APPENDIX I: LIST OF SUBSTANCES FOR BCS BASED BIOWAIVER

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
abacavir	200mg	high	low	3	5.3		antiretroviral	
acetazolamide	250 mg	low	Low (?)	4/2	Not eligible for biowaiver		Anti-glaucoma medicine	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
acetylsalicylic acid	500 mg	high	high	1	5.1		NSAID, anti-migraine medicine	
acetylsalicylic acid	100 mg	high	high	1	5.1		antithrombotic medicine	
acyclovir	200 mg	high	low	3	5.3		Anti-herpes medicines	
albendazole	400 mg	low	low (?)	4/2	Not eligible for biowaiver		Ant-helminthic	Chewable tablet; unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
allopurinol	100 mg	high	high	1	5.1		gout	
aluminium hydroxide	500 mg			NR	NA		antacid	Use for local effect
amiloride hydrochloride	5 mg	high	high	1	5.1		diuretic	
amitriptyline hydrochloride	25 mg (*I*)	high	high	1	5.1		Psychotherapeutic medicine	
amlodipine	5 mg	high	high	1	5.1		Anti-hypertensive medicine	
amodiaquine	200 mg	high	Borderline BA	3/1	5.3	CYP2C8	antimalarial	Extent of first pass

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
(base)			> 75%			polymorphism, increased risk for agranulocytosis and liver toxicity		metabolism uncertain
amoxicillin (a) + clavulanic acid (c)	(a) 500 mg + (c) 125 mg	(a) high + (c) high	(a) high + (c) borderline absorption >73% (radioactive excretion)	(a) 1 + (c) 3/1	5.3		antibacterial	combination should be tested according to clavulanic acid requirements
amoxicillin anhydrous	500 mg	high	high	1	5.1		antibacterial	
artemether (a) + lumefantrine (l)	(a) 20 mg + (l) 120 mg	(a and l) unknown	low (a and l)	(a) 4/3 + (l) 4/3	Not eligible for biowaiver		antimalarial	
ascorbic acid	50 mg	high	high	1	5.1		vitamin	
atenolol	100 mg	high	low	3	5.3		Anti-angina, antihypertensive, antiarrhythmic and used in heart failure	
azithromycin	500 mg	low	low (?)	4/2	Not eligible for biowaiver		antibacterial	Unknown whether poor BA is due to poor solubility or

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
								poor solubility and poor permeability
benznidazole	100 mg	high	low	3	5.3		American trypanosomiasis	
biperiden hydrochloride	2 mg	high	Insufficient literature	3/1	5.3		Anti-parkinson medicine	
carbamazepine	200 mg	Low (neutral)	high	2	Not eligible for biowaiver		Antiepileptic, psychotherapeutic medicine	scored tablet
cefixime	400 mg	low	low (?)	4/2	Not eligible for biowaiver		antibacterial	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
chloramphenicol	250 mg	high	low	3	5.3	Narrow therapeutic index	antibacterial	
chloroquine phosphate or sulfate	150 mg	high	high	1	5.1		DMARD, antimalarial	
chlorpheniramine hydrogen maleate	4 mg	high	BA 25-59%, first pass	3/1	5.3	CYP2D6 poly-morphism	antiallergic	Extent of first pass metabolism uncertain
chlorpromazine hydrochloride	100 mg	high	low	3	5.3		psychotherapeutic-tic medicine	
ciprofloxacin hydrochloride	250 mg	high	BA 70–82%, possible first pass, high in Caco-2 cells	3/1	5.3		antibacterial	Extent of first pass metabolism uncertain

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
clofazimine	100 mg	Insufficient literature	low	4/3	Not eligible for biowaiver at present		Antileprosy medicine	
clomifene citrate	50 mg	high	Insufficient literature	3/1	5.3		ovulation inducer	
clomipramine hydrochloride	25 mg	high	66% excreted in the urine, the remainder being eliminated in the faeces	3/1	5.3		Psychotherapeutic medicine	Lack of absolute bioavailability data
cloxacillin (as sodium salt)	1000 mg	high	low	3	5.3		antibacterial	
codeine phosphate	30 mg	high	low	3	5.3	risk of abuse	Opiod analgesic, diarrhoea in adults	
dapsone	100 mg	Low (weak base)	high	2	Not eligible for biowaiver	G6PD deficiency	Antileprosy medicine	
diazepam	5 mg	high	high	1	5.1		psychotherapeutic medicine	scored tablet
didanosine	200 mg	high	low	3	5.3		antiretroviral	Buffered chewable dispersible tablet
didanosine	400 mg	high	low	3	see comment		antiretroviral	Unbuffered enteric coated capsule →not eligible for biowaiver in this dosage form
digoxin	250 µg	high	high	1	5.1		Antiarrhythmic and used in heart failure	

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
diloxanide furoate	500 mg	low (*2*)	low (?)	4/2	Not eligible for biowaiver		antiprotozoal	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
doxycline hydrochloride	100 mg	high	high	1	5.1		antibacterial	
efavirenz	200 mg	low (*1*)	low (?)	4/2	Not eligible for biowaiver		antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
enalapril	2.5 mg	high	low	3	5.3		Antihypertensive medicine	
ergocalciferol	1.25mg (50 000 IU)	high	low	3	5.3		vitamin	
erythromycin stearate + ethylsuccinate	250 mg	low	low	4	Not eligible for biowaiver		antibacterial	
ethambutol hydrochloride	400 mg	high	low	3	5.3	Risk of dose related ototoxicity	Antituberculosis medicine	
ethinylestradiol	50 µg	high	Borderline, BA 40-50%, first pass	3/1	5.3		estrogen	Extent of first-pass metabolism uncertain
ethinylestradiol (e) + levonorgestrel (l)	30 µg + 150 µg	high	(e) borderline, BA 40–50%, first pass + (l) high	3/1 + 1	5.3		Hormonal contraceptive	Extent of first-pass metabolism uncertain; combination should be tested according to

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
								ethinylestradiol requirements
ethinylestradiol (e) + norethisterone (n)	35 µg + 1 mg	high	(e) borderline, BA 40–50%, first pass + (n) high	3/1 + 1	5.3		hormonal contraceptive	extent of first-pass metabolism un-certain; combination should be tested according to ethinylestradiol requirements
ferrous salt	equivalent to 60 mg iron	high (see footnote)	low	3	5.3		antianaemia medicine	commonly used salts: see footnote
ferrous salt (fs) + folic acid (fa)	equivalent to 60 mg iron + 400 µg folic acid	(fs) high + (fa) high	(fs) low + (fa) low (urinary recovery 28.5%) (2)	3 + 3/1	5.3		antianaemia medicine (during pregnancy)	lack of absolute bioavailability data; commonly used salts: see footnote; combination should be tested according to ferrous salt requirements
fluconazole	50 mg	high	high	1	5.1		antifungal	
folic acid	5 mg	high	low (?)	3/1	5.3		antianaemia medicine	lack of absolute bioavailability data
furosemide	40 mg	low	low (?)	4/2	Not eligible for biowaiver	highly variable BA	medicine used in heart failure, diuretic	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
glibenclamide	5 mg	low	low (?)	4/2	Not eligible for biowaiver		antidiabetic agent	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
glyceryl trinitrate	500 µg	high	sublingual application, permeability in the oral cavity more important than GI permeability	3/1	NA	local absorption	antianginal medicine	sublingual application
griseofulvin	250 mg	Low (neutral)	high	2	Not eligible for biowaiver		antifungal	
haloperidol	2 mg	Borderline <0.01 mg/ml2	low	4/3	Not eligible for biowaiver		Psychothepeutic tic medicine	
hydralazine hydrochloride	50 mg	high	low	3	5.3		Antihypertensive medicine	
hydrochlorothiazide	25 mg	high	low	3	5.3		Antihypertensive medicine, diuretic and used in heart failure	scored tablet
ibuprofen	400 mg	Low, weak acid (p*K* a4.4, 5.2)	high	2	5.2		NSAID, antimigraine medicine	
indinavir sulfate	400 mg	low	low (?)	4/2	Not eligible for biowaiver	CYP 450 3A4, food effect (–)	antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
iopanoic acid	500 mg	low, weak acid (p*K* a4.8) (2)	high	2	Not eligible for biowaiver		radiocontrast media	Insufficiently soluble in water (15 µg/ml) to be eligible for biowaiver

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
isoniazid	300 mg	high	borderline	3/1	5.3		Antitubercolusis medicine	
isoniazid (i) + ethambutol (e)	(i) 150 mg + (e) 400 mg	(i) high + (e) high	(i) borderline + (e) low	(i) 3/1 + (e) 3	See footnoteg	ocular toxicity	antituberculosis medicine	
isosorbide dinitrate	5 mg	high	Sublingual application, permeability in the oral cavity more important than GI permeability	3/1	NA		Antianginal medicine	sublingual
ivermectin	6 mg	Practically insoluble in water D:S > 6000 ml	low (?)	4/2	Not eligible for biowaiver		antifilarial	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
lamivudine	150 mg	high	high	1	5.1		antiretroviral	
levamisole hydrochloride	150 mg	high	borderline	3/1	5.3		anthelminthic	
levodopa (l) + carbidopa (c)	(l) 250 mg + (c) 25 mg	(l) high + (c) high	(l) high + (c) insufficient data (BAhumans58 %, BAdogs88%)	(l) 1 + (c) 3/1	5.3	narrow therapeutic index	antiparkinson medicine	extent of human first-pass metabolism; metabolism uncertain ; combination should be tested according to carbidopa requirements

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
levonorgestrel	30 µg	high	high	1	5.1		Hormonal contraceptive	
levonorgestrel	750 µg × 2 (pack of two)	high	high	1	5.1		Hormonal contraceptive	
levothyroxine sodium salt	100 µg	high	low	3	5.3	Narrow therapeutic index	thyroid hormone	
lithium carbonate	300 mg	high	high	1	5.1	Narrow therapeutic index	psychotherapeutic medicine	
lopinavir (l) + ritonavir (r)	(l) 133.3 mg + (r) 33.3 mg	(l) low + (r) low	(l) low (insufficient data) (?) + (r) low (?)	(l) 4/2 + (r) 4/2	Not eligible for biowaiver		antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
mebendazole	500 mg	low	low (?)	4/2	NA		anthelminthic	Chewable tablet, antihelminthics usually applied orally for local action in GI tract, solubility more important than permeability, but unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
mefloquine hydrochloride	250 mg	low2	low (?)	4/2	Not eligible for biowaiver		antimalarial	unknown whether poor BA is due to poor solubility or poor solubility and poor permeability

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
DL-methionine	250 mg	high	high	1	5.1		antidote	
metformin hydrochloride	500 mg	high	low	3	5.3		Antidiabetic agent	
methyldopa	250 mg	high	low	3	5.3		Antihypertensive medicine	
metoclopramide hydrochloride	10 mg	high	low	3	5.3		antiemetic	
metronidazole	500 mg	high	high	1	5.1		Abtiprotozoal antibacterial	
morphine sulfate	10 mg	high	insufficient data (BA ~ 30% but extensive first pass)	3/1	5.3	risk of abuse	Opiod analgesic	extent of first pass metabolism uncertain
nelfinavir mesilate	250 mg	low	low (?)	4	Not eligible for biowaiver	CYP 450 3A4, food effect (+)	antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
neostigmine bromide	15 mg	high	low	3	5.3		muscle relaxant	
nevirapine	200 mg	Low (weak base)	high	2	Not eligible for biowaiver		antiretroviral	
niclosamide	500 mg	low	low (?)	4/2	NA		anthelminthic	Chewable tablet, antihelminthics usually applied orally for local action in GI tract, solubility

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
								more important than permeability,
nicotinamide	50 mg	high	high	1	5.1		vitamin	
nifedipine	10 mg	Low, weak acid, solubility at pH 7 0.0056 mg/ml2	high	2	Not eligible for biowaiver		antioxytocic	
nifurtimox	250 mg	high	low	3	5.3		American trypanosomiasis	
nitrofurantoin	100 mg	low, weak acid, solubility at pH 7.0 0.374 mg/ml (p*K* a7.2 (25 °C)) (*2*)	high	2	Not eligible for biowaiver		antibacterial	Not soluble enough at pH 6.8 to be eligible for biowaiver
norethisterone	5 mg	high	high	1	5.1		progestogen	
nystatin	500 000 IU	–	–	NR	NA		antifungal	local effect
paracetamol	500 mg	high	high	1	5.1		NSAID, antimigraine medicine	
penicillamine	250 mg	high	low	3	5.3		antidote	
phenobarbital	100 mg	high	high	1	5.1	Narrow therapeutic	antiepileptic	

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
						index		
phenoxymethyl penicillin (as potassium salt)	250 mg	high	high	1	5.1		antibacterial	
phenytoin sodium salt	100 mg	low, weak acid, sol. at pH 6.8 1.7 mg/ml (*4*) p*K* a 8.3 (25 °C)) (*2*)	high	2	5.2	narrow therapeutic index, non-linear pharmaco-kinetics	antiepileptic	
potassium iodide	60 mg	high	high	1	5.1		thyroid hormones and antithyroid medicines	
praziquantel	600 mg	low (neutral)	high	2	Not eligible for biowaiver		anthelminthic, antischistosomal, antitrematode	
prednisolone	25 mg	high	high	1	5.1		antiallergic	
primaquine diphosphate	15 mg	high	high	1	5.1		antimalarial	
proguanil hydrochloride	100 mg	high	high	1	5.1		antimalarial	
promethazine hydrochloride	25 mg	high	high	1	5.1	CYP2D6 polymorphism	antiemetic	

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
propranolol hydrochloride	40 mg	high	high	1	5.1		antimigraine medicine	
propylthiouracil	50 mg	high	high	1	5.1		antithyroid medicine	
pyrantel embonate	250 mg	low	low (?)	4/2	NA		anthelminthic	chewable tablet; anthelminthics usually applied orally for action in GI tract: solubility more important than permeability
pyrazinamide	400 mg	high	borderline	3/1	5.3	Liver toxicity	antituberculosis medicine	
pyridoxine hydrochloride	25 mg	high	high	1	5.1		vitamin	
pyrimethamine	25 mg	borderline; < 0.1 mg/ml3	low	4/3	Not eligible for biowaiver		anti-pneumocystosis and antitoxoplasmosis medicine	
quinine bisulfate or sulfate	300 mg	high	high	1	5.1		antimalarial	
ranitidine hydrochloride	150 mg	high	low	3	5.3		Antiulcer medicine	
retinol palmitate	110 mg (200 000 IU)	low (*3*)	low (?)	4/2	Not eligible for biowaiver		vitamin	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
riboflavin	5 mg	high	high	1	5.1		vitamin	

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
rifampicin	300 mg	low (am-amphiphilic) (p*K* 1.7, 7.9) (*1*)	high	2	Not eligible for biowaiver		antileprosy and antituberculosis medicine	
rifampicin (r) + isoniazid (i)	(r) 300 mg + (i) 150 mg	(r) low + (i) high	(r) high + (i) borderline	(r) 2 + (i) 3/1	Not eligible for biowaiver		antituberculosis medicine	
rifampicin (r) + isoniazid (i) + pyrazinamide (p)	(r) 150 mg+ (i) 150 mg+ (p) 500 mg	(r) low + (i) high + (p) high	(r) high + (i) borderline + (p) borderline	(r) 2 + (i) 3/1 + (p) 3/1	Not eligible for biowaiver		antituberculosis medicine	
rifampicin (r) + isoniazid (i) + pyrazinamide (p) + ethambutol-(e)	(r) 150 mg+ (i) 75 mg + (p) 400 mg (e) 275 mg	(r) low + (i) high + (p) high + (e) high	(r) high + (i) borderline + (p) border-line + (e) low	(r) 2 + (i) 3/1 + (p) 3/1 + (e) 3	Not eligible for biowaiver		antituberculosis medicine	
ritonavir	100 mg	low	low (?)	4/2	Not eligible for biowaiver	CYP 450 3A4	antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor permeability
salbutamol sulfate	4 mg	high	high	1	5.1		Antiasthmatic and COPD	
saquinavir	200 mg	low	low (?)	4/2	Not eligible for biowaiver	CYP 450 3A4, food effect (+)	antiretroviral	Unknown whether poor BA is due to poor solubility or poor solubility and poor

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
								permeability
senna	7.5mg (sennoside)	–	–	NR	NA		laxative	local effect
spironolactone	25 mg	borderline	low	4/3	Not eligible for biowaiver		diuretic	
stavudine	40 mg	high	high	1	5.1		antiretroviral	
sulfamethoxazole (s) + trimethoprim (t)	(s) 400 mg + (t) 80 mg	(s) low (amphiphil) + (t) low (weak base)	(s) high + (t) high	(s) 2 + (t) 2	Not eligible for biowaiver	G6PD deficiency	antibacterial	
sulfasalazine	500 mg	low	low	4	NR		Gastrointestinal , anti-inflammatory medicine	Used for local action in the gastrointestinal tract
thiamine hydrochloride	50 mg	high	low	3	5.3		vitamin	
triclabendazole	250 mg	insufficient literature	low	4/3	Not eligible for biowaiver		Antischistosomal antitrematode	
trimethoprim	200 mg	Low (weak base)	high	2	Not eligible for biowaiver		antibacterial	
valproic acid sodium salt	500 mg	high	high	1	see comment		antiepileptic, psychotherapeutic-tic medicine	enteric-coated tablet □not eligible for biowaiver in this dosage form

Medicine	Highest oral strength[i]	Solubility	Permeability	BCS class	Dissolution test (for biowaiver)[ii]	Potential risks	Indication(s) according to WHO EML	Comments and special dosage form indications
verapamil hydrochloride	80 mg	low (weak base)	high	2	Not eligible for biowaiver		Antianginal and antiarrhythmic medicine	
warfarin sodium salt	5 mg	high (soluble in less than 1 of water) (*1*)	high	1	5.1	narrow therapeutic index	medicines affecting coagulation	
zidovudine	300 mg	high	high	1	5.1		antiretroviral	
zinc sulfate	10mg (per unit dosage form)	high	low	3	5.3		Diarrhoea in children	

Biowaivers not applicable or relevant, locally acting, no significant systemic absorption, absorption from the oral cavity or dosage form not designed for immediate release.

[i] The highest dose strength is based on the highest oral strength according to the WHO Essential medicines List

[ii] The dissolution testing procedure depends on the BCS classification of the API, based on solubility and permeability. The testing procedures are as defined in section 5 of the **Annex To Guideline On Submission Of Documentation For Registration Of A Multi-Source (Generic) Finished Pharmaceutical Products (Fpps):** *Guideline On Waiver Of In Vivo Bioequivalence Requirements For Immediate-Release Solid Oral Dosage Forms Rev 0_2008.*