Is Bioequivalence Established in Adults Relevant for Pediatrics?

Moderators

- Lanyan (Lucy) Fang, Ph.D., FDA
- Catherine Sherwin, Ph.D., University of Utah

Speakers

- Elin Matsson, Ph.D., Medical Products Agency
- Hannah Batchelor, Ph.D., University of Birmingham

Session Description and Objectives

Dialogue and Debate

- Two short focused presentations followed by discussions to explore the topic:

  “Is bioequivalence established in adults relevant for pediatrics?”

Learning Objectives

- Identify the drug products that are most at risk of lack of bioequivalence in pediatric populations
- Discuss tools that can be used to identify and mitigate such risks in development pathways to refine relative bioequivalence studies for pediatric products

Dr Elin Matsson
Medical Products Agency

- Pharmacokinetics Assessor, Medical Products Agency (MPA), Sweden

- ORISE Fellow (2016-2017), Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, CDER, FDA

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Disclaimer

The views expressed in this presentation are my own and do not necessarily reflect the official policy of the MPA, EMA or FDA.

For discussion today

- What is our degree of certainty that differences in oral absorption from the formulation in pediatric patients are correctly detected in adult volunteers?
- How do we identify drug products where we potentially should be cautious?
- What would be our approach if high risk products are identified?

Outline

- Background
  - New *vs* generic drug products
  - Current guidance recommendations
  - BCS concept in adults and children
  - Risk factors
- Moderated case study
- Discussion and wrap up

Background

Terminology used in this presentation

Bioequivalence

- 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
- Specified criteria for comparisons between test and reference products and predetermined BE limits for such criteria

Relative bioavailability

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

New drug products *vs* Generic drug products

New drug products: pediatric formulation development

Relative bioavailability studies

- 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

Differences from generic drug products include:

- Potentially greater changes in formulation
- Followed by determining the PK, safety and potentially efficacy in children

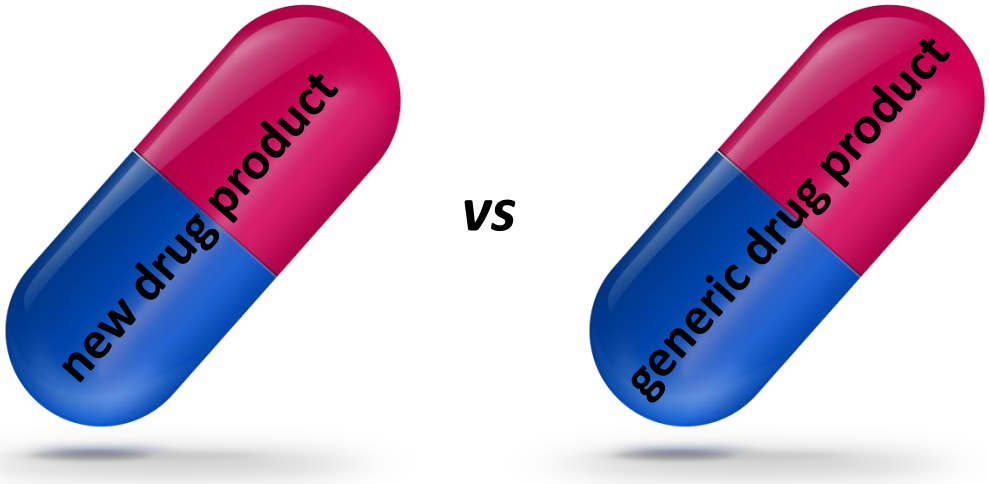
Similarities to generic drug products include:

- Biowaiver may be applicable for BCS I/III IR formulations

New drug products *vs* Generic drug products

Generic drug products with pediatric indication

- Approval frequently supported by bioequivalence studies with AUC and Cmax as pharmacokinetic endpoints
- Pharmacokinetic data are not collected in children
- Biowaiver may be applicable for BCS I/III IR formulations



Guidance recommendations

Relative bioavailability 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 paediatric 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 paediatric population**.

Guidance recommendations, cont.

EMA Bioequivalence studies for bridging paediatric 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 paediatric population**.

- *Do you consider that a justification for extrapolating PK bridging data from adults to children is needed?*
- *If so, what would you consider as appropriate justification?*

Guidance recommendations

Bioequivalence studies

(generic drug products)

FDA guidance

- 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**.
- If a drug products is intended for use in both sexes, the applicant should include similar proportions of males and females in the study.
- If the drug product is predominantly intended **for use in the elderly**, the applicant should include as many subjects as possible at or above the age 60.

EMA expert meeting on the development of fixed-dose combinations for the treatment of HIV infection in children

"…the predictive capacity of bioequivalence data in adults for paediatric formulations should be carefully considered in particular when a different formulation technology/composition is used in the paediatric formulation for a poorly soluble and/or permeable drug or where the dose mg/kg is higher in children (or a particular age-subset) than in adults due to higher clearance in children."

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 January 2016
EMA/766040/2015
Human Medicines Research and Development Support Division

Report of the expert meeting on paediatric development of fixed-dose combinations (FDCs) for the treatment of human immunodeficiency virus (HIV) infection

European Medicines Agency, London, 10 November 2015

The lamivudine case

- The ARROW trial provided an opportunity to post-approval collect PK data in children switching from solution to tablet
- In children, the bioavailability after the solution was ~40% lower compared to the tablet formulation
- In adults, the two formulations were bioequivalent

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

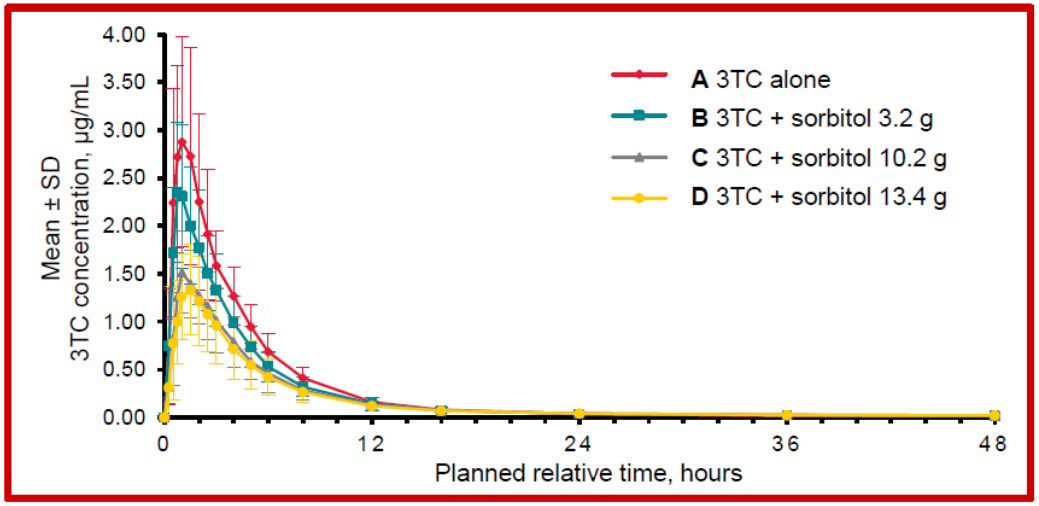
P Kasirye[1], L Kendall[2], KK Adkison[3], C Tumusiime[4], M Ssenyonga[4], S Bakeera-Kitaka[1], P Nahirya-Ntege[5], T Mhute[6], A Kekitiinwa[1], W Snowden[7], DM Burger[8], DM Gibb[2] and AS Walker[2]; on behalf of the ARROW Trial Team

The bioequivalence of formulations is usually evaluated in healthy adult volunteers. In our study in 19 HIV-1-infected Ugandan children (1.8–4 years of age, weight 12 to <15 kg) receiving zidovudine, lamivudine, and abacavir solutions twice a day for ≥24 weeks, the use of scored tablets allowed comparison of plasma pharmacokinetics of oral solutions vs. tablets. Samples were collected 0, 1, 2, 4, 6, 8, and 12 h after each child's last morning dose of oral solution before changing to scored tablets of Combivir (coformulated zidovudine + lamivudine) and abacavir; this was repeated 4 weeks later. Dose-normalized area under curve $(AUC)_{0-12}$ and peak concentration (C_{max}) for the tablet formulation were bioequivalent with those of the oral solution with respect to zidovudine and abacavir (e.g., dose-normalized geometric mean ratio (dnGMR) (tablet:solution) for zidovudine and abacavir AUC_{0-12} were 1.01 (90% confidence interval (CI) 0.87–1.18) and 0.96 (0.83–1.12), respectively). However, lamivudine exposure was ~55% higher with the tablet formulation (AUC_{0-12} dnGMR = 1.58 (1.37–1.81), C_{max} dnGMR = 1.55 (1.33–1.81)). Although the clinical relevance of this finding is unclear, it highlights the impact of the formulation and the importance of conducting bioequivalence studies in target pediatric populations.

Epivir, label 12.3

The relative bioavailability of EPIVIR oral solution is approximately 40% lower than tablets containing lamivudine in pediatric subjects despite no difference in adults. The mechanisms for the diminished absolute bioavailability of lamivudine and relative bioavailability of lamivudine solution are unknown.

The lamivudine case: an effect of sorbitol?



PK Parameter	Ratio of Geometric Least Squares Means (90% CI)		
	B vs A[a] N=16	C vs A[a] N=16	D vs A[a] N=16
$AUC_{(0-24)}$	0.803 (0.747, 0.864)	0.608 (0.566, 0.655)	0.557 (0.518, 0.599)
$AUC_{(0-\infty)}$	0.855[b] (0.799, 0.914)	0.677 (0.635, 0.721)	0.637[c] (0.594, 0.682)
C_{max}	0.724 (0.657, 0.798)	0.479 (0.434, 0.527)	0.454 (0.412, 0.500)

C_{max}, maximum observed concentration; T_{max}, time of C_{max}; $AUC_{(0-24)}$, area under concentration-time curve from time zero to 24 hours; $AUC_{(0-\infty)}$, AUC from time 0 extrapolated to infinity. [a]Treatment A: 3TC alone; treatment B: 3TC + sorbitol 3.2 g; treatment C: 3TC + sorbitol 10.2 g; treatment D: 3TC + sorbitol 13.4 g. [b]n=14. [c]n=13.

- Poster presented at the Conference on Retrovirus and Opportunistic Infections, Seattle, 2017
- Adkison et al., “Effect of sorbitol on lamivudine pharmacokinetics following administration of Epivir solution in adults”

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

Risk factors	Comment
Age of target population	
Exposure-Response	
Biowaiver approach applicable?	
Manipulation of products expected?	

Risk factors that are related to
- drug substance
- drug product
- patient population

We will get back to this slide during wrap up of the discussion

General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Gilbert J. Burckart at 301-796-2065.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2014
Clinical Pharmacology

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Ethical considerations!

Dr Hannah Batchelor
University of Birmingham

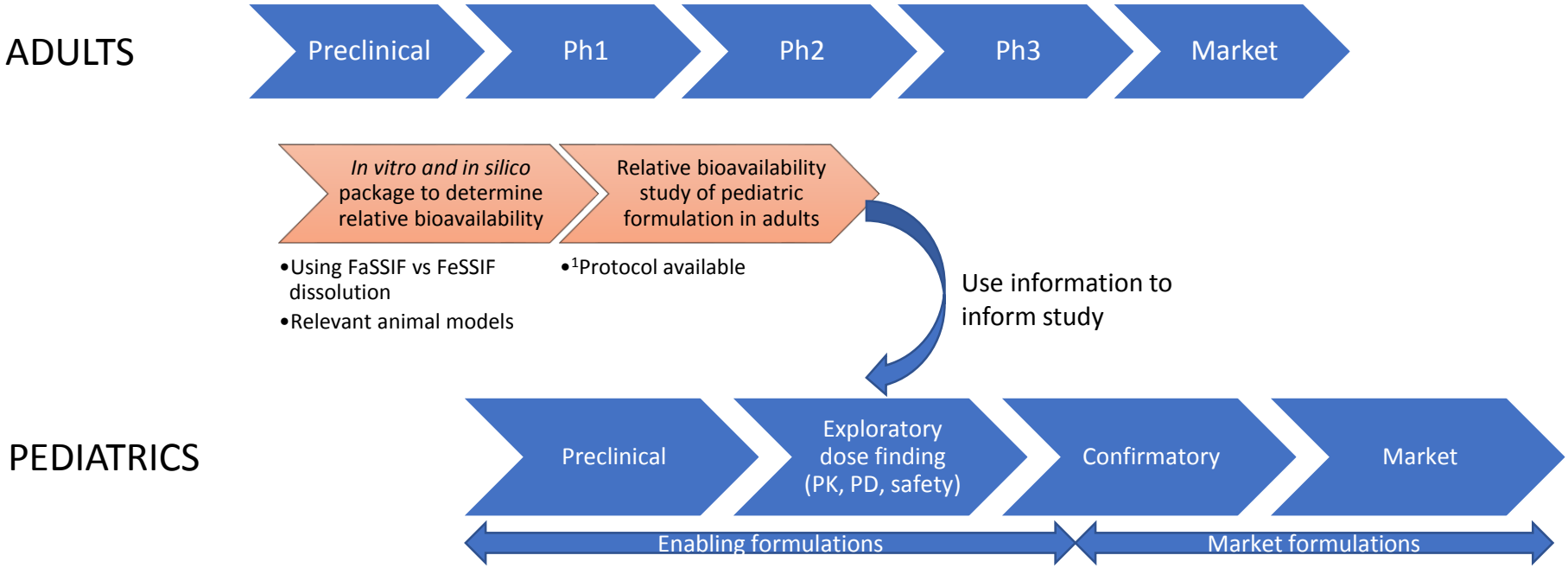
- Previously worked in Pharmaceutical Industry, Healthcare setting for clinical trials and within academia.
- Authored several papers on age-appropriate formulations for children
- Lead for the Biopharmaceutics workstream of the European Paediatric Formulation Initiative, EuPFI

UNIVERSITY OF BIRMINGHAM

EuPFI European Paediatric Formulation Initiative

What do we know about bioequivalence/ relative bioavailability in adults that is relevant to pediatrics?

Typical bridging from adult to pediatric formulation

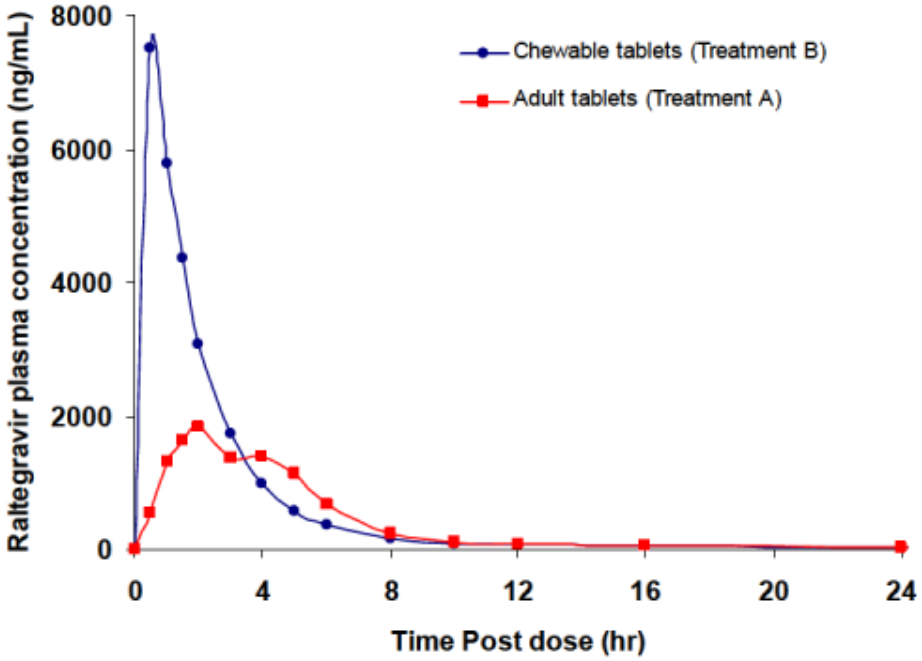


No guidance to support *in vitro* or *in silico* risk assessment to understand relative bioavailability

No clear protocol to undertake study

Key risks: Paediatric formulation effect

Figure 10 Mean plasma concentration-time profile of single dose 400 mg raltegravir administered under fasting conditions using poloxamer tablets (A) versus chewable tablets (B) (n=12).



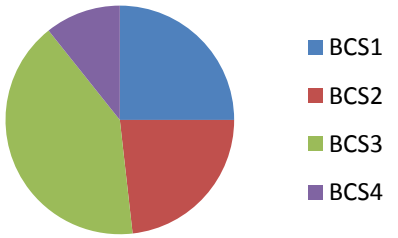
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/203045Orig1s000ClinPharmR.pdf

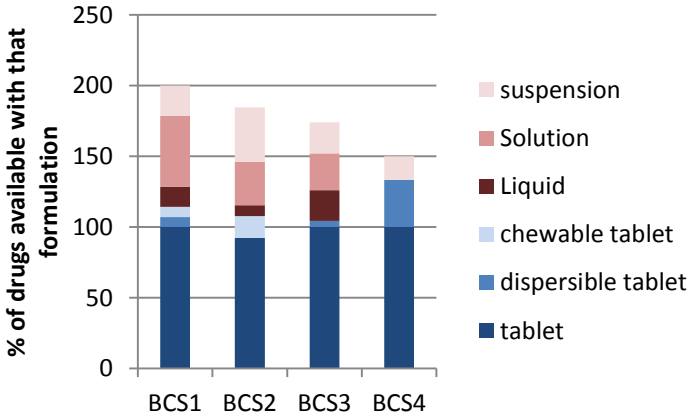
Are there any ways to predict “at risk” pediatric drug products?

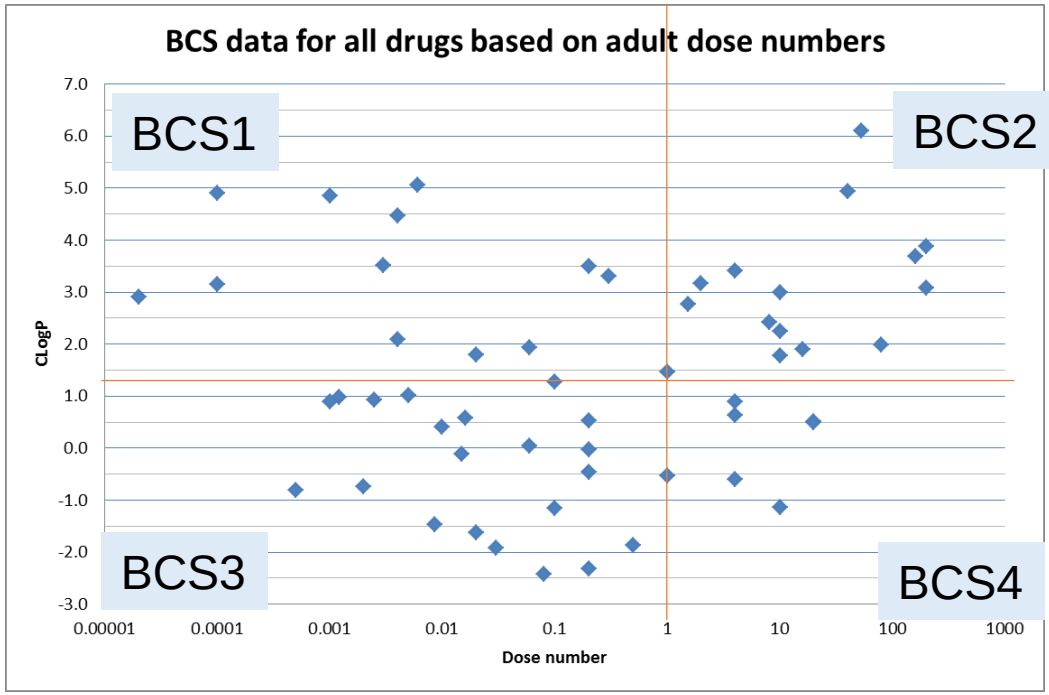
- Usually BCS is used as a tool for risk management
- Assessment of risk
  - Likelihood of occurrence and the severity of the consequences?
- Regulatory Decision
  - whether or not the risks are such that the project can continue with or without additional arrangements to mitigate the risk
- Acceptability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

BCS classification of paediatric drugs

- This chart combines drugs listed on the core WHO essential medicines list and those where a paediatric formulation is available according to the FDA website (n=56)



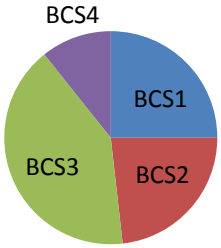




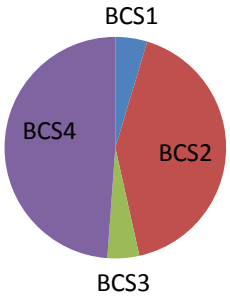
Adult vs Neonate

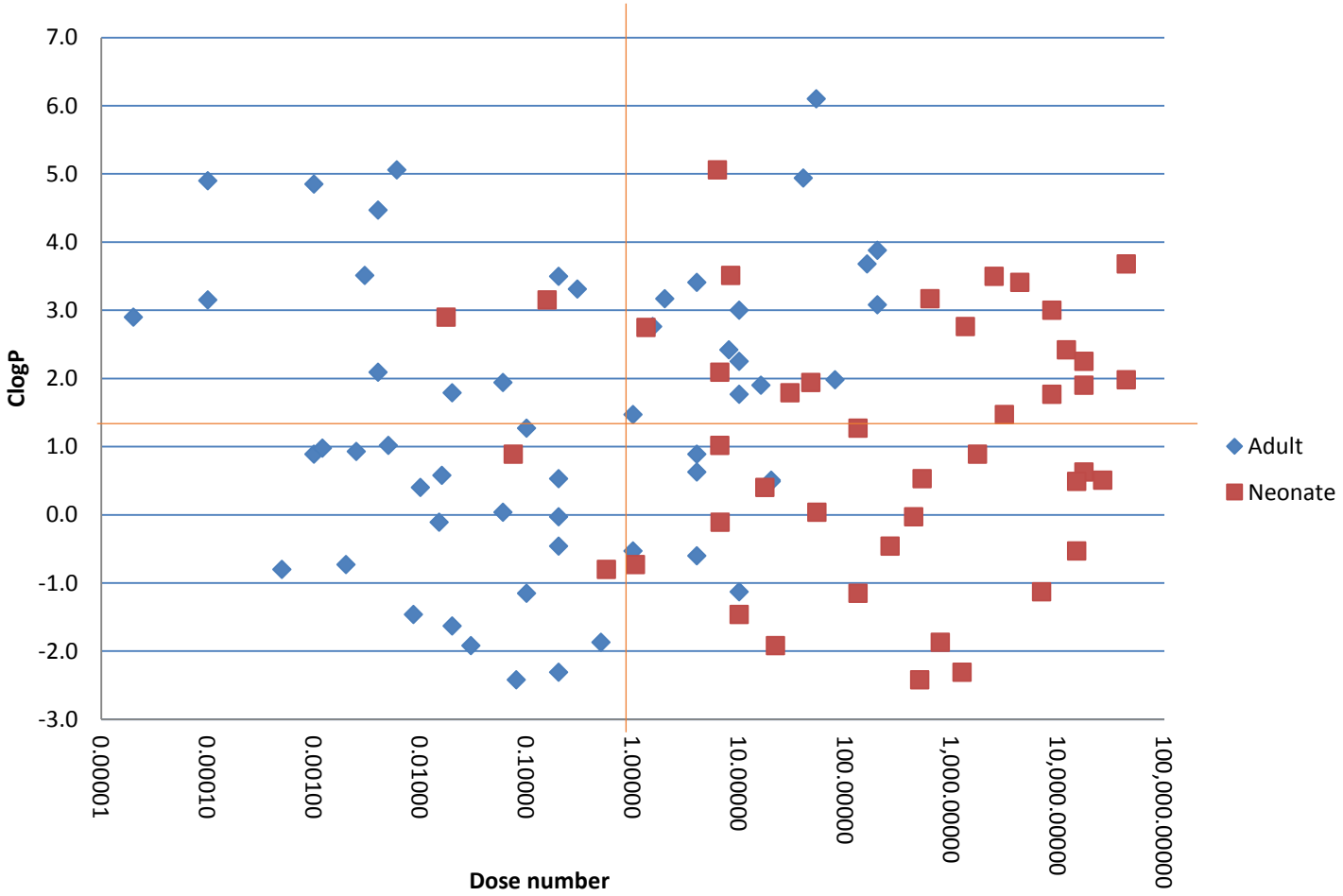
Amidon criteria of 25mL

Adult



Neonate





Key risks: Drug product
Regulatory Bioequivalence: An Overview

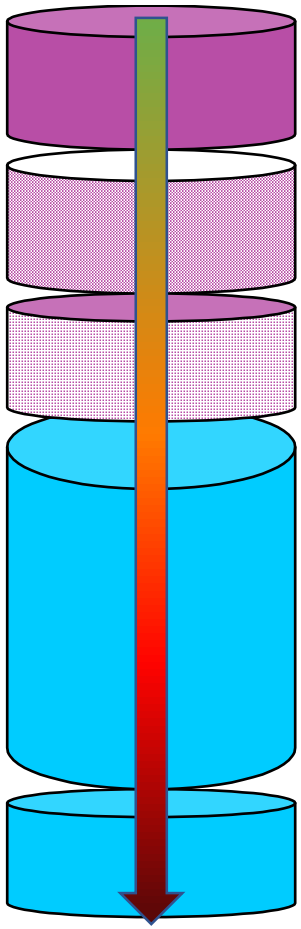
Solutions

Suspensions

Chewable, etc.

Conventional Tablets Capsules

MR Products



"Self-evident" - Biowaivers granted
Condition- excipients do not alter absorption (historical data)

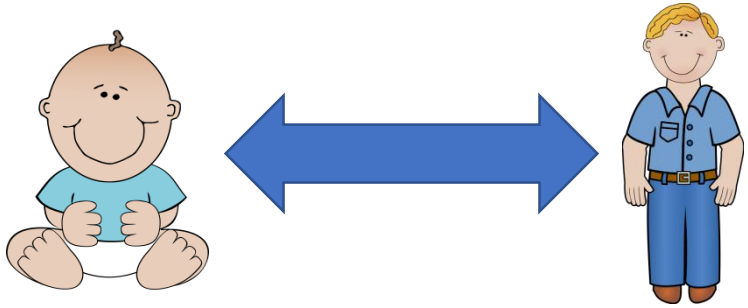
Pre-1962 DESI Drugs: *In Vivo* evaluation for "bio-problem" drugs (TI, PK, P-Chem)
Post-1962 Drugs: Generally *In Vivo* - some exceptions (IVIVC..)

SUPAC-IR (1995)
Dissolution-IR
BCS
(pre-/post approval)

In VIVO

SUPAC-MR
IVIVC

Key risks: patient



Absorption

Slow and irregular gastric emptying

Intestinal surface area

Intestinal transit time

Impact of food

Blood flow changes

Distribution

Increased total body water

Decreased total body fat

Altered blood flow

ADME

Metabolism

Ontogeny of intestinal transporters

Ontogeny of hepatic transporters

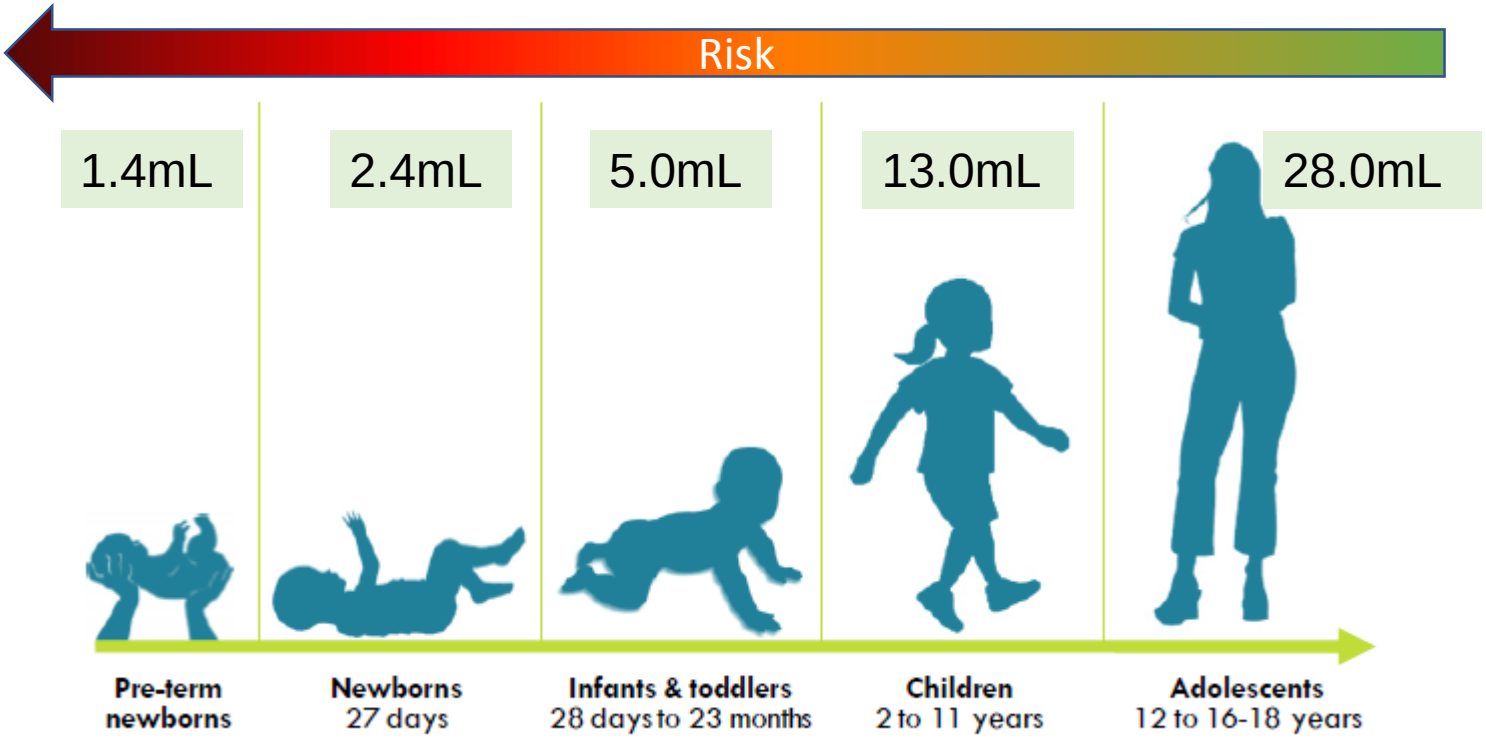
Elimination

Renal function

Hepatic function

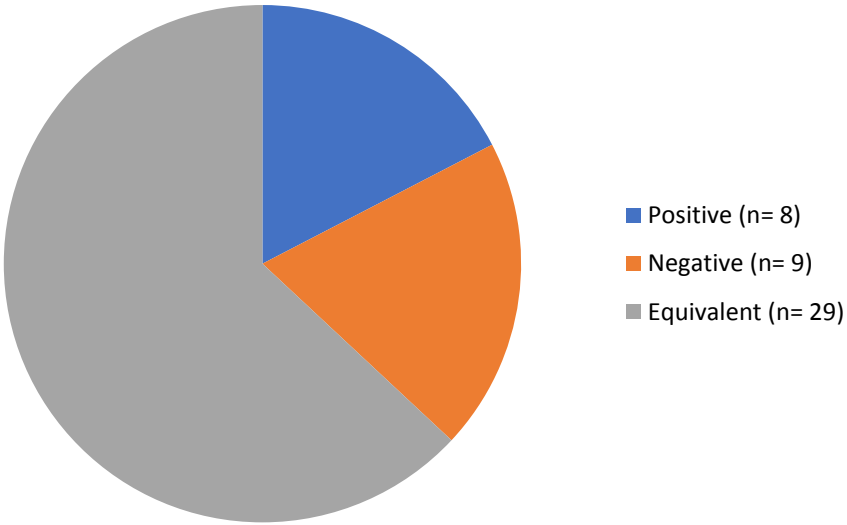
Key risks: Age

- *Example:* Solubility and dissolution media - volume
  - The volume of gastric fluids in children is not widely reported although a value of approximately 0.56mL/kg has been reported in fasted children
  - Equates to a volume of 37.1mL in adults



What information is in the literature?

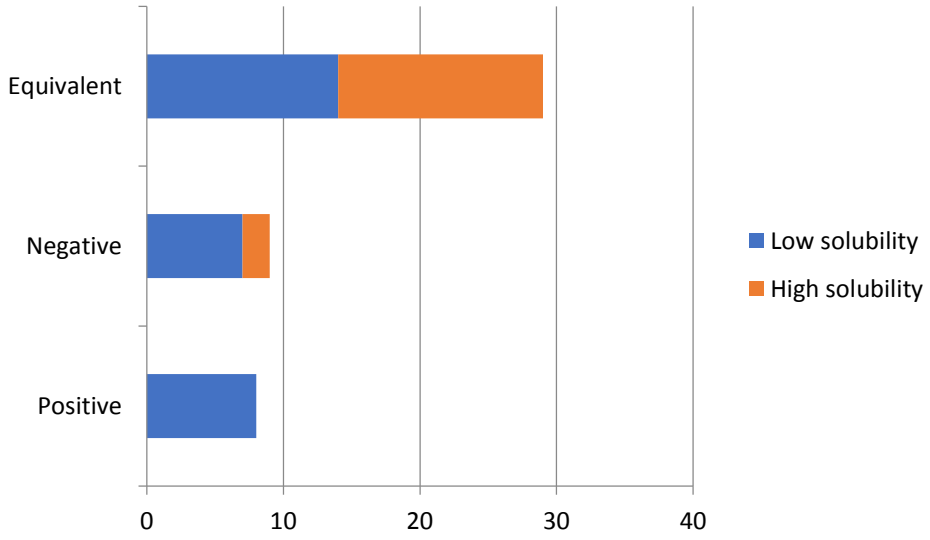
- 46 literature studies identified that compared the relative bioavailability of paediatric medicines



Positive effect means that the relative bioavailability of the pediatric formulation was higher than the reference

In total 63% of pediatric formulations showed comparable PK profiles

Did solubility affect likelihood of equivalence?

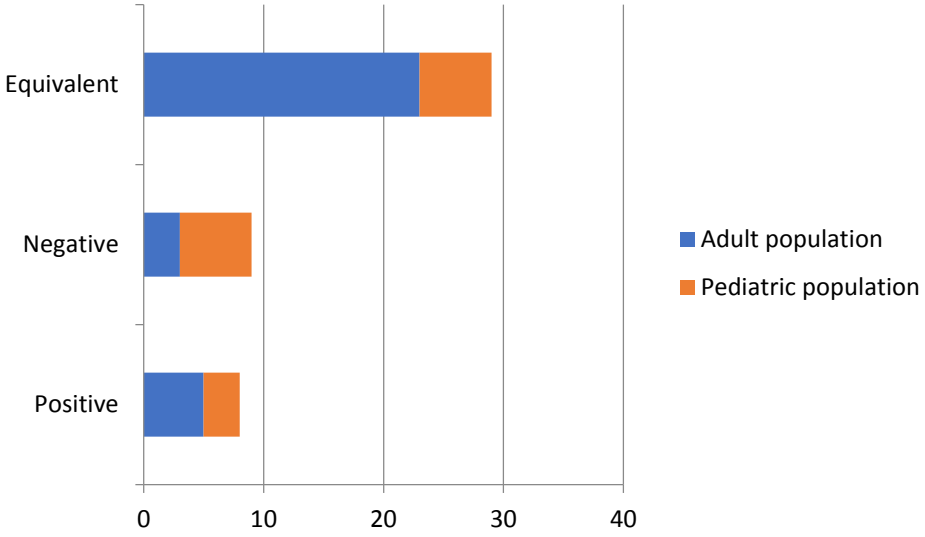


- Highly soluble compounds more likely to show equivalent PK profiles

Key risks: drug solubility

- 88% of studies (15/17) showed equivalence in paediatric to adult product where drug was high solubility
  - BCS 1 or 3
- 48% of studies (14/29) showed equivalence in paediatric to adult product where drug was low solubility
  - BCS 2 or 4

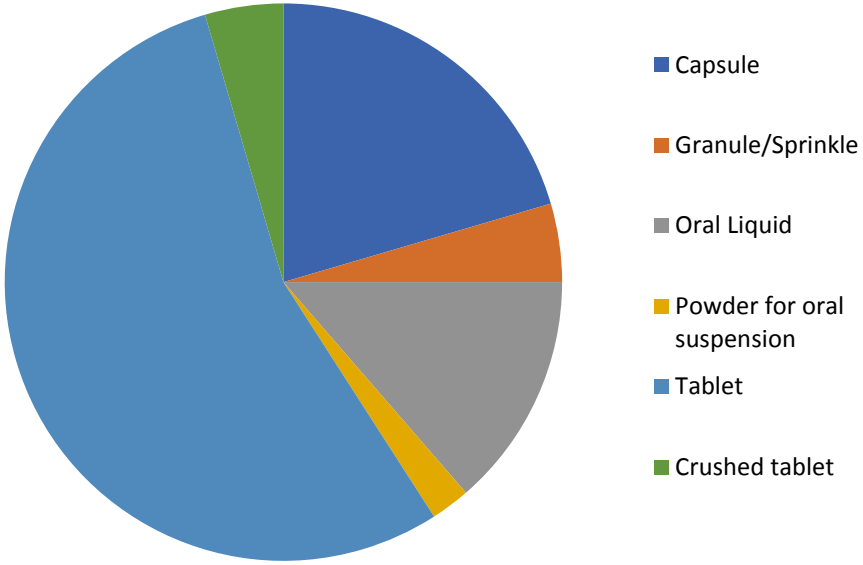
Did population affect likelihood of equivalence?



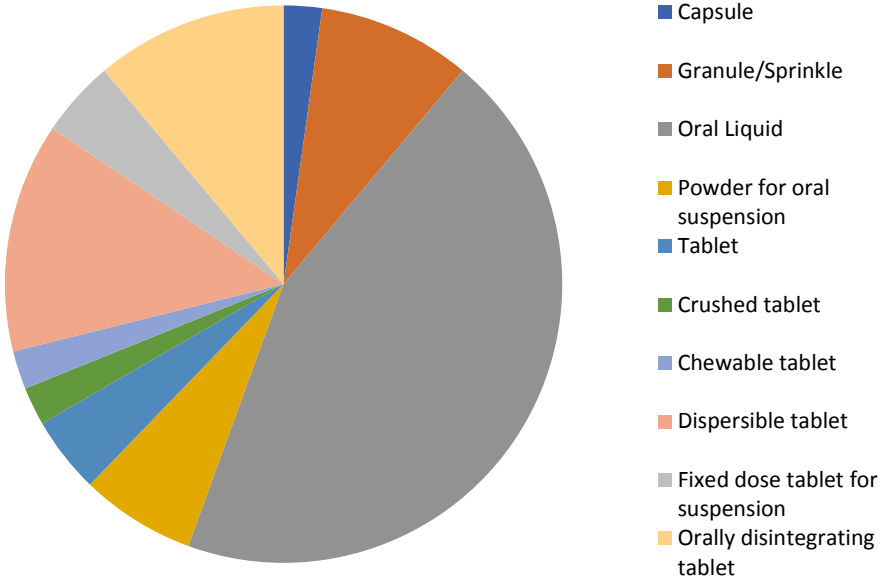
- In total 21/46 studies were conducted in pediatric populations
- Greater likelihood of showing equivalent PK in an adult population

Did formulation affect likelihood of equivalence?

Reference formulation

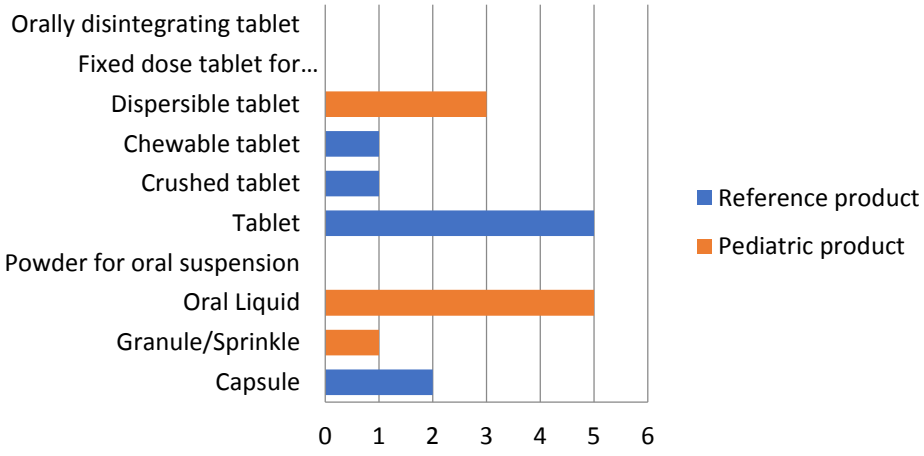


Pediatric formulation

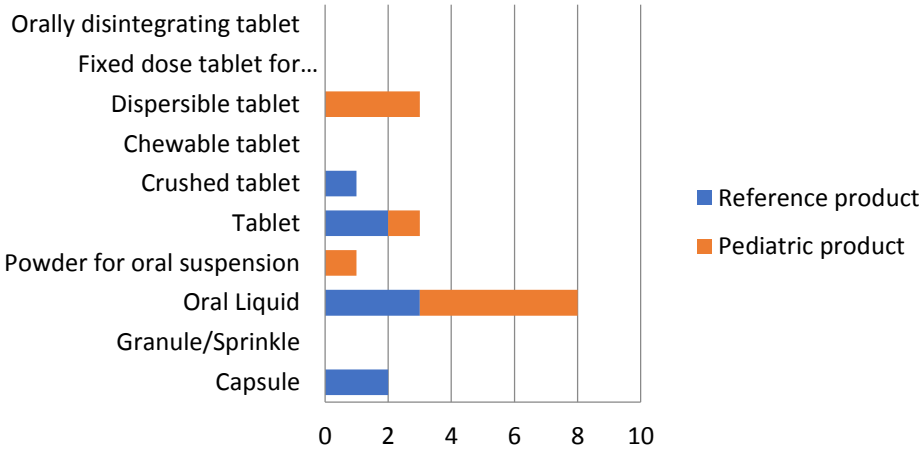


Did formulation affect likelihood of equivalence?

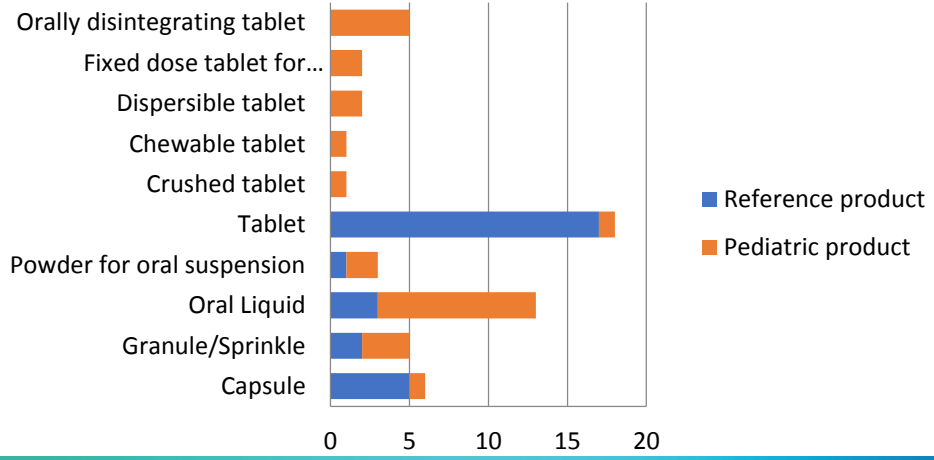
Pediatric showed lower exposure



Pediatric showed higher exposure



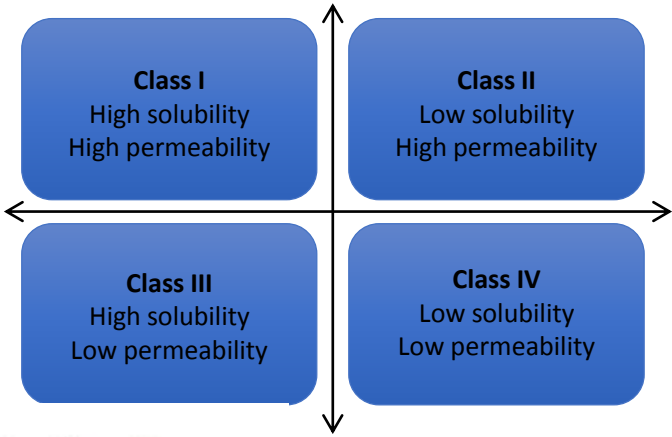
Pediatric showed equivalent exposure

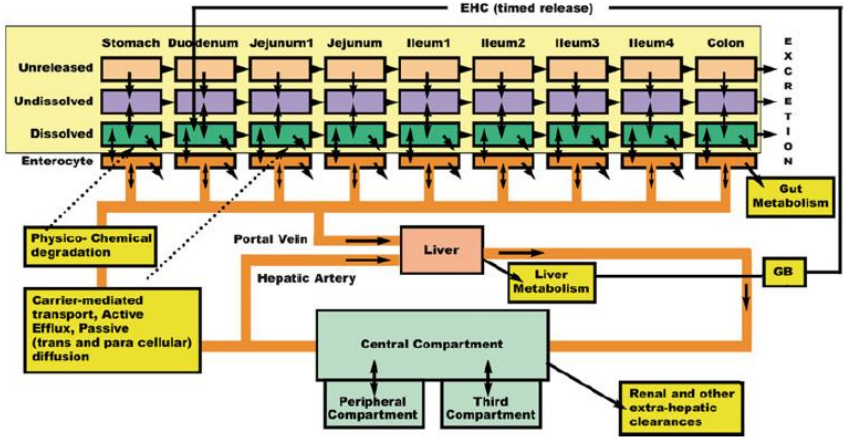


How to assess the biopharmaceutic risk in pediatric population?

complexity

- Biopharmaceutics Classification System
- Biorelevant in vitro dissolution testing
- PBPK modeling





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

Risk factors	Comment
Age of target population	
Exposure-Response	
Biowaiver approach applicable?	
Manipulation of products expected?	

Risk factors that are related to
- drug substance
- drug product
- patient population

We will get back to this slide during wrap up of the discussion

Moderated case study

This proposal is to work through a case study to look at the process to take to understand the likelihood of bioequivalence…..

Drug under development

- Adult product is a 100mg tablet

- Solubility = 0.45mg/mL with no physiologically relevant pH effect = highly soluble
- Permeability = >85% Fraction absorbed (highly permeable)

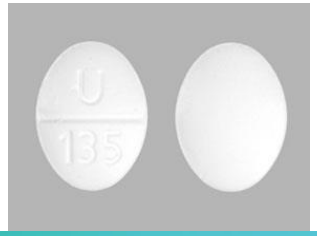
- BCS1

Pediatric product
Granule formulation based on the tablet

Tablet formulation

- Mannitol (E 421)
- Hyprolose (E 463)
- Magnesium stearate

- Coating: PVA based coating system (Opadry)



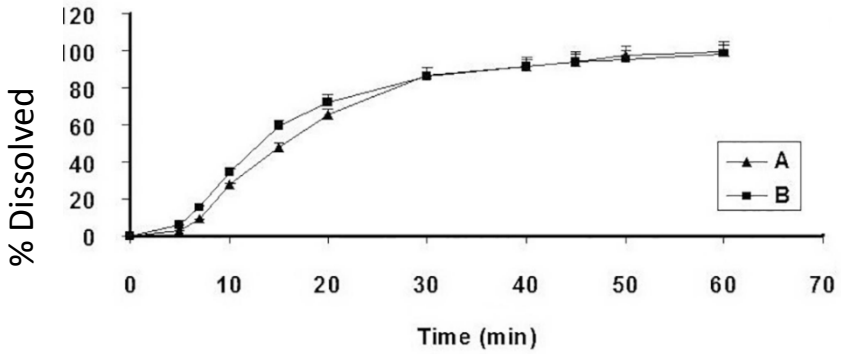
Granule formulation

- Mannitol (E 421)
- Hyprolose (E 463)
- Magnesium stearate

- Coating: PVA based coating system (Opadry)

Dissolution data

- Both products show rapid and complete dissolution across the pH range using BCS classification criteria



- Do you expect these products to be bioequivalent in an adult study?

The dosing for pediatrics

Population	Dose (mg)	Volume for dissolution (mL)	Highly soluble?	Likelihood of bioequivalence
Adult	100	250	Yes	
Adolescent	100	250		
Child (6-12 years)	50	121		
Child (2-5 years)	20	25		
Infant	12	25		
Neonate	5	25		

Solubility of the drug was 0.45 mg/mL

The dosing is on a mg/Kg basis

The dosing for pediatrics

Population	Dose (mg)	Volume for dissolution (mL)	Highly soluble?	Likelihood of bioequivalence
Adult	100	250	Yes	
Adolescent	100	250	Yes	
Child (6-12 years)	50	121	Yes (just!)	
Child (2-5 years)	20	25	No	
Infant	12	25	No	
Neonate	5	25	Yes	

Solubility of the drug was 0.45 mg/mL

The dosing is on a mg/Kg basis

Discussion and wrap-up

For discussion today

- What is our degree of certainty that differences in absorption from the formulation in pediatric patients are correctly detected in adult volunteers?
- How do we identify drug products where we potentially should be cautious?
- What would be our approach if high risk products are identified?

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

Risk factors	Comment
Age	
Exposure-Response	
Biowaiver	
Manipulation of products	

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

Risk factors	Comment
Age	Pediatric subgroups with varying degrees of concern based on changes in physiology
Exposure-Response	Narrow therapeutic index drug products Similar shape of the plasma concentration-time profile important?
Biowaiver	Is the biowaiver approach applicable? BCS classes at higher risk? “BCS migration”?
Manipulation of products	Is there a concern for off label manipulation of the product?

Acknowledgments

- EuPFI: European Paediatric Formulation Initative

EuPFI
European Paediatric Formulation Initiative

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Office of Clinical Pharmacology, FDA
Gilbert Burckart

Medical Products Agency
Ingrid Landberg
Eva Gil Berglund

Questions?

www.eupfi.org

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MEDICAL PRODUCTS AGENCY

U.S. FOOD & DRUG ADMINISTRATION

References

- Add your references. This slide is optional.

Back up Slides

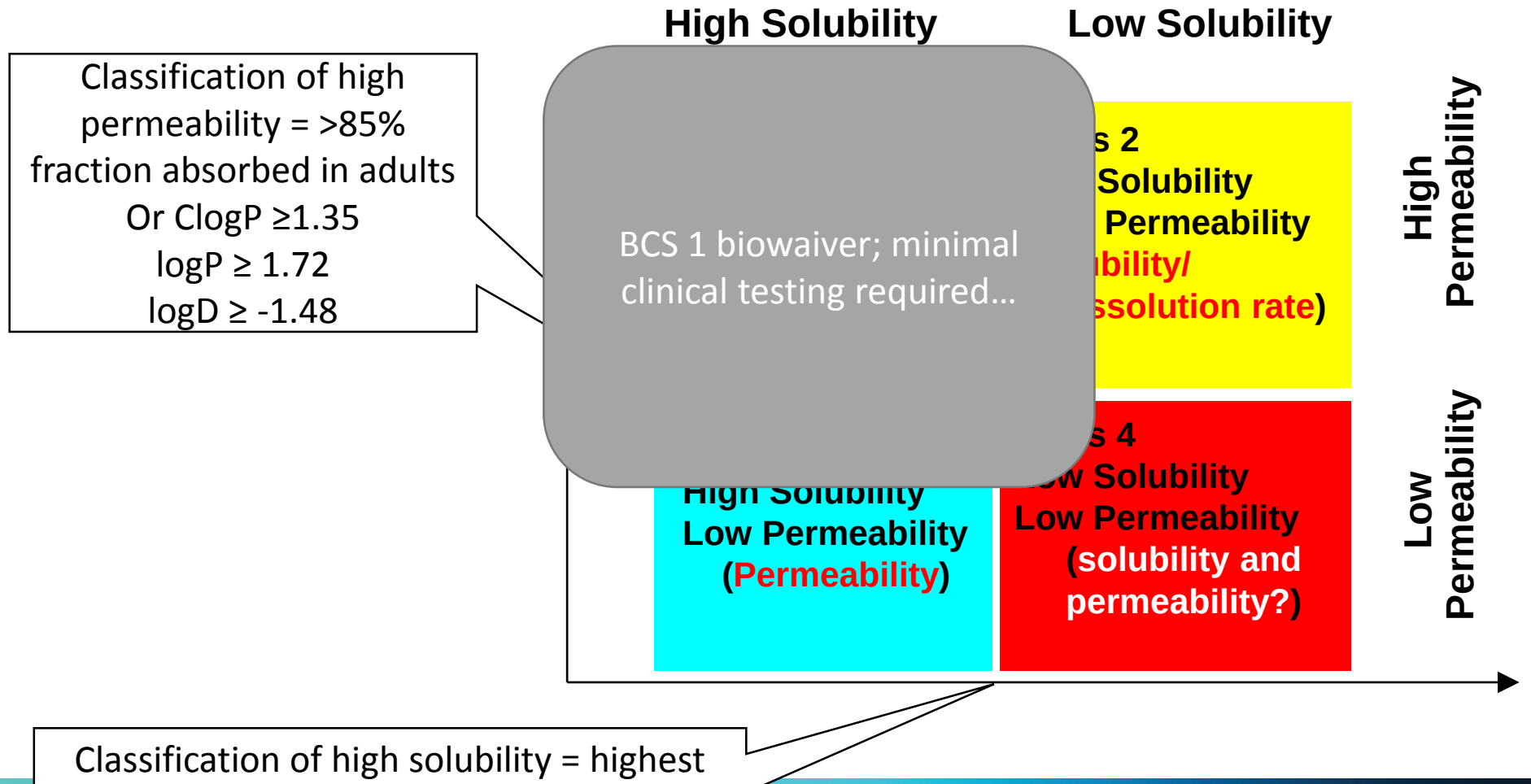
BCS a tool for risk management

- Assessment of risk
  - What is the risk of bio-in-equivalence between two pharmaceutical equivalent products when *in vitro* dissolution test comparisons are used for regulatory decisions?
    - Likelihood of occurrence and the severity of the consequences?
- Regulatory Decision
  - whether or not the risks are such that the project can be persued with or without additional arrangements to mitigate the risk
- Acceptability of the Decision
  - is the decision acceptable to society?

BCS based biowaivers

- Application of the BCS in waiving BA/BE requirements is based on premises that if
- (1) two immediate-release (IR) drug formulations/products behave as oral solutions within the GI tract due to high solubility and rapid dissolution,
- (ii) no precipitation occurs in the GI tract once the API is dissolved, and
- (iii) the two IR formulations have the same *in vivo* dissolution profile under all intestinal luminal conditions, then they should have the same rate and extent of absorption, and therefore be bioequivalent

BCS – in adults



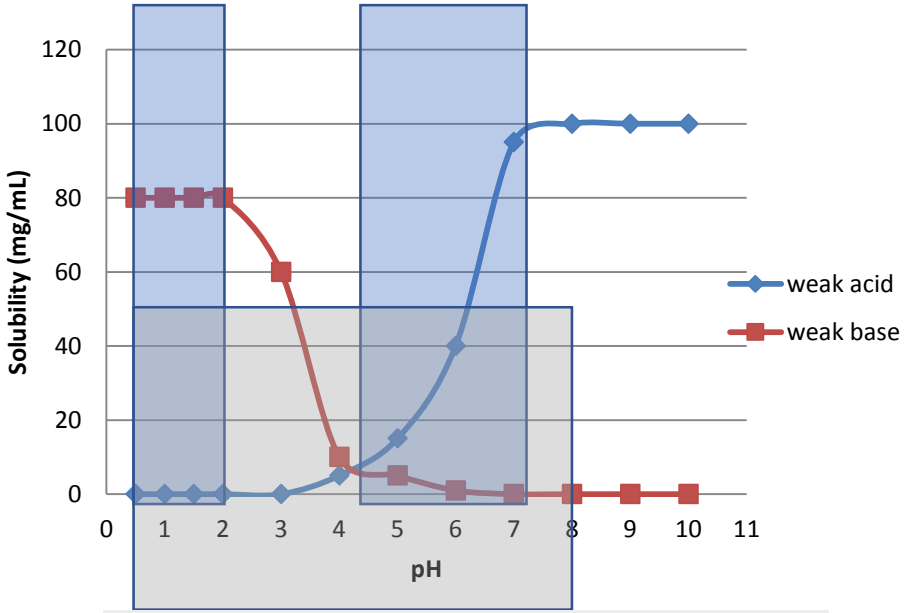
Regulatory considerations and comparisons

Table I. Similarities and Differences in Criteria for an Acceptable BCS-Based Biowaiver for the US-FDA, EMA, and WHO

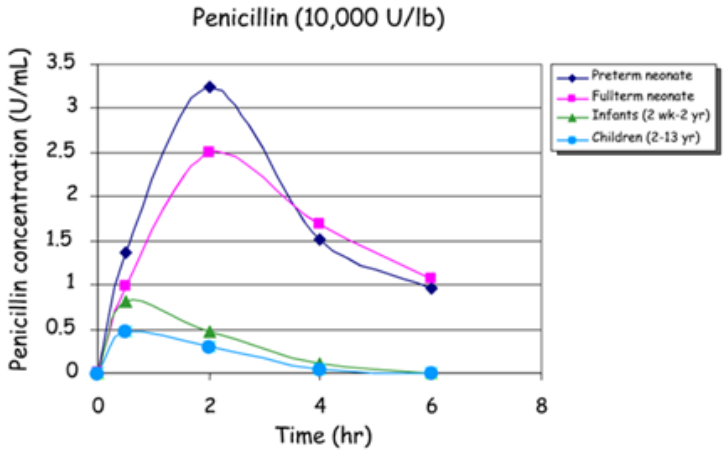
Attribute/criteria	Parameter	US-FDA	EMA	WHO	Common positions
Type of BCS biowaiver considered by agency		I and III	I and III	I and III	I and III
Formulation comparison to reference or to risk	Type	- IR solid oral dosage forms; - Applicable to pharmaceutical equivalents; - May be applicable to pharmaceutical alternatives with justification	- IR solid oral dosage forms; - Applicable to pharmaceutical equivalents or alternatives	- IR solid oral dosage forms; - Applicable to pharmaceutical equivalents or alternatives	- IR solid oral dosage forms; - Pharmaceutical equivalents or alternatives
	Excluded	- Any product designed to be absorbed in oral cavity (e.g., buccal or sublingual tablets); - Narrow therapeutic index drugs	- Buccal, sublingual, and orodispersable formulations with absorption in oral cavity; - Narrow therapeutic index drugs	- Orodispersible tablets are eligible if there is no sublingual or buccal absorption; - Narrow therapeutic index drugs	- Any product designed to be absorbed in oral cavity; - Narrow therapeutic index drugs
	Acceptable excipients	Class I: Usual excipients with quantity consistent with the intended function (e.g., lubricant); does not contain any excipients (e.g., surfactants and alcohol sugars like mannitol and sorbitol) that will affect the rate or extent of absorption of the drug; Class III: Qualitatively the same and quantitatively very similar	Class I: Well-established excipients in usual amount; qualitatively and quantitatively the same for critical excipients (e.g., surfactants, mannitol, and sorbitol) that affect bioavailability; Class III: Qualitatively the same and quantitatively very similar	Class I: well-known excipients in usual amounts; critical excipients (e.g., surfactants, mannitol, and sorbitol) should not differ qualitatively or quantitatively Class III: Qualitatively the same and quantitatively very similar	Class I: Well-established excipients in usual amount; qualitatively and quantitatively the same for excipients that affect bioavailability Class III: Composition must be qualitatively the same and quantitatively very similar
	API	Pharmaceutical alternatives not acceptable for ANDA; For prodrug, site of conversion will determine whether permeability of prodrug or active drug should be determined	Not eligible if different ester, ether, isomer, mixture of isomer, complex, or derivative	Not discussed	Not accepted if different ester, ether, isomer, mixture of isomer, complex, or derivative; site of conversion for prodrug must be discussed
Solubility/high solubility conditions	pH	Within 1 to 6.8. Base number of pH conditions on ionization characteristics of test drug substance to include pH = pKa; pH = pKa + 1; pH = pKa − 1, and at pH = 1 and 6.8	Within 1 to 6.8 (preferably at pH 1.2, 4.5, and 6.8 plus pKa if within 1–6.8)	Over the range of 1.2 to 6.8	Within 1 to 6.8; pH = pKa, pH = pKa + 1 and pKa − 1, and at pH 1 or 1.2, 4.5, and 6.8
	Method	Shake-flask or other justified method	Shake-flask or other justified method	Shake-flask or other justified method	Shake-flask or other justified method
	Volume	Soluble in 250 mL or less	Soluble in 250 mL	Soluble in 250 mL or less	Soluble in 250 mL or less
	temperature	37°C ± 1	37°C ± 1	37°C ± 1	37°C ± 1
	unit studied	Highest strength	Highest single therapeutic dose	Highest single therapeutic dose	Highest strength and highest single therapeutic dose
	timing of pH measure	After addition of the drug	Before and after addition of the drug	Not specified	Before and after addition of the drug
	Origin of data	Sponsor	Sponsor	Not specified	Sponsor
How to assess intestinal permeability	First choice	- High permeability if human Fa ≥ 85%; - Human Fa data based on absolute BA or mass balance studies; - *In vivo* intestinal perfusion studies in humans;	- High permeability if human Fa ≥ 85%; - Human Fa data based on absolute BA or mass balance studies;	- Human Fa ≥ 85%; - Human Fa data based on absolute BA or mass balance studies; - *In vivo* intestinal perfusion in humans is acceptable	- For high permeability, human Fa ≥ 85% - Human data preferred based on absolute BA or mass balance studies

Solubility and dissolution media – pH

Adult gastric and intestinal pH



Variability in neonatal gastric pH

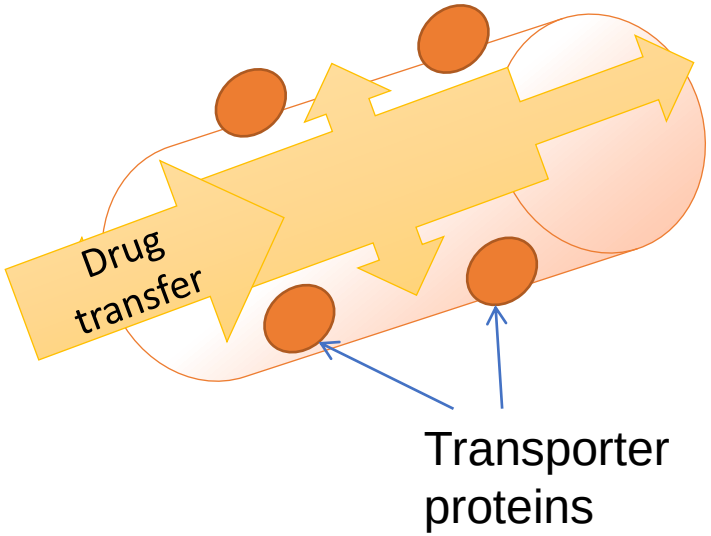


Huang et al J Pediatr 1953:42:657

Is there justification for a broader pH range in paediatric populations…?

Permeability

- Certain references to a more “leaky” membrane in the very young
- Differences in transporter proteins on the SI membrane may influence permeability of certain drugs



Biopharmaceutics test/parameter	Adult	Neonate	Infant	Child (2-5)	Child (6-12)	Adolescent	Comments
Permeability							
Considerations in permeability measurements		Only include passive permeability data	Only include passive permeability data	Use adult reference value	Use adult reference value	Use adult reference value	Efflux transporters in the intestine reach adult values at approx 2 years