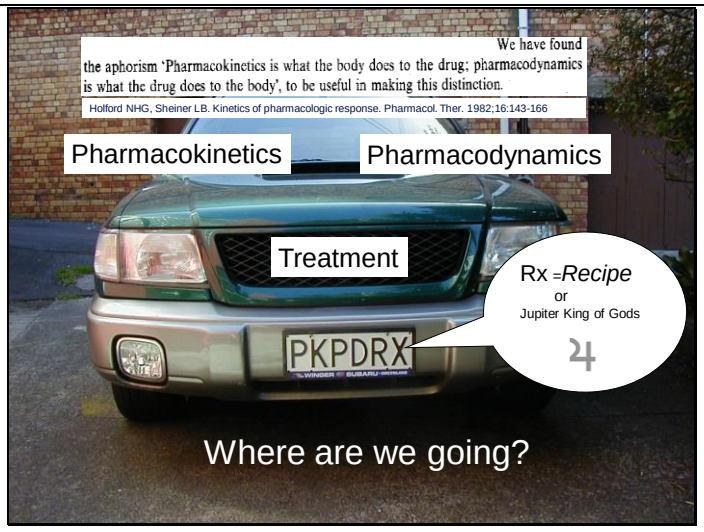
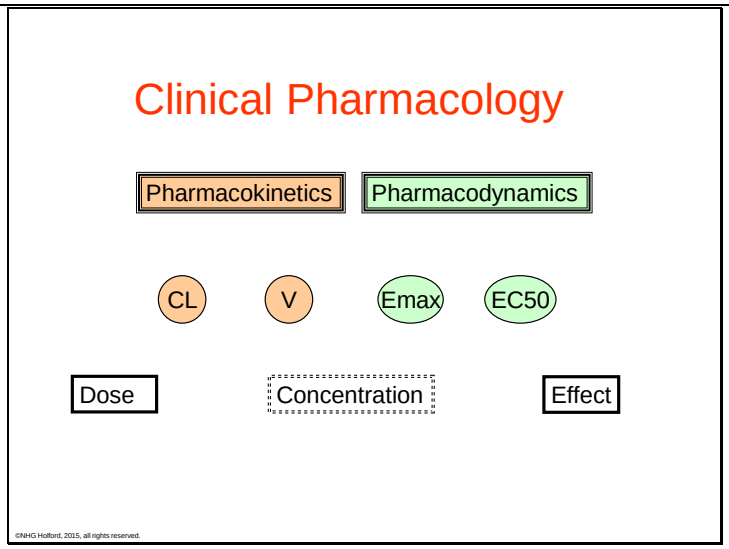
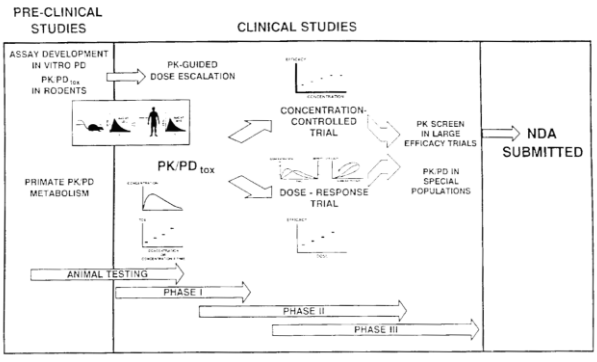
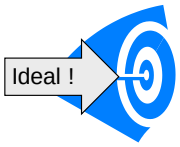
Slide 1	# Target Concentration Intervention ## Can we hit the targets? Nick Holford University of Auckland Auckland, New Zealand	
Slide 2	# Objectives 1) Appreciate how a target concentration (TC) strategy is essential for rational drug development and clinical use 2) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM) 3) Understand why safe and effective variability (SEV) has to be defined in order to make rational choices for dose individualization 	
Slide 3		PK = Pharmacokinetics: What the body does to the drug PD=Pharmacodynamics: What the drug does to the body Rx=Treatment: What the prescribed and patient need to know.

Slide 4		Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (EC50).
Slide 5	**Target Concentration** **Drug Development and Clinical Use** ● Effective drug development needs a plan » A good plan has a clear objective » TC provides a clear objective in all phases of drug development ● TC is the rational basis for dose individualization » Choose the target effect to determine the TC » Use TC to predict individual dose Holford NHG. The target concentration approach to clinical drug development. Clin Pharmacokinet. 1995;29(5):287-91. ©NHG Holford, 2015, all rights reserved.	
Slide 6	**Target Concentration in Drug Development**  Peck et al. 1992 ©NHG Holford, 2015, all rights reserved.	The 1992 view was based on using PKPD for drug development but did not explicitly include how to use medicines in patients.

Slide 7	**Target Concentration in Clinical Use of Medicines** **Target Conc = Target Effect x EC50 / (Emax-Target Effect)** **Target Conc** | **Dose Model** Initial Peak | Loading Dose = **Target Conc** x **Volume of Distribution** Average Steady State | Maintenance Dose Rate = **Target Conc** x **Clearance** Ideal dose prediction requires **individual** estimates of **Emax, EC50, V and CL** 	The target concentration approach links PKPD to prediction of the right dose for a patient.
Slide 8	**TDM or TCI?** ● 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  	
Slide 9	**How to Find the Target?** Clin. Pharmacokinet. 25 (6): 495-505, 1993 Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L? A Randomised Concentration-Controlled Trial *Nicholas Holford*[1], *Peter Black*[1], *Ron Couch*[2], *Julia Kennedy*[3] and *Robin Briant*[1] 1 Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Auckland, New Zealand 2 Department of Clinical Chemistry, Auckland Hospital, Auckland, New Zealand 3 Department of Pharmacy, School of Medicine, University of Otago, Dunedin, New Zealand ● Randomized concentration controlled trials are the gold standard 	

Slide 10

Why does PKPD vary?

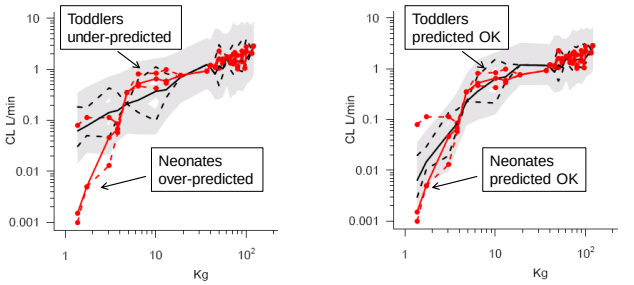
- Systematic (predictable)
  - » Body size
  - » Disease state (liver, kidney)
  - » Genotype
  - » etc...
- Random (not predictable)
  - » Between Subject Variability
  - » Within Subject Variability

Slide 11

Predictable Variability Size and Maturation

¾ Allometry Alone
explains 67% of CL variability

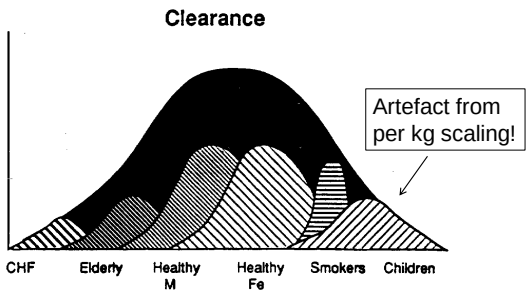
¾ Allometry + Maturation
explains 80% of CL variability



Original data from Peeters MY, Allegaert K, Blusse van Oud-Alblas HJ, Cella M, Tibboel D, Danhof M, et al. Prediction of propofol clearance in children from an allometric model developed in rats, children and adults versus a 0.75 fixed-exponent allometric model. Clin Pharmacokinet. 2010 Apr 1;49(4):269-75.

Slide 12

Covariates Do Not Explain All Variability



N.Sambol CDDS/SUMC1997

Slide 13

Unexplained Clearance Variability

Drug	BSV_U %	WSV_U %	Source
Metoprolol	53	35	Lunn (1997)
Fenoterol	12	16	Bouillon (1996)
Riluzole	51	28	Bruno (1997)
Felodipine	34	33	Wade (1995)
Drug A	57	29	Karlsson (1993)
Drug B	35	19	Karlsson (1993)
Drug B	33	19	Jonsson (1996)
Moxonidine	22	15	Karlsson (1998)
Artemisinin	48	53	Sidhu (1998)
Average	**41**	**30**	

BSV_U=Between Subject **WSV_U=Within Subject**

Slide 14

Safe and Effective Variability

- CLINICAL JUDGMENT
  Suppose medicine use is safe and effective if:
  1. Individual Css is on average at the Target Conc
     – Aim for the optimum target
  2. 90% of the time Css is within 80%-125% of Target Conc
     – 'therapeutic range' with optimum target
- STATISTICS
  Assume log-normal distribution for Css
  90% of Css must lie within ± 1.64 x SD
  – Therefore SD must be 0.136

The Safe and Effective Variability (SEV) is 13.6%

Slide 15

Three Ways to Dose

- Population
  » Same dose for everyone
  – The dream dosing method!
- Group (Covariate guided)
  » Same dose for similar group
  – e.g. same weight, CLcr, genotype
- Individual
  » Dose determined by individual response
  – e.g. BP, INR, blood conc

Slide 16

Dosing Individualization Method Depends on Safe and Effective Variability (SEV)

Suppose PPV_{total}=0.7, BSV_u=0.4, WSV_u=0.3

$PPV_U=sqrt(BSV_u^2 + WSV_u^2)=0.5$ $BSV_P=sqrt(PPV_{total}^2 - BSV_u^2)=0.57$

SEV	Method Criteria	Example	Dosing Strategy
0.9	SEV>PPV_{total}	**0.9>0.7**	Population dosing
0.55	PPV_{total} > SEV SEV>PPV_u	0.7>0.55 **0.55>0.5**	Group dosing (WT, CLcr, etc) (BSV_P ⇨ 0)
0.35	PPV_u > SEV SEV>WSV_u	0.5>0.35 **0.35>0.3**	Individual response dosing (TCI) (BSV_U ⇨ 0)

Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68

Slide 17

Safe and Effective Variability (SEV) Aminoglycosides

PPV_U	BSV_U	WSV_U
0.33	0.30	0.13

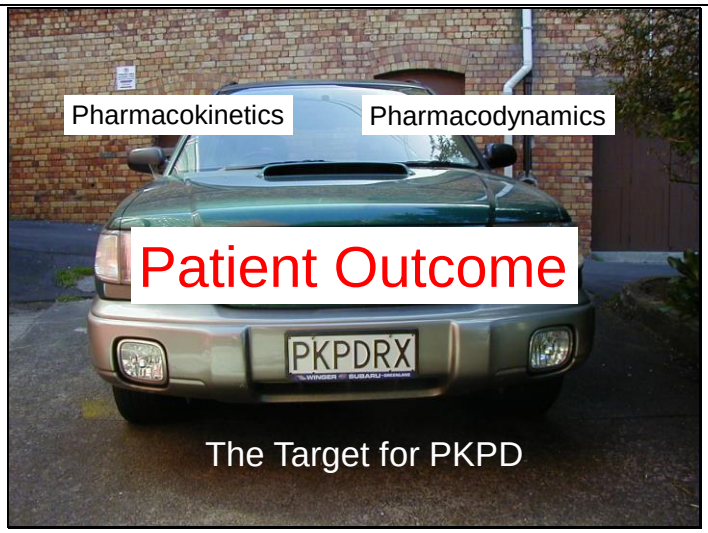
- Suggested Therapeutic Success Criterion
  90% of Concs Within 80%-125% of Target Css
  ∴ SEV is 0.136 (log normal SD)
- Unpredictable PPV_U is 0.33 and is > SEV
  ∴ Covariate (WT, CLcr) prediction alone will be inadequate
- Unpredictable WSV_U is 0.13 and is < SEV (just!)
  ∴ TCI can achieve safe and effective target

Matthews I, Kirkpatrick C, Holford NHG. Quantitative justification for target concentration intervention - Parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. British Journal of Clinical Pharmacology 2004;58(1):8-19

Slide 18

Know Your Target Be Courageous

- Target for drug development is to learn
  - » **the concentration effect relationship**
  - » **safe and effective variability**
- Target for clinical practice is to confirm
  - » **Target effect and target concentration**
  - » **Best method for achieving the target effect for the patient**
- PKPD provides the tools to achieve the targets
  - » **time to move away from traditional empirical approaches**.
  - » **drug developers and clinicians must have courage to change**
- **Take Aim and Hit the Target!**

Slide 19	# Which Way to Aim? ● Phase 2 Drug Development » PK and PKPD relationships (Target Effect ⟶ Target Conc) » Predictable and Unpredictable variability (PPV_T) » Between (BSV_U) and within subject (WSV_U) ● Phase 3 Drug Development » Safe and effective variability (SEV) » The BIG difficulty is deciding on SEV ! ● Clinical Use of Medicines » Use quantitative criteria to decide on dosing method » Covariate Dosing if PPV_T>SEV>PPV_U » TCI Dosing if PPV_U>SEV>WSV_U 	
Slide 20		The target for PKPD is improving patient outcome by developing medicines which can achieve the target effect
Slide 21	# References Bouillon T, Meineke I, Port R, Hildebrandt R, Günther K, Gundert-Remy, U. Concentration-effect relationship of the positive chronotropic and hypokalaemic effects of fenoterol in healthy woimen of childbearing age. Eur J Clin Pharmacol 1996;51:153-160. Bruno R, Vivier N, Le Libouix A, Powe LK, Delumeau JC, Rhodes GR. Population pharmacokinetics of riluzole in patients with amuyotrophic lateral sclerosis. Clin Pharmacol Ther 1997;62:518-526. Holford NHG, Tett S. Therapeutic Drug Monitoring. Chapter in Avery's Drug Treatment (4th Edition) Eds. Speight T, Holford NHG. 1997; Adis Intl, Auckland Holford NHG. Target Concentration Intervention: Beyond Y2K. British Journal Clinical Pharmacology 1999; 48: 9-13 Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68 Jonsson EN, Wade JR, Karlsson MO. Comparison of some practical sampling strategies for population pharmacokinetic studies. J Pharmacokin Biopharm 1996;24:245-263. Karlsson MO and Sheiner LB. The importance of modeling interoccasion variability in population pharmacokinetic analyses. J Pharmacokinet Biopharm 1993;21:735-750 Karlsson MO, Jonsson EN, Wilste CG, Wade JR. Assumption testing in population pharmacokinetic models: illustrated with an analysis of moxonidine data from congestive heart failure patients. J Pharmacokin Biopharm 1998;26:207-246. Lunn DJ and Aarons LJ. Markov Chain Monte Carlo techniques for studying interoccasion and intersubject variability: application to pharmacokinetics data. Appl Statist 1997;46:73-91 Sidhu JS, Ashton M et al. Artemisinin population pharmacokinetics in children and adults with uncomplicated falciparum malaria. Br J Clin Pharmacol 1998;45:347-354 Wade JR, Sambol NC. Felodipine population dose-response and concentration-response relationships in patients with essential hypertension. Clin Pharmacol Ther 57, 569-81, 1995 	