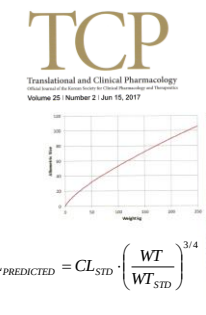
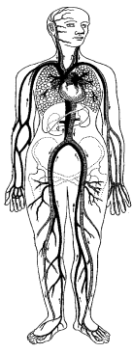
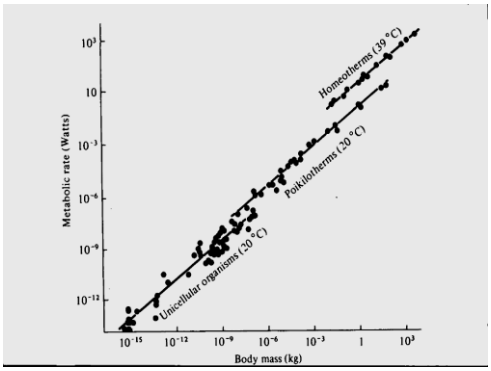
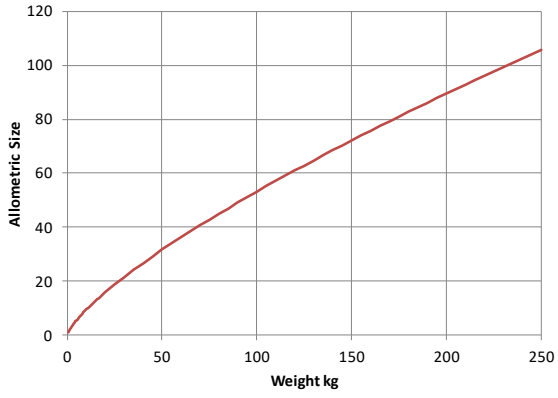
Slide 1	# Babies, Children, Adults Are All One Species Integrated Rational Dosing Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland	Presented at FDA, White Oak, Thursday 14 Sep 2017. Seminar on Dose Selection in Children. Participants were asked before this presentation: 1.) In children over 2 years of age, exposures can be reliably predicted and dosing can be derived based on adult PK data: (multiple choice) Responses YES 24 31.58% NO 52 68.42% The same question was asked aft the end of the seminar after the panel discussion and showed many of those present had changed their mind: YES 37 72.55% NO 14 27.45%
Slide 2	# **Body Size** is the most important quantitative determinant of drug dose ● The **human body weight range** varies from about 500 g to over 250 kg due to both biological variability and changes over the lifespan. • This more than **500 fold** range in size is directly translatable through volume of distribution into drug **loading dose** differences • Because of allometrically predictable relationships beween weight and clearance the corresponding range of **maintenance dose rates** is only about **100 fold** 	
Slide 3	# Theory Based Allometry     $CL_{PREDICTED} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}}\right)^{3/4}$ Note allometry is based on using **mass alone** to predict differences in structure and function. 	West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science. 1999;284(5420):1677-9. The fundamental assumption of West's allometric theory is that all cells are similar in size and have similar energy requirements. The structure of the energy delivery system e.g. blood vessels in humans, requires a certain mass e.g. bones in humans, to support the delivery system as well as the target cells. The mass overhead from these delivery and support systems increases total body mass without a linear increase in function. The allometric exponent value of ¾ describes this non-linear relationship for clearance. In contrast to functional processes such as clearance, allometric theory predicts a linear relationship between mass and structural properties such as volume of distribution. The allometric exponent for volume of distribution is 1.

		Holford N. Pharmacokinetic variability due to environmental differences. Transl Clin Pharmacol. 2017;25(2):59-62. Photo shows Nick Holford (41 y 80 kg) and Sam Holford (1 y 8 kg) on Fox Glacier, NZ 1987
Slide 4	**Allometric Size Matches Observations 18 Orders of Magnitude**  	Peters R. The ecological implications of body size. Cambridge: Cambridge University Press; 1983.
Slide 5	**Allometric Size for Clearance**  	The relationship between weight and clearance is non-linear. It is predictable from theory based allometry. Allometric size is scaled in this figure relative to a value of 1 at a weight of 0.5 kg. With weight varying 500 fold from 0.5 kg to 250 kg the equivalent allometric size varies by a factor of just over 100.

Slide 6

Allometric Size and Body Composition

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Review

Allometric size: The scientific theory and extension to normal fat mass

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Holford, N.H., European Journal of Pharmaceutical Sciences (2017), http://dx.doi.org/10.1016/j.ejps.2017.05.056

Slide 7

Allometry and Everything Else

Size is Not Everything

- Attempts to describe all differences using weight alone will fail if other factors are ignored (even if correlated with weight)
  - » Don't ignore species
  - » Don't ignore age
  - » Don't ignore genotype
  - » Don't ignore disease state
  - » Etc …

Allometry is about Mass

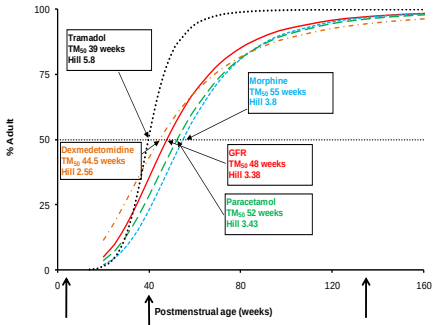
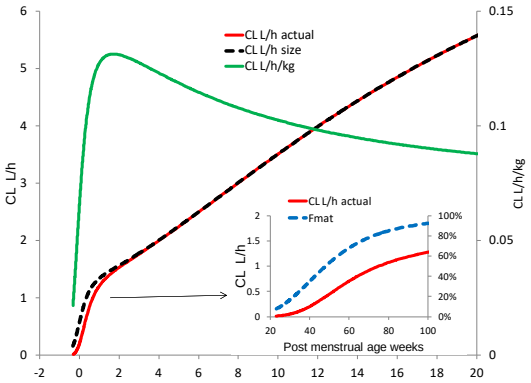
- Statements such as "allometry does not work" typically come from people who do not understand that allometry does not involve
  - » Species
  - » Age
  - » Genotype
  - » Disease state
  - » Etc…

Slide 8

How Old is a Baby?

- Post-natal age (PNA)
  - » Does not account for *in utero* maturation
- Post-menstrual age (PMA)
  - – On average 2 weeks longer than biological age
- Post-conception age (PCA)
  - – The biological age but not widely recorded

The age of a baby may be described using several kinds of "age".
Post-natal age (PNA). This is the age (e.g. days) since birth. It does not account for in utero maturation of body structure and function.
Post-menstrual age (PMA). This is the age (e.g. weeks) since the mother's last menstrual period. On average it is 2 weeks longer than biological age
Post-conception age (PCA). This is the age (e.g. weeks) since conception. This is the best description of biological age but it is not widely recorded because the date of conception is often difficult to identify.
Gestational age (GA). Defined by the PMA at birth. GA does not change with time.
Post menstrual age is the recommended way to describe biological age. This recommendation is pragmatic rather than theoretically correct.

Slide 9	**Clearance Maturation**  Conception Full Term 2 years old Maturation is complete by 2 years of age – – then weight is the sole predictive factor for drug clearance 	Post-menstrual age is the recommended way to describe the biological age in weeks after conception. It is based on the mother's recall of the date of the last menstrual period. It is therefore typically biased by overestimating the age since conception by 2 weeks.
Slide 10	**Weight and Age Explain Higher mg/kg Doses in Young Children**  Post natal age years 	Clearance increases with weight and age (red line). Allometric size predicts increasing clearance per kg with lower weights (green line). Below 2 years of age immaturity of drug clearance has a major effect on clearance (see inset) so clearance per kg decreases. This leads to a peak in clearance when expressed per kg around 2 years of age. Maintenance doses are commonly expressed per kg in clinical practice and are also higher around 2 years of age than in babies and adults.
Slide 11	**Standard Weight for Allometric Models** Concern is expressed sometimes that scaling parameter values estimated in neonates and children in terms of an adult size standard of 70 kg may bias the estimates or affect the precision of estimation. There is no basis for this concern. This can be seen by inspection of the allometric size model which may be re-arranged: $\text{allometric size} = \left(W/Wstd\right)^{3/4} = (W)^{3/4} \cdot \left(1/Wstd\right)^{3/4}$ The expression $\left(1/Wstd\right)^{3/4}$ is simply a constant that is determined by whatever weight is chosen for standardization. The precision of a parameter estimate will not be changed by multiplying the parameter value by an ad hoc constant. See Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. J Pharm Sci. 2013;102(9):2941-52 for the rationale for using a 70 kg standard. 	

Slide 12

Weight Used For Standardization Does Not Affect Parameter Estimation

	CL (%)	*V* (%)
Centered on 1 kg		
Bias		
Average	1.55	1.13
Median	1.40	0.80
RSE	5.43	3.26
2.5 percentile	91	95
97.5 percentile	113	108
Centered on 20 kg		
Bias		
Average	1.56	1.13
Median	1.33	1.15
RSE	5.42	3.25
2.5 percentile	91	95
97.5 percentile	113	108

	CL (%)	*V* (%)
Centered on 70 kg		
Bias		
Average	1.56	1.12
Median	1.40	1.00
RSE	5.42	3.27
2.5 percentile	91	95
97.5 percentile	113	108

Slide 13

Use of Age Categories for PK Study Analysis

	CL (%)	*V* (%)
Bias		
Average	3.6	2.2
Median	2.4	2.0
RSE	13	8
2.5 percentile	82	86
97.5 percentile	135	119

Analyzed using individual PMA and weight to describe differences in clearance and volume.

Don't Use Categories!

	CLP	VP	CLN	VN	CLI	VI	CLC	VC
Bias								
Average	5.1	3.8	4.4	7.4	−12	0.5	6.9	18
Median	2.7	2.9	4.1	6.4	−12	−0.3	6.3	16
RSE	22	15	13	14	13	18	13	22
2.5 percentile	69	77	81	84	62	66	83	80
97.5 percentile	152	136	130	136	114	137	135	163

Slide 14

The Compromise between Science and Clinical Practice

- Biology and pharmacology are strong sciences

Do the science first then make it practical for clinical use

Compromise should be made transparent to clinicians

- Clinical practice is often a compromise because of:
  - » Lack of computational tools
  - » Limited formulation flexibility

Slide 15

Rules of PNA and PMA

Fraction of adult maintenance dose

Typical Weight Kg	PMA or PNA	Fraction Adult Dose	Rule of PMA+PNA Error	'true' % Adult Dose
1	25 weeks	1/300	10%	0.3
1	30 weeks	1/120	1%	0.8
3	Full Term	1/30	1%	3.3
6	3 mo	1/10	8%	9.3
7	6 mo	1/6	24%	13.4
9	1 year	1/5	3%	19.5
12	2 years	1/4	-4%	26.1
19	5 years	1/3	-11%	37.4
34	10 years	1/2	-14%	58.5
50	15 years	3/4	-3%	77.4
70	Adult	1		100.0

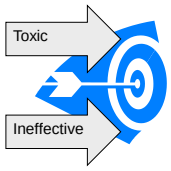
Weight is combined with post-natal age (PNA) and post-menstrual age (PMA) to predict the typical dose as a % of the adult dose.
The coloured areas of the table show the fraction of adult maintenance dose that would be expected for infants and children. The fractions are based on the theoretical size and maturation model for typical drug clearance with some approximation to make the numbers easier to remember. The 'rule of PMA+PNA' has an acceptable error for clinical dose prediction.
Although maturation is best described by a non-linear relationship it is quite well approximated by a linear function of PMA.

Slide 16

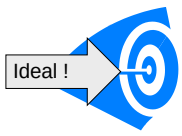
Slide 17

First Pick A Target

- Therapeutic Drug Monitoring
  - » TDM Therapeutic Range
  - ☹ Imprecise
  - » Sub-optimal at borders of the range



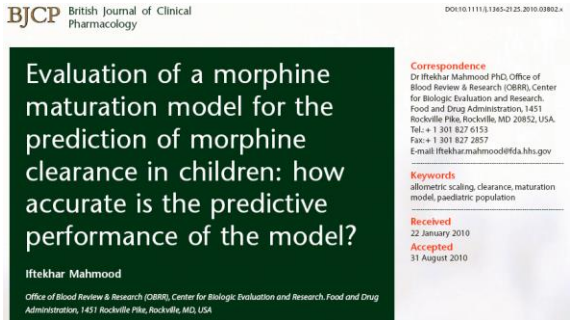
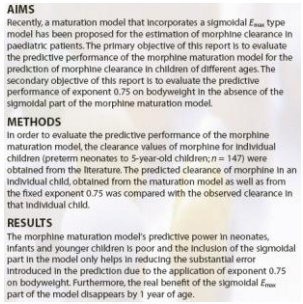
- Target Concentration Intervention
  - » TCI Single Target
  - ☺ Accurate
  - » Optimal – do the best you can



Therapeutic drug monitoring is a traditional concept associated with empirical 'seat of the pants' dose adjustment determine by a measurement being outside a 'therapeutic range'. The therapeutic range is hard to identify and is often mistakenly justified because it seems to be similar to the normal reference range for endogenous substances. A concentration at the bottom of the range has a very different meaning (close to being ineffective) from one at the top (close to being toxic) but TDM proponents usually ignore this and are happy to do nothing as long as the concentration is 'within range'.

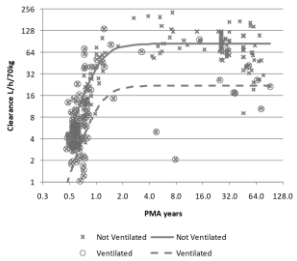
Target concentration intervention is a science based method that uses pharmacokinetic and pharmacodynamic principles to identify how patients are different and uses PK guided dose individualization to achieve a precise therapeutic target. It has been shown to improve clinical outcome as well as being a cost-effective use of health resources.

Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with

		individualized chemotherapy for childhood acute lymphoblastic leukemia. N Engl J Med. 1998;338(8):499-505. van Lent-Evers NAEM, MathÃ´t RAA, Geus WP, van Hout BA, Vinks AATMM. Impact of Goal-Oriented and Model-Based Clinical Pharmacokinetic Dosing of Aminoglycosides on Clinical Outcome: A Cost-Effectiveness Analysis. Ther Drug Monit. 1999;21(1):63-73. Le Meur Y, Buchler M, Thierry A, Caillard S, Villemain F, Lavaud S, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant. 2007;7(11):2496-503.
Slide 18	Check to See If You Can Hit the Target  BJCP British Journal of Clinical Pharmacology Evaluation of a morphine maturation model for the prediction of morphine clearance in children: how accurate is the predictive performance of the model? Iftekhar Mahmood Office of Blood Review & Research (OBRR), Center for Biologic Evaluation and Research, Food and Drug Administration, 1451 Rockville Pike, Rockville, MD, USA Correspondence Dr Iftekhar Mahmood PhD, Office of Blood Review & Research (OBRR), Center for Biologic Evaluation and Research, Food and Drug Administration, 1451 Rockville Pike, Rockville, MD 20852, USA. Tel.: + 1 301 827 6153 Fax: + 1 301 827 2857 E-mail: Iftekhar.mahmood@fda.hhs.gov Keywords allometric scaling, clearance, maturation model, paediatric population Received 22 January 2010 Accepted 31 August 2010 Mahmood I. Evaluation of a morphine maturation model for the prediction of morphine clearance in children: How accurate is the predictive performance of the model? Br J Clin Pharmac. 2011;71(1):88-94. ©NHG Holford, 2017 all rights reserved.	The most important parameter determining a regular maintenance dose rate is clearance. It is important to check proposed methods for predicting clearance to see how well they match with reality. However some methods of performing this check may not be appropriate as illustrated by this paper from Dr Mahmood at the US FDA.
Slide 19	Some Surprising Claims  AIMS Recently, a maturation model that incorporates a sigmoidal E_{max} type model has been proposed for the estimation of morphine clearance in paediatric patients. The primary objective of this report is to evaluate the predictive performance of the morphine maturation model for the prediction of morphine clearance in children of different ages. The secondary objective of this report is to evaluate the predictive performance of exponent 0.75 on bodyweight in the absence of the sigmoidal part of the morphine maturation model. METHODS In order to evaluate the predictive performance of the morphine maturation model, the clearance values of morphine for individual children (preterm neonates to 5-year-old children; $n = 147$) were obtained from the literature. The predicted clearance of morphine in an individual child, obtained from the maturation model as well as from the fixed exponent 0.75 was compared with the observed clearance in that individual child. RESULTS The morphine maturation model's predictive power in neonates, infants and younger children is poor and the inclusion of the sigmoidal part in the model only helps in reducing the substantial error introduced in the prediction due to the application of exponent 0.75 on bodyweight. Furthermore, the real benefit of the sigmoidal E_{max} part of the model disappears by 1 year of age. CONCLUSIONS The morphine maturation model has a poor predictive power of morphine clearance in preterm and term neonates, infants and very young children and may not be of any practical value for the prediction of morphine clearance in this age group. A theory based allometric model with sigmoid maturation (Anand et al. 2008) was evaluated with these claims about its performance: 1. "**substantial error due to exponent 0.75**" 2. "**not of any practical value for prediction of morphine clearance**" Anand KJS, Anderson BJ, Holford NHG, Hall RW, Young T, Barton BA. Morphine Pharmacokinetics and Pharmacodynamics in Preterm Neonates: Secondary Results from the NEOPAIN Multicenter Trial 2008. ©NHG Holford, 2017 all rights reserved.	Mahmood made two negative assertions about a model for predicting clearance of morphine based on size and maturation. He said that the use of a theory based allometric exponent of ¾ caused a substantial error. Furthermore he indicated that the model was unlikely to be of any practical value for predicting morphine clearance in clinical practice.

Slide 20

Morphine External evaluation



- **Patients:** 257 human morphine 'observed' CL
- **Age:** 24 PMA week to 91 year
- **Target**: 10 mcg/L

- **Acceptable: if dose <= 25% ideal**
- **Unacceptable: if >= than 100%**

Model	Data	Premature	Neonate	Infant	Child	Adult
	N	83	35	26	23	90
Textbook mg/kg	Reich	-18		31	-11	21
CL^3/4 MF,ventilated	Holford	-23	12	-32	-25	-1
CL^PWR PNA 10 d	Knibbe	37	33	-4	24	224
CL^(f(WT)) Ventilated	Wang	-31	74	6	6	106
CL^PWR, V^PWR Ventilated	Mahmood	-31	149	-16	-11	101

Only theory based allometry + maturation predicted adult dose (better than clinical textbook?)
All empirical allometric models unacceptable!

Holford NH, Ma SC, Anderson BJ. Prediction of morphine dose in humans. Paediatr Anaesth. 2012;22(3):209-22.

A population approach to evaluation of the predictions of morphine clearance showed that the theory based allometric model proposed by Anand et al. was somewhat better than standard empirical textbook recommendations. All the empirical models for prediction were unacceptable for some age group. 1Holford NHG, Ma S, Anderson BJ. Prediction of morphine dose in humans. Pediatric Anesthesia. 2011;Accepted

Reich A, Beland B, Van Aken H. Intravenous narcotics and analgesic agents. In: Pediatric Anesthesia, eds. Bissonnette B, Dalens B, London McGraw-Hill, 2002.
Wang C, Peeters MYM, Allegaert K, Tibboel D, Danhof M, Knibbe CAJ. Scaling clearance of propofol from preterm neonates to adults using an allometric model with a bodyweight-dependent maturational exponent [www.page-meeting.org/?abstract=1818]. PAGE 2010; 19.
Knibbe CA, Krekels EH, van den Anker JN, DeJongh J, Santen GW, van Dijk M, Simons SH, van Lingen RA, Jacqz-Aigrain EM, Danhof M, Tibboel D. Morphine glucuronidation in preterm neonates, infants and children younger than 3 years. Clin Pharmacokinet 2009; 48: 371-85.
Mahmood I. Prediction of drug clearance in children from adults: a comparison of several allometric methods. Br J Clin Pharmacol 2006; 61: 545-57.

Slide 21

Why Estimated Allometric Exponents are A Bad Idea without Good Design

Estimation of exponents is imprecise

Table 4 Imprecision of estimates of allometric coefficient for clearance (true value 0.75)

Weight distribution	5%CI	95%CI
Log normal median 70 kg, 20%CV	0.48	1.01
Log normal median 70 kg, 50%CV	0.64	0.86
Uniform 0–140 kg	0.69	0.81

Estimation was performed using NONMEM V 1.1 with the FOCE interaction method. Empirical confidence interval (CI) and CV (standard deviation/average) from parametric bootstrap distribution of 1000 replications. One hundred subjects were drawn from each weight distribution for each

Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303-32.