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Annex 8

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

Introduction

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Introduction

This proposal is closely linked to the *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7). It aims to give national authorities sufficient background information on the various orally administered active pharmaceutical ingredients (APIs) on the *WHO Model List of Essential Medicines* (EML), also taking into account local usage of the API, to enable them to make an informed decision as to whether generic formulations should be subjected to in vivo bioequivalence (BE) studies or whether a biowaiver can be granted. 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.

1. Background

1.1 Initiatives to allow biowaivers based on the Biopharmaceutics Classification System

In 1995 the American Department of Health and Human Services, US Food and Drug Administration (HHS-FDA) instigated the Biopharmaceutics

Classification System (BCS), with the aim of granting so-called biowaivers for scale-up and post-approval changes (SUPAC) (www.fda.gov/cder/guidance/cmc5.pdf). A biowaiver means that in vivo bioavailability and/or bioequivalence studies may be waived (i.e. 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 two pharmaceutical products are equivalent. At that time the biowaiver was only considered for 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 of the product approval process and the reduction of the time required, thus reducing the cost of bringing new products to market.

1.2 What is the Biopharmaceutics Classification System?

The Biopharmaceutics Classification System (BCS) was proposed in 1995 by Amidon et al.[1] It is a scientific framework which divides APIs into four groups, according to their solubility and permeability properties.

1.3 Classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System

According to the HHS-FDA definitions in the documents cited above, the four possible categories 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 being heavily dependent on the formulation and manufacturing method (e.g. Class II APIs: poorly soluble yet highly permeable) to being mostly dependent on the API permeability properties (e.g. Class III APIs: highly soluble yet poorly permeable).

[1] Amidon GL, Lennemas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutics Research*, 1995, 12:413–420.

1.4 How is high or low solubility currently defined by the Department of Health and Human Services, US Food and Drug Administration?

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 250 ml or lower*.
  — This criterion is met over the pH range 1–7.5 at 37 °C.

According to HHS-FDA guidances, the determination of the equilibrium solubility should be carried out with the shake-flask method (other methods such as acid or base titration are permitted when their ability to predict the equilibrium solubility is justified). The experiments should be carried out at a temperature of 37 ± 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 *United States Pharmacopeia* (USP) are appropriate for the tests, but other buffers are also allowed for these 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 be reported together 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 API in the small intestine.

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

1.5 How is high or low permeability currently defined by the Department of Health and Human Services, US Food and Drug Administration?

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

Permeability can be assessed by pharmacokinetic studies (for example, mass balance studies), or intestinal permeability methods, e.g. intestinal perfusion in humans, animal models, 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 fraction absorbed (as opposed to the bioavailability, which can be reduced substantially by first-pass metabolism).

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

1.6 Which pharmaceutical formulations can currently be considered for a biowaiver according to the Department of Health and Human Services, US Food and Drug Administration?

To be considered bioequivalent according to the HHS-FDA biowaiver procedure, a pharmaceutical product:

- should contain a Class I API;
- should be rapidly dissolving, meaning it should release at least 85% of its content in 30 minutes in three different media (pH 1.2, pH 4.5 and pH 6.8, composition see "Multisource document")[1] 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 API;
- should not contain an API with a narrow therapeutic index; and
- should not be designed to be absorbed from the oral cavity.

The reasoning for the above-mentioned dissolution restrictions is that when a highly soluble, highly permeable API 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 ensures the complete uptake (> 90%) of the API during its passage through the small intestine. The rapid dissolution of the product guarantees that the API is available long enough for the uptake in the small intestine (the passage time in the small intestine is approximately four 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, because the risk to 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 APIs which are absorbed from the small intestine; drugs absorbed from other sites (e.g. from the oral cavity) are not eligible for a biowaiver.

It is clear that the HHS-FDA requirements for the classification of APIs and eligibility criteria for the biowaiver are very strict. During the last decade,

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

several publications and continuing scientific discussions have suggested that the original HHS-FDA criteria for application of the biowaiver procedure could be relaxed without substantially increasing the risk to public health or to the individual patient. On the basis of these publications and dialogue, WHO has proposed revised BCS criteria and additional considerations for the eligibility of a pharmaceutical product for the biowaiver procedure in the "Multisource document".[1]

2. WHO revisions to the criteria for BCS classification

WHO revisions to the BCS criteria are as follows:

- **WHO high-solubility definition**
  When an API shows a dose:solubility ratio of 250 ml or lower 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 it reaches the mid-jejunum to ensure absorption from the gastrointestinal tract.
- Furthermore, the dose that is to be used for the calculation is the **highest dose indicated in the Model List of Essential Medicines (EML)**. In some countries, products may be available at doses exceeding the highest dose on the *EML*. In such cases, the classification given in the tables at the end of this Annex may no longer be appropriate and the dose:solubility ratio and the permeability will have to be reassessed at the product dose.
- **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 guidance to 85% in the WHO "Multisource document". Some examples of APIs now included in BCS Class I that were previously considered to be in Class III are paracetamol, acetylsalicylic acid, allopurinol, lamivudine and 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 *supersede those in previous publications*. As new APIs appear on the EML, it will be necessary to classify them according to the revised BCS; so it is therefore anticipated that the tables will be revised regularly. In addition, some APIs have not yet been sufficiently characterized to assign them a BCS classification. As the tables evolve, it is anticipated that more concrete information will be generated for these APIs as well.

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

The potential impact of the revised guidelines on registration requirements to establish interchangeability is that many of the 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".[1]

3. WHO extensions to the scope of application of the biowaiver

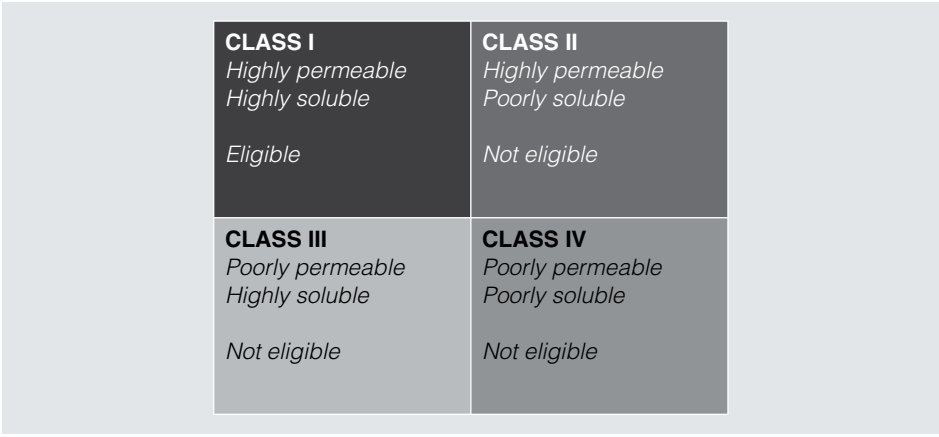
In the "Multisource document",[1] the WHO has broadened the scope of application of the biowaiver in three directions:

(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 requirements allow pharmaceutical products containing Class III APIs to be considered for a biowaiver, under application of more stringent dissolution criteria.
(3) The document further allows pharmaceutical products containing BCS Class II APIs that are weak acids which have a dose:solubility ratio of 250 ml or less at pH 6.8 to be eligible for the biowaiver procedure, provided that they dissolve rapidly at pH 6.8 and similarly to the comparator product at pH 1.2 and 4.5.

Diagrams depicting the products eligible for the biowaiver procedure under the HHS-FDA guidance and those eligible according to the WHO "Multisource document" are presented in Fig. 1.

Figure 1.
Eligibility for the biowaiver procedure based on solubility and permeability characteristics of the active pharmaceutical ingredient

a. according to HHS-FDA



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

b. according to WHO

4. WHO additional criteria for application of the biowaiver procedure

For all APIs on the EML, it is imperative to consider not only the physical, chemical and absorption properties of the API when evaluating them for biowaiver, but (as outlined in the "Multisource document")[1] to perform a benefit–risk analysis in view of the products' usage at the national level. As an example, in some countries amoxicillin is used primarily for the treatment of ambulatory patients with mild-to-moderate infections of the upper respiratory tract, urinary tract and other sites. In other countries, amoxicillin might also be used to treat 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 risks to individual patients is outweighed by the potential benefits accrued from the biowaiver approach may 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

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

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/or Class II APIs which are weak acids and meet the 250 ml dose:solubility requirement at pH 6.8).

(4) **Considerations relating to excipients**

The national authority should be aware 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 relating to 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 these excipients will have no unexpected consequences for the bioavailability of the product. If, however, the formulation contains different excipients, or amounts of the same excipients that are very different from usual, the national authority may choose to declare the biowaiver procedure inapplicable.

A list of usual and acceptable excipients can be found at the following web site: www.fda.gov/cder/iig/iigfaqWEB.htm; formulations of some products can be found on the web sites of some national drug regulatory authorities.

5. 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 API, its pharmacokinetic 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 excipients composition in the multisource product are 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). The relevant documents can also be downloaded from the FIP web site at: http://www.fip.org/. These monographs provide detailed information which should be taken into account whenever available in the biowaiver consideration.

5.1 Which active pharmaceutical ingredients are included in the tables?

The substances listed in the 14th *WHO Model List of Essential Medicines* (EML) of March 2005 have been evaluated and classified according to the revised criteria given above.

5.2 Where do the data come from?

The solubility and permeability values were found in the publicly available literature, such as Martindale's, the Merck Index and scientific journals.

Please note that the doses used for the calculation of the dose:solubility ratio are those stated in the EML.

The indications given in the tables are reproduced directly from the EML. If the EML specifies the dosage form (e.g. sublingual tablet) this is indicated under "comments".

5.3 "Worst case" approach to the Biopharmaceutics Classification System

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 conditions for BCS Class III substances have 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 III/1), because amoxicillin is a BCS Class I drug. This combination would therefore be tested according to BCS Class III requirements.

The results of the revised classification can be found in Tables 1–3.

5.4 Why are there three Tables?

Table 1 lists all APIs on the EML that are administered orally, with the exception of the APIs listed as complementary. Table 2 summarizes the APIs listed as complementary in the EML and Table 3 lists the APIs for which no classification had previously been assigned, or that had been introduced with the 14th EML (March 2005), together with a more detailed explanation of their classification.

5.5 Risk assessment

To minimize the risks of an incorrect biowaiver decision in terms of public health and risks to individual patients, 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.

6. 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 section 9.2.1 of the "Multisource document"[1]:

6.1 For pharmaceutical products containing Biopharmaceutics Classification System Class I (highly soluble, highly permeable) APIs

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

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

6.2 For pharmaceutical products containing Biopharmaceutics Classification System Class III (highly soluble, low permeability) APIs

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

Generally, the risks of an inappropriate biowaiver decision should be more critically reviewed (e.g. site-specific absorption, induction/competition at the absorption site, excipient composition and therapeutic risks) for products containing BCS Class III APIs than for BCS Class I drugs.

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

6.3 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:

- is *rapidly dissolving,* i.e. 85% or more dissolution of the labelled amount of the API should be achieved within 30 minutes in standard media at pH 6.8 using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm; ***and***
- 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 BCS Class II APIs with dose:solubility ratios of 250 ml or less, at pH 6.8, the excipients should also be critically evaluated in terms of type and amounts of surfactants in the formulation.

Further details of eligibility for the biowaiver and appropriate test procedures can be found in sections 5 and 9 of the "Multisource document".[1]

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

Table 1
Substances on 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]	Comments and special dosage form indications[a]
abacavir	200 mg	high	low	3	9.2.1.2		antiretroviral	
acetazolamide	250 mg	low	low (?)	4/2	Not eligible for biowaiver		antiglaucoma medicine	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
acetylsalicylic acid	500 mg	high	high	1	9.2.1.1		NSAID, antimigraine medicine	
acetylsalicylic acid	100 mg	high	high	1	9.2.1.1		antithrombotic medicine	
aciclovir	200 mg	high	low	3	9.2.1.2		antiherpes medicines	
albendazole	400 mg	low	low (?)	4/2	Not eligible for biowaiver		anthelminthic	chewable tablet; unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
allopurinol	100 mg	high	high	1	9.2.1.1		gout	
aluminium hydroxide	500 mg			NR	NA		antacid	used for local effect

NSAID, Non-steroidal anti-inflammatory drug; BA, bioavailability.

amiloride hydrochloride	5 mg	high	high	1	9.2.1.1		diuretic	
amitriptyline hydrochloride	25 mg (*1*)	high	high	1	9.2.1.1		psychotherapeutic medicine	
amlodipine	5 mg	high	high	1	9.2.1.1		antihypertensive medicine	
amodiaquine (base)	200 mg	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) 500 mg + (c) 125 mg	(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	500 mg	high	high	1	9.2.1.1		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	9.2.1.1		vitamin	
atenolol	100 mg	high	low	3	9.2.1.2		antianginal, antihypertensive, antiarrhythmic medicine and used in heart failure	

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[a]	Comments and special dosage form indications[a]
azithromycin	500 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
benznidazole	100 mg	high	low	3	9.2.1.2		American trypanosomiasis	
biperiden hydrochloride	2 mg	high	insufficient literature	3/1	9.2.1.2		antiparkinson 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	9.2.1.2	narrow therapeutic index	antibacterial	
chloroquine phosphate or sulfate	150 mg	high	high	1	9.2.1.1		DMARD, antimalarial	

BA, bioavailability; DMRD, disease modifying antirheumatic drug.

chlorphenamine hydrogen maleate	4 mg	high	BA 25-59%, first pass	3/1	9.2.1.2	CYP2D6 polymorphism	antiallergic	extent of first-pass metabolism uncertain
chlorpromazine hydrochloride	100 mg	high	low	3	9.2.1.2		psychotherapeutic medicine	
ciprofloxacin hydrochloride	250 mg	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	100 mg	insufficient literature	low	4/3	Not eligible for biowaiver at present		antileprosy medicine	
clomifene citrate	50 mg	high	insufficient literature	3/1	9.2.1.2		ovulation inducer	
clomipramine hydrochloride	25 mg	high	66% 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)	1000 mg	high	low	3	9.2.1.2		antibacterial	
codeine phosphate	30 mg	high	low	3	9.2.1.2	risk of abuse	opioid 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	9.2.1.1		psychotherapeutic medicine	scored tablet

BA, Bioavailability; G6PD, glucose-6-phosphate dehydrogenase.

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]	Comments and special dosage form indications[a]
didanosine	200 mg	high	low	3	9.2.1.2		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[i]
digoxin	250 µg	high	high	1	9.2.1.1		antiarrhythmic and used in heart failure	
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
doxycycline hydrochloride	100 mg	high	high	1	9.2.1.1		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	9.2.1.2		antihypertensive medicine	

BA, Bioavailability.

ergocalciferol	1.25 mg (50 000 IU)	high	low	3	9.2.1.2		vitamin	
erythromycin stearate + ethylsuccinate	250 mg	low	low	4	Not eligible for biowaiver		antibacterial	
ethambutol hydrochloride	400 mg	high	low	3	9.2.1.2	risk of dose-related ototoxicity	antituberculosis medicine	
ethinylestradiol	50 µg	high	borderline, BA 40–50%, first pass	3/1	9.2.1.2		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	9.2.1.2		hormonal contraceptive	extent of first-pass metabolism uncertain; combination should be tested according to ethinylestradiol requirements
ethinylestradiol (e) + norethisterone (n)	35 µg + 1 mg	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 60 mg iron	high (see footnote)	low	3	9.2.1.2		antianaemia medicine	commonly used salts: see footnote

BA, Bioavailability; 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]	Comments and special dosage form indications[a]
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	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	50 mg	high	high	1	9.2.1.1		antifungal	
folic acid	5 mg	high	low (?)	3/1	9.2.1.2		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

NSAID, Non-steroidal anti-inflammatory drugs; GI, gastrointestinal.

glyceryl trinitrate	500 µg	high	sublingual application, permeability in the oral cavity more important than GI permeability	3/1	NA[h]	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/ml[2]	low	4/3	Not eligible for biowaiver		psychotherapeutic medicine	
hydralazine hydrochloride	50 mg	high	low	3	9.2.1.2		antihypertensive medicine	
hydrochlorothiazide	25 mg	high	low	3	9.2.1.2		antihypertensive medicine, diuretic and used in heart failure	scored tablet
ibuprofen	400 mg	low, weak acid (pK_a 4.4, 5.2)	high	2	9.2.1.3		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

D:S, Dose:solubility ratio; 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[a]	Comments and special dosage form indications[a]
iopanoic acid	500 mg	low, weak acid (pK_a 4.8) (*2*)	high	2	Not eligible for biowaiver		radiocontrast media	Insufficiently soluble in water (15 µg/ml) to be eligible for biowaiver
isoniazid	300 mg	high	borderline	3/1	9.2.1.2		antituberculosis 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 footnote[g]	ocular toxicity	antituberculosis medicine	
isosorbide dinitrate	5 mg	high	sublingual application, permeability in the oral cavity more important than GI permeability	3/1	NA[h]		antianginal medicine	sublingual
ivermectin	6 mg	practically insoluble in water[3] D:S > 6000 ml	low (?)	4/2	Not eligible for biowaiver		antifilarial	scored tablet; unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
lamivudine	150 mg	high	high	1	9.2.1.1		antiretroviral	

BA, bioavailability; GI, gastrointestinal; D:S, Dose: solubility ratio.

levamisole hydrochloride	150 mg	high	borderline	3/1	9.2.1.2		anthelminthic	
levodopa (l) + carbidopa (c)	(l) 250 mg + (c) 25 mg	(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	30 µg	high	high	1	9.2.1.1		hormonal contraceptive	
levonorgestrel	750 µg × 2 (pack of two)	high	high	1	9.2.1.1		hormonal contraceptive	
levothyroxine sodium salt	100 µg	high	low	3	9.2.1.2	narrow therapeutic index	thyroid hormone	
lithium carbonate	300 mg	high	high	1	9.2.1.1	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 <u>and</u> poor permeability

NSAID, Non-steroidal anti-inflammatory drugs.

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]	Comments and special dosage form indications[a]
mebendazole	500 mg	low	low (?)	4/2	NA		anthelminthic	chewable tablet; anthelminthics 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 poor permeability
mefloquine hydrochloride	250 mg	low[2]	low (?)	4/2	Not eligible for biowaiver		antimalarial	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
DL-methionine	250 mg	high	high	1	9.2.1.1		antidote	
metformin hydrochloride	500 mg	high	low	3	9.2.1.2		antidiabetic agent	
methyldopa	250 mg	high	low	3	9.2.1.2		antihypertensive medicine	
metoclopramide hydrochloride	10 mg	high	low	3	9.2.1.2		antiemetic	

metronidazole	500 mg	high	high	1	9.2.1.1		antiprotozoal, antibacterial	
morphine sulfate	10 mg	high	insufficient data (BA ~ 30% but extensive first pass)	3/1	9.2.1.2	risk of abuse	opioid 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	9.2.1.2		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; anthelminthics usually applied orally for action in GI tract: solubility more important than permeability
nicotinamide	50 mg	high	high	1	9.2.1.1		vitamin	
nifedipine	10 mg	low, weak acid, solubility at pH7 0.0056 mg/ml[2]	high	2	Not eligible for biowaiver		antioxytocic	

BA, bioavailability; 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]	Comments and special dosage form indications[a]
nifurtimox	250 mg	high	low	3	9.2.1.2		American trypanosomiasis	
nitrofurantoin	100 mg	low, weak acid, solubility at pH 7.0 0.374 mg/ml (pK_a 7.2 (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	9.2.1.1		progestogen	
nystatin	500 000 IU	–	–	NR	NA		antifungal	local effect
paracetamol	500 mg	high	high	1	9.2.1.1		NSAID, antimigraine medicine	
penicillamine	250 mg	high	low	3	9.2.1.2		antidote	
phenobarbital	100 mg	high	high	1	9.2.1.1	narrow therapeutic index	antiepileptic	
phenoxymethyl penicillin (as potassium salt)	250 mg	high	high	1	9.2.1.1		antibacterial	
phenytoin sodium salt	100 mg	low, weak acid, sol. at pH 6.8 1.7 mg/ml (*4*) pK_a 8.3 (25 °C)) (*2*)	high	2	9.2.1.3	narrow therapeutic index, non-linear pharmacokinetics	antiepileptic	

potassium iodide	60 mg	high	high	1	9.2.1.1		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	9.2.1.1		antiallergic	
primaquine diphosphate	15 mg	high	high	1	9.2.1.1		antimalarial	
proguanil hydrochloride	100 mg	high	high	1	9.2.1.1		antimalarial	
promethazine hydrochloride	25 mg	high	high	1	9.2.1.1	CYP2D6 polymorphism	antiemetic	
propranolol hydrochloride	40 mg	high	high	1	9.2.1.1		antimigraine medicine	
propylthiouracil	50 mg	high	high	1	9.2.1.1		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	9.2.1.2	Liver toxicity	antituberculosis medicine	
pyridoxine hydrochloride	25 mg	high	high	1	9.2.1.1		vitamin	

NSAID, Non-steroidal anti-inflammatory drugs.

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]	Comments and special dosage form indications[a]
pyrimethamine	25 mg	borderline; < 0.1 mg/ml[3]	low	4/3	Not eligible for biowaiver		anti-pneumocystosis and antitoxoplasmosis medicine	
quinine bisulfate or sulfate	300 mg	high	high	1	9.2.1.1		antimalarial	
ranitidine hydrochloride	150 mg	high	low	3	9.2.1.2		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	9.2.1.1		vitamin	
rifampicin	300 mg	low (amphiphilic) (pK_a 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	See footnote[g]		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	See footnote[g]		antituberculosis medicine	

BA, bioavailability.

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) borderline + (e) low	(r) 2 + (i) 3/1 + (p) 3/1 + (e) 3	See footnote[g]		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	9.2.1.1		antiasthmatic and medicine for 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 permeability
senna	7.5 mg (sennoside)	–	–	NR	NA		laxative	local effect
spironolactone	25 mg	borderline	low	4/3	Not eligible for biowaiver		diuretic	
stavudine	40 mg	high	high	1	9.2.1.1		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	

G6PD, Glucose-6-phosphate dehydrogenase; BA, bioavailability; COPD: Chronic Obstructive Pulmonary Disease.

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]	Comments and special dosage form indications[a]
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	9.2.1.2		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 medicine	enteric-coated tablet → not eligible for biowaiver in this dosage form[l]
verapamil hydrochloride	80 mg	low (weak base)	high	2	Not eligible for biowaiver		antianginal and antiarrhythmic medicine	
warfarin sodium salt	5 mg	high (soluble 1 in less than 1 of water) (*1*)	high	1	9.2.1.1	narrow therapeutic index	medicines affecting coagulation	
zidovudine	300 mg	high	high	1	9.2.1.1		antiretroviral	
zinc sulfate	10 mg (per unit dosage form)	high	low	3	9.2.1.2		diarrhoea in children	

[a] *14th WHO Model List of Essential Medicines*, 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 > 250 ml 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 listed in the EML.
[d] The acceptance criteria that have been adapted by WHO are explained in Section 2 ("WHO revisions to the criteria for BCS classification").
[e] 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 often indicates lack of availability of 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 individual national authority based on local conditions of use.
[g] The possibility of biowaiving fixed-dose combinations of antituberculosis drugs is still under consideration because of their specific stability, toxicity and interaction issues.
[h] Medicine is applied sublingually, major site of absorption is from the oral cavity.
[i] Dosage form not designed for immediate release.

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

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

1. *Clarke's analysis of drugs and poisons*. 3rd ed. London, Pharmaceutical Press, Royal Pharmaceutical Society of Great Britain, 2004.
2. Brittain K, Florey HG. *Analytical profiles of drug substances and excipients*. Oxford University Press.
3. Sweetman S. *Martindale: the complete drug reference*, 34th ed. London, Pharmaceutical Press, 2004.
4. Stippler E. [Dissertation]. Biorelevant Dissolution Test Methods to Assess Bioequivalence of Drug Products. Germany, Johann-Wolfgang von Goethe University Frankfurt, 2004.
5. *Merck index*. New Jersey, USA, Merck Publishers, 2004.

Ferrous salts:
Commonly used iron salts:[3]
- ferrous ascorbate (anhydrous)
- ferrous aspartate (tetrahydrate)
- ferrous chloride (tetrahydrate)
- ferrous fumarate (anhydrous)
- ferrous gluconate (dihydrate)
- ferrous glycine sulfate
- ferrous orotate
- ferrous succinate (anhydrous)
- ferrous sulfate (dried)
- ferrous sulfate (heptahydrate)

Solubility of ferrous salts:
- lowest solubility of all commonly used iron salts: ferrous succinate anhydrous, sparingly soluble in water[5] (dose:solubility ratio 6ml)

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).

1. Sweetman S. *Martindale: the complete drug reference*, 34th ed. London, Pharmaceutical Press, 2004.
2. *Clarke's analysis of drugs and poisons*. 3rd ed. London, Pharmaceutical Press, Royal Pharmaceutical Society of Great Britain, 2004.
3. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine. Clinical implications. *Clinical Pharmacokinetics*, 1996,30:263–299.
4. Naisbitt DJ et al. Metabolism-dependent neutrophil cytotoxicity of amodiaquine: A comparison with pyronaridine and related antimalarial drugs. *Chemical Research in Toxicology,* 1998, 11:1586–1595.
5. Bolton GC et al. The disposition of clavulanic acid in man. *Xenobiotica*, 1986, 16:853–863.
6. *The International Pharmacopoeia,* 3rd ed. *General methods of analysis, quality specifications for pharmaceutical substances, excipients and dosage forms*. Geneva, World Health Organization, 2004.
7. Newton PN et al. Comparison of oral artesunate and dihydroartemisinin antimalarial bioavailabilities in acute falciparum malaria. *Antimicrobial Agents Chemotherapy*, 2002, 46:1125–1127.
8. Newton P et al. Antimalarial bioavailability and disposition of artesunate in acute falciparum malaria. *Antimicrobial Agents Chemotherapy*, 2000, 44:972–977.
9. Luke DR, Foulds G. Disposition of oral azithromycin in humans. *Clinical Pharmacology and Therapeutics*, 1997, 61:641–648.
10. Singlas E [Clinical pharmacokinetics of azithromycin]. *Pathologie-biologie* (Paris), 1995, 43:505–511 (in French).
11. Lalak NJ, Morris DL. Azithromycin clinical pharmacokinetics. *Clinical Pharmacokinetics*, 1993, 25:370–374.
12. McGuire BW et al. Absorption kinetics of orally administered leucovorin calcium. *NCI Monographs*, 1987, 5:47–56.
13. McGuire BW et al. Pharmacokinetics of leucovorin calcium after intravenous, intramuscular, and oral administration. *Clinical Pharmacy*, 1988, 7:52–58.
14. DeVito JM et al. Bioequivalence of oral and injectable levoleucovorin and leucovorin. *Clinical Pharmacy*, 1993, 12:293–299.
15. Greiner PO et al. Pharmacokinetics of (-)-folinic acid after oral and intravenous administration of the racemate. *British Journal of Clinical Pharmacology*, 1989, 28:289–295.
16. Yeh KC et al. Pharmacokinetics and bioavailability of Sinemet CR: a summary of human studies. *Neurology*, 1989, 39 (11 Suppl 2):25–38.
17. Obach R, Menargues A, Valles JM. The pharmacokinetic profile of carbidopa in dogs. *Journal of Pharmacy and Pharmacology*, 1984, 36:415–416.
18. McLean A et al. Pharmacokinetics and metabolism of chlorambucil in patients with malignant disease. *Cancer Treatment Reviews*, 1979, 6 (Suppl):33–42.
19. Newell DR et al. The clinical pharmacology of chlorambucil and prednimustine. *British Journal of Clinical Pharmacology*, 1983, 16:762–763.
20. Newell DR et al. Studies on the pharmacokinetics of chlorambucil and prednimustine in man. *British Journal of Clinical Pharmacology*, 1983, 15:253–258.
21. Nicolle A, Proctor SJ, Summerfield GP. High dose chlorambucil in the treatment of lymphoid malignancies. *Leukaemia & Lymphoma*, 2004, 45:271–275.
22. 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.
23. Brittain K, Florey HG. *Analytical profiles of drug substances and excipients*. Oxford University Press.
24. Dickstein K. Pharmacokinetics of enalapril in congestive heart failure. *Drugs*, 1986, 32 (Suppl) 5:40–44.
25. Rippley RK et al. Pharmacokinetic assessment of an oral enalapril suspension for use in children. *Biopharmaceutics & Drug Disposition*, 2000, 21:339–344.
26. Chen CL et al. Bioavailability and pharmacokinetic features of etoposide in childhood acute lymphoblastic leukemia patients. *Leukaemia & Lymphoma*, 2001, 42:317–327.
27. 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.
28. 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.
29. Frick A, Moller H, Wirbitzki E. Biopharmaceutical characterization of oral immediate release drug products. In vitro/in vivo comparison of phenoxymethylpenicillin potassium, glimepiride and levofloxacin. *European Journal of Pharmaceutics and Biopharmaceutics*, 1998, 46:305–311.
30. Van Bambeke F et al. Quinolones in 2005: an update. *Clinical Microbiology and Infection*, 2005, 11:256–280.
31. *Summary report on mebendazole*. London, European Agency for the Evaluation of Medicinal Products (EMEA), 1999.
32. Product Information Vermox®.

33. *WHO data sheet on pesticides, No. 63.* Geneva, World Health Organization, 2002.
34. Sigma-Aldrich Product Information.
35. Aquaron R et al. Bioavailability of seaweed iodine in human beings. *Cellular and Molecular Biology* (Noisy-le-grand), 2002, 48:563–569.
36. Jahreis G et al. Bioavailability of iodine from normal diets rich in dairy products – results of balance studies in women. *Experimental and Clinical Endocrinology & Diabetes*, 2001,109:163–167.
37. Bjorn H, Hennessy DR, Friis C. The kinetic disposition of pyrantel citrate and pamoate and their efficacy against pyrantel-resistant Oesophagostomum dentatum in pigs. *International Journal for Parasitology*, 1996, 26:1375–1380.
38. Roberts CJ. Clinical pharmacokinetics of ranitidine. *Clinical Pharmacokinetics*, 1984, 9:211–221.
39. Morello KC, Wurz GT, DeGregorio MW. Pharmacokinetics of selective estrogen receptor modulators. *Clinical Pharmacokinetics*, 2003, 42:361–372.