WORLD HEALTH ORGANIZATION
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PROPOSAL TO WAIVE *IN VIVO* BIOEQUIVALENCE REQUIREMENTS FOR THE WHO MODEL LIST OF ESSENTIAL MEDICINES IMMEDIATE RELEASE, SOLID ORAL DOSAGE FORMS

This document has been revised by Professor Jennifer B. Dressman, Institut für Pharmazeutische Technologie, Biozentrum, Johann Wolfgang Goethe-Universität, Frankfurt/Main, Germany. It has followed the steps given in the schedule on page 2 herein. It has been very widely distributed and numerous comments have been incorporated.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/04.109/REV.1:

Proposal to waive *in vivo* bioequivalence requirements for the WHO Model List of Essential Medicines immediate release, solid oral dosage forms

	Deadline
Consolidation of first list for consideration of biowaiver	October 2004
Consolidation of comments	March 2005
Discussion during consultation	July 2005
Additional studies and review	August-September 2005
Mailing of revised version for comments	September 2005
Presentation to Fortieth WHO Expert Committee on Specifications for Pharmaceutical Preparations	24-28 October 2005

Proposal to waive *in vivo* bioequivalence requirements for WHO Model List of Essential Medicines immediate release, solid oral dosage forms

ABBREVIATIONS USED

API	Active Pharmaceutical Ingredient
BE	Bioequivalence
BCS	Classification System
Biowaiver	Approval of a generic oral solid formulation of an API based on strictly defined dissolution criteria as a surrogate for an in vivo bioequivalence test (provided other aspects of the dossier are deemed acceptable according to the usual criteria).
EML	WHO Model List of Essential Medicines
HHS-FDA	Department of Human Health: Federal Drug Agency, the United States of America
Multisource document	WHO working document QAS/04.093 entitled "Revision of multi-source (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability"
SUPAC	Scale-up and post-approval changes

INTRODUCTION

This proposal is closely linked to the working document QAS/04.093/Rev.4, entitled *Revision of multi-source (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability ("Multisource document").* It aims to give national authorities sufficient background information on the various orally applied APIs on the WHO Model List of Essential Medicines (EML) to enable them to make an informed decision, also taking into account

local usage of the API, as to whether generic formulations should be subjected to *in vivo* bioequivalence (BE) studies or whether a Biowaiver can be applied. In light of scientific work and discussion in the last decade, some of the criteria used to evaluate the API in terms of potential for a Biowaiver have been revised to allow a broadened scope of application. The result is that many APIs on the EML can now be considered for the Biowaiver procedure, subject to the usage and risks in the national setting.

BACKGROUND: HHS-FDA INITIATIVES TO ALLOW BIOWAIVERS BASED ON THE BCS

In 1995 the American HHS-FDA instigated the Biopharmaceutics Classification System (BCS), with the aim of granting so-called Biowaivers for SUPAC changes (www.fda.gov/cder/guidance/cmc5.pdf). A Biowaiver means that *in vivo* bioavailability and/or bioequivalence studies may be waived (not considered necessary for product approval). Instead of conducting expensive and time consuming *in vivo* studies, a dissolution test could be adopted as the surrogate basis for the decision as to whether the two pharmaceutical products are equivalent. At that time the Biowaiver was only considered for scale-up and post approval changes (SUPAC) to pharmaceutical products.

More recently, the application of the Biowaiver concept has been extended to approval of certain orally administered generic products (www.fda.gov/cder/guidance/3618fnl.htm).

Within the context of the documents cited above, only APIs with high solubility and high permeability and which are formulated in solid, immediate release (IR) oral formulations can be approved on the basis of the Biowaiver procedure. A major advantage of the Biowaiver procedure is the simplification and reduction of time required for product approval, thus reducing the cost of bringing new products to market.

What is the BCS?

The Biopharmaceutics Classification System or BCS was proposed in 1995 by Amidon et al. (Pharm. Res. 1995 March; 12(3):413-20). It is a scientific framework which divides APIs into four groups, according to their solubility and permeability properties.

Classification of APIs according to the BCS

According to the HHS-FDA definitions in the documents cited above, the four different categories possible for an API according to the BCS are:

- BCS class I: "high" solubility – "high" permeability
- BCS class II: "low" solubility" – "high" permeability
- BCS class III: "high" solubility – "low" permeability
- BCS class IV: "low" solubility – "low" permeability

Depending on the classification, the oral availability of the API may be expected to range from heavily dependent on the formulation and manufacturing method (e.g. class 2 APIs: poorly soluble yet highly permeable) to mostly dependent on the API permeability properties (e.g. Class III APIs: highly soluble yet poorly permeable).

How is high or low solubility currently defined by HHS-FDA?

The aqueous solubility of a drug substance is considered as high according to the HHS-FDA BCS criteria when:

- The ratio of the *highest orally administered dose (in mg) to the solubility (mg/ml) is less than 250 ml*

- This criterion is met over the pH range 1-7.5 at 37°C

According HHS-FDA guidances, the determination of the equilibrium solubility should be carried out with the shake-flask method (other methods like acid or base titration are permitted, when their ability to predict the equilibrium solubility is justified). The experiments should be carried out a temperature of 37$\pm$ 1°C. Further, a sufficient number of pH conditions should be chosen to cover the pH range of 1-7.5 and each determination should be carried out at least in triplicate. The buffer solutions given in the USP are appropriate for the tests, but other buffers are also allowed for the experiments. The pH value of each buffer solution should be checked before and after each experiment. Degradation of the API due to pH or buffer composition should also be reported along with other stability data.

The reason for the 250 ml cut-off criterion for the dose:solubility ratio is that in pharmacokinetic bioequivalence studies, the API formulation is to be ingested with a large glass of water (8 ounces corresponds to about 250 ml). If the highest orally administered dose can be completely dissolved in this amount of water, independent of the physiological pH value (hence the determination over the pH range 1-7.5), solubility problems are not expected to hinder the uptake of the drug in the small intestine.

The other important parameter for the BCS is the intestinal permeability of the drug.

How is high or low permeability currently defined by HHS-FDA ?

According to HHS-FDA a drug is considered a highly permeable, when *more than 90% of the orally administered dose is absorbed in the small intestine.*

Permeability can be assessed by pharmacokinetic studies (mass balance studies for example), or intestinal permeability methods, e.g. intestinal perfusion in humans, animal models or Caco 2 cell lines or other suitable, validated cell lines. *In vivo* or *in situ* animal models or *in vitro* models (cell lines) are only considered appropriate by HHS-FDA for passively transported drugs. It should be noted that all of these measurements assess the faction absorbed (as opposed to the bioavailability, which can be reduced substantially by first pass metabolism).

HHS-FDA suggests use of two different methods if results with one method are inconclusive for the permeability classification.

Which pharmaceutical formulations can currently be considered for a biowaiver according to HHS-FDA?

In order to be considered bioequivalent according to the HHS-FDA Biowaiver procedure, a pharmaceutical product:

- should contain a class 1 substance
- should be rapidly dissolving, meaning it should release at least 85% of its content in 30 minutes in three different buffers (pH 1.2, pH 4.5 and pH 6.8, composition see multi source document) in a paddle (50 rpm) or basket (100 rpm) apparatus at 37°C and a volume of 900 ml
- should not contain excipients which could influence the absorption of the drug
- should not contain a drug with a narrow therapeutic index
- should not be designed to be absorbed from the oral cavity.

The reasoning for the above-mentioned dissolution restriction is that when a highly soluble, highly permeable drug dissolves rapidly, it behaves like a solution in the gastrointestinal tract. If this is the case, the pharmaceutical composition of the product is insignificant, provided that excipients which influence the uptake across the gut wall are excluded from the formulation. The API is not prone to precipitation after its dissolution due to its good solubility under all pH conditions likely to be found in the upper gastrointestinal tract. The high permeability assures the complete uptake (> 90%) of the API during its passage through the small intestine. The fast dissolution of the product guarantees that the API is available long enough for the uptake in small intestine (the passage time in the small intestine is approximately 4 hours) and negates any slight differences between the formulations.

Pharmaceutical products containing an API with a narrow therapeutic index should always be tested with *in vivo* methods, since the risk for the patient resulting from a possible incorrect bioequivalence decision using the Biowaiver procedure is considered too high with these kinds of APIs.

As the BCS is only applicable to drugs which are absorbed from the small intestine, drugs with different sites of absorption (oral cavity) are not eligible for a Biowaiver.

It can be easily seen that the HHS-FDA requirements for classification of APIs and eligibility criteria for the Biowaiver are very strict. In the last decade, several publications and continuing scientific discussions have suggested that the original HHS-FDA criteria for application of the Biowaiver procedure can be relaxed without substantially

increasing the risk to public health or to the individual patient. On the basis of these publications and dialogue, the WHO has proposed revised BCS criteria and additional considerations for the eligibility of a pharmaceutical product for the Biowaiver procedure in the Multisource document.

WHO REVISIONS TO THE CRITERIA FOR BCS CLASSIFICATION

Based upon numerous discussions and consultations, the WHO revisions to the BCS criteria are as newly suggested in the working document QAS/04.093, Rev. 4, entitled *Revision of multi-source (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability ("Multisource document")* as follows:

WHO high solubility definition

When an API shows a dose/solubility ratio of less than 250 ml at 37°C over a **pH range of 1.2-6.8**, it can be classified as “highly soluble”. The decrease in pH from 7.5 in the FDA Guidances to 6.8 reflects the need to dissolve the drug before mid-jejunum to ensure enough reserve length for absorption from the GI tract. Furthermore, the dose that is to be used for the calculation is the **highest dose indicated in the Model List**, even though in some countries other doses may be available on the market.

WHO permeability definition

When an API is absorbed to an extent of **85%** or more, it is considered to be “highly permeable”. The permeability criterion was relaxed from 90% in the FDA Guidances to 85% in the WHO multisource document. Some examples of APIs now included in BCS class I that were previously considered to be Class III are: paracetamol, acetylsalicylic acid, allopurinol, lamivudine, promethazine.

Application of these revised criteria has changed the classification of some APIs in the list. Thus, the classifications in the tables attached to this document *supercede those in previous publications*. As new APIs on the Model List, it will be necessary to classify these according to the revised BCS, so it is anticipated that the Tables will be revised regularily. In addition, some APIs have not yet been sufficiently characterized to assign a BCS classification. As the Tables evolve, it is anticipated that more concrete information will be generated for these APIs as well.

The potential impact of the revised guidelines on registration requirements to establish interchangeability is that a large number of medicines on the EML could become eligible for approval based on *in vitro* bioequivalence testing in accordance with the dissolution tests prescribed in Section 9 of the Multisource document.

WHO EXTENSIONS TO THE SCOPE OF APPLICATION OF THE BIOWAIVER

In the "*Multisource document*" WHO has broadened the scope of application of the Biowaiver in three directions:

1) The criteria for classification as a Class I API have been relaxed with respect to both the dose: solubility ratio and permeability requirements.

2) The new version of the document allows pharmaceutical products containing Class III APIs to be considered for a Biowaiver, with application of more stringent dissolution criteria.

3) The new version of the document further allows pharmaceutical products containing BCS class II APIs that are weak acids which can meet a dose:solubility ratio of 250 ml or less at pH 6.8 to be eligible for a Biowaiver, with the requirement that they dissolve rapidly at pH 6.8 and similarly to the comparator product at pH 1.2 and 4.5.

WHO ADDITIONAL CRITERIA FOR APPLICATION OF THE BIOWAIVER PROCEDURE

For all APIs on the EML, it is imperative to consider not only the physical and absorption properties of the API when evaluating the API for Biowaiver, but (as outlined in the Multisource document) to perform a benefit/risk analysis in view of usage at the national level. As an example, in some countries amoxicillin is used primarily for ambulatory patients with mild to moderate upper respiratory tract, urinary tract and other infections. In other countries, amoxicillin might also be used for severe or even life-threatening infections, in which case the risk to the patient of arriving at the wrong bioequivalence decision would be far greater.

Thus, the eligibility criteria according to WHO are

1. The **BCS classification** (according to the revised criteria) of the API.

2. **Risk assessment:** Only if the risk of an incorrect biowaiver decision and an evaluation of the consequences (of an incorrect, Biowaiver-based equivalence decision) in terms of public health and individual patient risks outweighed by the potential benefits of the Biowaiver approach should the Biowaiver procedure be applied.

3. **Dissolution requirements** for the pharmaceutical product:

   - *Very rapidly dissolving* (release of >85% of the labelled amount of drug in 15 minutes) in standard media at pH 1.2, 4.5 and 6.8, at a rotational speed of 75 rpm in the paddle apparatus or 100 rpm in the basket apparatus (applies to pharmaceutical products containing Class III APIs).

   - *Rapidly dissolving* (release of >85% of the labelled amount of drug in 30 minutes) in standard media at pH 1.2, 4.5 and 6.8, at a rotational speed of 75 rpm in the paddle apparatus or 100 rpm in the basket apparatus (applies to pharmaceutical products containing Class I APIs and Class II APIs

which are weak acids and meet the 250 ml dose:solubility requirement at pH 6.8).

4. Excipient considerations

The national authority should be mindful that some excipients can influence motility and/or permeability in the gastrointestinal tract. Therefore, the excipients used in the multisource product formulation should be scrutinized. In this regard, the national authority can draw on the experience of formulations which have been approved on the basis of human bioequivalence studies in their own or in other jurisdictions.

If the multisource product under consideration contains excipients that have been used before in similar amounts in other formulations of the same API, it can be reasonably concluded that the excipients will have no unexpected influence on the bioavailability of the product. If, however, the formulation contains different excipients or very different amounts of the same excipients, the national authority may choose not to allow the Biowaiver procedure to be used.

A list of usual and acceptable excipients can be found e.g. at the following website: (www.fda.gov/cder/iig/iigfaqWEB.htm), formulations of some products can be found on national websites of national drug regulatory authorities.

Explanation of the Tables

The decision of a national authority to allow a biowaiver based on the BCS should take into consideration the solubility and permeability characteristics as well as the therapeutic use and therapeutic index of the active pharmaceutical ingredient (API), its pharmaco-kinetic properties, the similarity of the dissolution profiles of the multisource and the comparator products in standard buffers with a pH of 1.2, pH 4.5 and pH 6.8 at 37°C. Data related to the excipient composition of the multisource product is also required. A systematic approach to the biowaiver decision has been established by the International Pharmaceutical Federation (FIP) and published in the *Journal of Pharmaceutical Sciences*: http://www3.interscience.wiley.com/cgi-bin/jhome/68503813 . They can further be downloaded from the International Pharmaceutical Federation (FIP) website: http://www.fip.org/. These monographs provide detailed information which should be taken into account whenever available in the Biowaiver consideration.

Which APIs are included in the Tables?

The substances listed on the 14th EML as of March 2005 have been evaluated and classified according to the revised criteria given above.

Where do the data come from?

The solubility and permeability values were found in the literature open to the public domain, such as the Martindale, the Merck Index, scientific journals, etc.

Please note that the doses used for the calculation of the dose/solubility ratio are the doses given in the EML.

The indications given in the Tables are taken directly from the EML. If the EML specifies the dosage form (e.g. sublingual tablet) this is indicated under “comments”.

“Worst case” approach to BCS classification

The drugs listed in the EML were classified according to the criteria explained above. Where no clear classification could be made, the “worst case” was assumed, for example if a substance is highly soluble but absolute bioavailability data were not available, the test for BCS class III substances has been proposed. The same procedure was adopted for fixed combinations, for example amoxicillin and clavulanic acid, the testing procedure was always fixed according to the “worst” BCS classification, in this example clavulanic acid (BCS class 3/1), since amoxicillin is a BCS class I drug. So this combination would be tested according to BCS class III requirements.

The results of the revised classification can be found in Tables A – C.

Why are there three Tables?

In Table A, all APIs on the EML that are applied orally are listed, with the exception of the APIs listed as complementary. In Table B, the APIs listed as complementary in the EML are summarized and in Table C, APIs for which there had previously been no classification or had been introduced with the 14th edition version of the EML (March 2005) are listed, along with a more detailed explanation of their classification.

Risk assessment

In order to minimize the risks of an incorrect biowaiver decision in terms of public health and individual patient risks the therapeutic indications of the API, known pharmacokinetic variations, food effects, etc should be evaluated based on local clinical experience, taking into account the indications for which the API is prescribed in that country as well as specific pharmacokinetic population variations (for example CYP polymorphisms). Known potential risks are listed under “potential risks” in the Tables. The absence of an entry under “potential risks” should not however be misconstrued as meaning that there are no risks associated with the use of the medicine.

BIOWAIVER TESTING PROCEDURE ACCORDING TO WHO

Depending on the BCS classification of the API, based on solubility and permeability characteristics listed in the accompanying Tables, the testing procedure is defined in 9.2.1 of the "*Multisource document*".

For pharmaceutical products containing **BCS class I** (highly soluble, highly permeable) APIs:

For *rapidly dissolving* (as defined above) pharmaceutical products containing **BCS class I** APIs, greater than 85% dissolution of the labelled amount is required within 30min in standard media at pH 1.2, 4.5 and 6.8 using the paddle apparatus at 75rpm or alternatively the basket apparatus at 100rpm. The dissolution profiles of the comparator and the multisource products should be compared by an $f_2 > 50$ or an equivalent statistical criterion.

If after 15 min more than 85% are released from the comparator and the multisource formulation under the above-mentioned conditions the product will be considered *very rapidly dissolving***.** In this case the products are deemed to be equivalent and a profile comparison is not required.

For pharmaceutical products containing **BCS class III** (highly soluble, low permeability) APIs:

A biowaiver can be only considered if both the multisource and the comparator product are *very rapidly dissolving*; 85% or more dissolution of the labelled amount of the API should be achieved within 15min in standard media at pH 1.2, 4.5 and 6.8 using the paddle apparatus at 75rpm or alternatively the basket apparatus at 100 rpm.

Generally the risks of an inappropriate biowaiver decision should be more critically reviewed (side specific absorption, induction/competition at the absorption side, excipient composition and therapeutic risks, etc.) than for BCS class I drugs.

For pharmaceutical products containing APIs with high solubility at pH 6.8 but not at pH 1.2 or 4.5 and with high permeability (by definition, **BCS class II compounds with weak acidic properties**):

These are eligible for a Biowaiver provided that the multisource product:

(i) is *rapidly dissolving* i.e. 85% or more dissolution of the labelled amount of the API should be achieved within 30 min in standard media at pH 6.8 using the paddle apparatus at 75 rpm or alternatively the basket apparatus at 100rpm, ***and***

(ii) The multisource product exhibits similar dissolution profiles, as determined with the f_2 value or equivalent statistical evaluation, to those of the comparator product in buffers at all three pH values (pH 1.2, 4.5 and 6.8).

For multisource products containing Class 2 APIs with dose:solubility ratios of 250 ml or less at pH 6.8, the excipients should additionally be critically evaluated in terms of type and amounts of surfactants in the formulation.

Further details about eligibility for the Biowaiver and appropriate test procedures can be found in Section 5 and 9 of the *Multisource* document.

Table A. Substances on the WHO Essential Medicines List (EML)

Drug[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)[g]	Comments and special dosage form indications[a]
abacavir	200mg	high	low	3	9.2.1.2		antiretroviral	
acetazolamide	250mg	low	low	4	no biowaiver		antiglaucoma medicine	unknown whether poor BA is due to poor solubility or poor solubility and permeability
acetylsalicylic acid	500mg	high	high	1	9.2.1.1		NSAID, antimigraine medicine	
acetylsalicylic acid	100mg	high	high	1	9.2.1.1		antithrombotic medicine	
aciclovir	200mg	high	low	3	9.2.1.2		antiherpes medicines	
albendazole	400mg	low	low	4	no biowaiver		anthelminic	chewable tablet; unknown whether poor BA is due to poor solubility or poor solubility and permeability
allopurinol	100mg	high	high	1	9.2.1.1		gout	
aluminium hydroxide	500mg			N.R.	N.A.		antacid	local effect
amiloride hydrochloride	5mg	high	high	1	9.2.1.1		diuretic	
amitriptyline hydrochloride	25mg[1]	high	high	1	9.2.1.1		psychotherapeutic medicine	
amlodipine	5mg	high	high	1	9.2.1.1		antihypertensive medicine	

amodiaquine (base)	200mg	high	borderline BA > 75%	3/1	9.2.1.2	CYP2C8 polymorphism, increased risk for agranulocytosis and liver toxicity	antimalarial	extent of first pass metabolism uncertain
amoxicillin (a) + clavulanic acid (c)	(a) 500mg + (c) 125mg	(a) high + (c) high	(a) high + (c) borderline absorption > 73% (radioactive excretion)	(a) 1 + (c) 3/1	9.2.1.2		antibacterial	combination should be tested according to clavulanic acid requirements
amoxicillin anhydrous	500mg	high	high	1	9.2.1.1		antibacterial	
artemether (a) + lumefantrine (l)	(a) 20mg + (l) 120mg	(a and l) unknown	low (a and l)	(a) 4/3 + (l) 4/3	no biowaiver		antimalarial	
ascorbic acid	50mg	high	high	1	9.2.1.1		vitamin	
atenolol	100mg	high	low	3	9.2.1.2		antianginal, antihypertensive, antiarrhythmic, medicine and used in heart failure	
azithromycin	500mg	low	low	4	no biowaiver		antibacterial	unknown whether poor BA is due to poor solubility or poor solubility and permeability
benznidazole	100mg	high	low	3	9.2.1.2		american tripanosomiasis	
biperiden hydrochloride	2mg	high	insufficient literature	3/1	9.2.1.2		antiparkinson medicine	

carbamazepine	200mg	low (neutral)	high	2	no biowaiver		antiepileptic, psychotherapeutic medicine	scored tablet
cefixime	400mg	low	low	4	no biowaiver		antibacterial	unknown whether poor BA is due to poor solubility or poor solubility and permeability
chloramphenicol	250mg	high	low	3	9.2.1.2	narrow therapeutic index	antibacterial	
chloroquine phosphate or sulfate	150mg	high	high	1	9.2.1.1		DMARD, antimalarial	
chlorphenamine hydrogen maleate	4mg	high	BA 25-59%, first pass	3/1	9.2.1.2	CYP2D6 polymorphism	antiallergic	extent of first pass metabolism uncertain
chlorpromazine hydrochloride	100mg	high	low	3	9.2.1.2		psychotherapeutic medicine	
ciprofloxacin hydrochloride	250mg	high	low/high, BA 70-82%, possible first pass, high in CaCo 2 cells	3/1	9.2.1.2		antibacterial	extent of first pass metabolism uncertain
clofazimine	100mg	insufficient literature	low	4/3	no biowaiver at present		antileprosy medicine	
clomifene citrate	50mg	high	insufficient literature	3/1	9.2.1.2		ovulation inducer	

clomipramine hydrochloride	25mg	high	Some 66% of a dose is excreted in the urine, the remainder being eliminated in the faeces	3/1	9.2.1.2		psychotherapeutic medicine	lack of absolute bioavailability data
cloxacillin (as sodium salt)	1000mg	high	low	3	9.2.1.2		antibacterial	
codeine phosphate	30mg	high	low	3	9.2.1.2	risk of abuse	opionid analgesic, diarrhoea in adults	
dapsone	100mg	low (weak base)	high	2	no biowaiver	G6PD defiency	antileprosy medicine	
diazepam	5mg	high	high	1	9.2.1.1		psychotherapeutic medicine	scored tablet
didanosine	200mg	high	low	3	9.2.1.2		antiretroviral	buffered chewable, dispersible tablet
didanosine	400mg	high	low	3	9.2.1.2		antiretroviral	unbuffered enteric coated capsule
digoxin	250µg	high	high	1	9.2.1.1		antiarrhythmic and used in heart failure	
diloxanide furoate	500mg	low[2]	low	4	no biowaiver		antiprotozoal	unknown whether poor BA is due to poor solubility or poor solubility and permeability
DL-methionine	250mg	high	high	1	9.2.1.1		antidote	
doxycycline hydrochloride	100mg	high	high	1	9.2.1.1		antibacterial	

efavirenz	200mg	low[1]	low	4	no biowaiver		antiretroviral	unknown whether poor BA is due to poor solubility or poor solubility and permeability
enalapril	2,5mg	high	low	3	9.2.1.2		antihypertensive medicine	
ergocalciferol	1.25mg (50 000 IU)	high	low	3	9.2.1.2		vitamin	
erythromycin stearate + succinate	250mg	high	low	3	9.2.1.2		antibacterial	
ethambutol hydrochloride	400mg	high	low	3	9.2.1.2	risk of dose related ototoxicity	antituberculosis medicine	
ethinylestradiol	50µg	high	borderline, BA 40-50%, first pass	3/1	9.2.1.2		estrogen	extent of first pass metabolism uncertain
ethinylestradiol (e) + levonorgestrel (l)	30µg + 150µg	high	(e) borderline, BA 40-50%, first pass + (l) high	3/1 + 1	9.2.1.2		hormonal contraceptive	extent of first pass metabolism uncertain; combination should be tested according to ethinylestradiol requirements
ethinylestradiol (e) + norethisterone (n)	35µg + 1mg	high	(e) borderline, BA 40-50%, first pass + (n) high	3/1 + 1	9.2.1.2		hormonal contraceptive	extent of first pass metabolism uncertain; combination should be tested according to ethinylestradiol requirements

ferrous salt	equivalalent to 60mg iron	high (see footnote)	low	3	9.2.1.2		antianaemia medicine	commonly used salts: see footnote
ferrous salt (fs) + folic acid (fa)	equivalent to 60mg iron + 400µg folic acid	(fs) high + (fa) high	(fs) low + (fa) low (urinary recovery 28.5%[2])	3 + 3/1	9.2.1.2		antianaemia medicine (during pregnancy)	lack of absolute bioavailability data; commonly used salts: see footnote; combination should be tested according to ferrous salt requirements
fluconazole	50mg	high	high	1	9.2.1.1		antifungal	
folic acid	5mg	high	low	3/1	9.2.1.2		antianaemia medicine	lack of absolute bioavailability data
furosemide	40mg	low	low	4	no biowaiver	highly variable BA	medicine used in heart failure, diuretic	unknown whether poor BA is due to poor solubility or poor solubility and permeability
glibenclamide	5mg	low	low	4	no biowaiver		antidiabetic agent	unknown whether poor BA is due to poor solubility or poor solubility and permeability
glyceryl trinitrate	500µg	high	sublingual application, permeability in the oral cavity more important than GI permeability	3/1	N.A.	local absorption	antianginal medicine	sublingual application

griseofulvin	250mg	low (neutral)	high	2	no biowaiver		antifungal	
haloperidol	2mg	borderline, < 0.01 mg/ml[2]	low	4/3	no biowaiver		psychotherapeutic medicine	
hydralazine hydrochloride	50mg	high	low	3	9.2.1.2		antihypertensive medicine	
hydrochlorothiazide	25mg	high	low	3	9.2.1.2		antihypertensive medicine, diuretic and used in heart failure	scored tablet
ibuprofen	400mg	low, weak acid [pK_a4.4, 5.2]	high	2	9.2.1.3		NSAID, antimigraine medicine	
indinavir sulfate	400mg	low	low	4	no biowaiver	CYP 450 3A4, food effect (-)	antiretroviral	unknown whether poor BA is due to poor solubility or poor solubility and permeability
iopanoic acid	500mg	low, weak acid, [pk_a 4.8][2] (see footnote)	high	2	no biowaiver		radiocontrast media	
isoniazid	300mg	high	borderline	3/1	9.2.1.2		antituberculosis medicine	
isoniazid (i) + ethambutol (e)	(i) 150mg + (e) 400mg	(i) high + (e) high	(i) borderline + (e) low	(i) 3/1 + (e) 3	9.2.1.2		antituberculosis medicine	
isosorbide dinitrate	5mg	high	sublingual application, permeability in the oral cavity more important than GI permeability	3/1	N.A.		antianginal medicine	sublingual

ivermectin	6mg	insufficient literature, practically insoluble in water[3] D/L>6000ml	low	4/3	no biowaiver		antifilarial	scored tablet; unknown whether poor BA is due to poor solubility or poor solubility and permeability
lamivudine	150mg	high	high	1	9.2.1.1		antiretroviral	
levamisole hydrochloride	150mg	high	borderline	3/1	9.2.1.2		anthelminic	
levodopa (l) + carbidopa (c)	(l) 250mg + (c) 25mg	(l) high + (c) high	(l) high + (c) insufficient data (BA_{humans} 58%, BA_{dogs} 88%)	(l) 1 + (c) 3/1	9.2.1.2	narrow therapeutic index	antiparkinson medicine	extent of human first pass metabolism uncertain; combination should be tested according to carbidopa requirements
levonorgestrel	30µg	high	high	1	9.2.1.1		hormonal contraceptive	
levonorgestrel	750µg * 2 (pack of two)	high	high	1	9.2.1.1		hormonal contraceptive	
levothyroxine sodium salt	100µg	high	low	3	9.2.1.2	narrow therapeutic index	thyroid hormone	
lithium carbonate	300mg	high	high	1	9.2.1.1	narrow therapeutic index	psychotherapeutic medicine	
lopinavir (l) + ritonavir (r)	(l) 133.3mg + (r) 33.3mg	(l) low + (r) low	(l) low (insufficient data) + (r) low	(l) 4/2 + (r) 4	no biowaiver		antiretroviral	unknown whether poor BA is due to poor solubility or poor solubility and permeability
mebendazole	500mg	low	low	4	N.A.		anthelminic	chewable tablet; anthelmintics usually applied 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 permeability

mefloquine hydrochloride	250mg	low[2]	low	4	no biowaiver		antimalarial	unknown whether poor BA is due to poor solubility or poor solubility and permeability
metformin hydrochloride	500mg	high	low	3	9.2.1.2		antidiabetic agent	
methyldopa	250mg	high	low	3	9.2.1.2		antihypertensive medicine	
metoclopramide hydrochloride	10mg	high	low	3	9.2.1.2		antiemetic	
metronidazole	500mg	high	high	1	9.2.1.1		antiprotozoal, antibacterial	
morphine sulfate	10mg	high	insufficient data (BA ~ 30% but extensive first pass)	3/1	9.2.1.2	risk of abuse	opionid analgesic	extent of first pass metabolism uncertain
nelfinavir mesilate	250mg	low	low	4	no biowaiver	CYP 450 3A4, food effect (+)	antiretroviral	unknown whether poor BA is due to poor solubility or poor solubility and permeability
neostigmine bromide	15mg	high	low	3	9.2.1.2		muscle relaxant	
nevirapine	200mg	low (weak base)	high	2	no biowaiver		antiretroviral	
niclosamide	500mg	low	low	4	N.A.		anthelminic	chewable tablet; anthelmintics usually applied orally for action in GI tract: solubility more important than permeability
nicotinamide	50mg	high	high	1	9.2.1.1		vitamin	
nifedipine	10mg	low, weak acid, solubility at pH 7 0.0056 mg/ml[2]	high	2	no biowaiver		antioxytocic	

nifurtimox	250mg	high	low	3	9.2.1.2		american tripanosomiasis	
nitrofurantoin	100mg	low, weak acid, solubility at pH 7.0 0.374 mg/ml [pK_a 7.2 (25°)][2]	high	2	no biowaiver		antibacterial	
norethisterone	5mg	high	high	1	9.2.1.1		progestogen	
nystatin	500 000 IU			N.R.	N.A.		antifungal	local effect
paracetamol	500mg	high	high	1	9.2.1.1		NSAID, antimigraine medicine	
penicillamine	250mg	high	low	3	9.2.1.2		antidote	
phenobarbital	100mg	high	high	1	9.2.1.1	narrow therapeutic index	antiepileptic	
phenoxymethylpenicillin (as potassium salt)	250mg	high	high	1	9.2.1.1		antibacterial	
phenytoin sodium salt	100mg	low, weak acid, sol. at pH 6.8 1.7 mg/ml[4] [pK_a8.3 (25°)])	high	2	9.2.1.3	narrow therapeutic index, non-linear pharmacokinetics	antiepileptic	
potassium iodide	60mg	high	high	1	9.2.1.1		thyroid hormones and antithyroid medicines	
praziquantel	600mg	low (neutral)	high	2	no biowaiver		anthelminic, antischistosomal, antitrematode	
prednisolone	25mg	high	high	1	9.2.1.1		antiallergic	
primaquine diphosphate	15mg	high	high	1	9.2.1.1		antimalarial	
proguanil hydrochloride	100mg	high	high	1	9.2.1.1		antimalarial	
promethazine hydrochloride	25mg	high	high	1	9.2.1.1	CYP2D6 polymorphism	antiemetic	
propranolol hydrochloride	40mg	high	high	1	9.2.1.1		antimigraine medicine	

propylthiouracil	50mg	high	high	1	9.2.1.1		antithyroid medicine	
pyrantel embonate	250mg	low	low	4	N.A.		anthelminic	chewable tablet; anthelmintics usually applied orally for action in GI tract: solubility more important than permeability

pyrazinamide	400mg	high	borderline	3/1	9.2.1.2		antituberculosis medicine	
pyridoxine hydrochloride	25mg	high	high	1	9.2.1.1		vitamin	
pyrimethamine	25mg	borderline; <0.1 mg/ml[3]	low	4/3	no biowaiver		antipneumocystosis and antitoxoplasmosis medicine	
quinine bisulfate or sulfate	300mg	high	high	1	9.2.1.1		antimalarial	
ranitidine hydrochloride	150mg	high	low	3	9.2.1.2		antiulcer medicine	
retinol palmitate	110mg (200 000 IU)	low[3]	low	4	no biowaiver		vitamin	unknown whether poor BA is due to poor solubility or poor solubility and permeability
riboflavin	5mg	high	high	1	9.2.1.1		vitamin	
rifampicin	300mg	low (amphiphil) [pK_a1.7, 7.9][1]	high	2	no biowaiver		antileprosy & antituberculosis medicine	
rifampicin (r) + isoniazid (i)	(r) 300mg + (i) 150mg	(r) low + (i) high	(r) high + (i) borderline	(r) 2 + (i) 3/1			antituberculosis medicine	
rifampicin (r) + isoniazid (i) + pyrazinamide (p)	(r) 150mg + (i) 150mg + (p) 500mg	(r) low + (i) high + (p) high	(r) high + (i) borderline + (p) borderline	(r) 2 + (i) 3/1 + (p) 3/1			antituberculosis medicine	
rifampicin (r) + isoniazid (i) + pyrazinamide (p) + ethambutol (e)	(r) 150mg + (i) 75mg + (p) 400mg + (e) 275mg	(r) low + (i) high + (p) high + (e) high	(r) high + (i) borderline + (p) borderline + (e) low	(r) 2 + (i) 3/1 + (p) 3/1 + (e) 3			antituberculosis medicine	
ritonavir	100mg	low	low	4	no biowaiver	CYP 450 3A4	antiretroviral	unknown whether poor BA is due to poor solubility or poor solubility and permeability
salbutamol sulfate	4mg	high	high	1	9.2.1.1		antiasthmatic and medicine for COPD	

saquinavir	200mg	low	low	4	no biowaiver	CYP 450 3A4, food effect (+)	antiretroviral	unknown whether poor BA is due to poor solubility or poor solubility and permeability
	7,5mg (sennoside)			N.R.	N.A.		laxative	local effect
spironolactone	25mg	borderline	low	4/3	no biowaiver		diuretic	
stavudine	40mg	high	high	1	9.2.1.1		antiretroviral	
sulfamethoxazole (s) + trimethoprim (t)	(s) 400mg + (t) 80mg	(s) low (amphiphil) + (t) low (weak base)	(s) high + (t) high	(s) 2 + (t) 2	no biowaiver	G6PD deficiency	antibacterial	
sulfasalazine	500mg	low	low	4	N.R.		gastrointestinal, anti-inflammatory medicine	local effect; unknown whether poor BA is due to poor solubility or poor solubility and permeability
thiamine hydrochloride	50mg	high	low	3	9.2.1.2		vitamin	
triclabendazole	250mg	insufficient literature	low	4/3	no biowaiver		antischistosomal, antitrematode	
trimethoprim	200mg	low (weak base)	high	2	no biowaiver		antibacterial	
valproic acid sodium salt	500mg	high	high	1	9.2.1.1		antiepileptic, psychotherapeutic medicine	enteric coated tablet

verapramil hydrochloride	80mg	low (weak base)	high	2	no biowaiver		antianginal and antiarrhythmic medicine	
warfarin sodium salt	5mg	low (soluble 1in less than 1 of water)[1]	High	1	9.2.1.1	narrow therapeutic index	medicines affecting coagulation	
zidovudine	300mg	high	high	1	9.2.1.1		antiretroviral	
zinc sulfate	10mg (per unit dosage form)	high	low	3	9.2.1.2		diarrhoea in children	

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a WHO Essential Medicines List, 14th edition, march 2005 can be found under: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf.

b Solubility based on the lowest solubility in the pH range from 1-6.8 at 37°C. "Low" indicates a dose[a] solubility ratio > 250ml at 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 were absorbed commensurate with the highest oral strength according to the EML[a].

d The original Biopharmaceutics Classification System (BCS) can be found under: http://www.fda.gov/cder/guidance/3618fnl.pdf Note that the acceptance criteria have been adapted according to WHO requirements as explained in footnotes 1-3.

e See WHO multisource document: www.who.int/medicines/library/qsm/manual-on-marketing/multisource-contents.html.

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

N.R. not relevant: locally acting, no significant systemic absorption

N.A. not applicable, locally acting

clavulanic recently classified, references see list of new compounds on the EML (List c)

fixed-dose combination of antituberculosis drugs, will be reviewed by the Expert Committee

compounds introduced to the EML since March 2005 or no certain classification had been previously reported

BA bioavailability

Medicine is applied sublingual, major absorption in the oral cavity

Ferrous salts

Commonly used iron salts[3]:

- ferrous ascorbate (anhydrous)
- ferrous aspartate (tetrahydrate)
- ferrous chloride (tetrahydrate)
- ferrous fumarate (anhydrous)
- ferrous gluconate (dihydrate)
- ferrous glycine sulphate
- ferrous orotate
- ferrous succinate (anhydrous)
- ferrous sulfate (dried)
- ferrous sulfate (heptahydrate)

Ferrous salts solubility:

- lowest solubility of all commonly used iron salts: ferrous succinate anhydrous,

  sparingly soluble in water[5], D/L 6ml).

Iopanoic acid:

not sufficient solubility at pH 6.8 expected: 0.015 mg/ml in water.

Table B. Substances on the Complementary list of WHO Essential Medicines List (EML)

Drug[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)[g]	Comments and special dosage form indications[a]
artesunate	50mg	high	borderline (BA_{abs} 82 + 88%) but dependant on severity of disease[1,2]	3/1	9.2.1.2	extent of abs. depends on severity of disease	antimalarial	
azathioprine sodium salt	50mg	low	low	4	no biowaiver	immunosuppressive, TDM recommended	immunosuppressive, DMARD	unknown whether poor BA is due to poor solubility or poor solubility and permeability
calcium folinate	15mg	high	high	1	9.2.1.1		anti-cytotoxic medicine	
chlorambucil	2mg	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	myolosuppression (leucopenia) = dose limiting toxicity	cytotoxic medicine	
cyclosporine	25mg	borderline	low	4/3	no biowaiver	immunosuppressive, TDM recommended	immunosuppressive	
clindamycin	150mg	high	high	1	9.2.1.1		antibacterial	
cyclophosphamide	25mg	high	high	1	9.2.1.1	myolosuppression (leucopenia) = dose limiting toxicity, accelerated metabolism leading to reduced oral BA after repeated treatment	cytotoxic medicine	

						cycles		
cylcoserine	250mg	high	insufficient literature (urinary recovery 65%[5], 70-90% of the dose absorbed[6])	3/1	9.2.1.3	serum levels > 30µg/ml associated with CNS toxicity	antituberculosis medicine	
diethylcarbamazine dihydrogen citrate	100mg	high	high	1	9.2.1.2	myolosuppression (leucopenia) = dose limiting toxicity, accelerated metabolism leading to reduced oral BA after repeated treatment cycles	antifilarial	
doxycycline hydrochloride	100mg	high	high	1	9.2.1.1		antimalarial	
ethionamide	250mg	high	insufficient literature (readily abs. from the GI tract[7])	3/1	9.2.1.3		antituberculosis medicine	
ethosuximide	250mg	high	insufficient literature	3/1	9.2.1.2		antiepileptic	
etoposide	100mg	low	low	4	no biowaiver	myolosuppression (leucopenia) = dose limiting toxicity, accelerated metabolism leading to reduced oral BA after repeated treatment cycles	cytotoxic medicine	unknown whether poor BA is due to poor solubility or poor solubility and permeability
flucytosine	250mg	high	borderline (BA_{abs} 76-89%)[8,9]	3/1	9.2.1.2		antifungal	
levamisole hydrochloride	50mg	high	no human data available	3/1	9.2.1.2		cytotoxic medicine	
levofloxacin	500mg	high	high	1	9.2.1.1		antituberculosis medicine	
mefloquine hydrochloride	250mg	low	insufficient literature (well absorbed[7])	4/2	no biowaiver	pharmacokinetics of mefloquine may be altered by malaria infection[7]	antimalarial	

mercaptopurine	50mg	low	low	4	no biowaiver		cytotoxic medicine	unknown whether poor BA is due to poor solubility or poor solubility and permeability
methotrexate sodium salt	2,5mg	high	low	3	9.2.1.2	severity of adverse effects depends on dose and indication	cytotoxic medicine, DMARD	
mifepristone - misoprostol	200mg	no literature data available	low	4/3	no biowaiver		oxytocic	
ofloxacin	400mg	high	high	1	9.2.1.1		antituberculosis medicine	
oxamniquine	250mg	low	insufficient literature (urinary recovery as single acid 70%[7])	4/2	no biowaiver		antischistosomal, antitrematode	
p-aminosalicylic acid	500mg	low	borderline (80% urinary recovery[7])	4/2	no biowaiver		antituberculosis medicine	
penicillamine	250mg	high	low	3	9.2.1.2		DMARD	
pentamine	300mg	high	no literature data	3/1	9.2.1.2		anti-pneumocystosis and antitoxoplasmosis medicine	
prednisolone	25mg	high	high	1	9.2.1.1		hormone/ antihormone	
procarbazine hydrochloride	50mg	high	insufficient literature (urinary recovery 70%, 24h[5])	3/1	9.2.1.2	myolosuppression (leucopenia) = dose limiting toxicity	cytotoxic medicine	
pyridostigmine bromide	60mg	high	low	3	9.2.1.2		muscle relaxant	
quinidine sulfate	200mg	high	insufficient literature (BA 70% but first pass[5])	3/1	9.2.1.2		antiarrhythmic	

sulfadiazine	500mg	borderline	low	4/3	no biowaiver		antibacterial	
sulfadoxine (s) + pyrimethamine (p)	(s) 500mg + (p) 25mg	(s) high + (p) borderline (< 0.1 mg/ml[7])	(s) insufficient data + (p) low	(s) 3/1+ (p) 4/3	no biowaiver		antimalarial	combination should be tested according to pyrimethamine requirements
sulfasalazine	500mg	low	low	4	no biowaiver		DMARD	unknown whether poor BA is due to poor solubility or poor solubility and permeability
tamoxifen citrate	20mg	high	high	1	9.2.1.1		antihormone	

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a WHO Essential Medicines List, 14th edition, march 2005 can be found under: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf.

b Solubility based on the lowest solubility in the pH range from 1-6.8 at 37°C. "Low" indicates a dose[a] solubility ratio > 250ml at 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 were absorbed commensurate with the highest oral strength according to the EML[a].

d The original Biopharmaceutics Classification System (BCS) can be found under: http://www.fda.gov/cder/guidance/3618fnl.pdf . Note that the acceptance criteria have been adapted according to WHO requirements as explained in footnotes 1-3.

e See WHO multisource document: www.who.int/medicines/library/qsm/manual-on-marketing/multisource-contents.html.

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

N.R. not relevant: locally acting, no significant systemic absorption

N.A. not applicable, locally acting

compounds introduced to the EML since March 2005 or no certain classification had been previously reported

cytotoxic medicines, possibility of a biowaiver procedure should be reviewed by the Expert Committee

BA bioavailability

Table C. Compounds introduced to the EML since March 2005 or where no certain classification had been previously reported (these compounds also appear in Table A and Table B)

Drug[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)[g]	Comments and special dosage form indications[a]
amlodipine	5mg	slightly soluble[1], D/L 5ml	BA_{abs} 60-65%, excretion of drug metabolites urine 90-95%[2]	1	9.2.1.1		antihypertensive medicine	BA_{abs} < 85% ascribed to first pass metabolism
amodiaquine (base)	200mg	45mg/ml[2], D/L 4.4ml	BA > 75%[3]	3/1	9.2.1.2	CYP2C8 polymorphism, increased risk for agranulocytosis and hepatotoxicity[4]	antimalarial	
amoxicillin + clavulanic acid	500mg + 125mg	freely soluble in water[1], D/L 1.25ml	absorption > 73% (radioactive excretion)[5]	1 + 3/1	9.2.1.2		antibacterial	combination should be tested accordin to clavulanic acid requirements
artesunate	50mg	very slightly soluble[6], D/L 500ml; (weak acid, pk_a ~ 6,4)	BA_{abs} 82%[1], BA_{abs} 88%[7], BA_{abs} 61%[8]	4/2	no biowaiver or 9.2.1.3		antimalarial	permeability depends on severity of disease

azithromycin	500mg	practically insoluble in water[1] < 0.01mg/ml, D/L 50000ml	BA_{abs} 16%[9]; BA 37%[10,11];	4/2	no biowaiver		antibacterial	unknown whether poor BA is due to poor solubility or poor solubility and permeability
calcium folinate	15mg	sparingly soluble in water (Ph. Eur. 5.2); very soluble (USP 28); D/L 15ml and 0,015ml, respectively	BA_{abs} 92% 25mg[12,13]; BA_{abs} 73.4% (15mg)[14]; fully absorbed; AUC & $t_{1/2}$ similar after i.v. & p.o[15]	1	9.2.1.1		anti-cytotoxic medicine	
levodopa (l) + carbidopa (c)	(l) 250mg + (c) 25mg	(l) high + (c) soluble 1 in 500 of water, freely soluble in 3M 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	combination should be tested according to carbidopa requirements
cefixime	400mg	slightly soluble[2], D/L 400ml	22-54%[2]	4/2	no biowaiver		antibacterial	unknown whether poor BA is due to poor solubility or poor solubility and permeability

chlorambucil	2mg	practically insoluble in water[1], D/L ~ 20ml	i.v. vs. p.o similar analytical profile urine = high degree of absorption[18], BA_{abs} > 70% after repeated oral dosage[19,20]	3/1	9.2.1.3(weak acid, pk_a ~ 5,8)	myolosuppression (leucopenia) = dose limiting toxicity; accelerated metabolism leading to reduced oral BA after repeated treatment cycles[21,22]	cytotoxic medicine	
clindamycin	150mg	500mg/ml[2], D/L 0.3ml	about 90% of the dose absorbed[1]	1	9.2.1.1	diarrhoea/ nausea	antibacterial	
cylcoserine	250mg	soluble 100mg/ml[2], D/L 2.5ml	65% urinary excreation[2], 70-90% of a p.o. dose absorbed[23]	3/1	9.2.1.2	serum levels > 30µg/ml associated with CNS toxicity	antituberculosis medicine	
enalapril	2,5mg	sparingly soluble in water[1], D/L 0.25ml; 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	9.2.1.3		antihypertensive medicine	

ethionamide	250mg	slightly soluble in water at 25°C[2], D/L < 250ml	readily absorbed from the gastrointestinal tract, extensively metabolised, 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	
etoposide	100mg	practically insoluble in water[2], D/L 1000ml	excretion 30-50% unchanged in the urine, 20% as metabolites = 50-70%[2], absorption 48,4% and 57%[23], 60,6% absorption in children[26]	4/2	no biowaiver	myolosuppression (leucopenia) = dose limiting toxicity; great variability in absorption (all references)	cytotoxic medicine	unknown whether poor BA is due to poor solubility or poor solubility and permeability
ferrous salt	equivalent to 60mg iron	high (see footnote)	low	3	9.2.1.2		antianaemia medicine	commonly used salts: see footnote
ferrous salt (fs) + folic acid (fa)	equivalent to 60mg iron + 400µg folic acid	(fs) high (see footnote) + very slightly soluble in water[2], D/L 2,5ml; 0,0016mg/ml	(fs) low + (fa) low (urinary recovery 28,5%[23])	(fs) 3 + (fa) 3/1	9.2.1.2		antianaemia medicine (during pregnancy)	combination should be tested according to requirements for BCS class 3 compounds; commonly used iron salts: see footnote

		(25°C) water[23], D/L 250ml						
flucytosine	250mg	soluble 15mg/ml[2], D/L 17ml; 14,2mg/ml[23]; D/L 17,6ml	BA_{abs} 76-89%[27,28]	1(borderline)	9.2.1.1		antifungal	
levofloxacin	500mg	high (30-300 mg/ml)[29] D/L: 16.7 ml	high (oral vs. iv 100% BA; CaCo2 permeability high)[29]	1	9.2.1.1	for main side effects refer to[30]	antituberculosis medicine	
mebendazole	500mg	practically insoluble in water (both monohydrate and anhydrous[1], also both permitted in Pharm. Int.), D/L > 50000ml	BA_{abs} 2%[31]; urinary recovery 2% of a orally administered dose [32]	4/2	N.A.		anthelminic	anthelmintics usually applied orally for action in GI tract: solubility more important than permeability
medroxyprogesterone acetate	5mg	practically insoluble in water[2], 1 g in >10 000 ml, < 0.1 mg/ml, D/L >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

mercaptopurine	50mg	low (insoluble in water pka 7.7/ 11.0, < 0.1 mg/ml)[2], D/L >500 ml[2]	BA_{oral} von aza 47%, first pass, 50% in urine[2]	4/2	no biowaiver	antimetabolite, TDM suggested by Lennard (1)	cytotoxic medicine	unknown whether poor BA is due to poor solubility or poor solubility and permeability
mifepristone - misoprostol	200mg	no information available	BA 70%; also reported 40% after 100 mg oral dose[2]	4/3	no biowaiver		oxytocic	insufficient information available
niclosamide	500mg	5-8mg/l (20°C)[33], D/L 77000ml	2-25% of a dose of 2g radiolabeled drug recovered in the urine, rest faeces[33]	4	N.A.	local use	anthelminic	anthelmintics usually applied orally for action in GI tract: solubility more important than permeability
ofloxacin	400mg	high (30-300 mg/ml)[29], D/L 13 ml	dose prop. 100% BA[29]	1	9.2.1.1	for main side effects refer to[30]	antituberculosis medicine	
oxamniquine	250mg	low (1 in 3300 at 27°C, 0.3 mg/ml)[23], D/L 825 ml, weak acid (?) pk_a not located	readily absorbed, urinary excretion 70% as single acid[1]	4/3	no biowaiver	no significant toxic effects on liver, kidney or heart, dose 15 mg/kg[1]	antischistosomal, antitrematode	
p-aminosalicylic acid	500mg	low (1 g in 600 ml, 1.66 mg/ml)[23]; D/L 301 ml, weak acid, pka not located	borderline, 80% excretion in urine[1]	4/2	no biowaiver		antituberculosis medicine	borderline in both solubility and permeability

pentamine	300mg	high (1 in 10 -> 100 mg/ml)[2], D/L 3 ml	No information available	3/1	9.2.1.2		anti-pneumocystosis and antitoxoplasmosis medicine	
potassium iodine	60mg	very soluble in water, D/L > 0.06ml, 133mg/ml[34], D/L 0.45ml	BA 96.4%[35]; urinary recovery 89%, faeces 11%[36]	1	9.2.1.1		thyroid hormones and antithyroid medicines	
procarbazine hydrochloride	50mg	high (200 mg/ml)[23], D/L 0.25 ml	readily absorbed, 70% dose -> urine after 24h[2]	3/1	9.2.1.2	tumour inhibitor, hematologic[2]	cytotoxic medicine	
pyrantel embonate	250mg	low (practically insoluble in water, 1 g in >10 000 ml[2], < 0.1 mg/ml), D/L >2500 ml	16 % BA_{oral} (palmoate), 41% oral BA (citrate)[37]	4	N.A.	local use	anthelminic	chewable tablet; anthelmintics usually applied orally for action in GI tract: solubility more important than permeability
quinidine sulfate	200mg	high (10 mg/ml)[23], D/L 20 ml	rapidly abs. BA 70%; varies widely, first pass[2]	3/1	9.2.1.2	narrow therapeutic index	antiarrhythmic	
ranitidine hydrochloride	150mg	high (freely soluble in water[2] > 1000 mg/ml), D/L 0.15	50% BA, first pass[2,38]	3/1	9.2.1.2		antiulcer medicine	

sulfadoxine	25mg	very slightly soluble in water[2], D/L < 250ml	readily absorbed after oral administration[2]	3/1	9.2.1.2		antimalarial	
tamoxifen citrate	20mg	high (very slightly soluble in water[1], 0.1 mg/ml -1 mg/ml), D/L 200 ml	BA_{abs} ~ 100%[39]	1	9.2.1.1	endometrical cancer, uterine sarcoma [1]	antihormone	
zinc sulfate	10mg (per unit dosage form)	high (very sol in water)[1], D/L 0.01, same solubility for all hydrates of the sulfate	11 % absorbed, with meal versus iv., abs. 20-30%	3	9.2.1.2		diarrhoea in children	

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a WHO Essential Medicines List, 14th edition, march 2005 can be found under: http://whqlibdoc.who.int/hq/2005/a87017_eng.pdf

b Solubility based on the lowest solubility in the pH range from 1-6.8 at 37°C. "Low" indicates a dose[a] solubility ratio > 250ml at 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 were absorbed commensurate with the highest oral strength according to the EML[a].

d The original Biopharmaceutics Classification System (BCS) can be found under: http://www.fda.gov/cder/guidance/3618fnl.pdf Note that the acceptance criteria have been adapted according to WHO requirements as explained in footnotes 1-3.

e See WHO multisource document: www.who.int/medicines/library/qsm/manual-on-marketing/multisource-contents.html

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

N.R. not relevant: locally acting, no significant systemic absorption

N.A. not applicable, locally acting

clavulanic newly classified, references see list of new compounds on the EML

fixed dose combination of antituberculosis drugs, will be reviewed by the Expert Committee

cytotoxic medicines, possibility of a biowaiver procedure should be reviewed by the Expert Committee

BA bioavailability

Ferrous salts

Commonly used iron salts[1]:

- ferrous ascorbate (anhydrous)
- ferrous aspartate (tetrahydrate)
- ferrous chloride (tetrahydrate)
- ferrous fumarate (anhydrous)
- ferrous gluconate (dihydrate)
- ferrous glycine sulphate
- ferrous orotate

- ferrous succinate (anhydrous)
- ferrous sulfate (dried)
- ferrous sulfate (heptahydrate)

Ferrous salts solubility:

- lowest solubility of all commonly used iron salts: ferrous succinate anhydrous, sparingly soluble in water[40], D/L 6ml)

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