Annex 11

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

1. Introduction and background

The World Health Organization (WHO) recognizes the possibility of waiving in vivo bioequivalence studies for immediate-release, solid oral dosage forms with active pharmaceutical ingredients (APIs) belonging to classes I and III according to the Biopharmaceutical Classification System (BCS), using comparative dissolution studies as surrogate proof of bioequivalence (*1*).

The WHO solubility classification, also referred to as the WHO Biowaiver List, is a tool for national regulatory authorities and pharmaceutical manufacturing companies, suggesting medical products that are eligible for a waiver from in vivo bioequivalence studies, which are usually necessary to establish the therapeutic equivalence with the originator (comparator). For exemption from an in vivo bioequivalence study, an immediate-release, multisource (generic) product should exhibit very rapid or rapid in vitro dissolution characteristics that are comparable to those of the reference product. A risk-based evaluation should also account for the excipients used in the formulation of the finished pharmaceutical product.

In addition, the present list replaces the existing literature-based compilation published in 2006 that is reported in the *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* (*2*) based on data extracted from the public domain (that is, solubility data published by different authors using inconsistent experimental conditions).

The WHO Biowaiver Project is organized into study cycles. Previous and current cycles are summarized below in order to provide an outline of the project development:

- 2018: cycle I, also referred to as the pilot phase
- 2019: cycle II
- 2020: cycle III
- 2021: cycle IV – The new results presented in this updated document (in Tables A11.1 and A11.2, highlighted in bold) originate from cycle IV.

2. WHO solubility classification for biowaiver

In 2017, the Fifty-second Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat revise the existing list using verifiable laboratory data that are generated according to consistent WHO criteria. Acting on this directive from the ECSPP, the WHO Secretariat initiated a multicentre research project, the Biowaiver Project, aimed at experimentally determining the equilibrium solubility profile of medicines

listed in the WHO Model List of Essential Medicines, using a harmonized approach (*3*).

To classify APIs according to the BCS framework, two critical properties are usually evaluated: (a) an API's aqueous solubility; and (b) its absorption or permeability. The initial phase of the WHO Biowaiver Project centres on unambiguous experimental assessment of the solubility parameter, as only highly soluble APIs are eligible for biowaiver. Once experimental solubility data are available, the exact BCS class assignment can be determined by utilizing quantitative absorption and permeability data. However, since high solubility within an aqueous environment is a necessary prerequisite for an API to be eligible for a waiver from bioequivalence studies, the current focus on solubility is justified to guide the regulatory decision.

The WHO classification should be considered a living document and is meant to be regularly updated in accordance with new quality requirements and progress in scientific development.

3. Scope

The aim of the WHO Biowaiver List is to enable an informed decision as to whether or not a waiver from in vivo bioequivalence studies could be granted safely according to the WHO guidance *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*1*).

The WHO Biowaiver List is expected to promote access to standard-quality essential medicines by shortening the time required to develop a multisource (generic) product, thereby supporting optimized pharmaceutical development.

The WHO Biowaiver List has been recognized by WHO regional and country offices as a "global good" – a normative work essential to strengthening global health in WHO Member States.

4. Methodology

The WHO *Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* (*4*) is a tool available to all participants in this research. It was developed for the purpose of providing a harmonized methodology for equilibrium solubility experiments, thereby minimizing a potential source of variability among centres and studies.

APIs studied in cycles I, II, III and IV were received primarily as in-kind donations from pharmaceutical manufacturers supporting WHO in this scientific work. Equilibrium solubility experiments were conducted by universities, official national control laboratories and WHO collaborating centres.

5. Results

Table A11.1 provides an overview of the APIs studied by WHO during cycles I, II, III and IV. The new APIs studied in cycle IV are reported in bold. Fixed-dose combination products, where all APIs contained in the combination drug product were studied as monocomponents (Table A11.1), are also reported in Table A11.2.

Table A11.1

WHO solubility classification of active pharmaceutical ingredients prioritized from the WHO Model List of Essential Medicines

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
abacavir (sulfate)	**Antiretrovirals**	**Antiretrovirals (HIV)**	**600**	**Yes**	**I/III**
aciclovir	Antiviral medicines	Antiherpes medicines	800	No	II/IV*
amoxicillin (trihydrate)	Antibacterials	Antibiotics	3000	Yes	II/IV*
azithromycin (dihydrate)	Antibacterials	Antibiotics	2000	Yes	II/IV
cefixime (trihydrate)	Antibacterials	Antibiotics	400	No	II/IV
chloroquine phosphate	Antiprotozoal medicines	Antimalarial medicines	1000 mg salt (= 600 mg base)	No	I/III
codeine (phosphate hemihydrate)	Medicines for pain and palliative care	Opioid analgesics	60	No	I/III
cycloserine	Antibacterials	Antituberculosis medicines	1000	Yes	I/III
daclatasvir (dihydrochloride)	Antiviral medicines	Medicines for hepatitis C	60	Yes	II/IV**
darunavir (ethanolate)	Antiviral medicines	Antiretrovirals (HIV)	800	Yes	II/IV**

Table A11.1 *continued*

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
dexamethasone	1. Gastrointestinal medicines 2. Immunomodulators and antineoplastics 3. Medicines for pain and palliative care 4. Corticosteroids for COVID-19[c]	1. Antiemetic medicines 2. Acute lymphoblastic leukaemia, multiple myeloma 3. Medicines for other common symptoms in palliative care 4. Treatment of patients with severe and critical COVID-19[c]	1, 3: 0.5 to 10 mg a day, depending on the disease being treated 2: 40 mg 4: 6 mg a day[c]	Yes	I/III**
dolutegravir	Antiviral medicines	Antiretrovirals (HIV)	50	Yes	II/IV**
doxycycline (hyclate)	**1. Antiprotozoals** **2. Antibacterials**	**1. Antimalarial medicines** **2. Antibiotics (access group)**	**100**	**No**	**I/III****
efavirenz	Antiviral medicines	Antiretrovirals (HIV)	600	Yes	II/IV
emtricitabine	Antiviral medicines	Antiretrovirals (HIV)	200	Yes	I/III**
entecavir	Antiviral medicines	Antihepatitis medicines	1	Yes	I/III**
ethambutol (hydrochloride)	**Antibacterials**	**Antituberculosis medicines**	**2000**	**Yes**	**I/III**
ethionamide	Antibacterials	Antituberculosis medicines	500–1000	Yes	II/IV*

Table A11.1 *continued*

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
furosemide	Cardiovascular medicines	Medicines used in heart failure	80	No	II/IV
hydroxychloroquine (sulfate)	**Disease-modifying antirheumatic drugs (DMARDs)**	**Lupus erythematosus**	**600**	**No**	**I/III****
isoniazid	**Antibacterials**	**Antituberculosis medicines**	**300**	**Yes**	**I/III**
lamivudine	**Antiviral medicines**	**Antiretrovirals (HIV)**	**300**	**Yes**	**I/III**
levonorgestrel	**Medicines for reproductive health and perinatal care**	**Oral hormonal contraceptives**	**1.5**	**Yes**	**II/IV***
mefloquine (hydrochloride)	Antiprotozoal medicines	Antimalarial medicines	1250 (as hydrochloride)	Yes	II/IV
methyldopa (sesquihydrate)	Cardiovascular medicines	Pregnancy-induced hypertension	500	No	I/III
oseltamivir (phosphate)	Antiviral medicines	Influenza virus	75 (as phosphate)	Yes	I/III**
paracetamol	Medicines for pain and palliative care, antimigraine medicines	Non-opioids and nonsteroidal antiinflammatory medicines, treatment of acute attack	1000	No	I/III

Table A11.1 *continued*

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
primaquine (phosphate)	Antiprotozoal medicines	Antimalarial medicines (curative treatment of *Plasmodium vivax* and *P. ovale* infections)	15	Yes	I/III
proguanil (hydrochloride)	**Antiprotozoal medicines**	**Antimalarial medicines**	**200**	**No**	**I/III**
pyrimethamine	Antiprotozoal medicines	Antimalarial medicines	75	Yes	II/IV
raltegravir (potassium)	Antiviral medicines	Antiretrovirals (HIV in pregnant women and in second line)	400	Yes	II/IV**
rifampicin	Antibacterials	Antituberculosis, antileprosy medicines	750	Yes	II/IV
sofosbuvir	Antiviral medicines	Medicines for hepatitis C	400	Yes	II/IV**
tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	300	Yes	I/III**

API: active pharmaceutical ingredient; PQ: prequalification; EOI-PQ: expression of interest for prequalification.

Note: In the table, the new APIs studied in cycle IV are reported in *bold text*.

[a] 22nd WHO Model List of Essential Medicines (2021) (*3*).

[b] According to the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*1*), APIs belonging to classes I and III are eligible for biowaiver. Once experimental permeability data are available, the exact class attribution will be possible (that is, either class I or class III). The present solubility characterization is already sufficient to provide an indication as to whether or not an API is eligible for biowaiver.

[c] Therapeutic area indication not reported on 22nd WHO Model List of Essential Medicines (2021) but in the WHO guidance *Corticosteroids for COVID-19: living guidance* (*5*).

* Change in solubility class with respect to WHO 2006 classification.

** APIs characterized for the first time within the WHO Biowaiver Project.

Table A11.2

WHO solubility classification of fixed-dose combination products prioritized from the WHO Model List of Essential Medicines

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)	API PQ, EOI-PQ	WHO classification[b]
efavirenz + emtricitabine + tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	600 + 200 + 300	Yes	II/IV**
efavirenz + lamivudine + tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	600 + 300 + 300	Yes	II/IV**
emtricitabine + tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	200 + 300	Yes	I/III**

API: active pharmaceutical ingredient; PQ: prequalification; EOI-PQ: expression of interest for prequalification.

[a] 22nd WHO Model List of Essential Medicines (2021) (*3*).

[b] According to the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*1*), APIs belonging to classes I and III are eligible for biowaiver. Once experimental permeability data are available, the exact class attribution will be possible (that is, either class I or class III). The present solubility characterization is already sufficient to provide an indication as to whether or not an API is eligible for biowaiver.

* Change in solubility class with respect to WHO 2006 classification.

** APIs characterized for the first time within the WHO Biowaiver Project.

Establishing a new WHO Biowaiver List that is based on unambiguous verifiable experimental solubility data is a critical project with tremendous public health implications for patients, procurers, United Nations agencies, national and regional regulatory authorities, payers, ethics committees and manufacturers worldwide. The involvement and support of WHO stakeholders and partners is highly encouraged and appreciated.

References

1. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. WHO Technical Report Series No. 1003, Annex 6. Geneva: World Health Organization; 2017.
2. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. WHO Technical Report Series No. 937, Annex 8. Geneva: World Health Organization; 2006.
3. WHO Model List of Essential Medicines, 22nd list. Geneva: World Health Organization; 2021.
4. Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. WHO Technical Report Series No. 1019, Annex 4. Geneva: World Health Organization; 2019.
5. Corticosteroids for COVID-19: living guidance. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1, accessed 5 September 2022).

Further reading

- Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. WHO Technical Report Series No. 992, Annex 8. Geneva: World Health Organization; 2015.
- Guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. WHO Technical Report Series No. 996, Annex 9. Geneva: World Health Organization; 2016.
- General background notes on the list of international comparator pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. WHO Technical Report Series No. 1003, Annex 5. Geneva: World Health Organization; 2017.