SUPPORTING INFORMATION FOR:

AN ACCURATE IN VITRO PREDICTION OF HUMAN VD_{ss} BASED ON THE ØIE-TOZER EQUATION AND PRIMARY PHYSICOCHEMICAL DESCRIPTORS. 3. ANALYSIS AND ASSESSMENT OF PREDICTIVITY ON A LARGE DATASET.

Giuliano Berellini and Franco Lombardo*

Drug Metabolism and Bioanalysis Group, Alkermes Inc., Waltham, MA, 02451

SUPPLEMENTAL TABLE 1. Prediction performance for VD_{ss} and f_{ut} using Model 1 for the 8 compounds with human $f_{ut} < 0$.

Compound	f_{up}	$logD^{7.4}$	Observed f_{ut}	Predicted f_{ut}	Observed VDss (L/kg)	Predicted VD_{ss} (L/kg)	Fold-Error VD_{ss}
Cephalothin	0.22	-2.2	-1.54	1.36	0.07	0.19	2.65
Diflunisal	0.0016	0.76	-0.08	0.007	0.097	0.20	2.02
Fenoprofen	0.02	1.74	-1.18	0.02	0.1	0.42	4.17
Glyburide	0.021	2.18	-0.30	0.02	0.08	0.51	6.40
Indomethacin	0.01	0.89	-0.40	0.02	0.096	0.26	2.76
Naproxen	0.002	0.33	-0.05	0.01	0.09	0.18	2.00
Suprofen	0.006	-0.52	-0.03	0.04	0.04	0.17	4.18
Tiaprofenic acid	0.015	-0.74	-0.22	0.08	0.08	0.18	2.19

SUPPLEMENTAL TABLE 2. Prediction performance for VD_{ss} and f_{ut} using Model 2 for the 13 compounds with human $f_{ut} > 1$.

Compound	fup	logD7.4	Observed fut	Predicted fut	Observed VDss (L/kg)	Predicted VDss (L/kg)	Fold-Error VDss
Acetylsalicylic Acid	0.68	-2.57	4.77	2.70	0.22	0.26	1.19
Amoxicillin	0.85	-3.2	4.69	1.71	0.25	0.37	1.48
Ampicillin	0.85	-1.8	8.30	0.99	0.22	0.51	2.31
Cephalexin	0.85	-1.1	11.18	0.81	0.21	0.58	2.77
Cephaloridine	0.8	-1.62	1.07	1.84	0.46	0.34	1.34
Cephradine	0.95	-1.15	18.14	0.63	0.21	0.77	3.64
Dicloxacillin	0.033	-0.17	5.24	0.09	0.11	0.25	2.31
Enalaprilat	0.62	-1	1.07	0.23	0.38	1.19	3.13
Metronidazole	0.96	0.12	1.75	0.83	0.4	0.63	1.57
Penicillin G	0.4	-0.82	1.53	0.73	0.24	0.35	1.46
Piperacillin	0.5	-2	1.58	1.60	0.27	0.27	1.01
Tolbutamide	0.05	0.36	1.75	0.09	0.12	0.33	2.73
Valproic Acid	0.08	0.13	1.08	0.14	0.14	0.33	2.37

SUPPLEMENTAL TABLE 3. Prediction performance for VD_{ss} and f_{ut} using Model 3 for the 15 compounds with human $f_{up} < 0.01$.

Compound	f_{up}	$logD^{7.4}$	Observed f_{ut}	Predicted f_{ut}	Observed VDss (L/kg)	Predicted VD_{ss} (L/kg)	Fold-Error VD_{ss}
Amiodarone	0.0002	5.95	0.0000013	0.0000124	60	6.25	9.59
Candesartan	0.002	-1.35	0.0302	0.0252	0.13	0.14	1.04
Carprofen	0.001	1.09	0.0033	0.0042	0.22	0.19	1.13
Diclofenac	0.005	1.22	0.0165	0.0125	0.22	0.26	1.17
Felodipine	0.0036	4.52	0.0003	0.0017	4.4	0.90	4.92
Fluvastatin	0.0079	1.4	0.0095	0.0158	0.42	0.30	1.42
Ibuprofen	0.006	1	0.051	0.016	0.15	0.25	1.65
Itraconazole	0.002	5.9	0.000104	0.000549	7.4	1.49	4.97
Ketoprofen	0.008	0.19	0.123	0.030	0.13	0.21	1.59
Meloxicam	0.003	0.07	0.0253	0.0159	0.15	0.18	1.18
Minocycline	0.005	-0.04	0.00127	0.00267	1.6	0.82	1.96
Sulfasalazine	0.004	0.8	0.304	0.013	0.11	0.22	1.99
Tebufelone	0.0007	5.63	0.000022	0.000298	12	0.996	12.05
Tenoxicam	0.0085	-0.32	0.0382	0.0412	0.19	0.18	1.03
Tolfenamic acid	0.003	2.1	0.0207	0.0054	0.16	0.31	1.96

SUPPLEMENTAL TABLE 4. Prediction performance for VD_{ss} using Model 1 and 1c for the 20 compounds compared with in vivo O-T prediction in 3 animal species.[a]

Compound	VD_{ss} human (L/kg)	f_{up} human	Predicted VDss O-T rat-dog-monkey[a] (L/kg)	Predicted VDss Model 1 (L/kg)	Predicted VDss Model 1c (L/kg)
Bisoprolol	2.4	0.66	1.66	2.45	3.77
Ciprofloxacin	2.1	0.7	2.32	1.67	2.39
Citalopram	12	0.2	5.24	4.48	7.78
Diclofenac	0.22	0.05	0.17	0.26	0.24
Fleroxacin	1.6	0.73	1.43	1.64	1.88
Furosemide	0.12	0.01	-	-	-
Gatifloxacin	1.7	0.8	1.77	2.12	2.65
Metoprolol	3.1	0.88	5.49	2.34	3.31
Midazolam	1.1	0.02	0.58	0.84	0.87
Morphine	2.3	0.65	2.72	2.66	2.68
Moxifloxacin	1.4	0.6	2.78	2.52	3.19
Pefloxacin	1.5	0.75	2.76	1.41	2.48
Piperacillin	0.27	0.5	-	-	-
Prednisone	0.57	0.27	1.09	0.59	0.70
Propranolol	3.1	0.13	8.57	3.25	3.27
Quinidine	2.9	0.26	2.89	3.65	4.95
Sulfinpyrazone	0.12	0.02	0.12	0.15	0.16

Theophylline	0.51	0.61	0.52	0.54	0.41
Trovafloxacin	1.3	0.24	1.34	4.29	2.01
Valproic acid	0.14	0.08	0.17	0.29	0.30
Venlafaxine	4.4	0.73	3.88	4.97	7.00
Verapamil	3.7	0.09	1.47	5.91	8.57
GMFE			**1.44**	**1.36**	**1.44**

a. In vivo data taken from Lombardo et al. 2013. The set comprises the compound from this work overlapping with the 60 compounds set reported in model V7 in that reference. Furosemide and piperacillin were excluded as in each case one species gave an aberrant ($f_{ut} < 0$) result.