Optimising PIPs through knowledge integration

For the motion:

Paediatric medicines development should be limited to pharmacokinetic bridging trials

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GSK Medicines for Children Advisory Network

1. Dose

It’s not does the drug work?

rather

What is the right dose?

Image source: Health Canada

Adverse Drug Reactions – 15 drugs ~ 41% of case reports

January 16, 2014 — Special Report on Children

Table 1. Most frequent suspect drugs in serious adverse drug events reported in normal medical use, 2008-2012

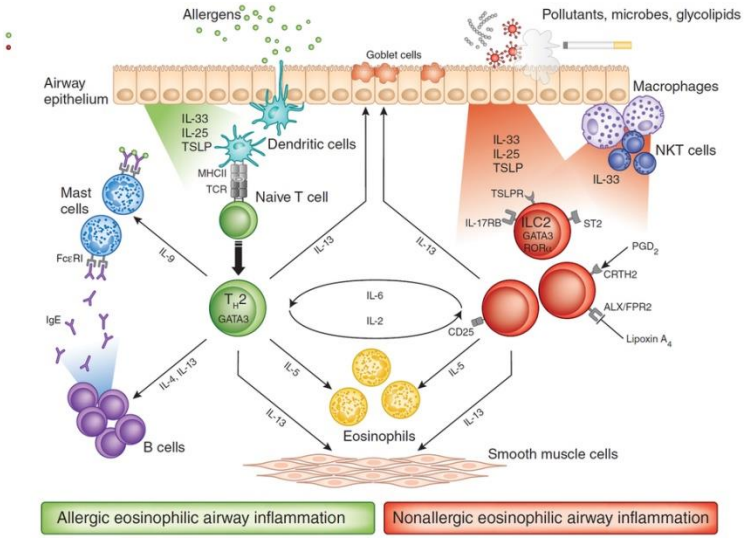
Rank	Drug name	Brand name*	Cases	Medical use*	Psych**	Most freq ADE	2d most freq ADE
1	Infliximab	REMICADE	1772	Crohn's Disease	N	Crohn's disease	Ulcerative colitis
2	Montelukast	SINGULAIR	944	Asthma	Y	Suicidal ideation	Aggression
3	Somatropin	NUTROPIN	606	GH deficiency	N	Headache	Convulsion
4	Baclofen	LIORESAL	579	Muscle spasticity	N	Hypertonia	Drug ineffective
5	Isotretinoin	CLARAVIS	447	Acne	Y	Suicidal ideation	Depression
6	Methylphenidate	CONCERTA	418	ADHD	Y	Sudden death	Aggression
7	Lamotrigine	LAMICTAL	335	Epilepsy	Y	Convulsion	Stevens-Johnson synd
8	Lisdexamfetamine	VYVANSE	314	ADHD	Y	Suicidal ideation	Aggression
9	Aripiprazole	ABILIFY	297	Bipolar disorder	Y	Weight increased	Dystonia
10	Ibuprofen	MOTRIN	242	Pyrexia	N	Hypersensitivity	Renal failure acute
11	Etanercept	ENBREL	231	Juvenile arthritis	N	Injection site pain	Vomiting
12	Atomoxetine	STRATTERA	227	ADHD	Y	Suicidal ideation	Chest pain
13	Quetiapine	SEROQUEL	210	Bipolar disorder	Y	Weight increased	Tardive dyskinesia
14	Levetiracetam	KEPPRA	206	Epilepsy	Y	Convulsions	Drug ineffective
15	Risperidone	RISPERDAL	195	Bipolar disorder	Y	Aggression	Weight increased

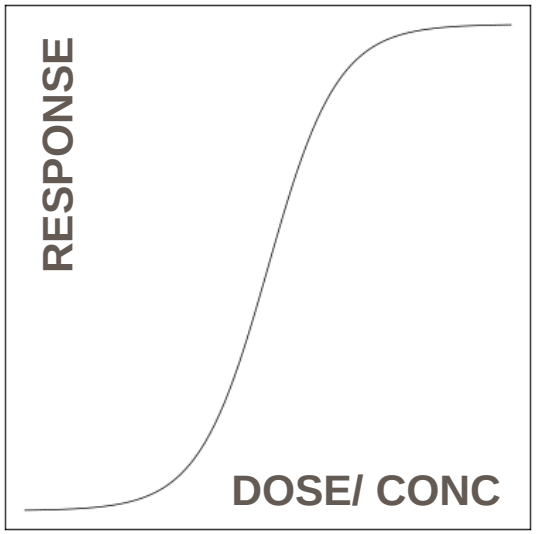
* Most frequently cited in case reports. **Psychiatric side effects > 25% of reports.

GH = Growth hormone. ADHD = Attention deficit hyperactivity disorder. Additional note in Methods Summary

2. Target

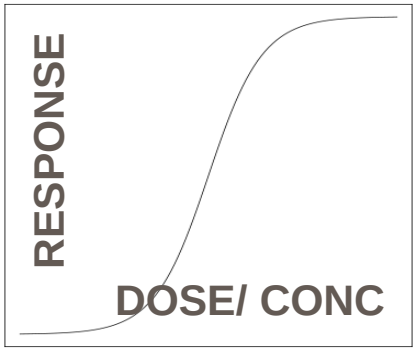
Drug target typically well defined

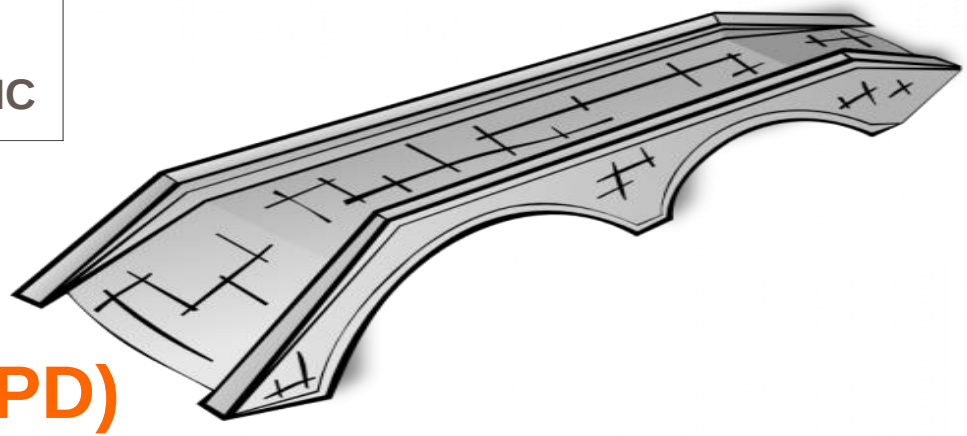




3. Efficiency

PK bridging is an efficient approach to select the **right dose**





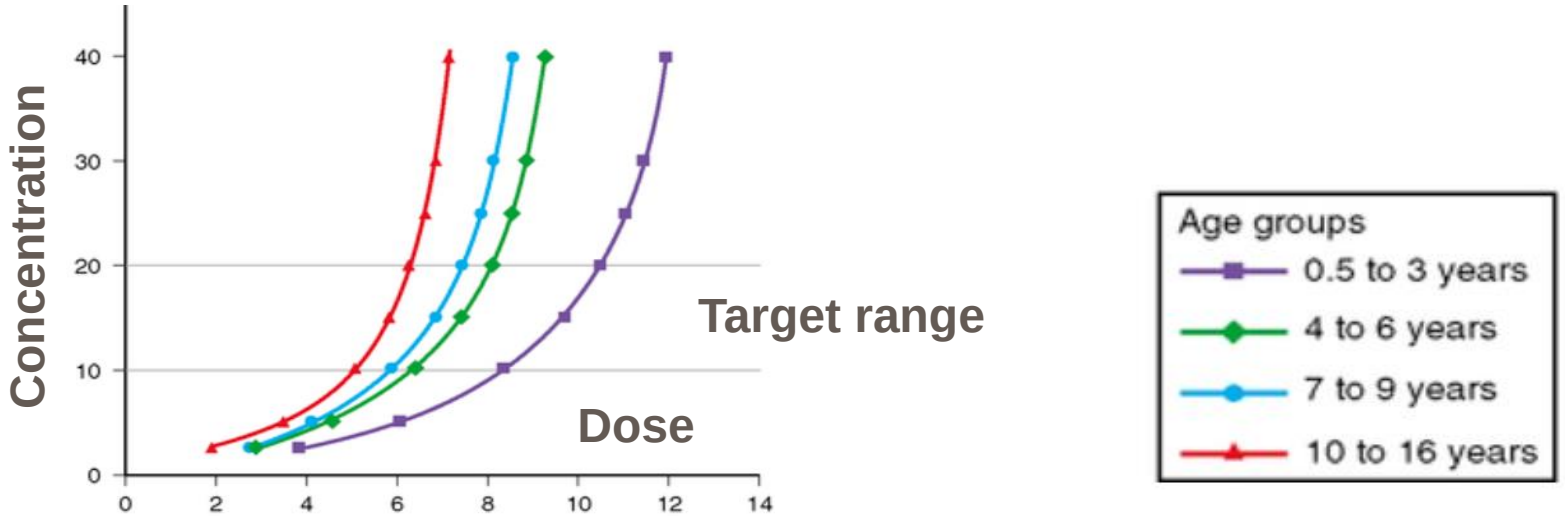
Efficacy & Safety

PK(/PD)

4. Application

PK bridging can account for majority of differences between adults and children

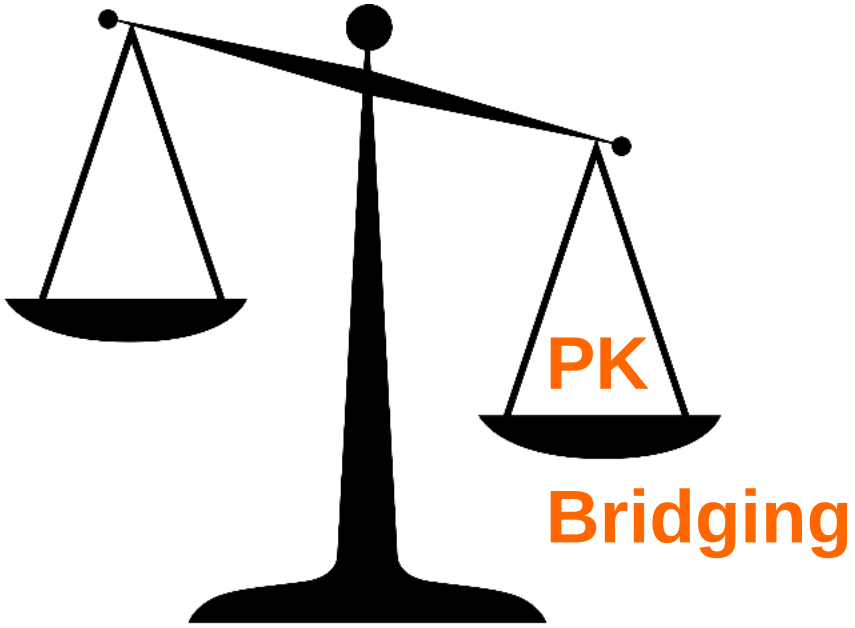
PKPD relationship often similar



https://clinicalgate.com/antiepileptic-drug-therapy-in-children/

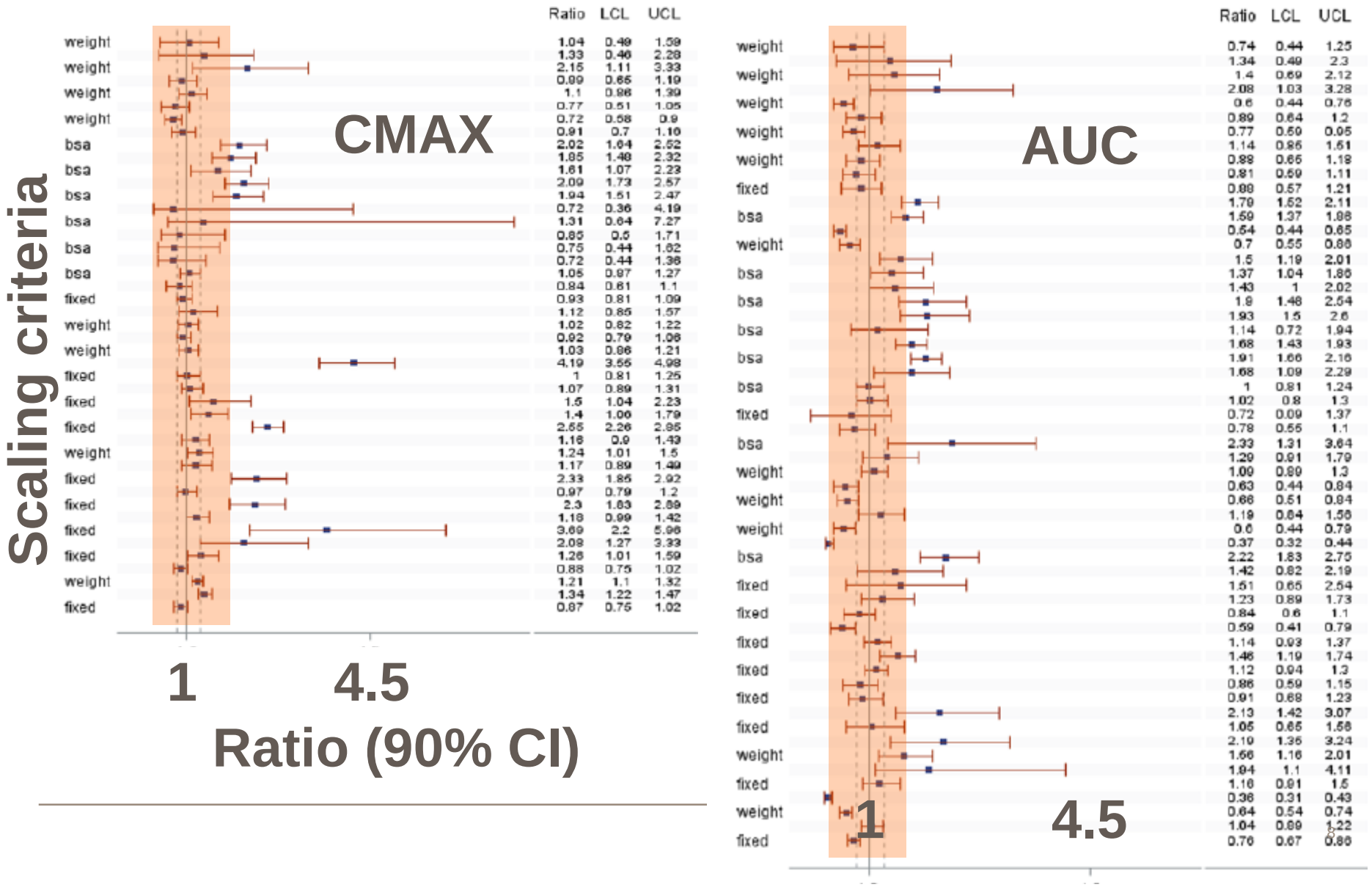
5. Evidence supporting approval

Precedence for PK bridging



Ratio (paed/adult) for products approved at the studied dose

Mulugeta et al: Journal of Clinical Pharmacology 2016, 56(11) 1326–1334



Pro: Paediatric medicines development should be limited to pharmacokinetic bridging trials

Right paediatric dose can be identified efficiently by PK bridging

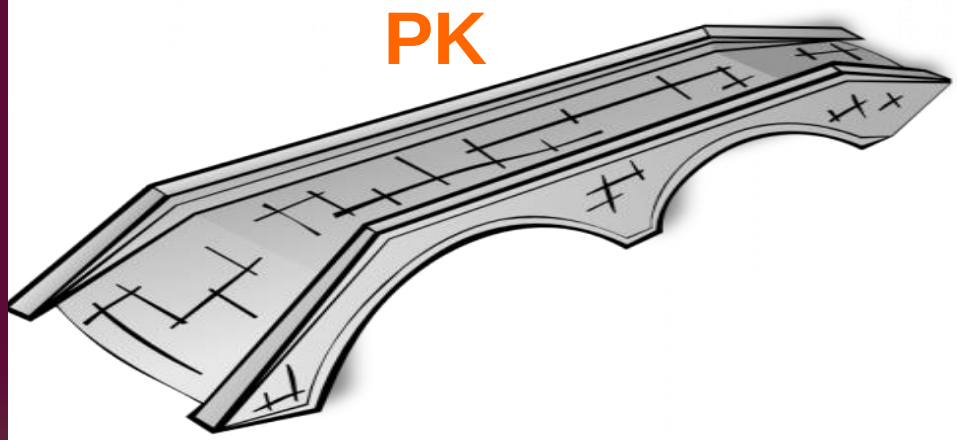
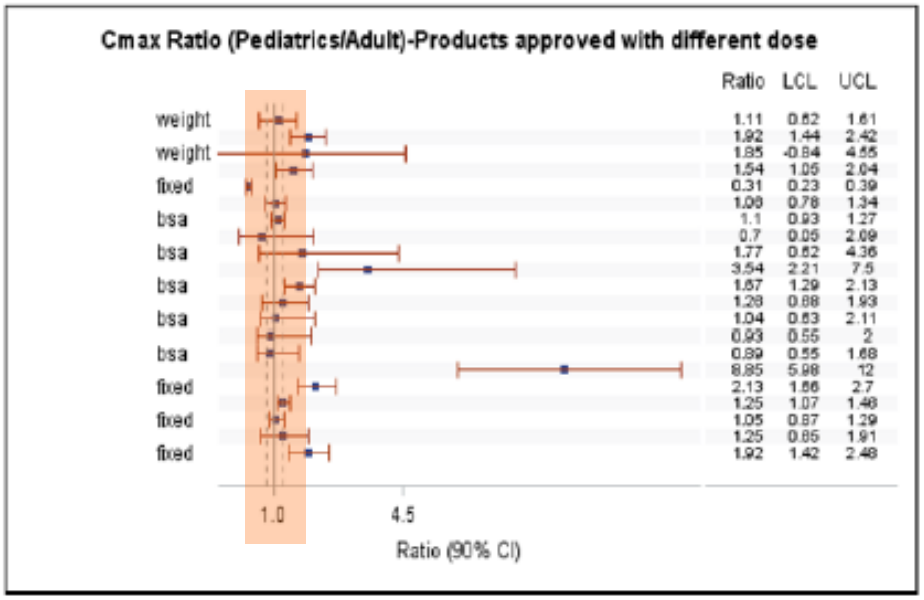


Image source: Certara

Thank you

Ratio (paed/adult) for products approved with different dose

Mulugeta et al: Journal of Clinical Pharmacology 2016, 56(11) 1326–1334



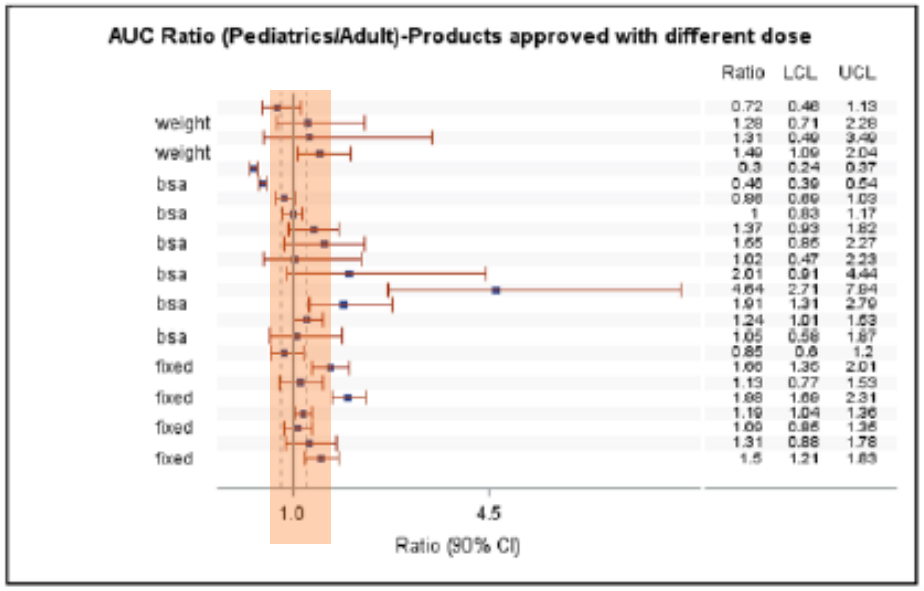
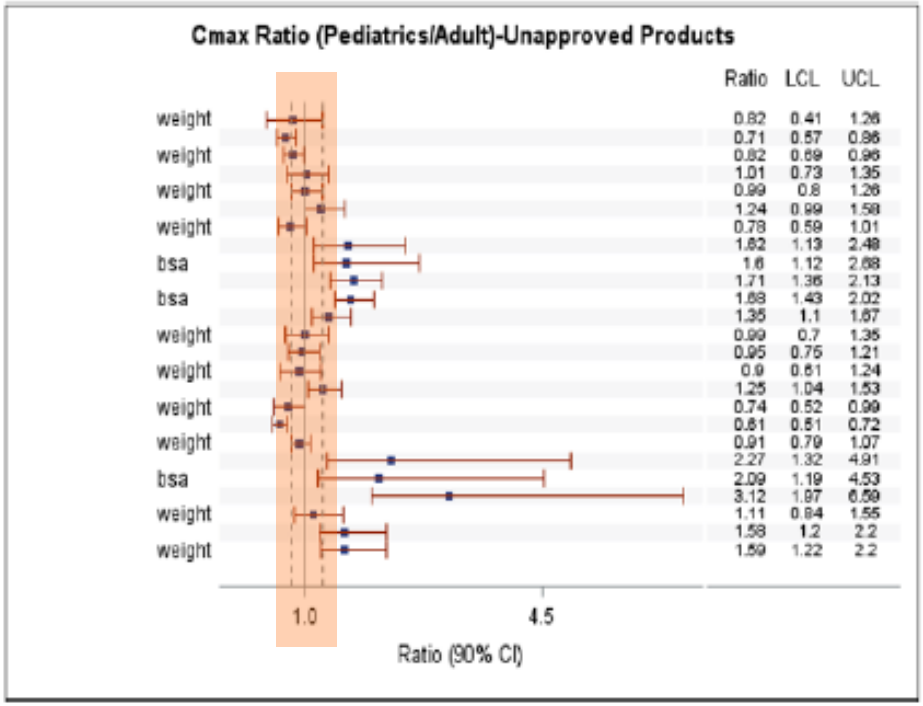


Figure 4. Forest plot of C_{max} and AUC ratios (pediatric/adult) for products approved with a different dose. The solid line corresponds to a ratio of 1. The 90% confidence intervals are based on the Fieller method.

Ratio (paed/adult) for products without pediatric indication

Mulugeta et al: Journal of Clinical Pharmacology 2016, 56(11) 1326–1334



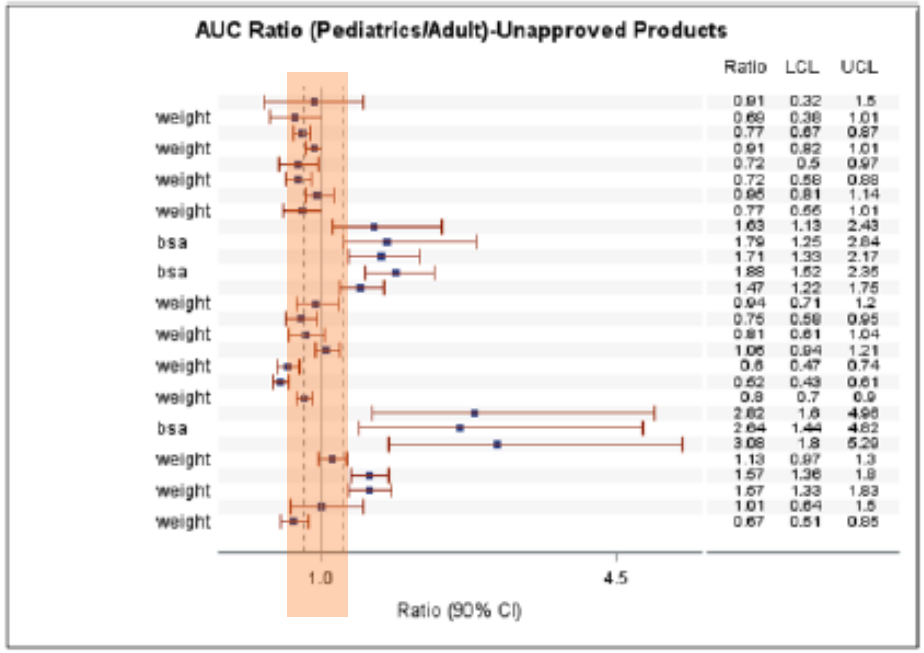


Figure 3. Forest plot of C_{max} and AUC ratios (pediatric/adult) for products without a pediatric indication. The solid line corresponds to a ratio of 1. The 90% confidence intervals are based on the Fieller method.