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Recommendes INN: List 86

International Nonproprietary Names for Pharmaceutical Substances



**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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- 684** Dolutegravir Dispersible Tablets (*dolutegraviri compressi dispersibiles*)
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- 701** Benzathine benzylpenicillin for injection (*benzathini benzylpenicillini ad injectionem*)

International Nonproprietary Names (INN)

- 707** Recommended INN List No. 86

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 | <i>The International Pharmacopoeia</i> (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 (ECSP) 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 ECSP (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 ECSP, 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.

预览已结束，完整报告链接和二维码如下：

https://www.yunbaogao.cn/report/index/report?reportId=5_23559

