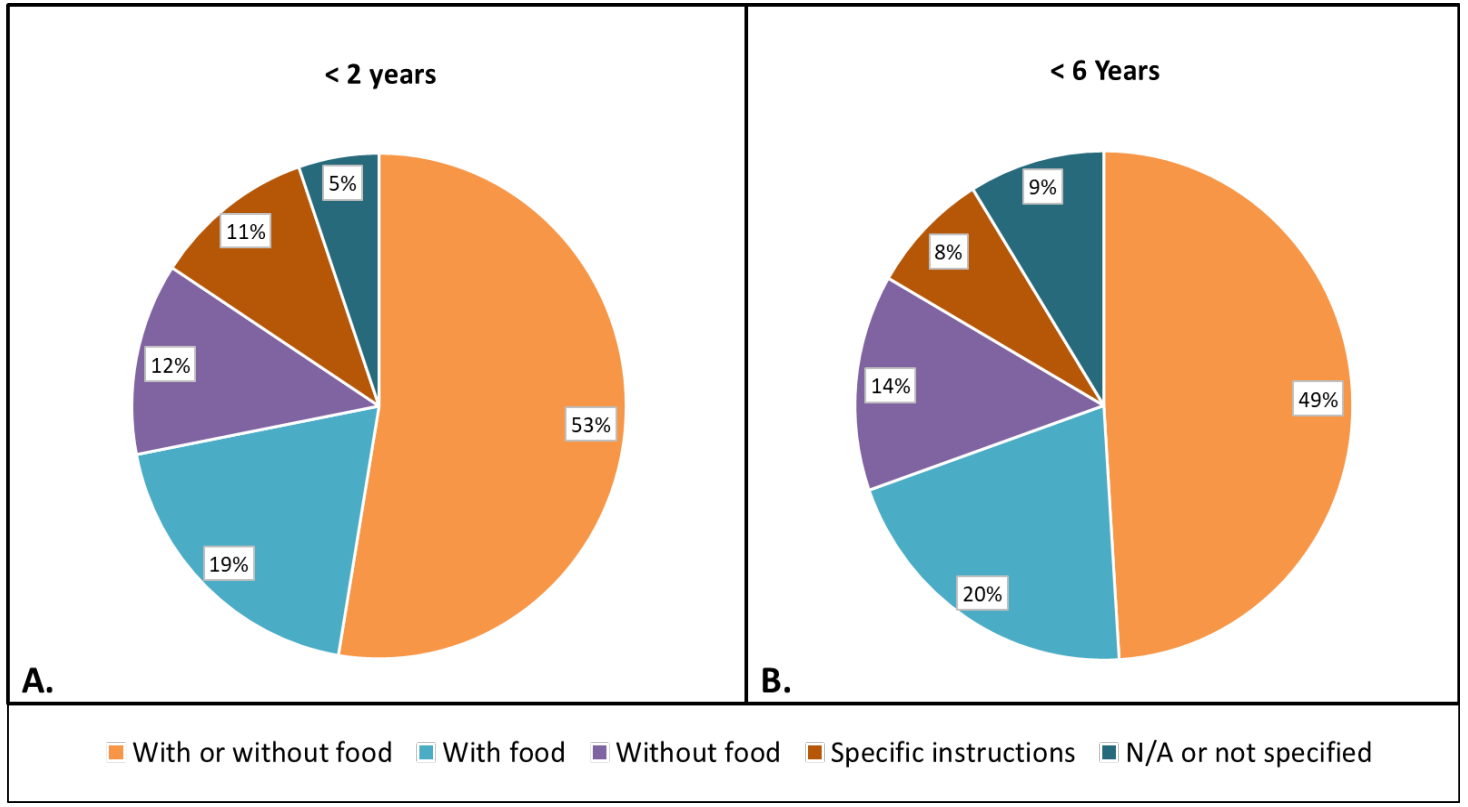
2008-2017 (n=254)

- Predict PK and propose dosage selection for pediatric trials
- Evaluate rBA prior to pediatric trial initiation
- Evaluate drug-drug interaction potentials in pediatric populations

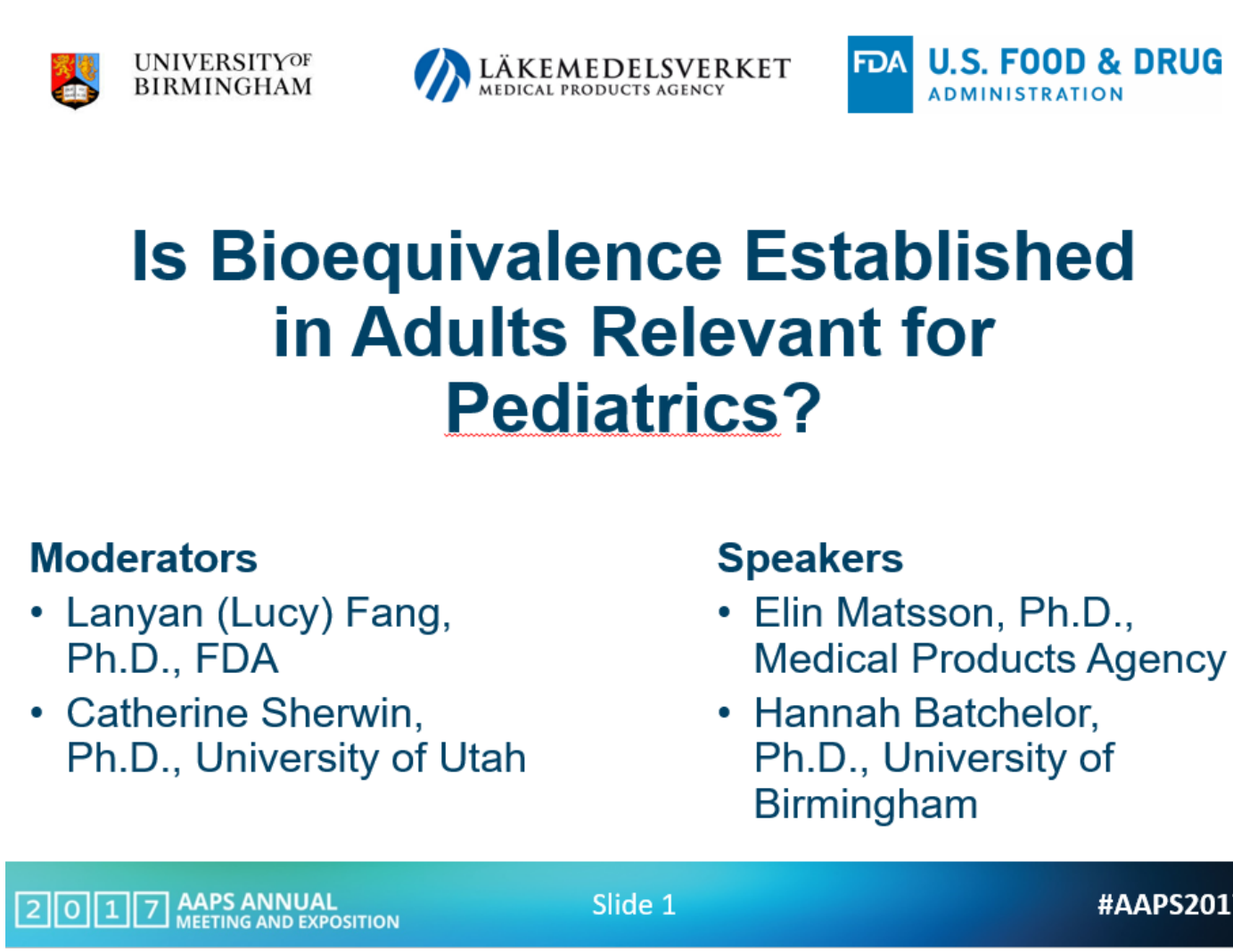
Grimstein et al. J Pharm Sci. 2019 Jan;108(1):21-25; PBPK: Physiological based pharmacokinetic modeling and simulation

PBPK to Assess Pediatrics Food Effect

- Food effect (FE) studies are conducted in healthy adults.
- Of 102 oral drug products approved for use in patients <6 years, 43 products recommended consideration of food intake in the drug labeling.
  - 65%: food or w/ specific instructions
  - 100% of those taken without food were approved for use in pediatric patients <2 years.
- Additional methods, such as a pediatric BCS classification system and pediatric PBPK absorption modeling, are needed to accurately assess pediatric FE



Food instructions in the label of oral drug products listed under BPCA-PREA between 2012-2022 approved in pediatric populations (**A**) < 2 years or < 12.6 kg (n = 57), and (**B**) < 6 years or < 20 kg (n = 102). Courtesy picture from Dr. Gil Burckart, OCP/CDER



Project initiated in 2017…

FDA's Proactive Research Efforts

- Grant: Generic Drug Substitution In Special Populations
  - https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-16-011.html
  - collected clinical data on approved generic drug substitution in pediatric population
- Contract: Risk mitigation in the evaluation of relative bioavailability of pediatric generic products, with University of Birmingham
  - Comprehensive literature research
  - Developing risk mitigation tools based on
    - Biopharmaceutics Classification System
    - Biorelevant in vitro dissolution testing
    - PBPK modeling

Putative Risk Factors: RLD vs. Test in Pediatrics

	Putative risk factors	Number of studies identified
Physiological factors (ADME effect)	Age-related absorption effects (e.g., GI motility, GI fluid volume or composition, and GI transit time)	28
	Age-related distribution effects (e.g., protein binding)	2
	Age-related metabolism or clearance effects	15
Drug substance or formulation effects	Drug substance effect (e.g., alternative salt or polymorphic form of drug substance)	5
	Drug product/formulation effects	12
Disease	Age-related disease progression and other disease-related effects	4
Population characteristics	High inter- and/or intra-individual variabilities	18
Study design	Non-equivalent dose effects	2
	Accuracy of administered dose	2
	Poor study design including small sample size	11

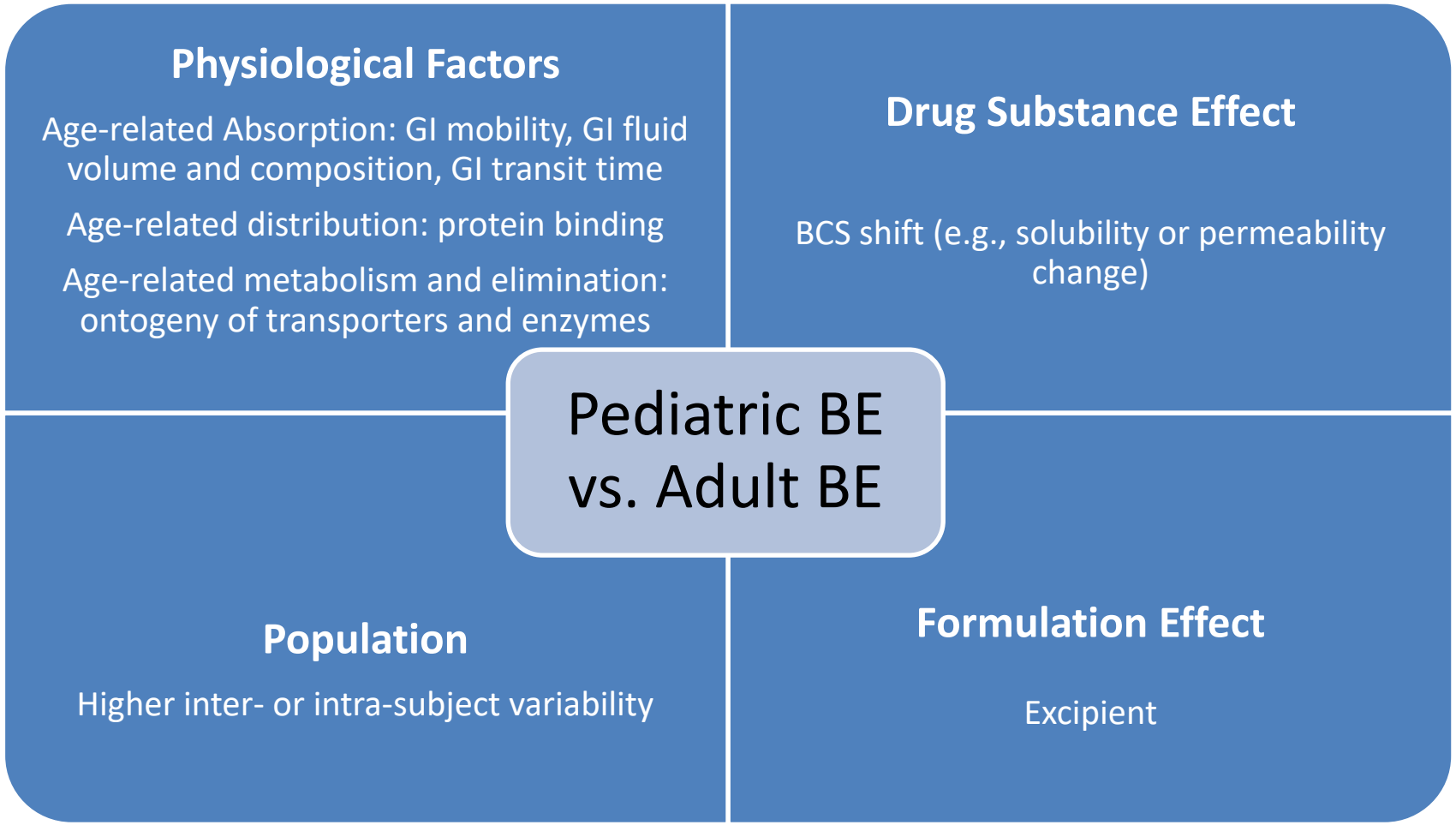
- *Note that multiple risk factors may have been extracted from one study*
- Risks were found being associated with products with API belonging to NTI drug category, The drug solubility is low (BCS class II or IV)

Research results from FDA contract: ORS-EXT-2018-09, Risk mitigation in the evaluation of relative bioavailability of pediatric generic products, with University of Birmingham

Pawar G, Wu F, Zhao L, Fang L, Burckart GJ, Feng K, Mousa YM, Naumann F, Batchelor HK. AAPS J. 2021 Apr 21;23(3):57. doi: 10.1208/s12248-021-00592-y. AAPS Journal, 2021

RLD: reference listed drug

PBPK: Evaluate Interplay between Populations & Formulations

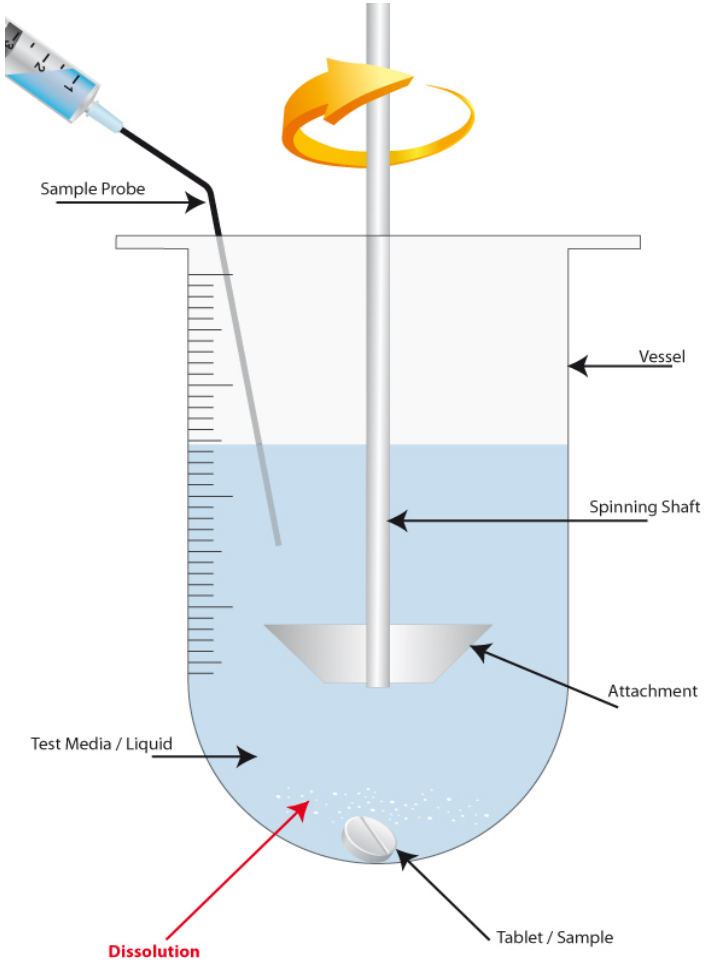


FDA contract: ORS-EXT-2018-09, Risk mitigation in the evaluation of relative bioavailability of pediatric generic products, with University of Birmingham

Dissolution and Risks of non-BE

There is known variability in GI fluids in children compared to adults

There is a known difference in fluid volume in children compared to adults



Can we use biorelevant dissolution testing integrated into PBPK modelling to predict a risk of bioinequvialence in pediatrics?

Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict In Vivo Performance and Bioequivalence of Generic Drugs in Pediatric Populations: a Carbamazepine Case Study

The AAPS Journal (2023) 25:67

Population (100 mg dose-Tegretol© and generic CBZ; simulation run time-24 h)	Cross-over design	Input dissolution datasets	VBE outcome: 90% CIs (GMR)-(lower limit-upper limit)		Bioequivalence Yes, or No?
			AUC (µg/mL h)	Cmax (µg/mL)	
Adult	$N=10$ trials; $n=12$ subjects	Only Ad-FaSSIF 500 mL	94.8 (94.6–95.0)	94.5 (94.3–94.7)	Yes
	$N=10$ trials, $n=12$ subjects	Ad-FaSSGF and FaSSIF 500 mL	105 (105–106)	105 (104–105)	Yes
	$N=10$ trials; $n=16$ subjects	Ad-FaSSGF and FaSSIF 500 mL	105 (105–106)	105 (105–105)	Yes
	$N=10$ trials; $n=24$ subjects	Ad-FaSSGF and FaSSIF 500 mL	105 (105–105)	105 (104–105)	Yes
	$N=10$ trials; $n=48$ subjects	Only adult FaSSIF 500 mL	94.8 (94.7–94.9)	94.5 (94.4–94.6)	Yes
	$N=10$ trials; $n=48$ subjects	Ad-FaSSGF and FaSSIF 500 mL	106 (105–106)	105 (105–105)	Yes
Pediatrics	$N=10$ trials; $n=12$ subjects	Only Ped-FaSSIF 200 mL_14 BS	98.9 (98.2–99.7)	101 (101–102)	Yes
	$N=10$ trials; $n=12$ subjects	Ped-FaSSGF and FaSSIF 200 mL_14 BS	112 (111–114)	113 (112–114)	Yes
	$N=10$ trials; $n=16$ subjects	Ped-FaSSGF and FaSSIF 200 mL_14 BS	113 (112–114)	113 (112–114)	Yes
	$N=10$ trials; $n=24$ subjects	Ped-FaSSGF and FaSSIF 200 mL_14 BS	112 (111–113)	113 (112–113)	Yes
	$N=10$ trials; $n=48$ subjects	Only Ped- FaSSIF 200 mL_14 BS	98.9 (98.5–99.3)	101 (101–102)	Yes
	$N=10$ trials; $n=48$ subjects	Ped-FaSSGF and FaSSIF 200 mL_14 BS	112 (111–113)	112 (112–113)	Yes

Take Home Messages

- Absorption modelling can incorporate characteristics of the drug substance and formulation as well as pediatric physiology to assess the potential differences in absorption of different formulations in pediatric patients (new and generic drugs).
- Little data, if any, are available showing that bioequivalent generic products in adults are in-equivalent in other populations, including children.
  - FDA awarded research projects to collect clinical data on generic drug substitution in pediatric population as well as risk evaluation of relative bioavailability/BE of pediatric generic products.
- The 2021 BE guidance for ANDAs recommends applicants conduct comprehensive formulation comparison, in vitro characterization, as well as modeling and simulation analysis as risk assessment.

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Terminologies

Bioequivalence (BE)

- Used in the context of generic drug products (ANDAs)
- To support a determination that a generic product may be substituted for its reference listed drug (RLD)
- Specified criteria for comparisons between test and reference products and predetermined BE limits for such criteria

Relative bioavailability (RBA)

- Used in the context of new drug products (INDs, NDAs)
- Bioequivalence, as defined by the conventional predetermined bioequivalence limits, does not necessarily have to be demonstrated
- Based on dose/concentration-response data, it can be justified that differences in rate and extent of absorption do not affect the safety and efficacy of the drug product

ANDA: Abbreviate New Drug Application; IND: Investigational New Drug; NDA: New Drug Applications