EMA EFPIA workshop
Break-out session no. 3

Case Study Title:

Revatio in Paediatric Pulmonary Arterial Hypertension (PAH), an Orphan Indication

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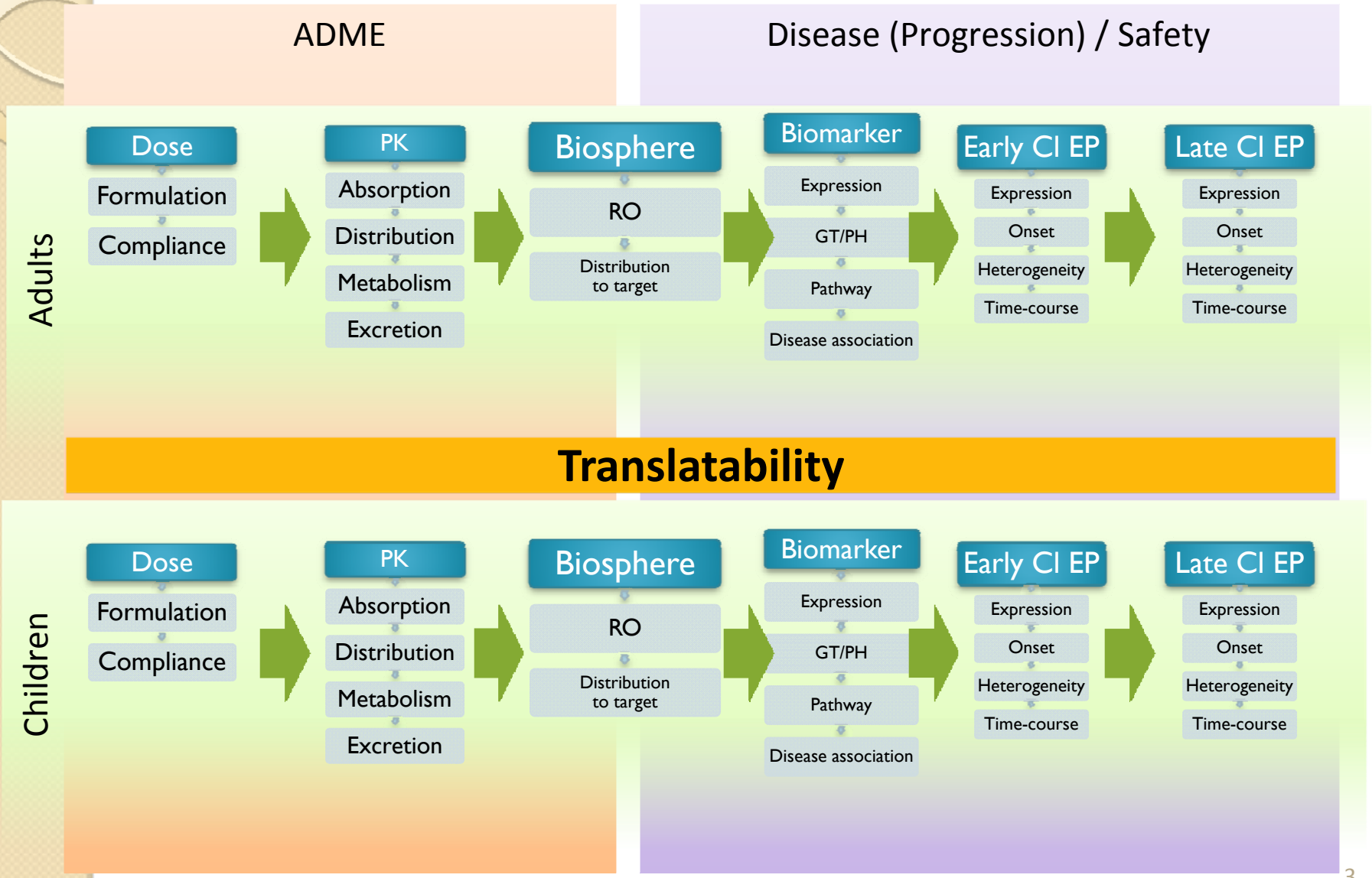
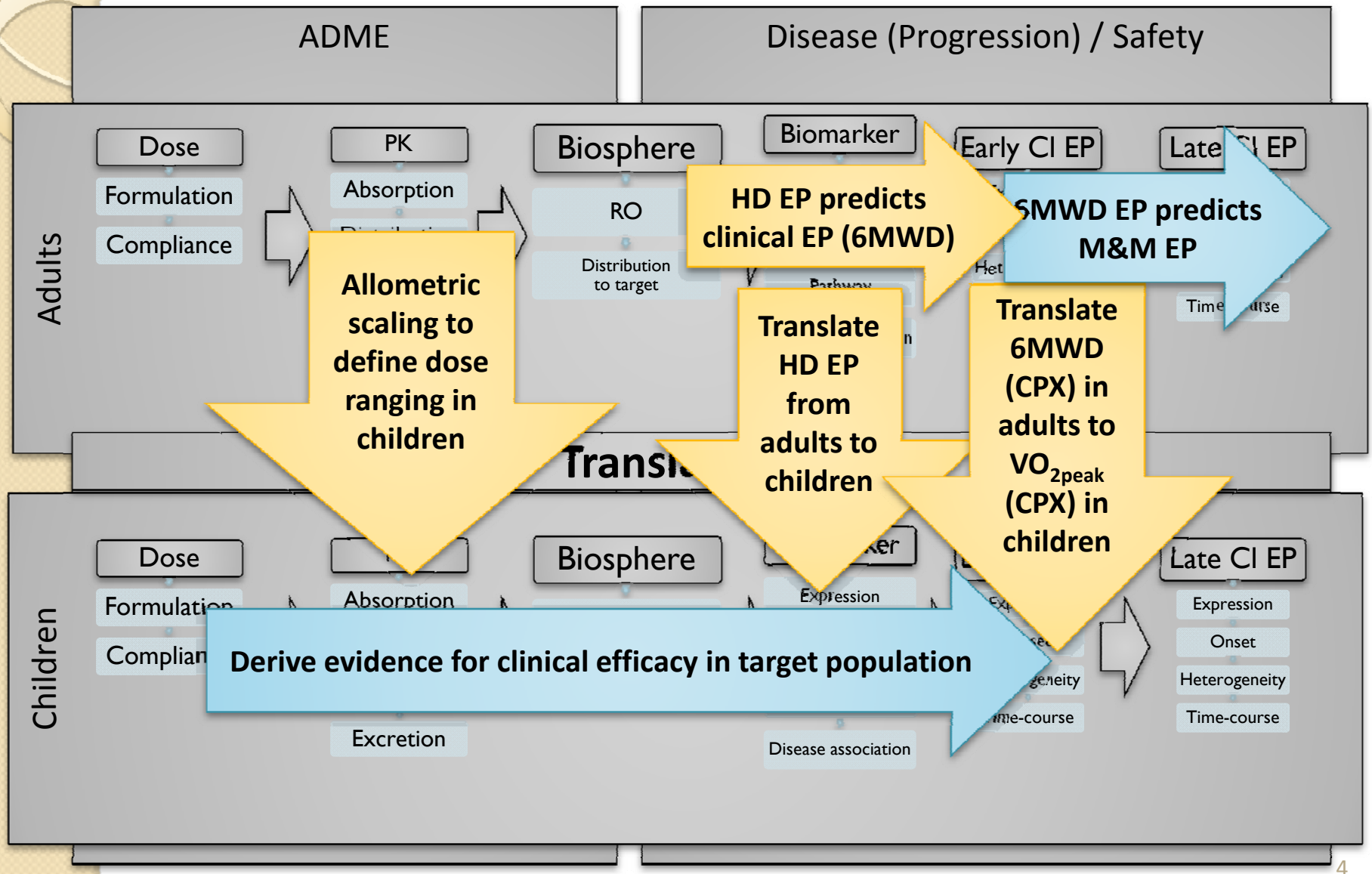
The Sildenafil Case

- Orphan Indication Pulmonary Arterial Hypertension (PAH)
  - Progressive life-threatening, prevalence 2-20:1M
- Aim: Assessment of Sildenafil efficacy and dose selection in children with PAH
  - Adult PAH program ran in parallel to single pediatric pivotal trial
  - Labelled adult oral dose regimen 20 mg TID
- Pediatric trial
  - Dose ranging (3 wt based treatment cohorts), plc controlled, in PAH patients, 1-17 years old
  - Primary PD EP (VO_{2peak} at week 16) only available in **7**-17 years
    - No widely accepted clinical effect size (~10-15% improvement on CFB), and different clinical EP (6MWD) compared to adults
  - Secondary PD EP in **1**-17 years (hemodynamics: PVRI)
    - Clinical relevance under debate, but allows scaling of PD from adults to children
  - Population PK scales adult to pediatric exposure from 1-17 years

Factors Predicting Treatment Response ...



…Translated to a Pediatric PAH Population

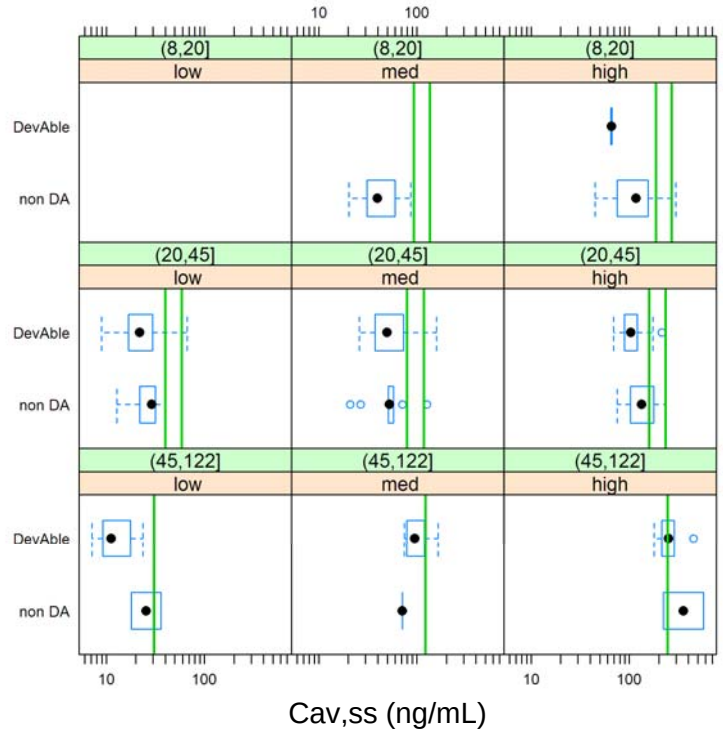


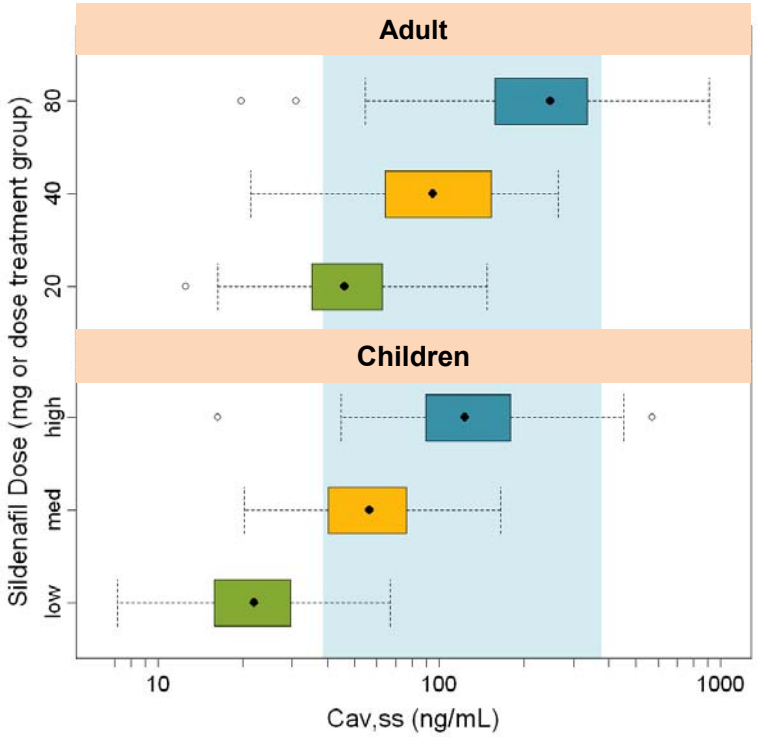
M&S Assumptions

- Minor assumptions on PK, since measured in pediatric population
  - fewer patients at lower weight/age range
  - maturation model on CYP3A4 and IV data in neonates to justify modelled CL intercept at low weight/age
- At design stage allometric PK/dose scaling used to project doses predicted to have similar exposure/PDE5 inhibition as 3 tested dose levels in adults
  - Population PK model of integrated adult/pediatric data discarded the "allometric" relationship
    - Assumption of equal exposure across weight range violated
    - → weight adjusted dose group comparison inconsistent in statistical analysis
- PD endpoint translation from adult to children
  - Bridging "hemodynamic" biomarker connects adults and children in response measure
  - But similarity of HD treatment response between adults and children not undisputed

Allometric Scaling Assumption Challenged

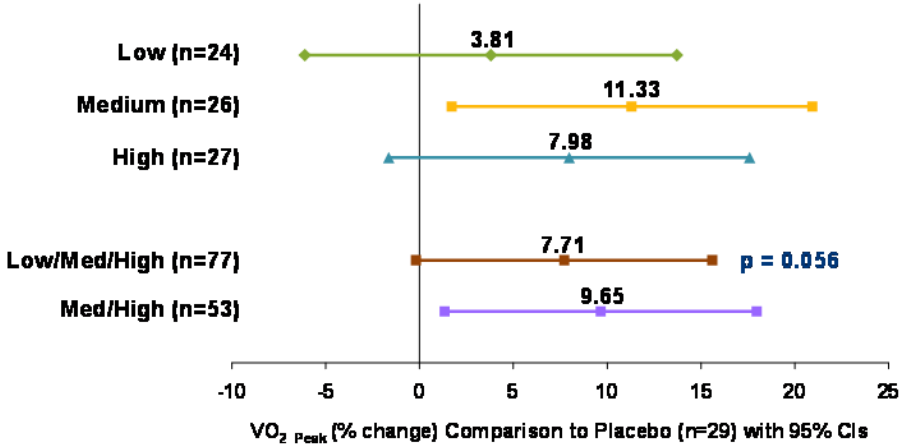
Exposure distribution across dose and weight groups in pediatric trial



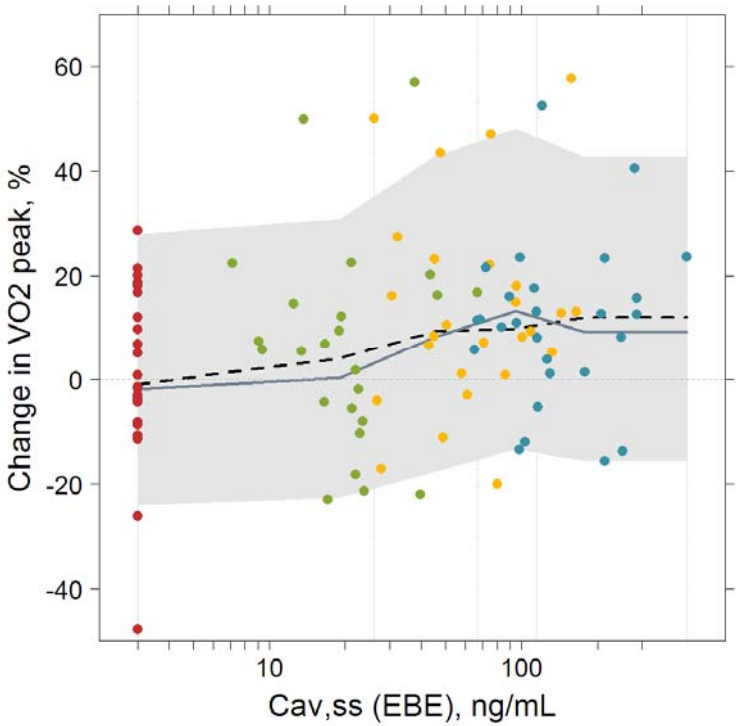


Primary EP Analysis for VO_{2peak}

Treatment Difference in Percentage Change from Baseline for VO_{2peak} at Week 16



VPC of Population PKPD Model

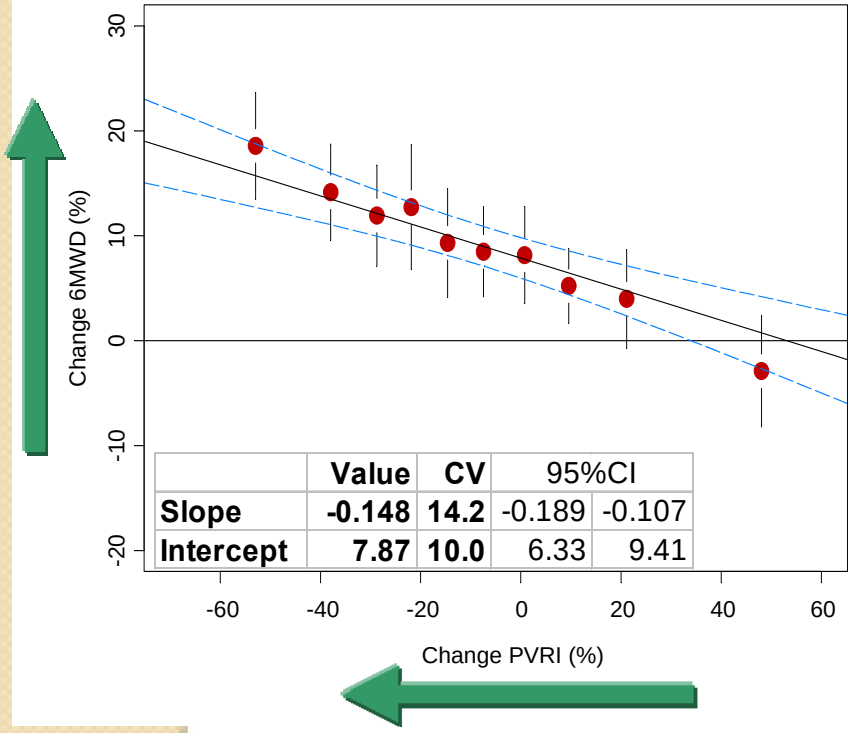


Population PKPD Parameter Estimates

Parameter	Mean	CV (%)	SD (%)	95%CI	
Baseline-VO_{2peak}, mL/kg/min	17.6	2.4	23.8	16.8	18.4
E_{max}, %	8.8	24.3		4.6	12.9
EC_{50}, ng/mL	31.1	19.5		19.2	43
HILL	8	Fixed			
Res-error, %	11.9				
EC_{90}, ng/mL	40.9	19.5		26.2	56.6

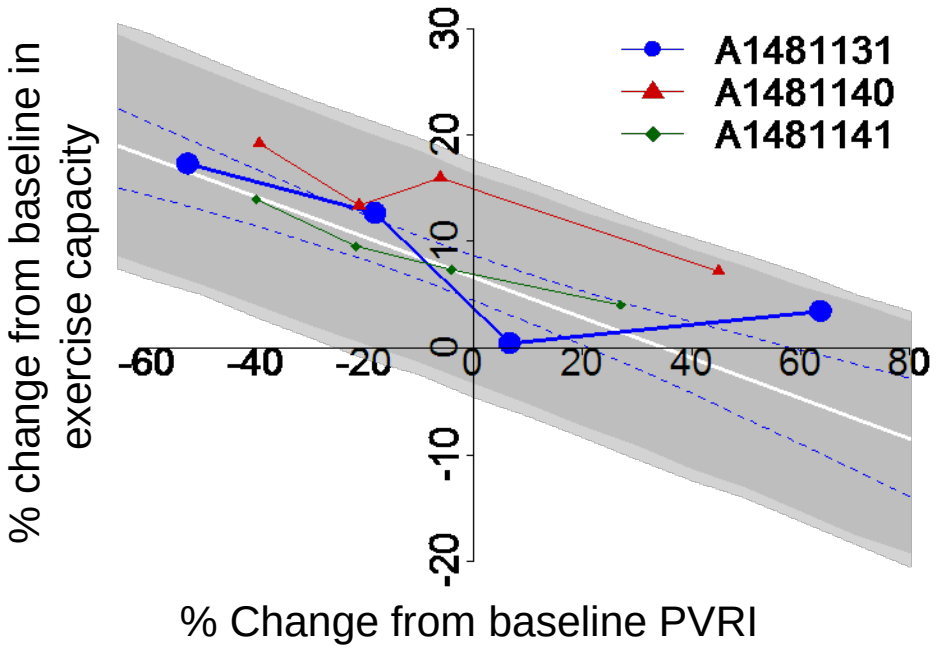
Sildenafil Data from Children are Consistent with Adult Data and the FDA Model

Univariate Regression of %Δ6MWD vs. %ΔPVRI for Pooled Analysis



	Value	CV	95%CI	
Slope	**-0.148**	**14.2**	-0.189	-0.107
Intercept	**7.87**	**10.0**	6.33	9.41

FDA based prediction interval + Sildenafil adult and children data

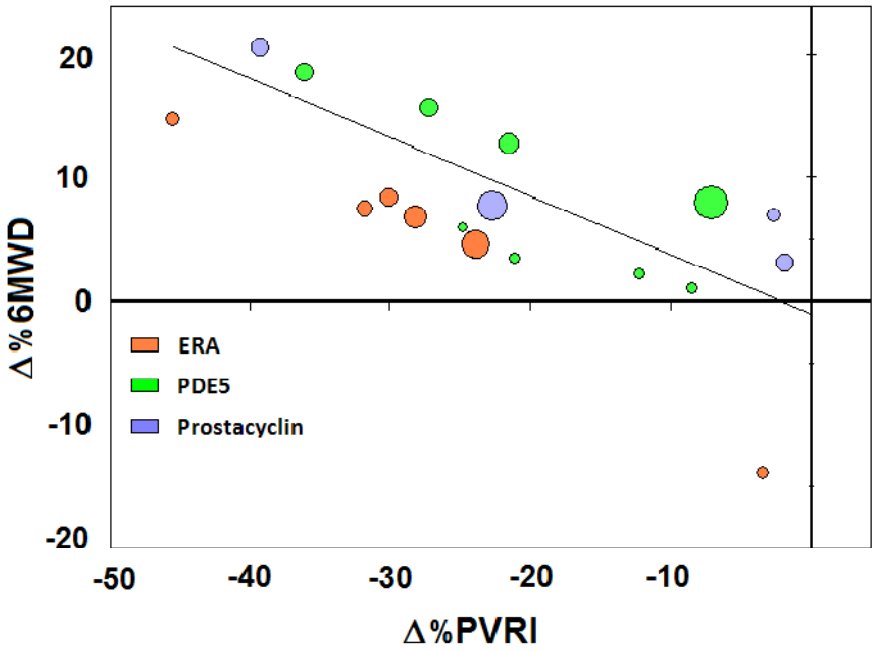


n=30/bin (dark grey)
n=24/bin (light grey)

Source: FDA-CDER-CDRAC, 29th July 2010, Satjit Brar, Pharm.D., Ph.D., Division of Pharmacometrics, "Use of Change in PVRI for Dosing Recommendations of Adult-Approved Drugs in Pediatric PAH Patients"

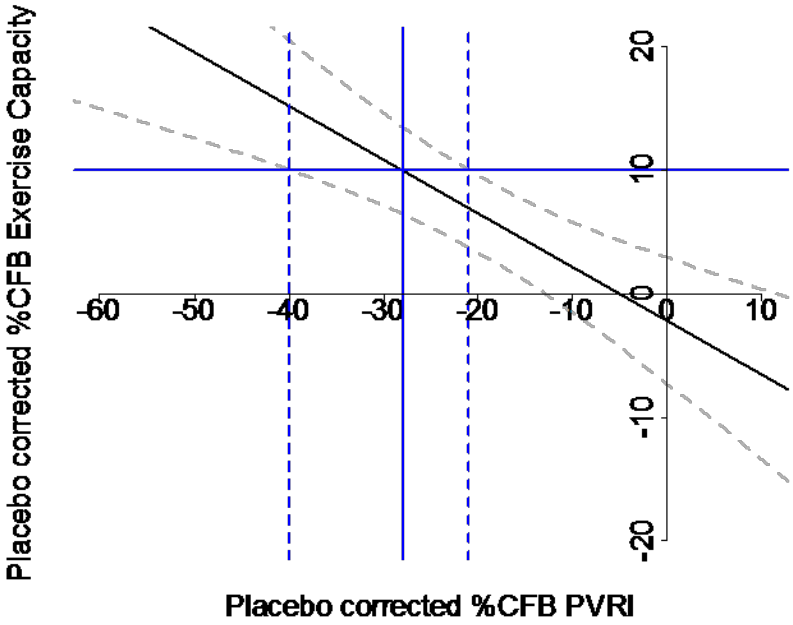
Target %Change PVRI Effect Size

FDA: Δ%6MWD-Δ%PVRI Relationship



	Value	CV	95%CI	
Slope	**-0.436**	**24.2**	-0.64	-0.23
Intcpt	**-2.23**	**116.6**	-7.33	2.87

Minimally Important Effect Target

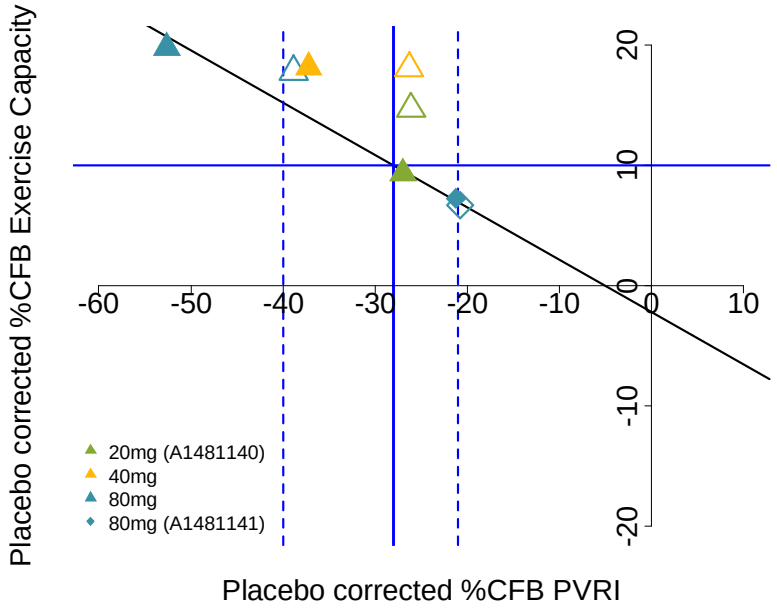


Δ% change in CPX	**Δ% change in PVRI**	
	Intercept	
	no	yes
5	11	**17**
10	23	**28**
15	34	**40**
20	46	**51**

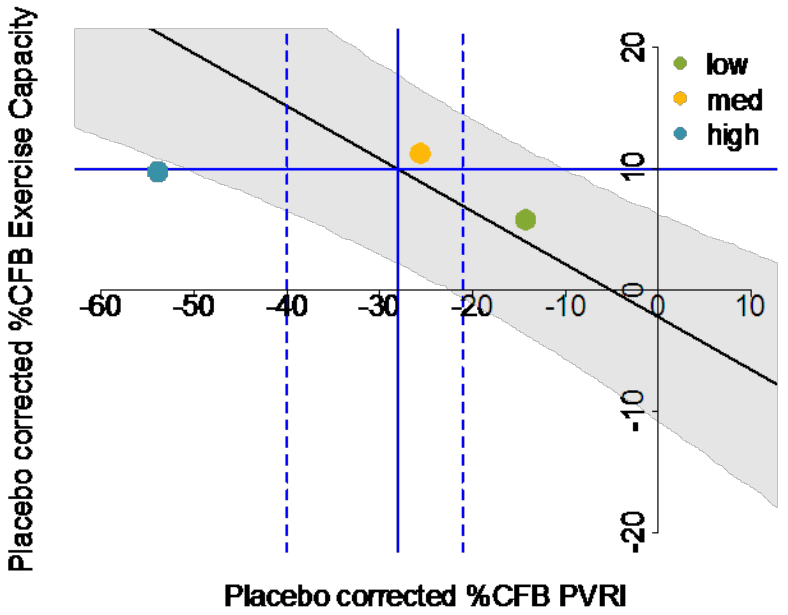
Source: FDA-CDER-CDRAC, 29th July 2010, Satjit Brar, Pharm.D., Ph.D., Division of Pharmacometrics, "Use of Change in PVRI for Dosing Recommendations of Adult-Approved Drugs in Pediatric PAH Patients"

Sildenafil Data Appear Consistent with ΔΔ-Model and Achieve Target PVRI Response

Adults

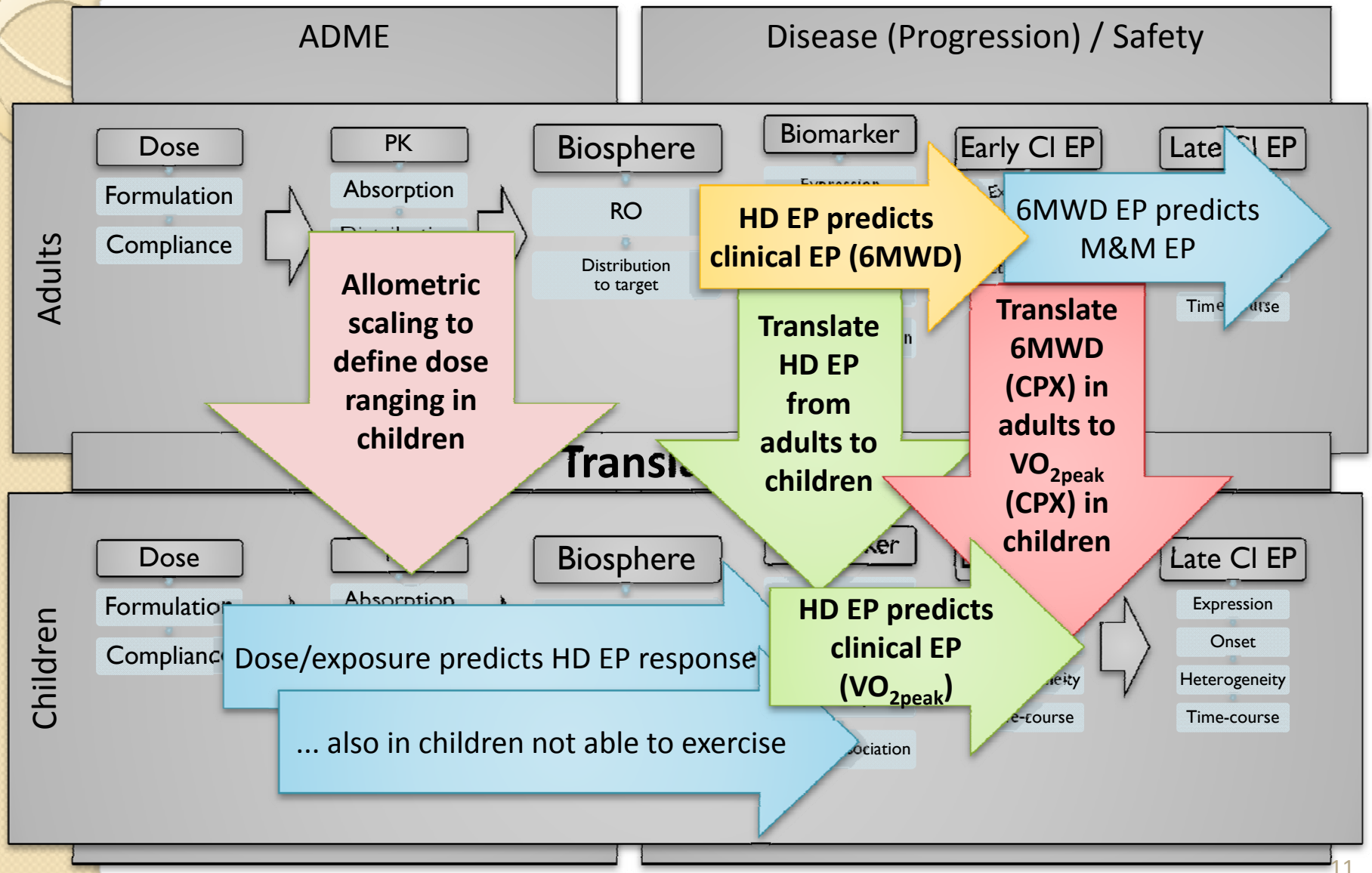


Pediatrics



Closed symbols: IPAH/SurgRep subpopulation
Open symbols: all (+CTD) adult patients

Assumption & Modelling vs "*Missing*" Evidence



Assumption Impact & Consequence

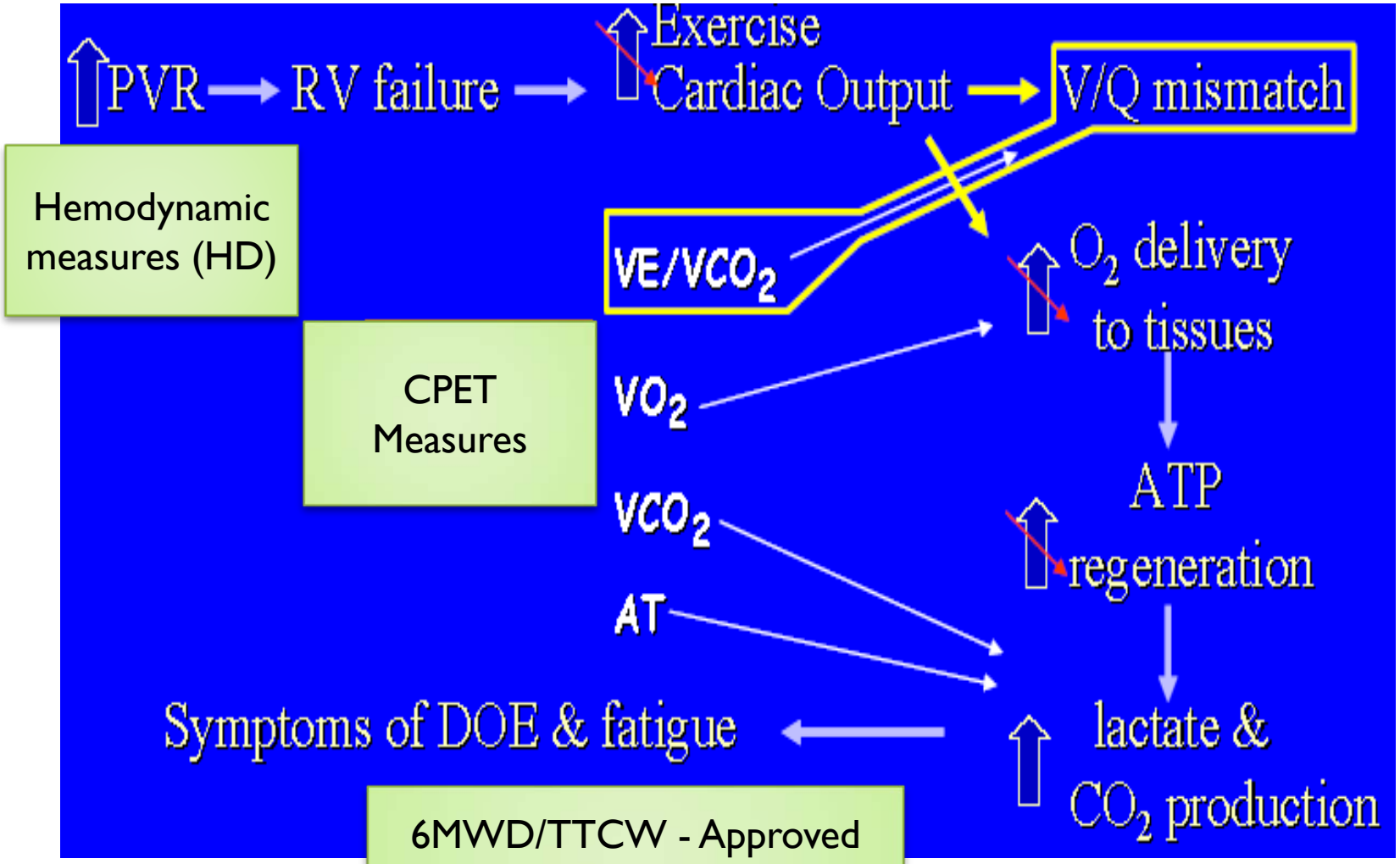
Assumption	Probability to violate (uncertainty)	Consequence	Potential M&S impact
	Based on biological/ pharmacological/clinical prior understanding	Needs to adjust for environmental condition	Generally depends on density of available data
AUC_{ped} = AUC_{adult} (assuming allometric scaling)	**likely (at design stage)**	**major (equal exposure assumption in stats analysis)**	**… allows regrouping … PKPD-model to define EC90**
AUC_{ped} ~ AUC_{adult}	**unlikely (post readout)**	**moderate**	**… quantifies confounding factors**
CPX_{ped} ~ CPX_{adult} (clinic. meaningful effect size)	**moderate**	**moderate**	**… allows bridging <u>only</u> in conjunction with HDs**
$(CPX\sim HD)_{ped}$ = $(CPX\sim HD)_{adult}$	**unlikely**	**major**	**… qualifies bridging of CPX~HD EPs between populations**
DP_{ped} = Dp_{adults}	unlikely	moderate	… justifies design in SP
HD-ER_{ped} = HD-ER_{adults}	unlikely	major	… justifies dose in children
HD-$ER_{<7y/non\text{-}able}$ = HD-$ER_{>7y/able}$	unlikely	major	… justifies dose in younger/non-able children
HD-ER_{strata} = HD-$ER_{major\text{-}group}$	moderate	moderate	… quantifies dose for strata
CPX-$ER_{<7y/non\text{-}able}$ = CPX-$ER_{>7y/able}$	very likely	major	No existing data, → future research

Conclusions

- Model based approach addressed efficacy evaluation of sildenafil in pediatric PAH
  - including dose selection and evaluation of sub-group performance (backups)
- Labelled dose is model based
  - but input at design stage could have strengthen analyses, especially could have accounted *a priori* against violating assumptions in the design and primary analyses
- M&S could alleviate the risk to violate some assumptions on translational EPs, but not all
  - might lead to further investigations (development of alternative EPs in very young patients)
  - led to discussion on label restrictions

BACKUPS

Cardiopulmonary Exercise Testing in PAH



PK Prior and Exploratory Dosing Regimen

Predicted Exposure Measures of Sildenafil in Paediatrics across weight groups at each dose level

Body Weight (kg)	Low Dose			Medium Dose			High Dose		
	Cmax (ng/mL)	C_{min} (ng/mL)	C_{avg} (ng/mL)	Cmax (ng/mL)	C_{min} (ng/mL)	C_{avg} (ng/mL)	Cmax (ng/mL)	C_{min} (ng/mL)	C_{avg} (ng/mL)
10	251.5	20.4	135.9	251.5	20.4	135.9	503.0	40.7	271.9
15	173.0	14.0	93.7	173.0	14.0	93.7	347.0	28.1	187.0
25	109.0	8.8	58.9	218.0	17.6	118.0	436.0	35.3	236.0
40	71.4	8.6	40.0	143.0	17.2	80.0	286.0	34.5	160.0
55	53.8	7.6	30.7	215.0	30.5	123.0	430.0	61.1	246.0

The predictions were obtained by scaling adult pharmacokinetic parameter values for sildenafil (oral clearance = 53.2 L/hr, apparent volume of distribution = 232 L, absorption rate constant = 4.24 hr^{-1}) based on body weight

Applied Dosing Regimen

Body Weight (kg)	Dose Low	Dose Medium	Dose High
≥8 - 20		10 mg	20 mg
>20 - 45	10 mg	20 mg	40 mg
>45	10 mg	40 mg	80 mg

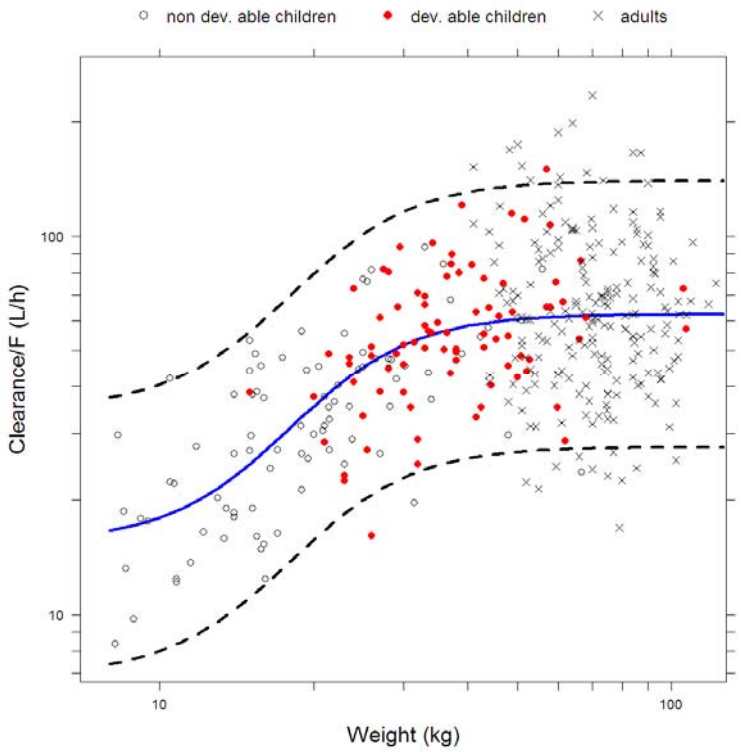
Pop PK: Parameter Estimates and CL Maturation Model

Parameter	Unit	Point Estimates	CovStep RSE %	95% CI	
Ka	1/h	4.51	19.6	2.78	6.24
CL_0/F	L/h	14.3	21.4	8.3	20.3
V/F	L	302	5.2	271	333
$ALAG_1$	H	0.24	1.93	0.23	0.25
CL_{max}	L/h	57.2	5.21	51.4	63.0
WT50	kg	21.7	13.3	16.0	27.4
WT on V/F		0.655	20.2	0.396	0.914
DoseExpo		-0.217	32.8	-0.357	-0.077
Gamma		3.76	17.6	2.46	5.06
MIX.ERR	ng/mL	2.47	20.7	1.47	3.47
H3A4 on CL/F		-0.298	15.4	-0.388	-0.208
BETAB on CL/F		-0.344	17.8	-0.464	-0.224
D3A4 on CL/F		3.12	42.6	0.51	5.73
CV_{KA}		1.12	11.6	0.87	1.37
$CV_{CL/F}$		0.493	4.9	0.446	0.540
$CV_{V/F}$		0.571	7.09	0.492	0.650
Res		0.263	4.75	0.239	0.288

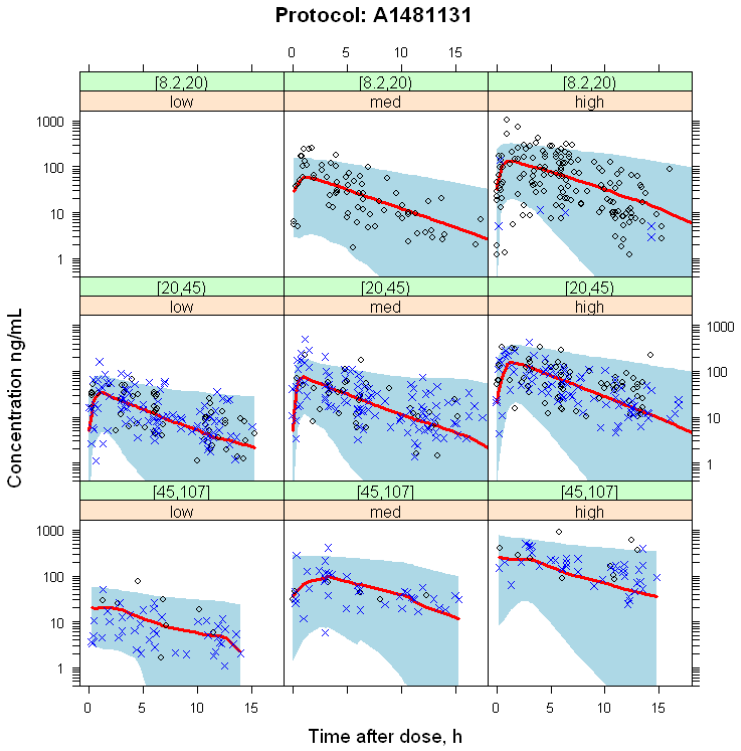
$$CL/F = \left[CL_0 + \frac{(CL_{max} - CL_0) * WT^{\gamma}}{WT^{\gamma} + WT_{50}{}^{\gamma}} \right] * (\mathrm{DOSE}/29.6)^{\theta 1}$$

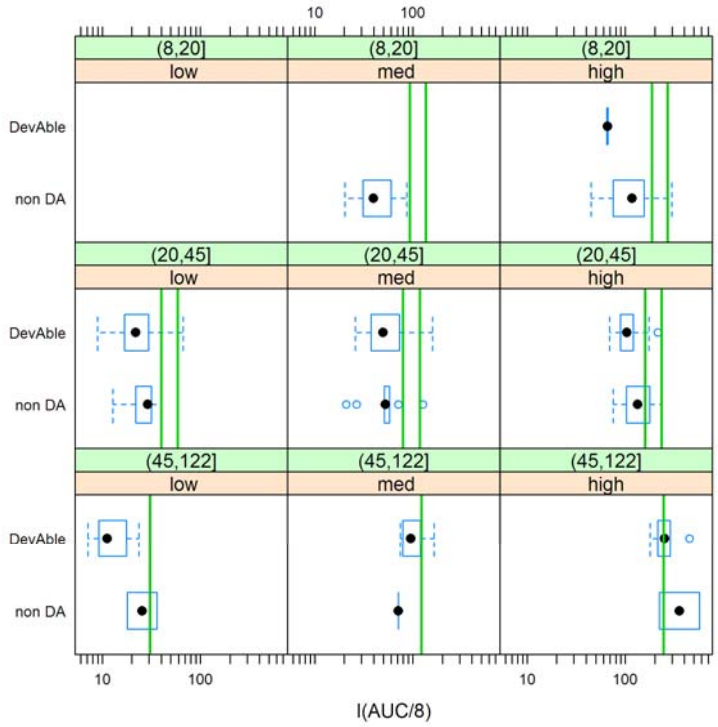
$$\mathrm{V/F} = TV * (\mathrm{WT}/53.1)^{\theta 2} * (\mathrm{DOSE}/29.6)^{\theta 1}$$

$$Ka = TVKa$$



VPC and Deviation from Allometric Scaling Model





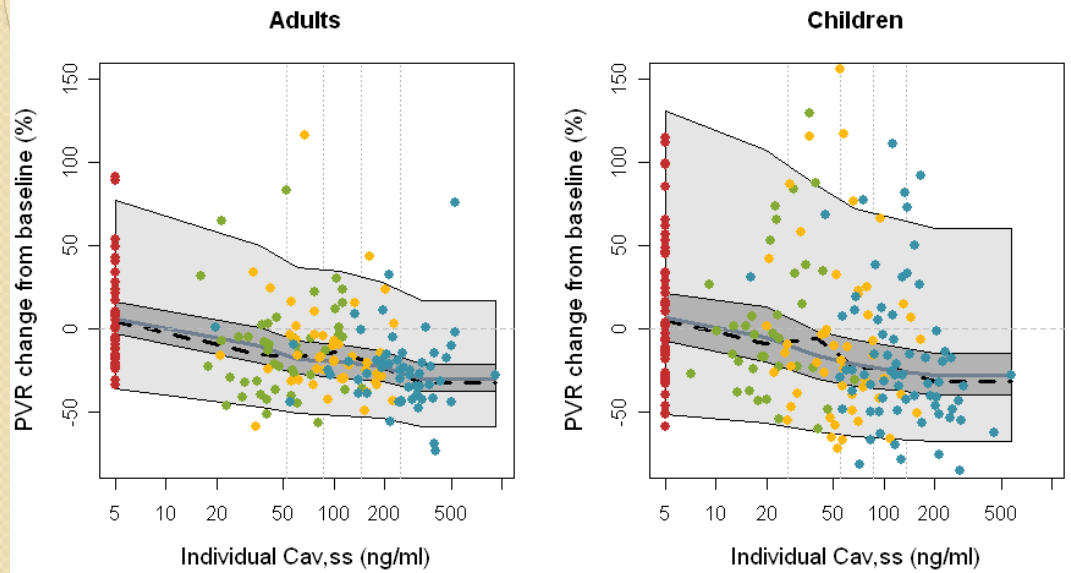
PK samples from 173 children (1-17 years) and 207 adult patients

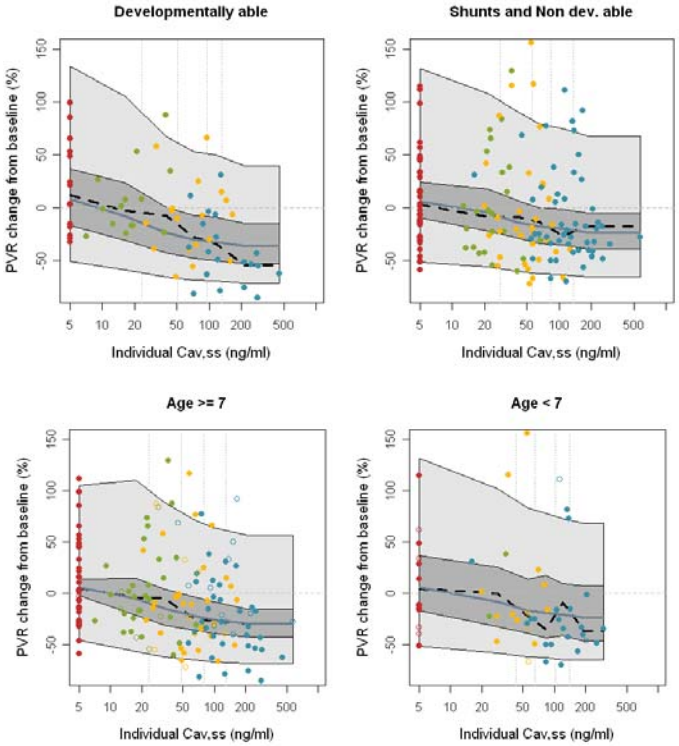
Population PK/PD Estimates for Final PVR Model

Parameter	*Theta*	*CV (%)*	*Value and unit on transformed parameter*		*95% CI*	
BASE	6.97	0.613	1064	$dyne.s/cm^5$	978.8	1157
$BASE_{CTD}$	6.71	1.26	820.6	$dyne.s/cm^5$	694.9	968.9
$BASE_{BSA}$	-0.0627	17.5	0.804	$/0.5m^2$	0.7433	0.8641
$BASE_{Age}$	-0.00122	22.3	0.919	/10y	0.8843	0.9526
$BASE_{FC}$	0.0444	14	1.363	/1 FC	1.247	1.479
E_0	0.0606	57.8	6.247	%	-0.7968	13.79
$Slope_1$	-0.00506	19.4	-22.35	%/50ng/mL	-29.47	-14.52
$Slope_{1,devable}$	-0.00829	24.4	-33.93	%/50ng/mL	-45.8	-19.47
$Slope_2$	-0.000525	42.1	-2.591	%/50ng/mL	-4.678	-0.4581
Thrs	48.9	0.00301	48.9	ng/mL	48.9	48.9
IIV_{ADULT}	0.47	5.21	47	%	42.2	51.8
IIV_{PED}	0.57	5.67	57	%	50.67	63.33
RV_{ADULT}	0.22	9.64	22	%	17.84	26.16
RV_{PED}	0.336	4.91	33.6	%	30.37	36.83

- Step-wise linear model. Threshold Cav,ss at 48.9 ng/mL with shallower response beyond
- Improvement of PVR of at least 22% among the adult and pediatric population at 50 ng/mL
- Response in the developmentally able or children >7 years around 5-10% larger than in the remainder of the population
- Covariates identified to be influential on PVR at baseline: BSA, AGE, and FC. While BSA and FC effects not different between adults and children, age appears only in the adults

HD Effects in PAH Populations





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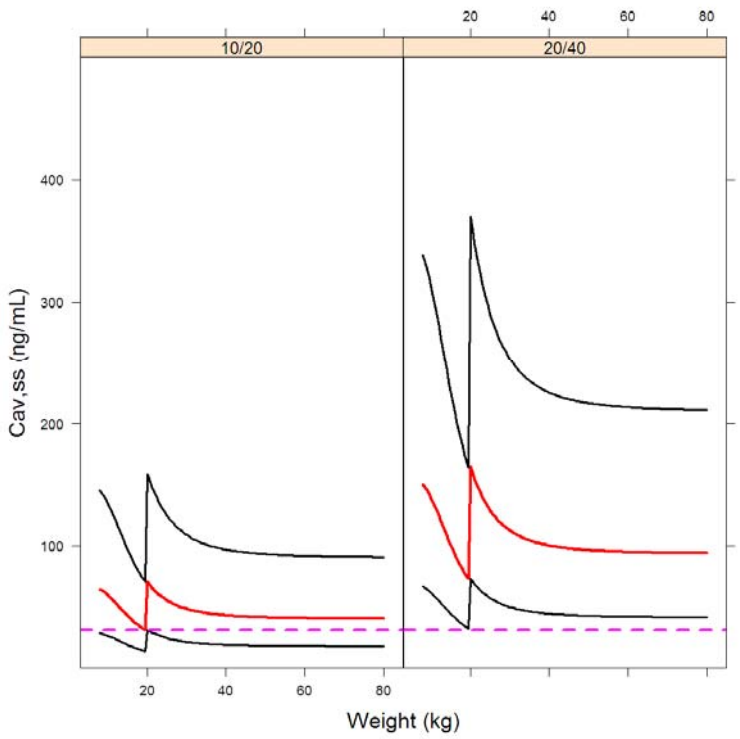
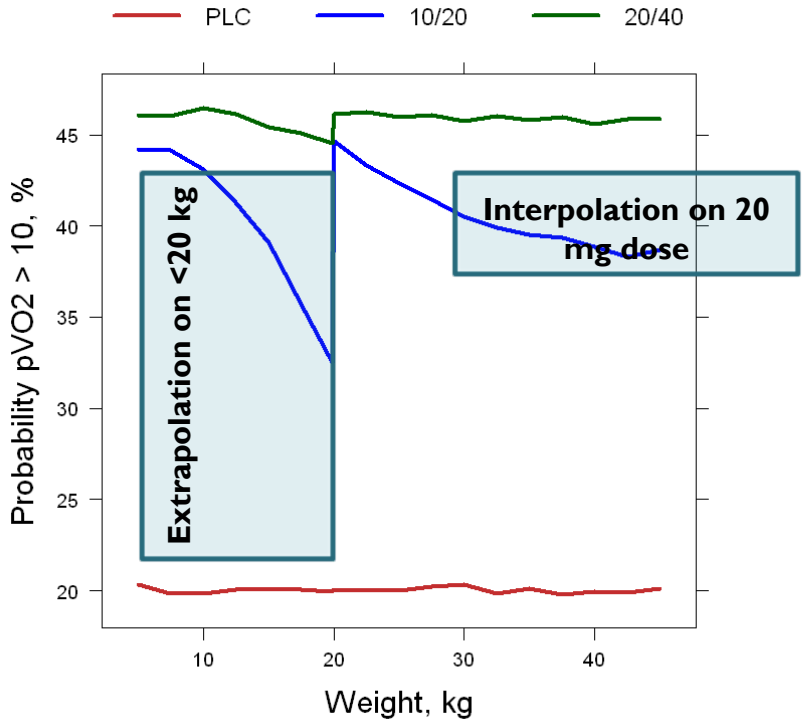
4 Way Dose Regimen Derivation

1: achieve concentration threshold

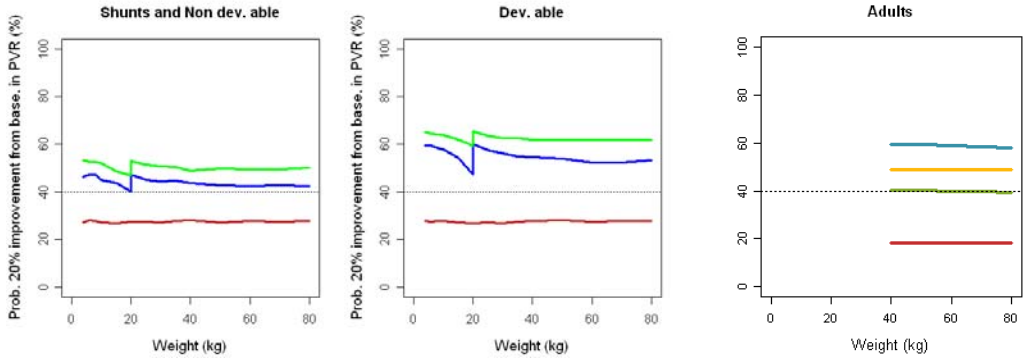


2: achieve VO_{2peak} 10% improvement



4 Way Dose Regimen Derivation

3: achieve HD threshold target



80 mg
40 mg
20 mg
10 mg
placebo

20/40 mg
10/20 mg
placebo

4: achieve HD equivalency target