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Risk Factors Related to Relative Bioavailability Studies for Pediatric Products

October 2021

Hannah Batchelor

Gopal Pawar

FDA Team: Fang Wu, Liang Zhao, Lanyan Fang, Gilbert J. Burckart, Kairui Feng, Youssef Mousa

University of Strathclyde Glasgow

Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies

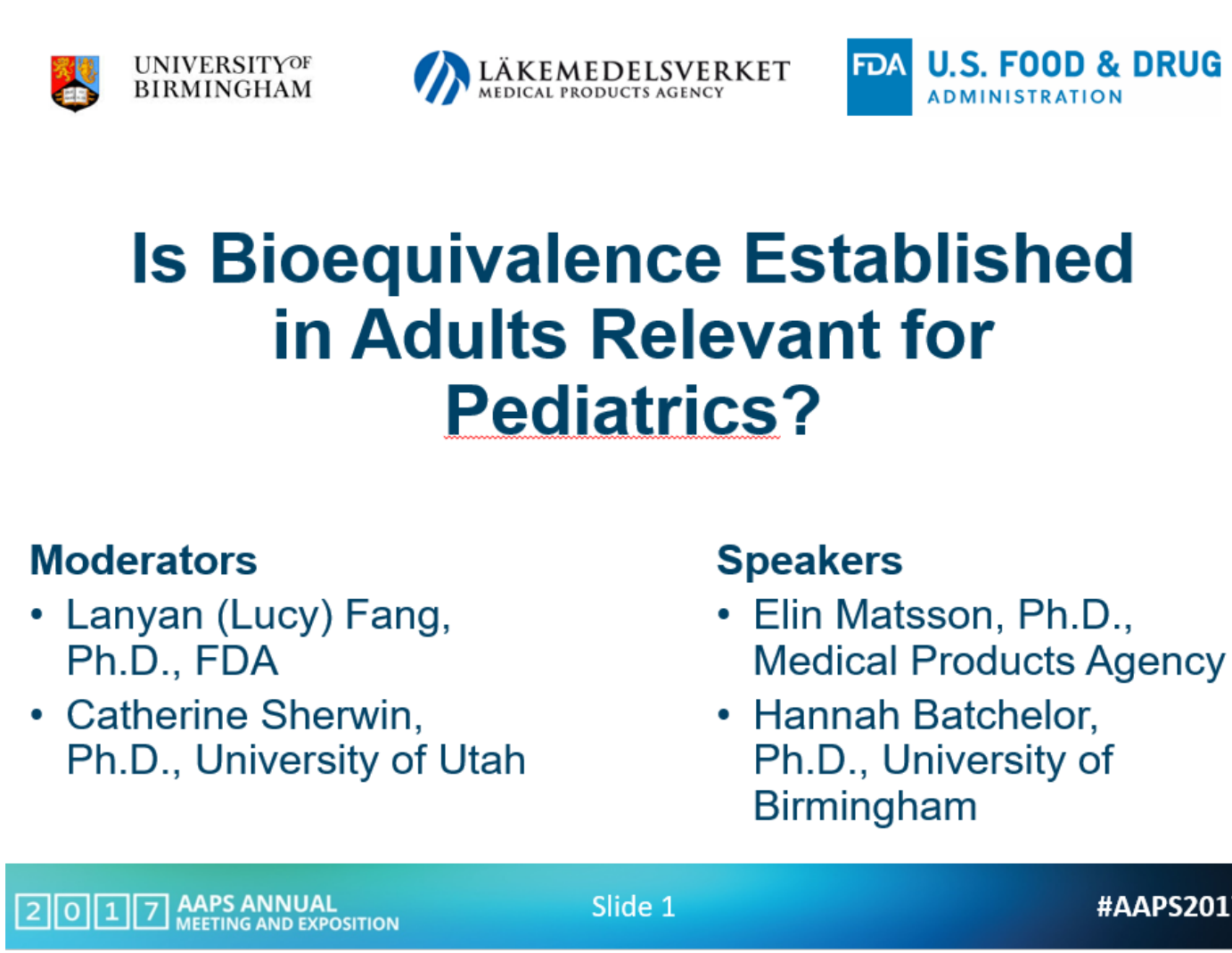
Session Description and Objectives

- This presentation will introduce a database containing the cases of pediatric products with reported bioinequivalence or disparities in pharmacokinetic (PK) profiles in bioequivalence and relative bioavailability studies conducted in pediatric populations to improve the understanding and identification of any common risk factors that may lead to PK differences observed.

- Upon completion, participants will be able to…..
- Explain the challenges and opportunities that we are facing when evaluating pediatric products during drug development
- List risk factors associated with the bioequivalence and relative bioavailability studies for pediatric products
- Implement in vitro biorelevant dissolution as well as modeling and simulations in assessing the risk for having undesired relative bioavailability or bioequivalence results in pediatrics

Biography and Contact Information

- Professor Hannah Batchelor is a pharmaceutical scientist who has worked in academia, the NHS and within pharmaceutical industry.
- She works on the design and manipulation of medicines to create age-appropriate drug formulations to maximise clinical efficacy in paediatric patients.
- Hannah is recognised as an expert in biopharmaceutics and leads the Academy of Pharmaceutical Scientists Focus group on biopharmaceutics in the UK as well as the European Paediatric Formulation Initiative's biopharmaceutics workstream.
- Hannah.batchelor@strath.ac.uk



Project initiated in 2017…

Are there any ways to predict “at risk” pediatric drug products?

- Usually BCS is used as a tool for risk management
- Assessment of risk
  - Likelihood of occurrence and the severity of the consequences?
- Regulatory Decision
  - Whether or not the risks are such that the project can continue with or without additional arrangements to mitigate the risk
- Acceptability of the Decision
  - Is the decision acceptable to society?

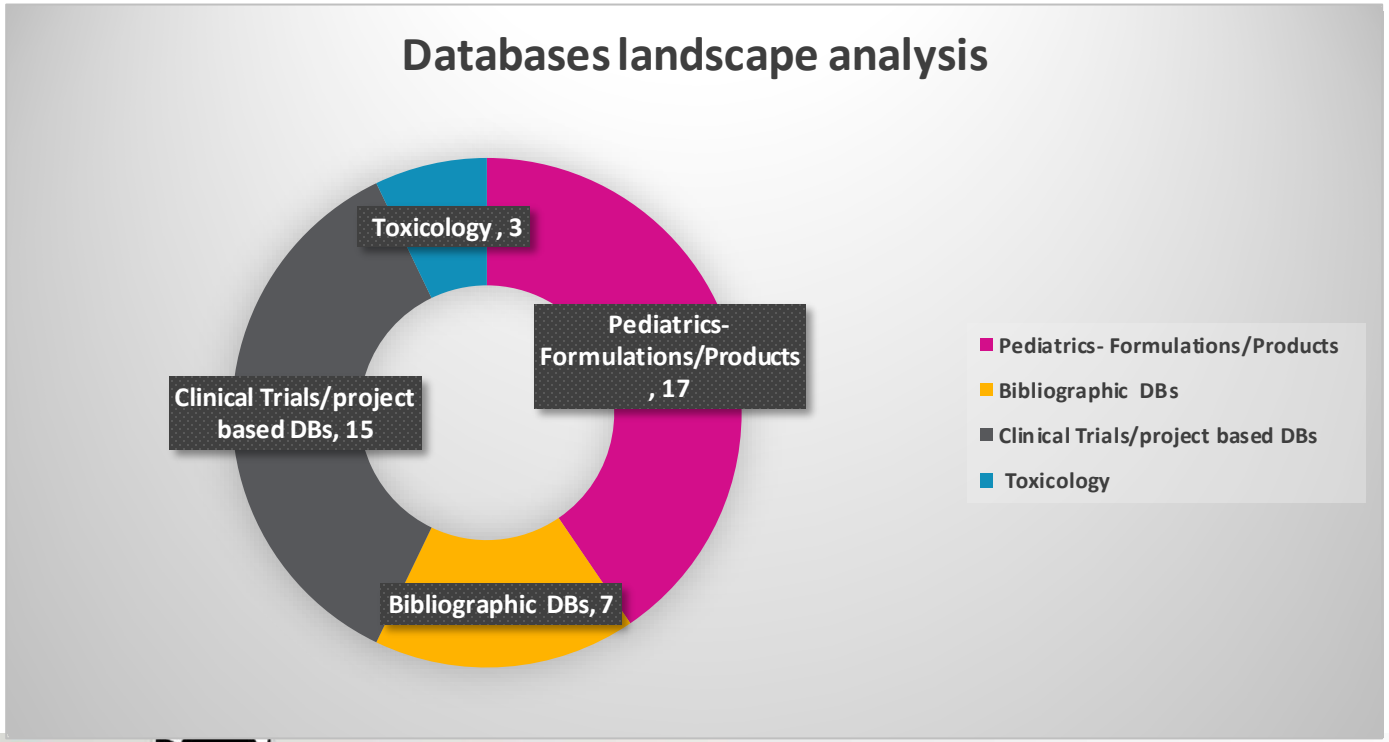
Key goals of project

Identify generic pharmaceutical products most at risk of suboptimal efficacy in pediatric patients

Use literature to scope evidence

Use *in vitro* and *in silico* models to generate additional evidence

Identification of literature



- We conducted a landscape analysis of databases/ datasets useful for data mining of relative bioavailability and bioinequivalence studies of adult and pediatric formulations.
- The scoping review helped to identify 42 databases.
- Example databases:
  - US FDA Databases, Clinical Trials.Gov, PubMed, Cochrane Library, FIP (BCS biowaivers monograph)

The following information was extracted:

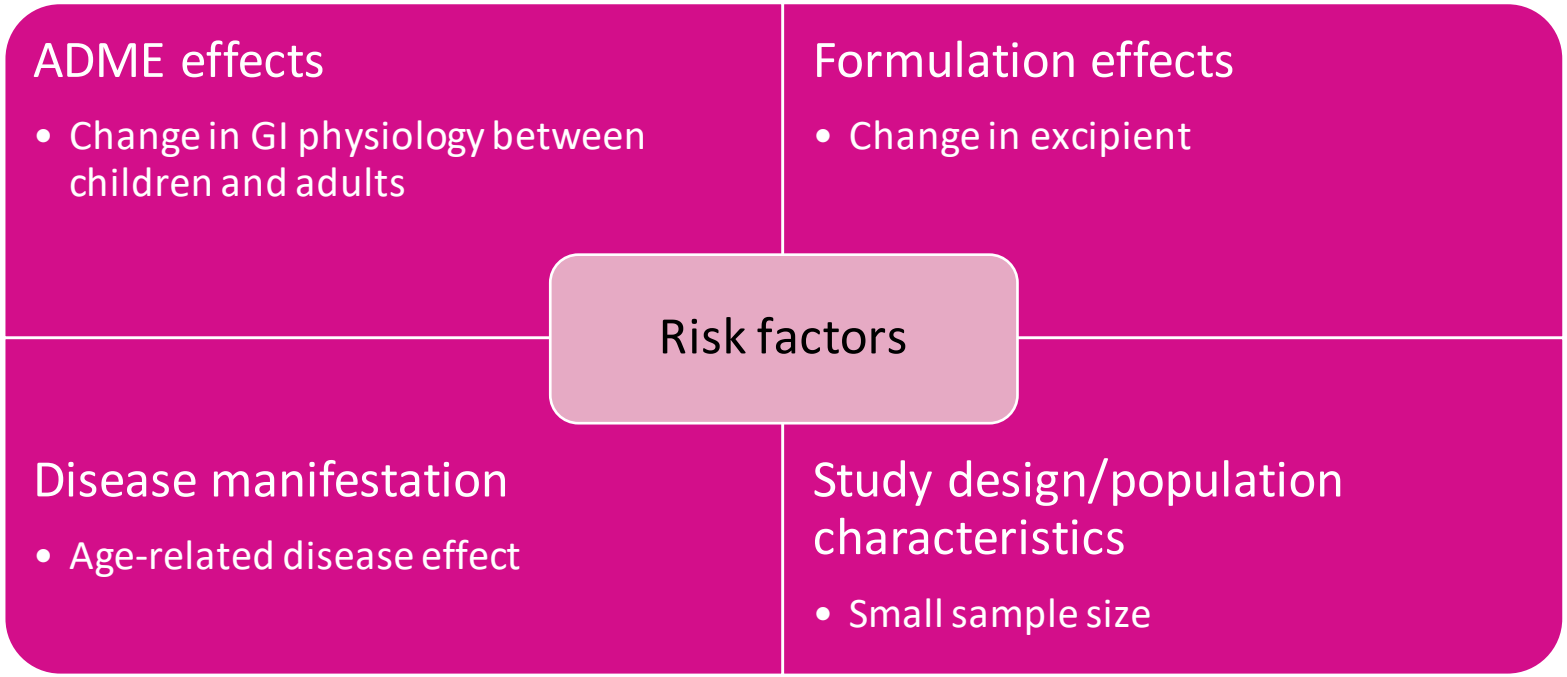
Study details	Study title; URL link; study design (i.e., randomized controlled, parallel or cross-over); sample size; dose administered; single or multiple dose
Study population	Age; Healthy/diseased state; Number of participants
Test and reference products	Dosage form and strength of the test and reference products (i.e. tablet, capsule etc.); pre-dosing manipulations (e.g. halving or quartering or crushing the tablets before administration)
Administration details	Fasted/Fed state; Volume of water consumed (mL)
Study results	90% CIs (80-125%) or geometric mean ratios (0.8-1.25) for both the test and reference medicines for the PK endpoints AUC and Cmax; statistics
Interpretations	Authors interpretation of data on product equivalence (Yes/No)
Risk factors for bioinequivalence	Original authors' reasons for bioinequivalence stated in the paper
Clinical impact of bioinequivalence	Authors interpretation of data on clinical equivalence (Yes/No)
Miscellaneous details	Clinical Trials registration ID.; Remarks; Reference

Risk factors for bioinequivalence

- The risk factors for bioinequivalence were extracted from the study data set based on the original authors' comments.
  - This could also include links to secondary references where authors interpreted their data in the context of wider literature.

The risk factors were then sorted into themes

ADME: Absorption, Distribution, Metabolism and Excretion.



Overview

- 78 clinical studies containing data from pediatric populations were identified using the search terms listed above and applying the inclusion and exclusion criteria

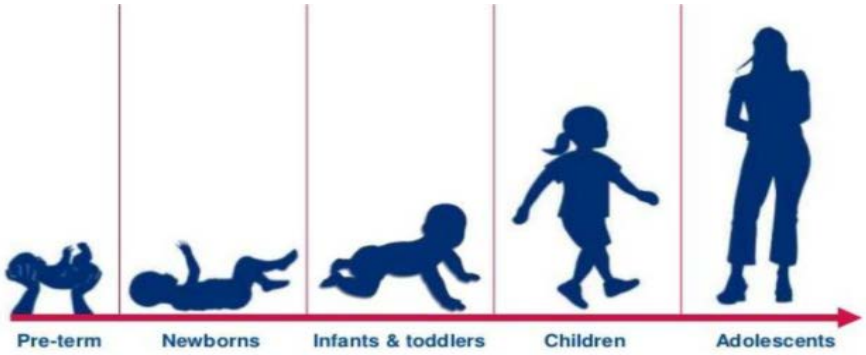
- A total of 40 studies with bioinequivalence results or different relative bioavailability between test and reference products remained for further analysis

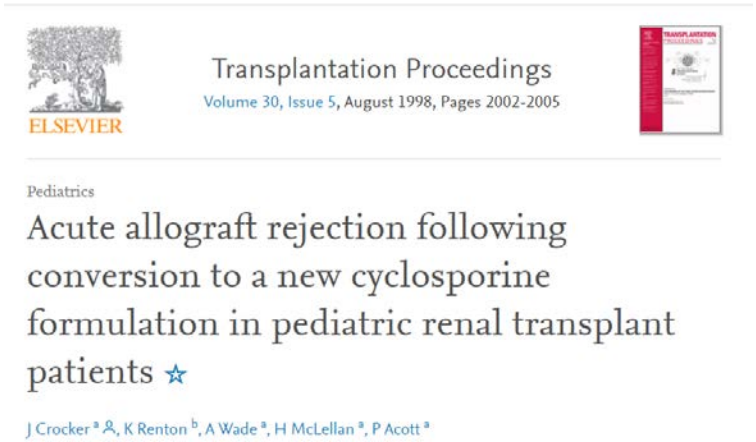
Putative risk factors reported to be associated with bioinequivalence or significant differences in PK parameters in relative BA studies in paediatrics

Physiological risk factors (ADME effect)

Age related absorption effects

- **GI Transit**




ELSEVIER
Transplantation Proceedings
Volume 30, Issue 5, August 1998, Pages 2002-2005
Pediatrics

Acute allograft rejection following conversion to a new cyclosporine formulation in pediatric renal transplant patients ☆

J Crocker [a] ✉, K Renton [b], A Wade [a], H McLellan [a], P Acott [a]

In children Neoral was rapidly absorbed and produced a high peak level of within 1 to 2 hours after dosing; Unique to pediatric patients, who generally have **increased GI motility**, and may be a feature unique to drugs like CyA with its dependence on metabolism in the GI tract

Drug substance and formulation effects

Our data demonstrate that not all liquid formulations of 6-MP are equivalent with respect to BA of parent drug. **Differences in formulation constituents, viscosity**, and potentially 6-MP concentration likely contribute to the variability observed in systemic drug availability from liquid formulations.

Pediatric Blood & Cancer

RESEARCH ARTICLE | Full Access

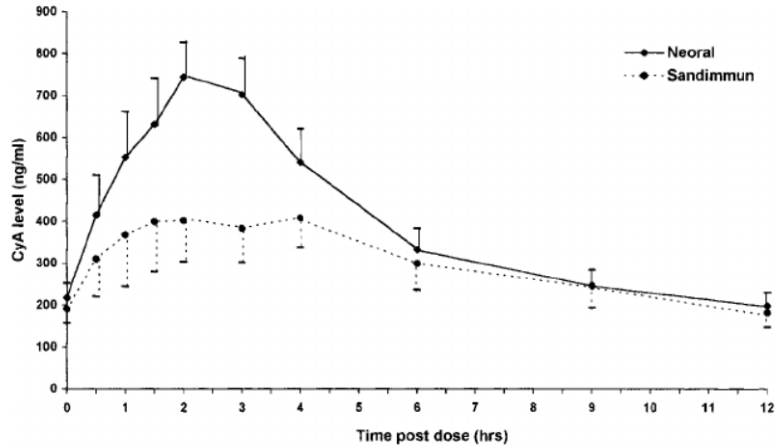
Pharmacokinetics of two 6-mercaptopurine liquid formulations in children with acute lymphoblastic leukemia

Jaszianne A. Tolbert, Shasha Bai, Susan M. Abdel-Rahman, Keith J. August, Scott J. Weir, Gregory L. Kearns, Kathleen A. Neville

First published: 10 March 2017 | https://doi.org/10.1002/pbc.26465 | Citations: 2

Disease manifestation and progression

The absorption of Sandimmune is affected by the type of biliary anastomosis and underlying disease



Comparison of Pharmacokinetics of Neoral and Sandimmune in Stable Pediatric Liver Transplant Recipients

Indra D.M. van Mourik, Mike Thomson,† and Deirdre A. Kelly**

Impaired gastrointestinal function, e.g., in cystic fibrosis where intestinal absorption is dependent on pancreatic enzyme supplementation, may also affect Sandimmune bioavailability.

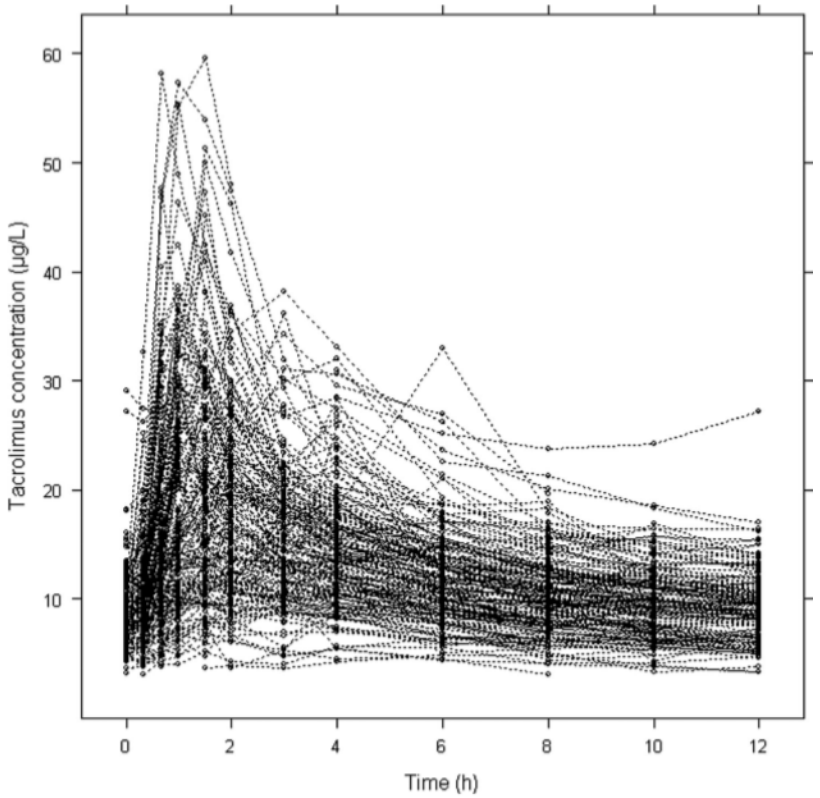
Population characteristics

High inter-individual variability was reported in several studies

Children are inherently variable due to maturation
Clinical studies conducted in children are not conducted in a “healthy” population

Examples of genetic polymorphism within the population

Inter and Intraindividual variabilities



Sikma et al., 2015

Non-equivalent dose and accuracy of administered dose

- Dose manipulation is common in pediatric studies
- Extemporaneous preparation is also common
- The use of divided adult FDC tablets in children therefore persists in many settings

J Antimicrob Chemother. 2009 Dec;64(6):1251-9. doi: 10.1093/jac/dkp358. Epub 2009 Oct 6.

Pharmacokinetics of nevirapine in HIV-infected children with and without malnutrition receiving divided adult fixed-dose combination tablets

Louisa Pollock [1], Laura Else, Goenke Poerksen, Elizabeth Molyneux, Peter Moons, Sarah Walker, William Fraser, David Back, Saye Khoo

Practical difficulties in dividing adult tablets, particularly into quarters, may also contribute to underdosing.

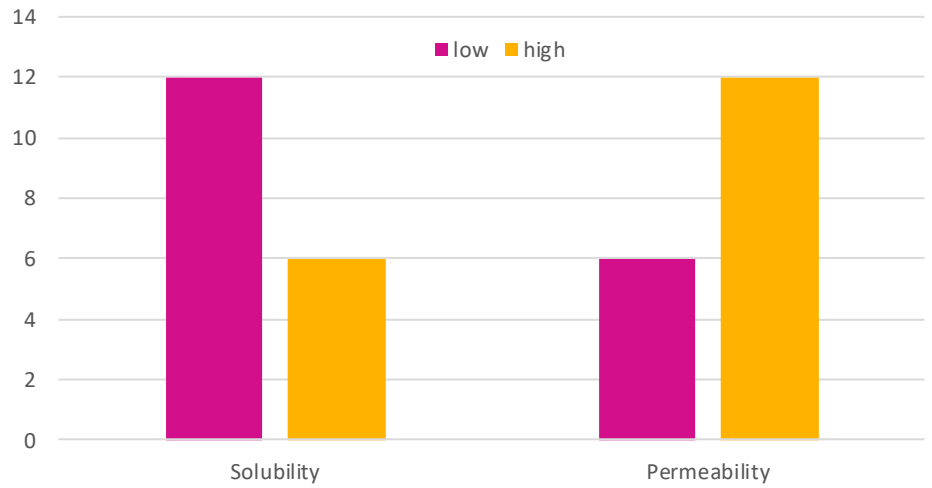
Overview of risk factors identified

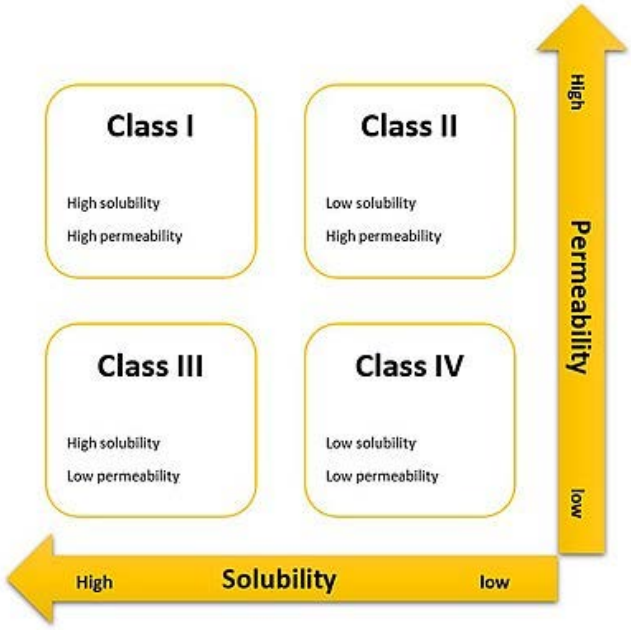
	Putative risk factors	Number of studies identified
Physiological factors (ADME effect)	Age-related absorption effects (e.g., Gastrointestinal (GI) motility, GI fluid volume or composition, GI transit time)	28
	Age-related distribution effects (e.g., protein binding)	2
	Age related metabolism or clearance 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 manifestation	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

Pawar G, Wu F, Zhao L, Fang L, Burckart GJ, Feng K, Mousa YM, Naumann F, Batchelor HK. Development of a Pediatric Relative Bioavailability/Bioequivalence Database and Identification of Putative Risk Factors Associated With Evaluation of Pediatric Oral Products. AAPS J. 2021 Apr 21;23(3):57. doi: 10.1208/s12248-021-00592-y.

Were there any common risk factors? BCS Classification

- Of those that showed bioinequivalence the following proportions were found:





Were there any common risk factors? NTI classification

- Narrow therapeutic index (NTI) drugs are defined as those drugs where small differences in dose or blood concentration may lead to dose and blood concentration dependent, serious therapeutic failures or adverse drug reactions.
- In this study NTI drugs identified were extracted from narrow therapeutic index drugs list from the Drug Bank
- ~28% of bioinequivalence studies were associated with NTI drugs (FDA listed)
- ~50% if we include other lists of NTI drugs

Figure 1A. Dose-Response Curves for Wide Therapeutic Index Medications

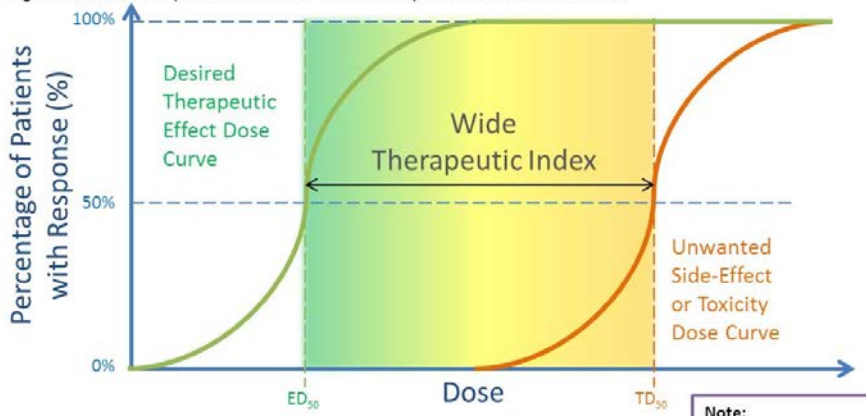
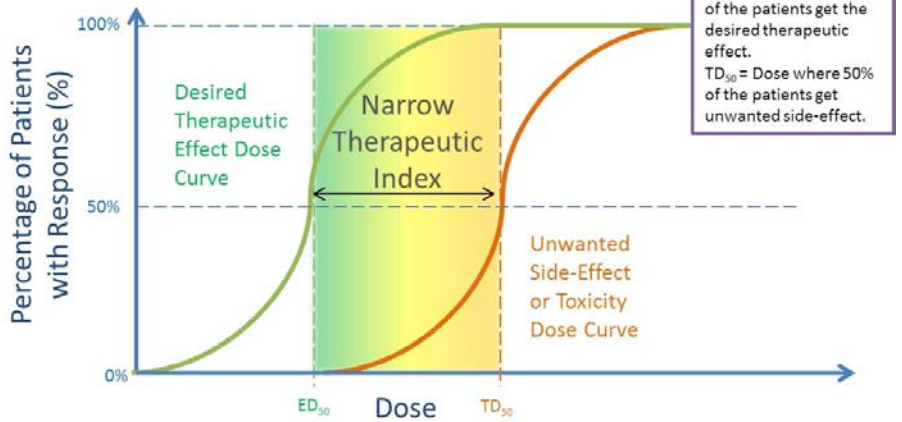
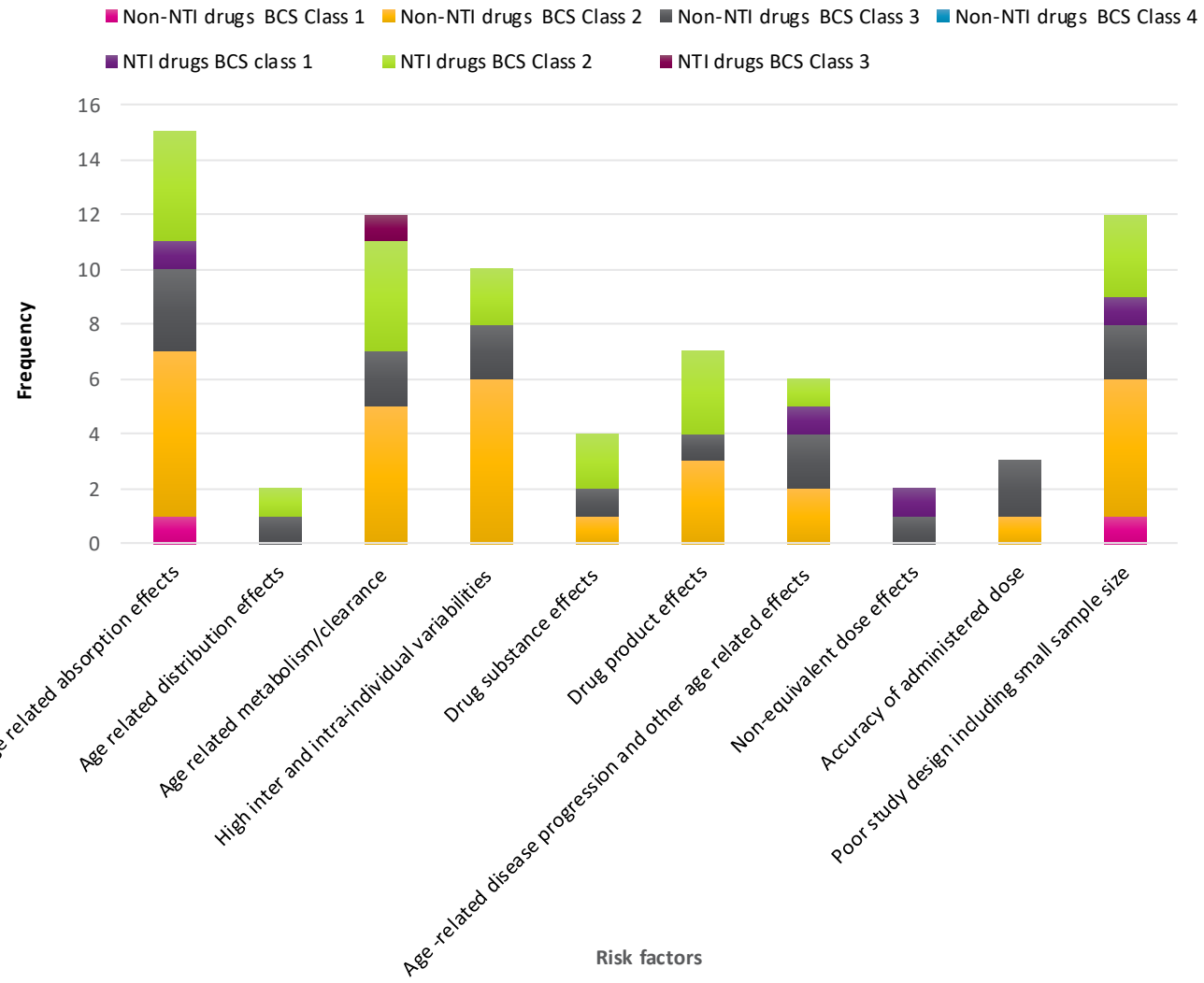


Figure 1B. Dose-Response Curves for Narrow Therapeutic Index Medications



Summary of risk factors



Limitations

- Risk factors are potential or putative and only based on the evidence reported within the literature.
- No proof-of-concept studies are conducted in children and it should also be borne in mind that bioinequivalence in due to the aforementioned risk factors does not mean therapeutic inequivalence of pediatric medicines
- It was not possible to generate sufficient data to stratify findings into subsets of the pediatric population (neonates, infants, children, and adolescents) yet this would be useful and additional data is needed to fully understand how risks of bioinequivalence change with age within the pediatric population

Future work

- Further work is required to also compare the magnitude of differences observed for the BE or rel BA data identified from the pediatric population with similar data from the adult population to fully evaluate the limitations of using adult data to predict the effects in pediatric populations.

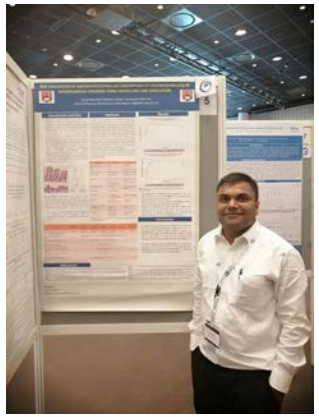
- Additional work is required to ensure that *in vitro* and *in silico* models account for subtle changes in GI physiology that can affect the absorption of drugs in pediatric populations; particularly GI motility and transit times.

Conclusion

This work has highlighted that particular care is required for poorly soluble, NTI drugs where bioinequivalence in pediatric populations was observed with greater frequency than in corresponding adult data sets. Drugs having low solubility are highly sensitive to bioinequivalence in pediatric populations.

Acknowledgments

- This work was supported by U.S. FDA Contract # HHSF223201810112C



Gopal Pawar

Marie-Christine Jones

Fang Wu,
Liang Zhao,
Lanyan Fang,
Gilbert J. Burckart,
Kairui Feng,
Youssef Mousa,

Questions

This slide will stay visible during your Q&A. You may add your contact information, a web address, or other information that participants would need to follow-up on your talk.

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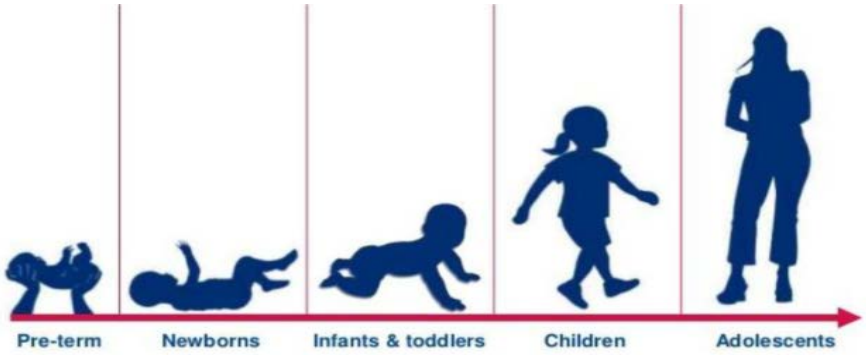
Putative risk factors reported to be associated with bioinequivalence or significant differences in PK parameters in relative BA studies in paediatrics

I. Physiological risk factors (ADME effect)

Age related absorption effects

- **GI Transit**



An emtricitabine capsule formulation provided 20% higher plasma exposure compared to the solution formulation in children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Antiviral Agents

Pharmacokinetics and Safety of Single Oral Doses of Emtricitabine in Human Immunodeficiency Virus-Infected Children

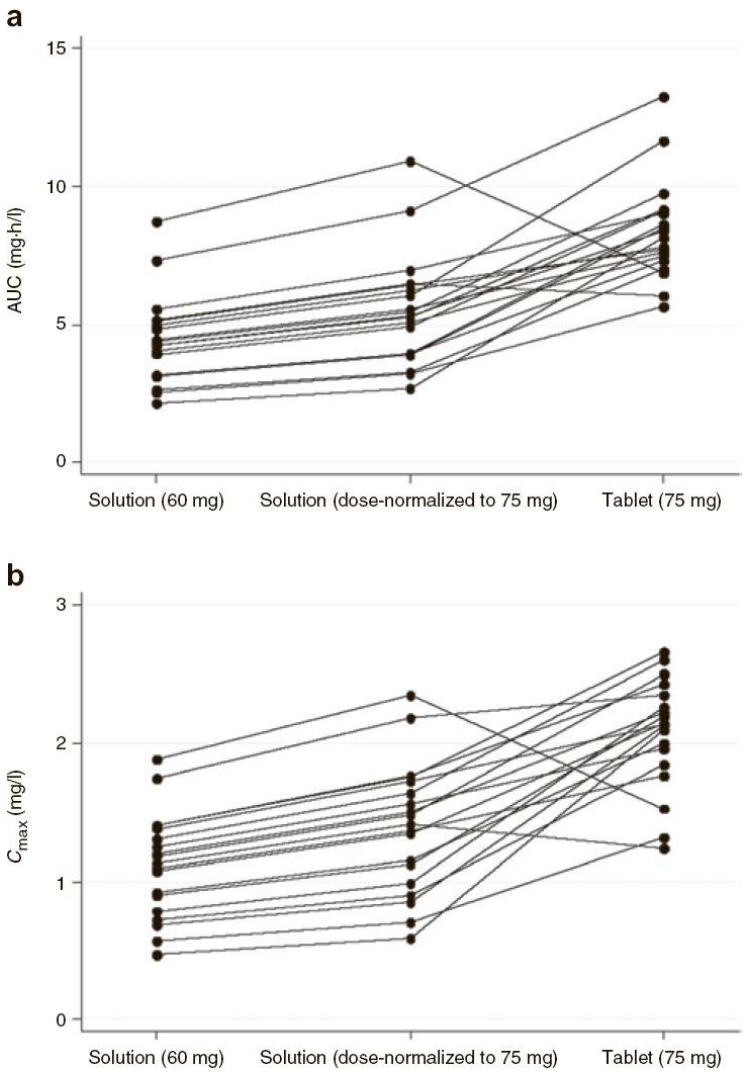
Laurene H. Wang, Andrew A. Wiznia, Mobeen H. Rathore, Gregory E. Chittick, Saroj S. Bakshi, Patricia J. Emmanuel, Patricia M. Flynn

DOI: 10.1128/AAC.48.1.183-191.2004

It is likely that the gastrointestinal transit time of the solution formulation is shorter than that of the capsule formulation, thereby reducing the mucosal contact time for emtricitabine to be absorbed.

- **Saturation of GI transporters**

The solution may lead to very high local concentrations of active components in children resulting in saturation of gastrointestinal membrane transporters.



Clinical Pharmacology & Therapeutics

Articles | Full Access

Pharmacokinetics of Antiretroviral Drug Varies With Formulation in the Target Population of Children With HIV-1

P Kasirye, L Kendall, K K Adkison, C Tumusiime, M Ssenyonga, S Bakeera-Kitaka, P Nahirya-Ntege, T Mhute, A Kekitiinwa, W Snowden, D M Burger, D M Gibb, A S Walker, ARROW Trial Team

First published: 21 December 2011 | https://doi.org/10.1038/clpt.2011.225 | Citations: 2

Age related distribution effects
Age related metabolism or clearance effects

Proposed reasons for these differences include differences in first pass metabolism; changes in hepatic metabolism including the cytochrome p450 system with age; volume of distribution; and blood protein binding

Absorption

Distribution (Blood)

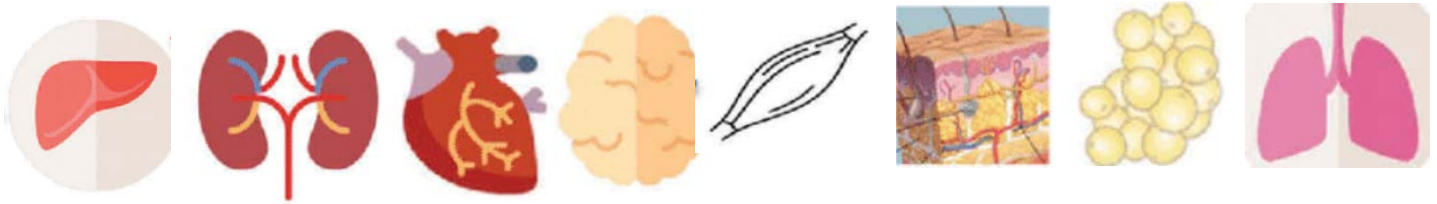
Plasma Level
Bound->-< Free
(Plasma protein)

- ⬇ Total body water
- ⬇ Lean body mass
- ⬆ Body fat
- ⬇ Serum albumin
- ⬇ Protein binding

Original Article | Full Access

Transition from brand to generic tacrolimus is associated with a decrease in trough blood concentration in pediatric heart transplant recipients

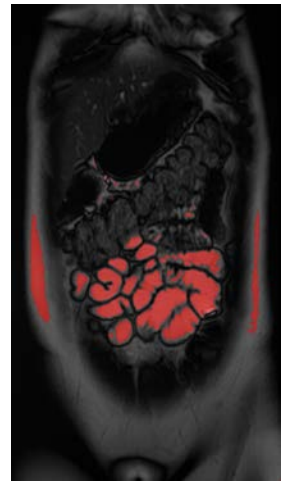
Son Q. Duong, Ashwin K. Lal, Rujuta Joshi, Brian Feingold, Raman Venkataramanan



Liver Kidney Heart Brain Muscle Skin Adipose Lung

I. Drug substance and formulation effects

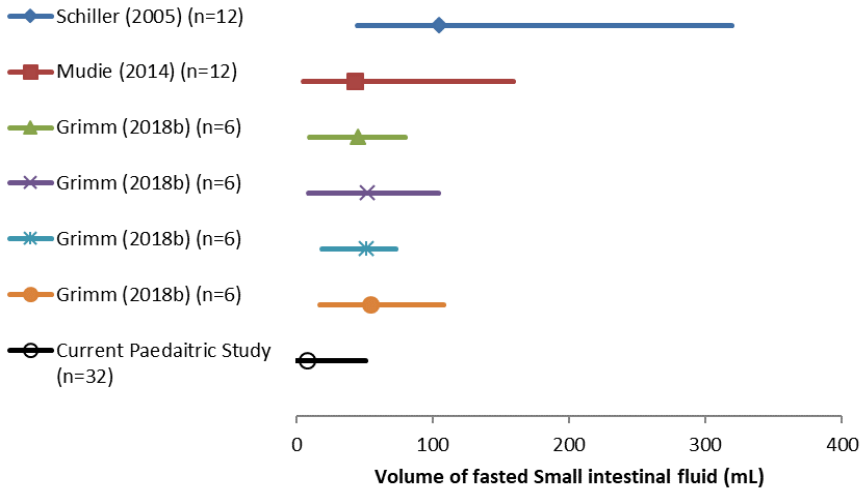
We therefore hypothesise that the differences observed in bioavailability are due to the **mixture of polymorphic forms** of RMP in R-Cin that was not favourable for absorption. The water **solubility** of RMP is reported to vary eight-fold depending on the crystalline state of the material, altered particle size affects solubility, and altered solubility is likely to affect **bioavailability**.



Published in final edited form as:
Int J Tuberc Lung Dis. 2016 July ; 20(7): 915–919. doi:10.5588/ijtld.15.0833.

Bioavailability of two licensed paediatric rifampicin suspensions: implications for quality control programmes

H. McIlleron*, H. Hundt*, W. Smythe*,†, A. Bekker‡, J. Winckler§, L. van der Laan‡, P. Smith*, H. J. Zar§,¶, A. C. Hesseling‡, G. Maartens*, L. Wiesner*, and A. van Rie#,**



Poor study design including small sample size

Risk factors include

- Underpowered study design
- Non-randomized study design
- Parallel study arms
- Retrospective study design