Supplementary example:

Example: Prediction of AUC of bosutinib in a subject with moderate hepatic impairment.

The sum of 5 parameters in subjects with moderate hepatic impairment is 5.02 and the log P value is 3.34 (19). The average of all 6 parameters is 1.39 and dividing by the liver mass = 1.39/0.81 = 1.72. The AUC in healthy subject is 714 ng·hr/mL therefore, AUC in a subject with moderate hepatic impairment = 714 × 1.72 = 1228 ng·hr/mL

Table S1. Predicted and observed AUCs by minimal and whole body PBPK in subjects with mild hepatic impairment

Drugs (n = 19)	Healthy subjects	Units	Observed (mild)	Predicted (MPBPK)	Predicted (PBPK)	Ratio (MPBPK)	Ratio (PBPK)
Bosutinib (S1)	714	ng·hr/mL	1720	991	1265	0.58	0.74
Eliglustat (S2)	69	ng·hr/mL	172	96	568	0.56	3.30
Tofacitinib (S3)	362	ng·hr/mL	369	402	615	1.09	1.67
Sildenafil (S4-5)	1328	ng·hr/mL					
Samidorphan (S6)	278	ng·hr/mL					
Olanzapine (S6)	276	ng·hr/mL					
Treprostinil (S7)	3.5	ng·hr/mL	5.05	4.7	7.62	0.92	1.51
Cabozantinib (S8-9)	32700	ng·hr/mL	61700	51491	51633	0.83	0.84
Atomoxetine (S10)	0.69	ug·hr/mL					
Alectinib (S11)	1995	ng·hr/mL					
Ruxolitinib (S11)	1077	ng·hr/mL	2017	1374	1044	0.68	0.52
Panobinostat (S11)	225	ng·hr/mL	215	278	364	1.29	1.69
Bosentan (S12)	11957	ng·hr/mL	10781	17426	13389	1.62	1.24
Olmesartan (S12)	5964	ng·hr/mL	6780	5448	5795	0.80	0.85
Repaglinide (S12)	92	ng·hr/mL					
Telmisartan (S12)	471	ng·hr/mL	1290	1031	785	0.80	0.61
Valsartan (S12)	21200	ng·hr/mL	46800	22355	26817	0.48	0.57
Pemafibrate (S13)	16	ng·hr/mL	19	29	21	1.50	1.11
Zidovudine (S14)	1388	ng·hr/mL	4715	1299	1868	0.28	0.40
Isavuconazole (S15)	39	ng·hr/L	72	58	41	0.80	0.57
Alprazolam (S16)	220	ng·hr/mL					
Sirolimus (S16)	970	ng·hr/mL	1439	1579	984	1.10	0.68
Nifedipine (S16)	0.03	1/CL (1/L/hr)					
Midazolam (S16)	0.04	1/CL (1/L/hr)	0.04	0.05	0.041	1.28	1.04
Felodipine IV (S16)	1.32	1/CL (1/L/hr/kg)	2.56	1.96	1.92	0.77	0.75
Felodipine Oral (S16)	0.12	1/CL (1/L/hr/kg)	0.36	0.28	0.39	0.78	1.08
Ibrutinib (S16)	67	ng·hr/mL	273	101	291	0.37	1.07
Oseltamivir (S17)	150	ng·hr/mL					

Blank space means data are not available. AUC = area under the curve. The clearance values of midazolam and felodipine were converted to AUC to accommodate as AUC values in the plot since other values were in AUC. The AUC values for felodipine following IV administration for

predicted values by mPBPK and PBPK were 21 and 20.6 ng·hr/mL, respectively. Following oral administration, the AUC values for predicted mPBPK and PBPK were 40 and 56 ng·hr/mL, respectively. For midazolam the AUC values for predicted mPBPK and PBPK were 50 and 41 ng·hr/mL, respectively

Table S2. Predicted and observed AUCs by minimal and whole body PBPK in subjects with moderate hepatic impairment

Drugs (n = 23)	Healthy subjects	Units	Observed (moderate)	Predicted (MPBPK)	Predicted (PBPK)	Ratio (MPBPK)	Ratio (PBPK)
Bosutinib	714	ng·hr/mL	1350	1228	1942	0.91	1.44
Eliglustat	69	ng·hr/mL	575	119	1760	0.21	3.06
Tofacitinib	362	ng·hr/mL	625	510	1099	0.82	1.76
Sildenafil	1328	ng·hr/mL	2450	1897	5312	0.77	2.17
Samidorphan	263	ng·hr/mL	408	311	527	0.76	1.29
Olanzapine	275	ng·hr/mL	424	519	378	1.22	0.89
Treprostinil	3.5	ng·hr/mL	11.7	6.1	11.9	0.52	1.02
Cabozantinib	32700	ng·hr/mL	58700	63129	47096	1.08	0.80
Atomoxetine	0.69	ug·hr/mL	1.16	1.27	4.63	1.09	3.99
Alectinib	1995	ng·hr/mL	3280	4221	3179	1.29	0.97
Ruxolitinib	1077	ng·hr/mL	1380	1718	1826	1.24	1.32
Panobinostat	225	ng·hr/mL	308	348	458	1.13	1.49
Bosentan	11957	ng·hr/mL					
Olmesartan	5964	ng·hr/mL	6972	7084	4965	1.02	0.71
Repaglinide	92	ng·hr/mL	369	207	236	0.56	0.64
Telmisartan	471	ng·hr/mL					
Valsartan	21200	ng·hr/mL	45400	28539	25436	0.63	0.56
Pemafibrate	16	ng·hr/mL	37	35	48	0.94	1.30
Zidovudine	1388	ng·hr/mL	4842	1728	2197	0.36	0.45
Isavuconazole	39	ng·hr/L	101	71	57	0.70	0.56
Alprazolam	220	ng·hr/mL	529	347	566	0.66	1.07
Sirolimus	970	ng·hr/mL	1899	1931	1549	1.02	0.82
Nifedipine	0.03	1/CL (1/L/hr)					
Midazolam	0.04	1/CL (1/L/hr)	0.1	0.06	0.05	0.60	0.51
Felodipine	1.32	1/CL (1/L/hr/kg)					
Felodipine	0.12	1/CL (1/L/hr/kg)					
Ibrutinib	67	ng·hr/mL	558	124	648	0.22	1.16
Oseltamivir	150	ng·hr/mL	227	186	238	0.82	1.05

Blank space means data are not available. Sildenafil observed data were taken from reference S5. In this study, dose of sildenafil was 50 mg but in PBPK model 100 mg dose was used. Therefore, for comparison purpose, the AUC and C_{max} were doubled from reference S5. For midazolam the AUC values for predicted mPBPK and PBPK were 60 and 51 ng·hr/mL, respectively

Table S3. Predicted and observed AUCs by minimal and whole body PBPK in subjects with severe hepatic impairment

Drugs (n = 11)	Healthy subjects	Units	Observed (severe)	Predicted (MPBPK)	Predicted (PBPK)	Ratio (MPBPK)	Ratio (PBPK)
Bosutinib	714	ng·hr/mL	1270	1586	2734	1.25	2.15
Eliglustat	69	ng·hr/mL					
Tofacitinib	362	ng·hr/mL					
Sildenafil	1328	ng·hr/mL					
Samidorphan	278	ng·hr/mL					
Olanzapine	276	ng·hr/mL					
Treprostinil	3.5	ng·hr/mL	18.2	7.5	14.5	0.41	0.80
Cabozantinib	32700	ng·hr/mL					
Atomoxetine	0.69	ug·hr/mL	2.54	1.64	10.4	0.64	4.09
Alectinib	1995	ng·hr/mL	4260	5431	4692	1.27	1.10
Ruxolitinib	1077	ng·hr/mL	1784	2222	3259	1.25	1.83
Panobinostat	225	ng·hr/mL	272	451	587	1.66	2.16
Bosentan	11957	ng·hr/mL					
Olmesartan	5964	ng·hr/mL					
Repaglinide	92	ng·hr/mL					
Telmisartan	471	ng·hr/mL					
Valsartan	21200	ng·hr/mL					
Pemafibrate	16	ng·hr/mL					
Zidovudine	1388	ng·hr/mL	6321	2262	2516	0.36	0.40
Isavuconazole	39	ng·hr/L					
Alprazolam	220	ng·hr/mL					
Sirolimus	970	ng·hr/mL	2597	2487	2292	0.96	0.88
Nifedipine	0.03	1/CL (1/L/hr)	0.06	0.06	0.08	1.00	1.24
Midazolam	0.04	1/CL (1/L/hr)	0.12	0.08	0.07	0.70	0.55
Felodipine	1.32	1/CL (1/L/hr/kg)					
Felodipine	0.12	1/CL (1/L/hr/kg)					
Ibrutinib	67	ng·hr/mL	620	160	1149	0.26	1.85
Oseltamivir	150	ng·hr/mL					

Blank space means data are not available. AUC = area under the curve. For midazolam the AUC values for predicted mPBPK and PBPK were 80 and 70 ng·hr/mL, respectively

Table S4. Predicted and observed C_{max} by minimal and whole body PBPK in subjects with mild hepatic impairment

Drugs (n = 9)	Healthy subjects	Units	Observed (mild)	Predicted (MPBPK)	Predicted (PBPK)	Ratio (MPBPK)	Ratio (PBPK)
Bosutinib (S1)	32	ng/mL	78	44	39	0.57	0.50
Eliglustat (S2)	10.4	ng/mL	22.4	14	64.2	0.65	2.87
Tofacitinib (S3)	62	ng/mL	62	69	79	1.11	1.27
Sildenafil (S4-5)	155	ng/mL					
Samidorphan (S6)	31	ng/mL					
Olanzapine (S6)	4.9	ng/mL					
Treprostinil (S7)	0.82	ng/mL	0.78	1.09	0.88	1.40	1.13
Atomoxetine (S10)	0.14	ng/mL					
Alectinib (S11)	106	ng/mL					
Ruxolitinib (S11)	413	ng/mL	379	527	490	1.39	1.29
Panobinostat (S11)	31	ng/mL	29	38	51	1.32	1.76
Pemafibrate (S13)	4.8	ng/mL	6.6	9	4.1	1.30	0.62
Alprazolam (S16)	18.4	ng/mL					
Sirolimus (S16)	78	ng/mL	79	127	116	1.61	1.47
Ibrutinib (S16)	8.7	ng/mL	46.7	13	99.8	0.28	2.14
Oseltamivir (S17)	90	ng/mL					

Blank space means data are not available. C_{max} = maximum plasma concentration

Table S5. Predicted and observed C$_{max}$ by minimal and whole body PBPK in subjects with moderate hepatic impairment

Drugs (n = 16)	Healthy subjects	Units	Observed (moderate)	Predicted (MPBPK)	Predicted (PBPK)	Ratio (MPBPK)	Ratio (PBPK)
Bosutinib	32	ng/mL	64	55	48	0.86	0.75
Eliglustat	10.4	ng/mL	39.5	18	173	0.45	4.38
Tofacitinib	62	ng/mL	93.7	87	86.7	0.93	0.93
Sildenafil	310	ng/mL	456	442	956	0.97	2.1
Samidorphan	31	ng/mL	51	38	56	0.74	1.10
Olanzapine	4.9	ng/mL	10.6	9	5.8	0.87	0.55
Treprostinil	0.82	ng/mL	1.98	1.41	1.35	0.71	0.68
Atomoxetine	0.14	ng/mL	0.12	0.26	0.32	2.27	2.78
Alectinib	106	ng/mL	111	224	73	2.02	0.66
Ruxolitinib	413	ng/mL	321	659	537	2.05	1.67
Panobinostat	31	ng/mL	34	48	55	1.41	1.62
Pemafibrate	4.8	ng/mL	11	10	6.5	0.95	0.59
Alprazolam	18.4	ng/mL	17.3	29	15.3	1.68	0.93
Sirolimus	78	ng/mL	75	155	126	2.07	1.68
Ibrutinib	8.7	ng/mL	67.2	16	161.9	0.24	2.41
Oseltamivir	90	ng/mL	99	112	92	1.13	0.93

C$_{max}$ = maximum plasma concentration

Table S6. Predicted and observed C$_{max}$ by minimal and whole body PBPK in subjects with severe hepatic impairment

Drugs (n = 8)	Healthy subjects	Units	Observed (severe)	Predicted (MPBPK)	Predicted (PBPK)	Ratio (MPBPK)	Ratio (PBPK)
Bosutinib	32	ng/mL	49	71	59	1.45	1.20
Eliglustat	10.4	ng/mL					
Tofacitinib	62	ng/mL					
Sildenafil	155	ng/mL					
Samidorphan	31	ng/mL					
Olanzapine	4.9	ng/mL					
Treprostinil	0.82	ng/mL	2.36	1.75	1.59	0.74	0.67
Atomoxetine	0.14	ng/mL	0.13	0.34	0.41	2.70	3.28
Alectinib	106	ng/mL	103	289	78	2.80	0.76
Ruxolitinib	413	ng/mL	352	852	579	2.42	1.64
Panobinostat	31	ng/mL	31	62	65	2.00	2.10
Pemafibrate	4.8	ng/mL					
Alprazolam	18.4	ng/mL					
Sirolimus	78	ng/mL	56	200	149	3.57	2.66
Ibrutinib	8.7	ng/mL	56.2	21	230.9	0.37	4.11
Oseltamivir	90	ng/mL					

Blank space means data are not available. C$_{max}$ = maximum plasma concentration

Table S7. Predicted and observed area under the curve by minimal PBPK model in subjects with mild hepatic impairment

Drugs (n = 18)	Healthy subjects	Units	Observed (Mild)	Predicted (Mild)	Ratio
Empagliflozin (S18)	10800	nmol·hr/L	13800	11962	0.87
Tedizolid (S19)	23	ug·hr/mL			
Cinacalcet (S20)	181	ng·hr/mL	186	357	1.92
Tigecycline (S21)	3749	ng·hr/mL	3835	3473	0.91
Amprenavir (S22)	12000	ng·hr/mL			
Clazosentan (S23)	174	ng·hr/mL	245	218	0.89
Brivanib (S24)	25414	ng·hr/mL	26817	35503	1.32
Voxelotor (S25)	200	ug·hr/mL	224	260	1.16
Temsavir (S26)	7884	ng·hr/mL	9420	7909	0.84
Itacitinib (S27)	2490	nmol·h/L			
Ribociclib (S28)	6170	ng·hr/mL	6330	7568	1.20
Cannabidiol (S29)	474	ng·hr/mL	699	908	1.30
Conivaptan (S30)	4111	ng·hr/mL			
Evacetrapib (S31)	10857	ng·hr/mL	10639	19860	1.87
Gepotidacin (S32)	16	ug·hr/mL			
Ondansetron (S33)	279	ng·hr/mL	633	340	0.54
Rucaparib (S34)	17000	ng·hr/mL	11900	20791	1.75
Zibotentan (S35)	5480	ng·hr/mL	7680	5949	0.77
Asciminib (S36)	4700	ng·hr/mL	5840	6454	1.11
Ipatasertib (S37)	318	ng·hr/mL	323	409	1.27
Oxycodone (S38)	106	ng·hr/mL			
Omeprazole (S39)	151	umol·h/L	241	179	0.74
Acetaminophen (S40)	39	ug·hr/mL			
Pomalidomide (S41)	493	ug·hr/mL	728	386	0.53
Atogepant (S42)	2780	ng·hr/mL	3495	3975	1.14

Blank space means data are not available

Table S8. Predicted and observed area under the curve by minimal PBPK model in subjects with moderate hepatic impairment

Drugs (n = 24)	Healthy subjects	Units	Observed (Moderate)	Predicted (Moderate)	Ratio
Empagliflozin	10800	nmol·hr/L	16100	15183	0.94
Tedizolid	23	ug·hr/mL	31	31	1.00
Cinacalcet	181	ng·hr/mL	442	430	0.97
Tigecycline	3749	ng·hr/mL	5636	4507	0.80
amprenavir	12000	ng·hr/mL	25761	17735	0.69
Clazosentan	174	ng·hr/mL	412	282	0.68
Brivanib	25414	ng·hr/mL	27869	43991	1.58
Voxelotor	200	ug·hr/mL	244	325	1.33
Temsavir	7884	ng·hr/mL	12780	10159	0.79
Itacitinib	2490	nmol·h/L	5550	3670	0.66
Ribociclib	6170	ng·hr/mL	7920	9499	1.20
Cannabidiol	474	ng·hr/mL	1163	1096	0.94
conivaptan	4111	ng·hr/mL			
evacetrapib	10857	ng·hr/mL	13940	24065	1.73
Gepotidacin	16	ug·hr/mL	20	18	0.94
ondansetron	279	ng·hr/mL	446	427	0.96
rucaparib	17000	ng·hr/mL	26800	26103	0.97
zibotentan	5480	ng·hr/mL	7940	7569	0.95
Asciminib	4700	ng·hr/mL	5020	8010	1.60
Ipatasertib	318	ng·hr/mL	808	511	0.63
Oxycodone	106	ng·hr/mL	135	125	0.93
Omeprazole	151	umol·h/L	280	226	0.81
Acetaminophen	39	ug·hr/mL	65	44	0.68
Pomalidomide	493	ug·hr/mL	764	514	0.67
Atogepant	2780	ng·hr/mL	3314	4915	1.48

Blank space means data are not available

Table S9. Predicted and observed area under the curve by minimal PBPK model in subjects with severe hepatic impairment

Drugs (n = 25)	Healthy subjects	Units	Observed (Severe)	Predicted (Severe)	Ratio
Empagliflozin	10800	nmol·hr/L	19000	19699	1.04
Tedizolid	23	ug·hr/mL	35	40	1.15
Cinacalcet	181	ng·hr/mL	769	552	0.72
Tigecycline	3749	ng·hr/mL	7656	5872	0.77
amprenavir	12000	ng·hr/mL	38656	22982	0.59
Clazosentan	174	ng·hr/mL	660	365	0.55
Brivanib	25414	ng·hr/mL	37688	56812	1.51
Voxelotor	200	ug·hr/mL	293	420	1.43
Temsavir	7884	ng·hr/mL	13606	13210	0.97
Itacitinib	2490	nmol·h/L	8960	4756	0.53
Ribociclib	6170	ng·hr/mL	7960	12298	1.55
Cannabidiol	474	ng·hr/mL	2439	1409	0.58
conivaptan	4111	ng·hr/mL	6574	12327	1.88
evacetrapib	10857	ng·hr/mL	17044	30943	1.82
Gepotidacin	16	ug·hr/mL	25	24	0.94
ondansetron	279	ng·hr/mL	1383	553	0.40
rucaparib	17000	ng·hr/mL	48300	33797	0.70
zibotentan	5480	ng·hr/mL	15900	9824	0.62
Asciminib	4700	ng·hr/mL	8680	10348	1.19
Ipatasertib	318	ng·hr/mL	920	661	0.72
Oxycodone	106	ng·hr/mL	218	163	0.75
Omeprazole	151	umol·h/L	323	293	0.91
Acetaminophen	39	ug·hr/mL	72	58	0.80
Pomalidomide	493	ug·hr/mL	822	672	0.82
Atogepant	2780	ng·hr/mL	3836	6345	1.65

Table S10. Predicted and observed maximum plasma concentration by minimal PBPK model in subjects with mild hepatic impairment

Drugs (n = 16)	Healthy subjects	Units	Observed (Mild)	Predicted (Mild)	Ratio
Empagliflozin	1370	nmol/L	1430	1517	1.06
Tedizolid	1.85	ug/mL			
Cinacalcet	11.9	ng/mL	13.7	23	1.71
Tigecycline	981	ng/mL	865	909	1.05
amprenavir	4901	ng/mL			
Brivanib	2107	ng/mL	3176	2943	0.93
Voxelotor	2.0	ug/mL	2.4	2.6	1.1
Temsavir	1473	ng/mL	1967	1478	0.75
Itacitinib	467	nmol/L			
Ribociclib	317	ng/mL	339	388.85	1.15
Cannabidiol	148	ng/mL	233	283	1.22
evacetrapib	605	ng/mL	609	1179	1.94
Gepotidacin	3.2	ug/mL			
ondansetron	97.2	ng/mL	68.6	119	1.73
rucaparib	685	ng/mL	604	838	1.39
zibotentan	566	ng/mL	526	614	1.17
Asciminib	578	ng/mL	731	794	1.09
Ipatasertib	45	ng/mL	53	58	1.09
Oxycodone	7.6	ng/mL			
Acetaminophen	16	ug/mL			
Pomalidomide	61	ug/mL	56	48	0.85
Atogepant	589	ng/mL	666	842	1.26

Blank space means data are not available

Table S11. Predicted and observed maximum plasma concentration by minimal PBPK model in subjects with moderate hepatic impairment

Drugs (n = 22)	Healthy subjects	Units	Observed (Moderate)	Predicted (Moderate)	Ratio
Empagliflozin	1370	nmol/L	1660	1926	1.16
Tedizolid	1.85	ug/mL	2.1	2.5	1.19
Cinacalcet (FDA)	11.9	ng/mL	18	28	1.57
Tigecycline	981	ng/mL	914	1179	1.29
amprenavir	4901	ng/mL	6483	7243	1.12
Brivanib	2107	ng/mL	3128	3647	1.17
Voxelotor	2.01	ug/mL	2.91	3.26	1.12
Temsavir	1473	ng/mL	2174	1898	0.87
Itacitinib	467	nmol/L	791	688	0.87
Ribociclib	317	ng/mL	455	488	1.07
Cannabidiol	148	ng/mL	354	342	0.97
evacetrapib	605	ng/mL	591	1422	2.41
Gepotidacin	3.2	ug/mL	3.91	3.69	0.94
ondansetron	97.2	ng/mL	105.5	149	1.41
rucaparib	685	ng/mL	694	1052	1.52
zibotentan	566	ng/mL	505	782	1.55
Asciminib	578	ng/mL	568	985	1.73
Ipatasertib	45	ng/mL	89	72	0.81
Oxycodone	7.6	ng/mL	7.8	9.0	1.15
Acetaminophen	16	ug/mL	21	18	0.87
Pomalidomide	61	ug/mL	58	64	1.10
Atogepant	589	ng/mL	529	1041	1.97

Table S12. Predicted and observed maximum plasma concentration by minimal PBPK model in subjects with severe hepatic impairment

Drugs (n = 22)	Healthy subjects	Units	Observed (Severe)	Predicted (Severe)	Ratio
Empagliflozin	1370	nmol/L	1970	2499	1.27
Tedizolid	1.85	ug/mL	2.2	3.2	1.47
Cinacalcet	11.9	ng/mL	14.6	36	2.49
Tigecycline	981	ng/mL	1207	1536	1.27
amprenavir	4901	ng/mL	9435	9386	0.99
Brivanib	2107	ng/mL	3586	4710	1.31
Voxelotor	2.01	ug/mL	2.96	4.22	1.43
Temsavir	1473	ng/mL	2529	2468	0.98
Itacitinib	467	nmol/L	1510	892	0.59
Ribociclib	317	ng/mL	419	632	1.51
Cannabidiol	148	ng/mL	381	440	1.15
evacetrapib	605	ng/mL	478	1827	3.82
Gepotidacin	3.2	ug/mL	5.54	4.81	0.87
ondansetron	97.2	ng/mL	93.7	193	2.06
rucaparib	685	ng/mL	827	1362	1.65
zibotentan	566	ng/mL	536	1015	1.89
Asciminib	578	ng/mL	746	1273	1.71
Ipatasertib	45	ng/mL	80	94	1.17
Oxycodone	7.6	ng/mL	13.1	11.7	0.89
Acetaminophen	16	ug/mL	20	24	1.19
Pomalidomide	61	ug/mL	49	83	1.70
Atogepant	589	ng/mL	543	1344	2.48