Frequently Asked Questions and Answers on Phase 2 Requirement of Bioavailability and Bioequivalence Studies

1. What are the requirements on the bioavailability and bioequivalence (BABE) studies for registration of the 38 Critical Dose Drugs / Narrow Therapeutic Range Drugs (NTRD)?

Applications of the 38 Critical Dose Drugs / NTRD **appended below** must include BABE studies in accordance with the World Health Organization (WHO) guidance document – Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability[1]. Other BABE studies can be accepted if official evidence of registration approval of the generic drugs in the following countries or region can be provided: Australia, Canada, the European Union, the United Kingdom, Japan or the United States.

38 Critical Dose Drugs / Narrow Therapeutic Range Drugs

Acetohexamide	Isoetharine
Aminophylline	Isoprenaline
Aprindine	Levodopa and Carbidopa
Chloramphenicol	Levothyroxine
Choline theophylline	Lithium
Clindamycin	Metaproterenol
Clonidine	Methotrexate
Cyclosporine	Minoxidil
Digitoxin	Phenobarbital
Digoxin	Prazosin
Diprophylline	Procainamide
Disopyramide	Proxyphylline
Ethinyl Estradiol	Quinidine
Flecainide	Sirolimus
Glibenclamide	Tacrolimus
Gliclazide	Theophylline
Glybuzole	Tolazamide
Glyclopyramide	Tolbutamide
Guanethidine	Warfarin

[1] WHO Technical Report Series, No. 1003, 2017: Annex 6 - republication of Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability, WHO Technical Report Series, No. 992, 2015: Annex 7 with a new Appendix 2

2. What is the timeline for the Phase 2 requirement of BABE studies for the registration of generic drugs?

A. New applications for registration received before 1 August 2016

For all new applications for registration of the 38 Critical Dose Drugs / NTRD **as listed under Question 1** received before 1 August 2016 but have not been completed for registration before 1 August 2017, the applicants must satisfy the Phase 2 requirement for BABE studies before the approval of the applications.

B. New applications for registration received on or after 1 August 2016

With effect from 1 August 2016, all new applications for registration of the 38 Critical Dose Drugs / NTRD **as listed under Question 1** must include evidence to satisfy the Phase 2 requirement for BABE studies. Otherwise, the applications will not be accepted for evaluation.

C. Renewal applications of registered generic drugs

With effect from 1 August 2017, all renewal applications for registration of the 38 Critical Dose Drugs / NTRD **as listed under Question 1** must include evidence to satisfy the Phase 2 requirement for BABE studies. Otherwise, the registration of the generic drugs will not be renewed.

3. What dose form will be affected by the Phase 2 requirement of BABE studies?

The Phase 2 requirement of BABE studies for the 38 Critical Dose Drugs / NTRD is applicable to only oral dose form except (i) clonidine which would be applicable to both oral dose form and transdermal patch; and (ii) isoetharine which would be applicable to only inhalation aerosol.

4. What is the bioequivalence acceptance range applicable for Critical Dose Drugs / NTRD?

The current WHO guidelines on BABE registration requirements[2], including the bioequivalence acceptance range of 90.00-111.11% will be applicable for 6

[2] WHO Technical Report Series, No. 1003, 2017: Annex 6 - republication of Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability, WHO Technical Report Series, No. 992, 2015: Annex 7 with a new Appendix 2

antiepileptic drugs subject to the Phase 1 requirement for BABE studies, namely carbamazepine, clonazepam, divalproex, phenytoin, valproates and zonisamide belonging to NTRD and the 38 Critical Dose Drugs / NTRD subject to the Phase 2 requirement of BABE studies according to the following timeline:

(i) 1 January 2018 for new applications and including applications for change of registered particulars of registered pharmaceutical products; and
(ii) 1 January 2023 for renewal applications.

For the current WHO guidelines on BABE registration requirements, please visit the following website:
https://extranet.who.int/pqweb/medicines/bioequivalence

5. Are there any arrangements to exempt BABE studies for some registered pharmaceutical products when their comparators cannot be identified nor available?

In order to address the concerns on the difficulties to identify comparators of some registered pharmaceutical products for BABE studies and to preserve the continuous supply of these registered products for the interests of patients, the following arrangements are provided for registered products affected by the Phase 2 requirement of BABE studies:

A. Exemption will be applicable:
for the renewal of registered products which have been registered with the Pharmacy and Poisons Board before 1 August 2016 if the applicants could provide evidence to prove that no comparators could be identified according to the current WHO guidelines on BABE registration requirements nor available in the market;

B. Exemption will not be applicable:
(i) when there are any changes in manufacturers of the registered products mentioned in 5A above, pharmacokinetic and/or pharmacodynamic studies will be required unless justified; and

(ii) when there is any addition of active ingredient(s) of the registered products mentioned in 5A above, new drug applications and including clinical studies will be required.