Table 2

Active pharmaceutical ingredients on the complementary list of the *WHO Model List of Essential Medicines* (EML)

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a,g]	Comments and special dosage form indications[a]
artesunate	50 mg	low	borderline (BA_{abs} 82–88%) but dependent on severity of disease (*1, 2*)	4/2	Not eligible for biowaiver	extent of absorption depends on severity of disease	antimalarial	
azathioprine sodium salt	50 mg	low	low (?)	4/2	Not eligible for biowaiver	immunosuppressive, TDM recommended	immunosuppressive, DMARD	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
calcium folinate	15 mg	high	high	1	9.2.1.1		anticytotoxic medicine	
chlorambucil	2 mg	high	insufficient literature (BA after repeated dosage > 70% but urinary analytical profile i.v. similar to p.o.) (*3, 4*)	3/1	9.2.1.2	myelosuppression (leukopenia) = dose-limiting toxicity	cytotoxic medicine[g]	
cyclosporine	25 mg	low	low	4/3	Not eligible for biowaiver	immunosuppressive, TDM recommended	immunosuppressive	

TDM: Therapeutic Drug Monitoring; DMARD, disease modifying antirheumatic drug; BA, bioavailability; i.v., intravenous; p.o. per orale.

clindamycin	150 mg	high	high	1	9.2.1.1		antibacterial	
cyclophosphamide	25 mg	high	high	1	9.2.1.1	myelosuppression (leukopenia) = dose-limiting toxicity, accelerated metabolism leading to reduced oral BA after repeated treatment cycles	cytotoxic medicine[g]	
cycloserine	250 mg	high	insufficient literature (urinary recovery 65% (*5*), 70–90% of the dose is absorbed (*6*))	3/1	9.2.1.3	serum levels > 30 µg/ml associated with CNS toxicity	antituberculosis medicine	
diethylcarbamazine dihydrogen citrate	100 mg	high	high	1	9.2.1.2	myelosuppression (leukopenia) = dose-limiting toxicity, accelerated metabolism leading to reduced oral BA after repeated treatment cycles	antifilarial	

BA, Bioavailability; CNS, central nervous system; GI gastrointestinal.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a,g]	Comments and special dosage form indications[a]
doxycycline hydrochloride	100 mg	high	high	1	9.2.1.1		antimalarial	
ethionamide	250 mg	high	insufficient literature ("readily absorbed from the GI tract") (*7*)	3/1	9.2.1.2		antituberculosis medicine	
ethosuximide	250 mg	high	insufficient literature	3/1	9.2.1.2		antiepileptic	
etoposide	100 mg	low	low (?)	4/2	Not eligible for biowaiver	myelosuppression (leukopenia) = dose-limiting toxicity, accelerated metabolism leading to reduced oral BA after repeated treatment cycles	cytotoxic medicine[g]	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
flucytosine	250 mg[3]	high	borderline (BA_{abs} 76–89%) (*8, 9*)	3/1	9.2.1.2		antifungal	

BA, Bioavailability; DMARD, disease modifying antirheumatic drug.

levamisole hydrochloride	50 mg	high	no human data available	3/1	9.2.1.2		cytotoxic medicine[g]	
levofloxacin	500 mg	high	high	1	9.2.1.1		antituberculosis medicine	
mefloquine hydrochloride	250 mg	low	insufficient literature ("well absorbed") (*7*)	4/2	Not eligible for biowaiver	pharmacokinetics of mefloquine may be altered by malaria infection (*7*)	antimalarial	
mercaptopurine	50 mg	low	low (?)	4/2	Not eligible for biowaiver		cytotoxic medicine[g]	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
methotrexate sodium salt	2.5 mg	high	low	3	9.2.1.2	severity of adverse effects depends on dose and indication	cytotoxic medicine[g], DMARD	
mifepristone – misoprostol	200 mg	no literature data available	low	4/3	Not eligible for biowaiver at present		oxytocic	
ofloxacin	400 mg	high	high	1	9.2.1.1		antituberculosis medicine	
oxamniquine	250 mg	low	insufficient literature (urinary recovery as single acid 70%) (*7*)	4/2	Not eligible for biowaiver		antischistosomal, antitrematode	

BA, Bioavailability; DMARD, disease modifying antirheumatic drug.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a,g]	Comments and special dosage form indications[a]
p-aminosalicylic acid	500 mg	low	borderline (80% urinary recovery (*7*)	4/2	Not eligible for biowaiver		antituberculosis medicine	
penicillamine	250 mg	high	low	3	9.2.1.2		DMARD	
pentamine	300 mg	high	no literature data	3/1	9.2.1.2		anti-pneumocystosis and anti-toxoplasmosis medicine	
prednisolone	25 mg	high	high	1	9.2.1.1		hormone/ antihormone	
procarbazine hydrochloride	50 mg	high	insufficient literature (urinary recovery 70%, 24 h) (*5*)	3/1	9.2.1.2	myelosuppression (leukopenia) = dose-limiting toxicity	cytotoxic medicine[g]	
pyridostigmine bromide	60 mg	high	low	3	9.2.1.2		muscle relaxant	
quinidine sulfate	200 mg	high	insufficient literature (BA 70% but first pass) (*5*)	3/1	9.2.1.2		antiarrhythmic	
sulfadiazine	500 mg	borderline	low	4/3	Not eligible for biowaiver		antibacterial	

BA, Bioavailability; DMARD, disease modifying antirheumatic drug.

sulfadoxine (s) + pyrimeth-amine (p)	(s) 500 mg + (p) 25 mg	(s) high + (p) border-line (< 0.1 mg/ml (*7*)	(s) insufficient data + (p) low	(s) 3/1+ (p) 4/3	Not eligible for biowaiver		antimalarial	
sulfasalazine	500 mg	low	low	4	NR		DMARD	Used for local action in the gastro-intestinal tract
tamoxifen citrate	20 mg	high	high	1	9.2.1.1		antihormone	

[a] *14th WHO Model List of Essential Medicines*, Geneva, World Health Organization, March 2005; available at: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf.

[b] Solubility based on the lowest solubility in the pH range from 1 to 6.8 at 37 °C. "Low" indicates a dose[a] :solubility ratio > 250ml for at least one pH value in this range.

[c] Permeability based on fraction of the dose absorbed after oral dosing in humans, except where otherwise indicated. "Low" indicates that less than 85% of the oral dose was absorbed at the highest oral strength in the EML.[a]

[d] The original Biopharmaceutics Classification System (BCS)is available at: http://www.fda.gov/cder/guidance/3618fnl.pdf .

Note: the acceptance criteria have been adapted according to WHO requirements as explained in Section 2 of this Annex.

[e] See WHO "Multisource document": *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

[f] Known potential risks are indicated where appropriate. Where no information is given, this may indicate lack of availability of relevant data and should not be construed as meaning that there are no risks associated with use of the compound. Assessment of risks should be made by the national authority based on local conditions of use.

[g] Cytotoxic medicines: the risks associated with applying the biowaiver procedure should be very carefully scrutinized by the national regulatory authority.

NR not relevant: locally acting, no significant systemic absorption.

Compounds introduced to the EML since March 2005 or for which no classification had been previously reported.

1. Newton P et al. Antimalarial bioavailability and disposition of artesunate in acute falciparum malaria. *Antimicrobial Agents and Chemotherapy*, 2000, 44:972-977.
2. Newton PN et al. Comparison of oral artesunate and dihydroartemisinin antimalarial bioavailabilities in acute falciparum malaria. *Antimicrobial Agents and Chemotherapy*, 2002, 46:1125-1127.
3. McLean A et al. Pharmacokinetics and metabolism of chlorambucil in patients with malignant disease. *Cancer Treatment Reviews,* 1979, 6, Suppl:33-42.
4. Silvennoinen R et al. Pharmacokinetics of chlorambucil in patients with chronic lymphocytic leukaemia: comparison of different days, cycles and doses. *Pharmacology & Toxicology,* 2000, 87:223-228.
5. *Clarke's Analysis of Drugs and Poisons*. 3rd ed. London, Pharmaceutical Press, 2004.
6. Brittain HG, Florey K. *Analytical Profiles of Drug Substances and Excipients*. ed. Oxford University Press.
7. Sweetman S. *Martindale: The complete drug reference*. 34 ed. London, Pharmaceutical Press, 2004.
8. Vermes A et al. Population pharmacokinetics of flucytosine: comparison and validation of three models using STS, NPEM, and NONMEM. *Therapeutic Drug Monitoring*, 2000, 22:676-687.
9. Vermes A, Guchelaar HJ, Dankert J. Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *Journal of Antimicrobial Chemotherapy*, 2000, 46:171-179.

Table 3

Compounds introduced to the *WHO Model List of Essential Medicines* since March 2005 for which no certain classification had been previously reported (these compounds also appear in Table 1 and Table 2)

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List (EML)[a]	Comments and special dosage form indications[a]
amlodipine	5 mg	slightly soluble (*1*), D:S 5 ml	BA_{abs} 60–65%, excretion of drug metabolites in urine 90–95% (*2*)	1	9.2.1.1		antihypertensive medicine	BA_{abs} < 85% ascribed to first-pass metabolism
amodiaquine (base)	200 mg	45 mg/ml[2], D:S 4.4 ml	BA > 75% (*3*)	3/1	9.2.1.2	CYP2C8 polymorphism, increased risk for agranulocytosis and hepatotoxicity (*4*)	antimalarial	
amoxicillin + clavulanic acid	500 mg + 125 mg	freely soluble in water (*1*), D:S 1.25 ml	absorption > 73% (*5*)	1 + 3/1	9.2.1.2		antibacterial	tests based on clavulanic acid classification
artesunate	50 mg	very slightly soluble (*6*), D:S 500 ml; (weak acid, pK_a ~ 6.4)	BA_{abs} 82% (*1*), BA_{abs} 88% (*7*), BA_{abs} 61% (*8*)	4/2	Not eligible for biowaiver		antimalarial	permeability depends on severity of disease

D:S, Dose: solubility; BA, Bioavailability.

azithromycin	500 mg	practically insoluble in water (*1*) < 0.01mg/ml, D:S 50 000 ml	BA_{abs} 16% (*9*); BA 37% (*10, 11*);	4/2	Not eligible for biowaiver		antibacterial	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
calcium folinate	15 mg	sparingly soluble in water (Ph. Eur. 5.2); very soluble (USP 28); D:S 15 ml and 0.015 ml, respec-tively	BA_{abs} 92% 25 mg (*12, 13*); BA_{abs} 73.4% (15 mg) (*14*); fully absorbed; AUC and $t_{1/2}$ similar after i.v. & p.o (*15*)	1	9.2.1.1		anticytotoxic medicine	
levodopa (l) + carbidopa (c)	(l) 250 mg + (c) 25 mg	(l) high + (c) soluble 1 in 500 of water, freely soluble in 3 M HCl (*1*)	(l) high + (c) BA 58% (16); BA_{abs} 88% (dogs) (*17*)	(l) 1 + (c) 3/1	9.2.1.2	narrow therapeutic index	antiparkinson medicine	tests based on carbidopa classification
cefixime	400 mg	slightly soluble (*2*), D:S 400 ml	22–54% (*2*)	4	Not eligible for biowaiver		antibacterial	

D:S, Dose: solubility; BA: Bioavailability; Ph.Eur., *European Pharmacopoeia*; USP, *United States Pharmacopoeia*; AUC, area under the curve; i.v., intravenous.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List (EML)[a]	Comments and special dosage form indications[a]
chlorambucil	2 mg	"practically insoluble in water" (*1*), but D:S ~ 20 ml	i.v. vs. p.o. similar analytical profile in urine = high degree of absorption (*18*), BA_{abs} > 70% after repeated oral dosage (*19, 20*)	3/1	9.2.1.2	myelosuppression (leukopenia) = dose-limiting toxicity; accelerated metabolism leading to reduced oral BA after repeated treatment cycles (*21, 22*)	cytotoxic medicine[g]	
clindamycin	150 mg	500 mg/ml[2], D:S 0.3 ml	about 90% of the dose absorbed (*1*)	1	9.2.1.1	diarrhoea/ nausea	antibacterial	
cylcoserine	250 mg	soluble 100 mg/ml[2], D:S 2.5 ml	65% urinary excretion (*2*), 70–90% of a p.o. dose absorbed (*23*)	3/1	9.2.1.2	serum levels > 30 µg/ml associated with CNS toxicity	antituberculosis medicine	

i.v., intravenous; p.o., per orale; BA: Bioavailability; D:S, Dose: solubility.

enalapril	2.5 mg	sparingly soluble in water (*1*), D:S 0.25 ml; dissolves in dilute solutions of alkali hydroxides (*1*)	absorption p.o. 69%, urinary recovery 77%, BA 38%, first pass 10% (*24*); p.o. children, urinary recovery ~ absorption 50% (*25*)	3	9.2.1.2		antihypertensive medicine	
ethionamide	250 mg	slightly soluble in water at 25° C (*2*) D:S < 250 ml	readily absorbed from the gastrointestinal tract, extensively metabolized, probably in the liver, less than 1% of a dose appears in the urine as unchanged drug (*1*)	3/1	9.2.1.2		antituberculosis medicine	

D:S, Dose: solubility; BA: Bioavailability; p.o., per orale.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List (EML)[a]	Comments and special dosage form indications[a]
etoposide	100 mg	practically insoluble in water (*2*), D:S 1000 ml	excretion 30–50% unchanged in the urine, 20% as metabolites = 50–70% (*2*), absorption 48–57% (*23*), 60% absorption in children (*26*)	4/2	Not eligible for biowaiver	myelosuppression (leukopenia) = dose-limiting toxicity; great variability in absorption (all references)	cytotoxic medicine[g]	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
ferrous salt	equivalent to 60 mg iron	high (see footnote, Table 1)	low	3	9.2.1.2		antianaemia medicine	applies to commonly used salts
ferrous salt (fs) + folic acid (fa)	equivalent to 60 mg iron + 400 µg folic acid	(fs) high (see footnote) + very slightly soluble in water (*2*), D:S 2.5ml; 0,0016 mg/ml (25 °C) water (*23*), D:S 250 ml	(fs) low + (fa) low (urinary recovery 28% (*23*))	(fs) 3 + (fa) 3/1	9.2.1.2		antianaemia medicine (during pregnancy)	combination should be tested according to requirements for BCS Class III compounds; applies to commonly used iron salts

D:S, Dose: solubility; BA: Bioavailability.

flucytosine	250 mg	soluble 15 mg/ml (*2*), D:S 17 ml; 14.2 mg/ml (*23*); D:S 17.6 ml	BA_{abs} 76–89% (*27, 28*)	3/1	9.2.1.2		antifungal	
levofloxacin	500 mg	high (30–300 mg/ml) (*29*) D:S 16.7 ml	high (oral vs i.v. 100% BA; Caco-2 permeability high) (*29*)	1	9.2.1.1	for main side-effects refer to (*30*)	antituberculosis medicine	
mebendazole	500 mg	practically insoluble in water (both monohydrate and anhydrous (*2*)), D:S > 50 000 ml	BA_{abs} 2% (*31*); urinary recovery 2% of orally administered dose (*32*)	4/2	NA		anthelminthic	Chewable tablet, anthelminthics usually administered orally for 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
medroxy-progesterone acetate	5 mg	practically insoluble in water (*2*), 1 g in >10 000 ml, < 0.1 mg/ml, D:S < 50 ml	in rats + dogs BA 27% first-pass metabolism, self-induced metabolism; 16% and very variable (*2*)	3/1	9.2.1.2		progestogen	extent of first-pass metabolism in humans uncertain

D:S, Dose: solubility; BA: Bioavailability; i.v., intravenous.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List (EML)[a]	Comments and special dosage form indications[a]
mercaptopurine	50 mg	low (insoluble in water; pK_a 7.7/ 11.0, < 0.1 mg/ml)[2], D:S > 500 ml (*2*)	BA_{oral} von aza 47%, first pass, 50% in urine (2)	4/2	Not eligible for biowaiver	antimetabolite, TDM suggested by Lennard (*1*)	cytotoxic medicine[g]	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
mifepristone – misoprostol	200 mg	no information available	BA 70%; also reported 40% after 100 mg oral dose (*2*)	4/3	Not eligible for biowaiver at present		oxytocic	insufficient information available
niclosamide	500 mg	5–8mg/l (20 °C) (*33*), D:S 77 000 ml	2–25% of a dose of 2 g radiolabelled drug recovered in the urine, rest in faeces (*33*)	4/2	NA		anthelminthic	chewable tablet, anthelminthics usually applied orally for action in GI tract: solubility more important than permeability
ofloxacin	400 mg	high (30–300 mg/ml) (*29*), D:S 13 ml	dose proportional 100% BA (*29*)	1	9.2.1.1	for main side- effects refer to (*30*)	antituberculosis medicine	

D:S, Dose: solubility; BA: Bioavailability; TDM, therapeutic drug monitoring; GI, gastrointestinal.

oxamniquine	250 mg	low (1 in 3300 at 27 °C, 0.3 mg/ml) (*23*), D:S 825 ml	"readily absorbed", urinary excretion 70% as single acid (*1*)	4/3	Not eligible for biowaiver	no significant toxic effects on liver, kidney or heart, dose 15 mg/kg (*1*)	antischistosomal, antitrematode	
p-aminosalicylic acid	500 mg	low (1 g in 600 ml, 1.66 mg/ml) (*23*); D:S 301 ml, weak acid, pK_a not found in literature	borderline, 80% excretion in urine (*1*)	4/2	Not eligible for biowaiver at present		antituberculosis medicine	borderline in both solubility and permeability – solubility profile needs to be better characterized
pentamine	300 mg	high (1 in 10 → 100 mg/ml)[2], D:S 3 ml	no information available	3/1	9.2.1.2		anti-pneumocystosis and antitoxoplasmosis medicine	
potassium iodide	60 mg	very soluble in water, D:S < 0.06 ml	BA 96.4% (*35*); urinary recovery 89%, faeces 11% (*36*)	1	9.2.1.1		thyroid hormones and antithyroid medicines	
procarbazine hydrochloride	50 mg	high (200 mg/ml) (*23*), D:S 0.25 ml	readily absorbed, 70% dose excreted in urine after 24h (*2*)	3/1	9.2.1.2	tumour inhibitor, haematologic (*2*)	cytotoxic medicine[g]	

D:S, Dose: solubility; BA: Bioavailability.

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List (EML)[a]	Comments and special dosage form indications[a]
pyrantel embonate	250 mg	low (practically insoluble in water, 1 g in >10 000 ml[2], < 0.1 mg/ml), D:S > 2500 ml	16% BA_{oral} (palmoate), 41% oral BA (citrate) (*37*)	4/2	NA		anthelminthic	chewable tablet, anthelminthics usually applied orally for action in GI tract:solubility more important than permeability
quinidine sulfate	200 mg	high (10 mg/ml) (*23*), D:S 20 ml	rapidly absorbed BA 70%; permeability varies widely, first pass (*2*)	3/1	9.2.1.2	narrow therapeutic index	antiarrhythmic	
ranitidine hydrochloride	150 mg	high (freely soluble in water (*2*) > 1000 mg/ml), D:S 0.15 ml	50% BA, first pass (*2, 38*)	3/1	9.2.1.2		antiulcer medicine	
sulfadoxine	25 mg	very slightly soluble in water (*2*), D:S < 250 ml	readily absorbed after oral administration (*2*)	3/1	9.2.1.2		antimalarial	

D:S, Dose: solubility; BA: Bioavailability; GI, gastrointestinal.

tamoxifen citrate	20 mg	high (very slightly soluble in water (*1*), 0.1 mg/ml -1 mg/ml), D:S 200 ml	BA_{abs} ~ 100% (*39*)	1	9.2.1.1	endometrial cancer, uterine sarcoma (*1*)	antihormone	
zinc sulfate	10 mg (per unit dosage form)	high (very soluble in water) (*1*), D:S 0.01, same solubility for all hydrates of the sulfate	11 % absorbed, with meal versus percentage of i.v. dose absorbed 20–30%	3	9.2.1.2		diarrhoea in children	

D:S, Dose:solubility; BA, bioavailability; i.v., intravenous.

[a] *14th WHO Model List of Essential Medicines*, Geneva, World Health Organization, March 2005; available at: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf.

[b] Solubility based on the lowest solubility in the pH range from 1 to 6.8 at 37 °C. "Low" indicates a dose[a] :solubility ratio > 250ml for at least one pH value in this range.

[c] Permeability based on fraction of the dose absorbed after oral dosing in humans, except where otherwise indicated. "Low" indicates that less than 85% of the oral dose was absorbed at the highest oral strength in the EML.[a]

[d] The original Biopharmaceutics Classification System (BCS) is available at: http://www.fda.gov/cder/guidance/3618fnl.pdf.

Note: the acceptance criteria have been adapted according to WHO requirements as explained in Section 2 of this Annex.

[e] See WHO "Multisource document": *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

[f] Known potential risks are indicated where appropriate. Where no information is given, this may indicate lack of availability of relevant data and should not be construed as meaning that there are no risks associated with use of the compound. Assessment of risks should be made by the national authority based on local conditions of use.

[g] Cytotoxic medicines: the risks associated with applying the biowaiver procedure should be very carefully scrutinized by the national regulatory authority.

NR not relevant: locally acting, no significant systemic absorption.

NA not applicable, locally acting.

Ferrous salts: (see footnote to Table 1).