

Annex 12

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	268
2. WHO solubility classification for biowaiver	268
3. Scope	269
4. Methodology	269
5. Results	269
References	272
Further reading	272



1. Introduction and background

The World Health Organization (WHO) recognizes the possibility to waive in vivo bioequivalence studies for immediate-release, solid oral dosage forms with active pharmaceutical ingredients (APIs) belonging to Class I and III according to the Biopharmaceutics 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 (NRAs) 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).

As part of its 2006 guidance on the waiving of bioequivalence requirements for immediate-release, solid oral dosage forms on the *WHO Model List of Essential Medicines* (2), WHO had provided a list of APIs based on data extracted from the public domain (i.e. solubility data published by different authors using inconsistent experimental conditions) (3).

2. WHO solubility classification for biowaiver

In 2017, the Fifty-second Expert Committee on Specifications for Pharmaceutical Preparations (ECSP) 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 ECSP, the WHO Secretariat initiated a multicentre research project, the Biowaiver Project, aimed at experimentally determining the equilibrium solubility profile of medicines listed in the EML, using a harmonized approach (4).

To classify APIs according to the BCS framework, two critical properties are usually evaluated: (i) an API's aqueous solubility; and (ii) its absorption/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/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. The list replaces the existing literature-based compilation 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* (3).

3. Scope

The aim of the WHO Biowaiver List is to enable an informed decision on 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 develop a multisource (generic) product supporting an 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 with the purpose of providing a harmonized methodology for the equilibrium solubility experiments, thereby minimizing the variability among centres and studies.

To date, all APIs studied in Cycles I and II are received 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 A12.1 provides an overview of the APIs studied by WHO during Cycles I and II.

Table A12.1

WHO solubility classification of active pharmaceutical ingredients prioritized from the WHO Model List of Essential Medicines (2)

Medicine	Therapeutic area	Indication ^a	Highest therapeutic dose (mg) ^b	API PQ EOI / PQ	2019 WHO classification
aciclovir	Antiviral medicines	Antiherpes medicines	800	No	II/IV
amoxicillin (trihydrate)	Antibacterials	Antibiotics	3000	No	II/IV
azithromycin (dihydrate)	Antibacterials	Antibiotics	2000	No	II/IV
cefixime (trihydrate)	Antibacterials	Antibiotics	400	No	II/IV
codeine (sulfate)	Medicines for pain and palliative care	Opioid analgesics	60	No	I/III
daclatasvir (dihydrochloride)	Antiviral medicines	Medicines for hepatitis C	60	Yes	II/IV
darunavir (ethanolate)	Antiviral medicines	Antiretrovirals (HIV)	800	Yes	II/IV
dolutegravir	Antiviral medicines	Antiretrovirals (HIV)	50	Yes	II/IV
efavirenz	Antiviral medicines	Antiretrovirals (HIV)	600	Yes	II/IV
ethionamide	Antibacterials	Antituberculosis medicines	500–1000	Yes	II/IV
furosemide	Cardiovascular medicines	Medicines used in heart failure	80	No	II/IV
primaquine (phosphate)	Antiprotozoal medicines	Antimalarial medicines (curative treatment of <i>P. vivax</i> and <i>P. ovale</i> infections)	15	No	I/III

Table A11.1 *continued*

Medicine	Therapeutic area	Indication ^a	Highest therapeutic dose (mg) ^b	API PQ EOI / PQ	2019 WHO classification
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
tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	300	Yes	I/III

API: active pharmaceutical ingredient; PQ: prequalification; PQ EOI: expression of Interest for prequalification (2); WHO: World Health Organization.

^a 21st WHO Model List of Essential Medicines (2019) (2).

^b According to the WHO guidelines, *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 (i.e. either Class I or Class III). The present solubility characterization is already sufficient to provide an indication on whether or not an API is eligible for biowaiver.

Note. 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.

Establishing a new WHO Biowaiver List that is based on unambiguous verifiable experimental solubility data is a critical project with a tremendous public health impact on patients; procurement/United Nations agencies; national and regional regulatory authorities; payers; ethics committees; and manufacturers worldwide. The involvement and support from 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. Geneva: World Health Organization; 2017: Annex 6 (WHO Technical Report Series, No. 1003; <http://apps.who.int/medicinedocs/documents/s23245en/s23245en.pdf>, accessed 18 November 2019).
2. WHO Model List of Essential Medicines, 21st list. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1>, accessed 4 November 2019).
3. 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. Geneva: World Health Organization; 2006: Annex 8 (WHO Technical Report Series, No. 937; <https://apps.who.int/medicinedocs/documents/s19640en/s19640en.pdf>, accessed 18 November 2019).
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. Geneva: World Health Organization; 2019: Annex 4 (WHO Technical Report Series, No. 1019; <https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1>, accessed 18 November 2019).

Further reading

- Guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 9 (WHO Technical Report Series, No. 996; <http://apps.who.int/medicinedocs/documents/s22406en/s22406en.pdf>, accessed 18 November 2019).
- General background notes and list of international comparator pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: Annex 5 (WHO Technical Report Series, No. 1003; <http://apps.who.int/medicinedocs/documents/s23244en/s23244en.pdf>, accessed 18 November 2019).
- 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. Geneva: World Health Organization; 2015; <http://apps.who.int/medicinedocs/documents/s21901en/s21901en.pdf>, accessed 18 November 2019).
- List of international comparator products (September 2016). Geneva: World health Organization; 2016 (http://www.who.int/medicines/areas/quality_safety/quality_assurance/list_int_comparator_prods_after_public_consult30.9.xlsx?ua=1, accessed 18 November 2019).