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World Health Organization

WHO Drug Information

WHO Drug Information provides an overview of topics relating to medicines development, regulation, quality and safety. The journal also publishes and reports on guidance documents and includes lists of International Nonproprietary Names for Pharmaceutical Substances (INN), ATC/DDD classification and monographs for The International Pharmacopoeia. It presents and describes WHO policies and activities while reflecting on technical and pharmaceutical topics of international and regional interest.

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International Nonproprietary Names (INN)

Abbreviations and websites

CHMP	Committee for Medicinal Products for Human Use (EMA)
EMA	European Medicines Agency (www.ema.europa.eu)
EU	European Union
FDA	U.S. Food and Drug Administration (www.fda.gov)
Health Canada	Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
HPRA	Health Products Regulatory Authority, Ireland(www.hpra.ie)
HSA	Health Sciences Authority, Singapore (www.hsa.gov.sg)
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (www.ich.org)
IGDRP	International Generic Drug Regulators Programme (https://www.igdrp.com)
INN	International Nonproprietary Names
MHLW	Ministry of Health, Labour and Welfare, Japan
MHRA	Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe	New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
Ph. Int	*The International Pharmacopoeia* (http://apps.who.int/phint/)
PMDA	Pharmaceuticals and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic	Swiss Agency for Therapeutic Products(www.swissmedic.ch)
TGA	Therapeutic Goods Administration, Australia(www.tga.gov.au)
WHO	World Health Organization (www.who.int)
WHO MHP	WHO Access to Medicines and Health Products Division (www.who.int/medicines/en/)
WHO RPQ	WHO Regulation and Prequalification Department
WHO PQT	WHO Prequalification Unit (https://www.who.int/topics/prequalification/en/)
WHO HPS	WHO Health Product Policy and Standards Department

Note: The online version of this issue is available at *https://www.who.int/our-work/access-to-medicines-and-health-products/who-drug-information*

WHO BIOWAIVER PROJECT - PREPARATION FOR CYCLE V (2022): PRIORITIZATION EXERCISE OF ACTIVE PHARMACEUTICAL INGREDIENTS ON THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR SOLUBILITY DETERMINATION AND BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED CLASSIFICATION

DRAFT FOR COMMENTS

Please send your comments to **Dr Steve Estevao Cordeiro**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (estevaos@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int).

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the "*Current projects*" link.

If you wish to receive all our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.

WHO BIOWAIVER PROJECT - PREPARATION FOR CYCLE V (2022): PRIORITIZATION EXERCISE OF ACTIVE PHARMACEUTICAL INGREDIENTS ON THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR SOLUBILITY DETERMINATION AND BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED CLASSIFICATION

Background

In October 2020, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparation (ECSPP) took note of the results achieved within the WHO Biowaiver Project and recommended continuing the Biopharmaceutical Classification System (BCS)-based classification of active pharmaceutical ingredients (APIs) contained in medicines listed in the WHO List of Essential Medicines (EML) *(1)* and prioritized according to public health priorities, Member States' and WHO partners' needs *(2)*.

This document is intended to support the prioritization exercise of APIs to be characterized in their solubility profile in cycle V of the WHO Biowaiver Project. Following a review of the comments received during the public consultation, a list of APIs for study in cycle V will be proposed for adoption at the next ECSPP *(2)*.

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

- 2018: cycle I; also referred to as the *pilot phase.*
- 2019: cycle II.
- 2020: cycle III.
- 2021: cycle IV; current study cycle.
- 2022: cycle V. *Note:* this prioritization exercise is propaedeutic to this study cycle.

1. Introduction
2. The revised WHO Biowaiver List
3. Prioritization exercise of active pharmaceutical ingredients for Biopharmaceutical Classification System-based classification in WHO Biowaiver Project

References

Further reading

1. Introduction

When evaluating multisource (generic) products, the goal is to ensure that they have a comparable *bioavailability* (BA) with respect to their originator in order to assume comparability in their efficacy and safety profiles.

The WHO recognizes the possibility to waive in vivo bioequivalence studies for immediate-release, solid oral dosage forms for APIs belonging to classes I and III according to the BCS, using comparative dissolution studies as surrogate proof of bioequivalence (*3*).

The aim of WHO biowaiver guidance documents is to reduce the risk of "*bioinequivalence*" to an acceptable level when granting biowaivers supporting pharmaceutical development and access to medicines. In this context, the solubility, the release from the drug product and the subsequent absorption phase are considered critical processes underlying the equivalence of the test and reference product.

Equilibrium solubility profiles of APIs contained in medicines in the EML (*1*) can be used in conjunction with absorption/permeability data, finished pharmaceutical products (FPP) dissolution studies and comparative consideration of FPP-excipient content in order to provide an informed decision as to whether or not a biowaiver could be granted safely.

2. The revised WHO Biowaiver List

According to the recommendations from the Fifty-second, Fifty-third, Fifty-fourth and Fifty-fifth ECSPP, the WHO Secretariat has published the revised *WHO Biowaiver List: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms (4)*. The List is published in the form of a living document and is updated annually with new data in accordance with the scientific and technical progress in this area. The 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 (5).*

The *WHO Protocol to conduct equilibrium solubility experiments for the purpose of biopharmaceutics classification system-based classification of active pharmaceutical ingredients for biowaiver (6)* is a tool available to all participants in this research. This protocol was developed with the purpose of providing a standardized methodology for the equilibrium solubility experiments, thereby minimizing the variability among centres and studies.

3. Prioritization exercise of active pharmaceutical ingredients for Biopharmaceutical Classification System-based classification in WHO Biowaiver Project

A fourth set of APIs is proposed for BCS-based classification within the WHO Biowaiver Project. The criteria underpinning the APIs prioritization are as follows:

- the API must be contained in medicines listed in the EML;
- the API must be intended to be formulated as an immediate-release, solid oral dosage form;
- the API must belong to therapeutic areas of major public interest; and
- the specific physical-chemical properties for the API must be known.

Consideration should be given to narrow therapeutic index drugs (NTIs) as the BCS-based biowaiver approach is not considered to be a suitable surrogate for the establishment of bioequivalence of NTIs. NTIs are defined in the WHO guidance Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability *(3)*.

Proposed list of active pharmaceutical ingredients for study in cycle V

Table 1 provides the proposed list of APIs to be prioritized for BCS-based classification in the next cycle of the project (cycle V - 2022) and comments are invited. APIs are listed in alphabetic order and, when providing comments, you might wish to indicate their order of priority.

Table 1. List of APIs to be prioritized for BCS-based classification in cycle V of the project - 2022

N	API contained in medicines on the EML	Therapeutic Area	Indication	Highest therapeutic single dose [mg]
1	Amitriptyline	Medicines for mental and behavioural disorders	Medicines used in depressive disorders	75 mg (as hydrochloride)
2	Amlodipine	Cardiovascular medicines	Antihypertensive medicines	10 mg
3	Bisoprolol	Cardiovascular medicines	Antihypertensive medicines	20 mg
4	Clindamycin	Anti-infective medicines	Access group antibiotics	450 mg

5	Hydralazine hydrochloride	Cardiovascular medicines	Antihypertensive medicines (pregnancy-induced hypertension)	100 mg
6	Zidovudine*	Anti-infective medicines	Nucleoside/Nucleotide reverse transcriptase inhibitors (HIV)	300 mg
7	Levofloxacin	Anti-infective medicines	Antituberculosis medicines (MDR-TB)	1500 mg
8	Moxifloxacin	Anti-infective medicines	Antituberculosis medicines (MDR-TB)	800 mg
9	Pyrazinamide**	Anti-infective medicines	Antituberculosis medicines	2000 mg
10	Quinine	Anti-infective medicines	Antimalarial	648 mg
11	Ribavirin	Anti-infective medicines	For the treatment of viral haemorrhagic fevers	600 mg
12	Valganciclovir	Anti-infective medicines	For the treatment of cytomegalovirus retinitis (CMVr)	900 mg

* Zidovudine as mono-component and in Fixed-dose combination (FDC) with lamivudine (under study in cycle IV)

**Pyrazinamide as mono-component and in FDCs with isoniazid (under study in cycle IV), ethambutol (under study in cycle IV) and rifampicin (listed in the *WHO Biowaiver List*)

***Note*:** For exemption from an in vivo bioequivalence study, an immediate release, multisource product should exhibit very rapid or rapid in vitro dissolution characteristics that are comparable to the reference product. The excipients used in the formulation must be considered together with a risk-based approach in terms of the therapeutic index and clinical indications.