APPENDIX 16

BIOEQUIVALENCE (BE) REQUIREMENTS

1. BIOEQUIVALENCE (BE) REQUIREMENTS

1.1 Overview

In applications for generic medicinal products, the concept of bioequivalence is fundamental. The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a comparator medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the comparator medicinal product. A generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same dosage form as the medicinal product, and whose bioequivalence with the comparator medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

Applicants are advised to refer to and be familiar with the latest ASEAN Guideline for The Conduct of Bioequivalence Studies regarding the recommendation for establishing the interchangeability of generic product with comparator product. In addition, other relevant and latest international guidelines, e.g. by EMA, USFDA, ICH should also be referred to complement the ASEAN Guideline. These guidelines are to be read in conjunction with pertinent directives, circulars and updates regarding implementation of bioequivalence requirements in Malaysia, which will be updated periodically on the *NPRA website*.

1.2. Scope of Implementation

Bioequivalence (BE) requirement is implemented by stages for generic product applications in Malaysia.

Currently, this requirement is applicable to all generic products in the form of oral solid dosage forms with systemic actions. The following **Table 1** summarizes types of dosage forms that are required to submit BE data for new application of generic product registration or product registration renewal. The scope of implementation is not exhaustive and will be reviewed accordingly from time to time upon scientific judgement and patient risk assessment by the National Drug Authority. As for now, dosage forms that are not covered within the scope are not required to submit BE data during product registration or product registration renewal.

Table 1: Implementation of BE Requirement

Types of dosage form	Directives
All generic products containing scheduled poison in the form of **modified release**, oral, solid dosage form.	*Keperluan Akreditasi Pusat Kajian Bioavailability/ Bioekuivalens Bagi Produk Dalam Bentuk* Modified Release, *Bil. (3) dlm. BPFK/ PPP/01/03 Jld.3* (12 June 2013)
All generic products containing scheduled poison in the form of **immediate release**, oral, solid dosage form.	Directive No. 1, 2011: *Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens bagi Semua Produk Generik* 'Immediate Release, Oral, Solid Dosage Form' *yang Mengandungi Bahan Aktif Racun Berjadual Serta Akreditasi Pusat Kajian Bioekuivalens*, *Bil. (10) dlm. BPFK/PPP/01/03 Jld.1* (2 March 2011)
Bioequivalence study report for all registered generic products containing scheduled poison with **effervescent, dispersible, orodispersible, sublingual, buccal and chewable** dosage forms	(i) Directive No, 3, 2015*: Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens (BE) Bagi Semua Produk Generik Dalam Bentuk Dos Oral Tablet/Kapsul Yang Bersifat* Effervescent, Dispersible, Orodispersible, Sublingual, Buccal *dan* Chewable *Yang Mengandungi Bahan Aktif Racun Berjadual*, *Bil. (27) dlm. BPFK/PPP/07/25* (23 February 2015) (ii) *Lanjutan Tarikh Penguatkuasaan Untuk Memenuhi Keperluan Kajian Bioekuivalens* (BE) *bagi Produk Generik dalam Bentuk Dos Oral Tablet/Kapsul yang Bersifat* Effervescent, Dispersible, Orodispersible, Sublingual, Buccal *dan* Chewable *yang Mengandungi Bahan Aktif Racun Berjadual*, *Bil. (45) dlm. BPFK/PPP/01/03 Jld.3* (31 May 2016)

Should further clarification be needed on the BE requirements, kindly contact **be_sug@npra.gov.my**

1.3 Documentation of BE Study Report

A complete BE report with all the appendices and comparative dissolution profile data/report according to the relevant guidelines shall be submitted during generic product registration application. The complete BE report should consist of BE study protocol, clinical study report, method validation report, bioanalytical report and pharmacokinetic & statistical report. Applicants are advised to refer to the *Bioequivalence Study Report Submission Checklist* in preparation of dossier for submission. The complete documentation should be submitted in QUEST3+ system under section P9 Product Interchangeability/ Equivalence Evidence. Hardcopy of the report shall be requested when deemed necessary.

1.4 Bioequivalence (BE) Study Centre Accreditation

As of 1 January 2012, all BE studies intended to support product registration review by the NPRA must be conducted at clinical and bioanalytical facilities that are listed under the NPRA BE Centre Compliance Programme. The list of accredited facilities is available on the *NPRA website*.

On 21 July 2020, a new Directive was issued that necessitates a risk assessment to be performed on BE studies conducted at facilities not listed on the NPRA BE Centre Compliance Programme or conducted outside the valid listing period. This risk assessment leverages on reliance mechanisms with other regulatory agencies via the *Evaluation on the Need for BE Study Inspection (BEDE)* pathway.

Effective 18 February 2025, the scope of facility accreditation requirements has been expanded to include BE study centres listed in the *ASEAN BE Centre List* (The link to the *ASEAN BE Centre List* will be made available once it has been established). Bioequivalence (BE) studies conducted at these facilities during their valid listing period are exempt from the BEDE application, provided they involve generic products that meet the eligibility criteria. This includes *immediate-release, oral, solid dosage forms, with systemic action* containing scheduled poisons. Additionally, products eligible for evaluation under the *Facilitated Registration Pathway (FRP)* are also exempt from the BEDE requirement.

BE studies conducted outside the valid listing period of facilities in the *NPRA BE Centre Compliance Programme* or *ASEAN BE Centre List* or at facilities not listed in either programme must undergo the BEDE evaluation pathway. The outcome of the BEDE application will determine if the BE study may be accepted to support product registration review or require a study-specific inspection with a satisfactory outcome for acceptance.

Regardless of the mechanism that accepts the BE study for product registration review, the NPRA reserves the right to inspect study sites if concerns arise regarding BE study data during the review. Refusals for the inspection or inspection with unsatisfactory outcomes will result in the product's rejection.

Applications for BE centre inspections and BEDE should be submitted to the Bioequivalence Centre and Ethics Committee Section, Centre of Compliance and Quality Control. Details on BE centre inspections, BEDE, and relevant guidance, including application forms and procedures for BEDE and study-specific inspections, are available on the NPRA website.

Applicable directives and circulars regarding the requirements above are as follows:

- *Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens Bagi Semua Produk Generik 'Immediate Release, Oral, Solid Dosage Form' yang Mengandungi Bahan Aktif Racun Berjadual Serta Akreditasi Pusat Kajian Bioekuivalens Bil. (10) dlm. BPFK/PPP/01/03 Jld.1* (2 March 2011)

- *Direktif Penguatkuasaan Keperluan Kajian Bioekuivalens (BE) Bagi Produk Generik Dalam Bentuk Dos Oral Tablet/ Kapsul Yang Bersifat Effervescent, Dispersible, Orodispersible,*

Sublingual, Buccal dan Chewable Yang Mengandungi Bahan Aktif Racun Berjadual Bil. (27) dlm. BPFK/PPP/07/25 (23 February 2015)

- *Direktif Pelaksanaan Penilaian Keperluan Pemeriksaan Kajian Bioekuivalens (BE) NPRA.600-1/9/13 (3)* (21 July 2020)

- Malaysian Guideline For Bioequivalence Inspection 2nd Edition

- *Direktif Perluasan Skop Keperluan Akreditasi Pusat Kajian Bioekuivalens (BE) dan Pengecualian Penilaian Keperluan Pemeriksaan Kajian BE Bagi Tujuan Pendaftaran Produk NPRA.600-1/9/13 (50) Jld. 1* (18 February 2025)

2. Investigational Products

2.1 Test Product

The test product used in the BE study should be manufactured at the same drug product manufacturing site by the same manufacturing process and manufactured with the same drug substance and formula as the generic product proposed for registration in Malaysia. The batch size of test product used in the BE study should also be at least 100,000 units or 1/10 of production scale, whichever is greater, unless otherwise justified. Any deviation from this requirement should be justified with additional documentation to ensure the sameness of both test product and product proposed for registration. Applicants are advised to refer to FAQ on the NPRA website for the additional documentation required.

2.2 Reference Product

The reference product used in the BE study must be the same as the innovator/ comparator products which have been registered with Drug Control Authority (DCA) in Malaysia. A generic product for which its innovator has never been registered in Malaysia will be classified under Hybrid application.

For purpose of product registration in Malaysia, applicants are advised to use Malaysia comparator product (MCP) to conduct the BE studies. The *list of Malaysia comparator product* is available on the NPRA website.

Applicant should provide a copy of the outer carton label which clearly showing batch number, manufacturer address, expiry date and the prescribing information (product leaflet) of the reference product used in the BE study for verification purposes.

Should the reference product use in the BE study was manufactured at a different site from the MCP, or manufacturer address was not stated on the outer carton, the applicant should justify and prove that the BE reference product is identical with the MCP in the following aspects:-

(i) The ingredients in the BE reference product are qualitatively identical to the Malaysia comparator product except minor differences in excipient (e.g. colouring and ink) that will not affect bioavailability of the reference product.

(ii) Comparative dissolution profile of the BE reference product is similar with the Malaysia comparator product. The CDP should be conducted as per requirement in Appendix I of ASEAN Guideline for the Conduct of Bioequivalence Study. It is highly recommended to conduct the CDP between reference product and MCP simultaneously to reduce potential variabilities and avoid comparison and compilation of historical data.

(iii) The drug substance does not have a narrow therapeutic index

Should the MCP be no longer available or could not be found on the list of comparators, kindly contact **be_sug@npra.gov.my** for further assistance.

3. Study Design

3.1 Immediate Release Product

For products where the Summary of Product Characteristic (SmPC) recommends intake of the comparator medicinal product on an empty stomach or irrespective of food intake, the BE study should be conducted under fasting conditions. BE study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations. For products where the SmPC recommends intake of the comparator medicinal product only in fed state, the BE study should generally be conducted under fed conditions.

3.2 Modified Release Product

Single dose BE studies under both fasting and fed conditions should be submitted. Multiple dose study in fasting or fed state will be requested when deemed necessary.

4. Dissolution Testing and Similarity of Dissolution Profile

4.1 General Aspects of Dissolution Testing as Related to Bioavailability

During the development of a medicinal product, a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug. As soon as the composition and the manufacturing process are defined, a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, in certain instances a dissolution test can be used to waive a BE study. Therefore, dissolution studies can serve several purposes:

(i) Testing on product quality

- To get information on the test batches used in bioequivalence studies and pivotal clinical studies to support specifications for quality control
- To be used as a tool in quality control to demonstrate consistency in manufacture

- To get information on the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies

(ii) Bioequivalence surrogate inference

- To demonstrate in certain cases similarity between different formulations of an active substance and the reference medicinal product (biowaivers e.g., variations, formulation changes during development and generic medicinal products)
- To investigate batch-to-batch consistency of the products (test and reference) to be used as basis for the selection of appropriate batches for the in-vivo study

4.2 Comparative Dissolution Profile (CDP)

In order to compare the dissolution profile of the products, the dissolution data should be generated under the same test conditions, if possible, on the same day. It is highly recommended to conduct the dissolution testing concurrently to reduce potential variabilities and avoid comparison and compilation of historical data

4.2.1 Usual Testing Conditions

(i) Media buffer

The in vitro dissolution test should be conducted at three different buffers (normally pH1.2, 4.5, 6.8) and the media intended for product release (QC media, if applicable and available).

Surfactants should be avoided in comparative dissolution testing.

A statement that the API is not soluble in any of the media is not sufficient, and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

(ii) Number of products to be tested

At least 12-unit of each investigative products should be used in CDP testing to enable statistical evaluation. The products should originate from batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified.

(iii) Agitation

Selection of speed of agitation should be properly justified. Stirrer used in paddle apparatus is usually at 50rpm for tablets and basket apparatus at 100rpm for capsules.

(iv) Sampling time points

Sampling time points should be sufficient to obtain meaningful dissolution profiles, and at least every 15 minutes. More frequent sampling during the period of greatest change in the dissolution profile is recommended. For rapidly dissolving products, where complete dissolution is within 30 minutes, generation of an adequate profile by sampling at 5- or 10-minute intervals may be necessary.

(v) Statistical comparison

Dissolution similarity may be determined using suitable statistical procedure e.g the f_2 similarity factor as described in ASEAN guideline or other international guidelines.

(vi) Documentation

Complete documentation of in vitro dissolution experiments is required including a study protocol, batch information on batches, detailed experimental conditions, validation of experimental methods, individual and mean results and respective summary statistics.

5. Biowaiver considerations

Generic products should demonstrate the bioequivalence evidence by in-vivo equivalence testing. Nevertheless, exemption on the submission of an in-vivo BE study can be considered in certain circumstances for generic products of oral solid dosage forms. Applicants should provide adequate data and justifications for not submitting the in-vivo data.

5.1 Waiver of Additional Strength(s)

In generic drug product application consists of several strengths, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths and BE test products. If bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, in-vivo BE studies for the other strengths may be waived provided that the following requirements are fulfilled: -

(a) the different strengths of the generic product are manufactured by the same manufacturing process,

(b) the qualitative composition of the different strengths is the same,

(c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule)

If there is some deviation from quantitatively proportional composition, condition (c) is still considered fulfilled if condition (i) and (ii) or (i) and (iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered

(i) the amount of the active substance(s) is less than 5 % of the tablet core weight or the weight of the capsule content;
(ii) the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed;
(iii) the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths

(d) appropriate comparative dissolution profile testing should confirm the adequacy of waiving additional in-vivo bioequivalence testing. Similarity of the dissolution profiles across the physiological pH range between additional strengths of the generic products and the strength of the generic product used in the BE study should be demonstrated. In addition, CDP testing demonstrating similar profiles at the same dose (e.g. two 10mg tablets versus one 20mg tablets) may be required.

If the data and justifications are considered not adequate, applicant will be required to provide relevant biopharmaceutics data, e.g. in-vivo BE study.

Applicants are advised to refer to the checklist "*Application For A Biowaiver: Additional Strength*" and submit relevant documents when requesting for biowaiver for additional strength.

5.2 BCS-based Biowaiver

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is intended to reduce the need for in-vivo bioequivalence studies if an assumption of equivalence in in-vivo performance can be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance(s). The BCS categorizes drug substances into one of four BCS classes as follows:

Class I : high solubility, high permeability

Class II : low solubility, high permeability

Class III: high solubility, low permeability

Class IV: low solubility, low permeability

5.2.1 Consideration for BCS-based Biowaiver Criteria

(i) BCS-based biowaivers are applicable for immediate-release oral solid dosage forms with systemic action.

(ii) For immediate release product in fixed dose combination, all the drug substances in the combination should meet the BCS-based biowaiver criteria.

(iii) Biowaiver may also be applicable if test and reference products contain different salts provided that both belong to BCS Class I (high solubility and high permeability).

(iv) Drug products with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application

(v) Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver

(vi) Biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of a drug substance from that of the reference product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept.

Currently NPRA allows only BCS-based class 1 biowaiver application. Applicants are advised to prove that the generic product and drug substances are highly soluble and highly permeable with sufficient data and documentation as per requirement on the checklist *Application For Biopharmaceutics Classification System (BCS) Biowaiver*.

BCS-based class 1 application should be product specific and should not based on list of substance in the particular BCS class. If a generic product is to be marketed in several strength(s) and the submission is based on a BCS-based biowaiver approach, a complete set of documents is required for each strength, as it will be evaluated independently.

In situation where the applicant is unable to provide satisfactory documents to support BCS-based class 1 biowaiver application, biowaiver request may not be considered and BE study should be conducted.

5.3 Waiver for Second Source Product

In general, for a second source application of a generic product (immediate release, oral solid dosage form), BE study report from the actual manufacturing site must be submitted during the submission of application for registration. The base of this requirement is due to the difference in manufacturing site from the first source that may change the characteristic and specifications of a second source product.

However, biowaiver may be considered as a surrogate to in-vivo BE study for the second source product, provided that all the following conditions are fulfilled:

(a) BE study conducted using the registered first source product has been evaluated by NPRA and found satisfactory.

(b) Comparative Dissolution Profile (CPD) data between the second source product against the registered first source product is submitted

(c) The second source product is the same as registered first source product used in the BE study in terms of:

- Product formulation.
- Equipment used in the manufacturing process.
- Source and supplier of raw material.
- Quality control and specifications of raw material.
- Manufacturing process of product and standard operating procedures.
- Environmental conditions during the manufacturing process of product.
- Quality control and specifications of finished product.

(d) CDP must be conducted in accordance to ASEAN Guidelines for The Conduct of Bioequivalence Studies including the calculation of similarity factor (f2) to prove the similarity of these two products.

(e) Process validation has been conducted on three pilot or commercial batches of the second source product and found satisfactory by the NPRA.

This exemption is not applicable for any new submission of application for registration of a first source product. BE study must be conducted for this product which is manufactured at the actual manufacturing site submitted for registration.

Disclaimer: NPRA reserves the right to request for any additional information required for evaluation if deemed appropriate, to determine the product interchangeability of the generic product to the MCP.

6. References

a. ASEAN Guideline for the Conduct of Bioequivalence Studies

b. ICH M9 Guideline on Biopharmaceutics Classification System-based Biowaivers

c. Annex 6 WHO Technical Report Series 1003, 2017