APPENDIX 10 *PRODUCT INTERCHANGEABILITY AND BIOWAIVER REQUEST FOR CHEMICAL GENERIC DRUG APPLICATIONS*

Applicants are advised to be familiar with the *ASEAN Guideline for the Conduct of Bioequivalence Studies* for the purposes of drug registration. Applicants are also advised to refer to the relevant international guidelines e.g. by EMA CHMP or US FDA for the conduct and analysis of bioequivalence (BE) studies.

In vivo BE data are required to support GDAs for Prescription Only Medicines (POM) in oral solid dosage forms.

1 PRODUCT INTERCHANGEABILITY

A generic product is considered to be interchangeable with the Singapore reference product if it demonstrates therapeutic and pharmaceutical equivalency. A BE study is generally the most appropriate method for demonstrating therapeutic equivalence between products that are pharmaceutically equivalent.

For generic products containing a ***different*** salt, ester, ether, isomer, mixture of isomer, complex or derivative of the active substance compared to the Singapore reference product, applicants are required to submit data to demonstrate that the different form does **not** differ from the active substance in the Singapore reference product in terms of efficacy and safety.

A generic POM in an oral solid dosage form is required to demonstrate product interchangeability with the Singapore reference product using BE study data and supplemented by comparative dissolution profile data.

2 BE STUDY

2.1 Overview

The report of a BE study should include the complete documentation of its protocol, conduct and evaluation in compliance with GCP and the related ICH E3 guideline.

Deviations, additions, or omissions from existing guidelines must be explained, either in the introductory remarks or within each relevant module/part of the submission, whichever is more appropriate. Examples of information to be included in the report are:

(a) Signature of the Principal Investigator to attest the authenticity of the report;

(b) Audit certificate(s);

(c) BE site inspection report(s) from national drug regulatory agencies or WHO, if available;

(d) Approval letter(s) from the Institutional Review Board/Independent Ethics Committee and, if available, the appropriate drug regulatory agency;

(e) Information about the reference and test products, including the product name, strength, dosage form, batch number, manufacturing site, expiry date and batch size (test product only);

(f) Certificates of Analysis of the reference and test products used in the BE study, including the batch size of the test product and manufacturing/expiry date of both products (where applicable);

(g) Bioanalytical study report and description of the bioanalytical method validation; and

(h) A signed statement confirming that the test product used in the BE study is the same formulation and is manufactured by the same process as that submitted for registration.

Applicants should ensure that the submitted BE study report is complete, including all appendices and data, according to the relevant guidelines.

2.2 BE Test Product vs Product Proposed for Registration

It is highly recommended that the generic or test product used in the BE study be the same as the generic product submitted for registration in Singapore. In other words, the test product should be manufactured at the same drug substance and drug product manufacturing sites and by the same manufacturing processes as

submitted in the GDA application dossier. The test product used in the BE study should also be from a batch of at least 100,000 units or 1/10 of production scale, whichever is greater, unless otherwise justified.

If the BE test product was manufactured at manufacturing site(s) other than the manufacturing site(s) proposed for registration in the GDA submission, the documents listed below have to be submitted. This is applicable to immediate release and modified release oral solid dosage forms. However, for submissions via the verification and verification-CECA evaluation routes, the BE test product must be manufactured by the same drug substance and drug product manufacturers at the same manufacturing site(s) as those proposed for registration in Singapore.

2.2.1 Different Drug Substance Manufacturing Sites

- **Quality documents from drug substance manufacturer of BE test product:**
  - 3.2.S.2.2 Brief process synthetic route with flow diagram, structure & solvents
  - 3.2.S.3.1 Characterisation of drug substance
  - 3.2.S.3.2 Impurity
  - 3.2.S.4.1 Drug substance specification
  - 3.2.S.4.4 Batch analysis (1 batch each from drug substance and drug product manufacturers)
- Scientific justification showing that characteristics of the drug substance that may have an impact on bioavailability (e.g. polymorphism, particle size) are identical.
- Comparative dissolution profile testing (to be performed in at least 3 pH media) between the drug products manufactured using the drug substance sourced from the drug substance manufacturer of the BE test product and the drug substance manufacturer proposed for registration.

2.2.2 Different Drug Product Manufacturing Sites

- **Quality documents from drug product manufacturer of BE test product:**
  - 3.2.P.1 Composition of Drug Product
  - 3.2.P.2 Dissolution profile over multiple time points, (including the BE test product) (12 units in product release medium* or at least 3 pH media**)
  - 3.2.P.3 Manufacture (process validation to be submitted, if available)
  - 3.2.P.5.4 Batch Analyses (including the BE test product)
  - 3.2.P.8 Stability (This is only required if the stability data from the drug product manufacturer proposed for registration in Singapore do not meet the submission requirements: 2 batches of 12-month stability data from the drug product manufacturer of the BE test product are required to support the proposed shelf life.)

- Scientific justifications that the BE test product is representative of the product proposed for registration in Singapore in terms of:
  - Product formula, specifications, manufacturing process and equipment type;
  - Excipient characteristics which may have an impact on the bioavailability of the active substance;
  - Comparison of batch analysis data; and
  - Similarity of comparative dissolution profiles (release profile/data, f_2) in product release medium* or at least 3 pH media**.

  *Site change within a single facility, within a contiguous campus, between facilities in adjacent city blocks

  **Site change to a different campus or country

For instances where both the drug substance and drug product manufacturers of the BE test product differ from those proposed for registration in Singapore, the above documentary requirements should be combined.

2.3 BE Reference Product vs Singapore Reference Product

It is highly recommended that the reference product used in the BE study be the same as the Singapore reference product – i.e. the BE reference product should be of the same strength as the generic product and manufactured from the Singapore-

registered drug product manufacturing site. Details of the manufacturing source of the Singapore reference product can be found by searching HSA's Register of Therapeutic Products.

If the BE reference product was manufactured by a non-Singapore-registered manufacturer, the following criteria must be fulfilled in order for the BE reference product to be accepted:

(a) The BE reference product is registered in the country where the product is sourced from;

(b) It is documented that the BE reference product is marketed in the country of origin

  (i) by the same innovator company or corporate entity that markets the same drug product (same dosage form and strength) in Singapore; or

  (ii) through a licensing arrangement with the innovator company or corporate entity that markets the same product in Singapore;

(c) The ingredients in the BE reference product are qualitatively identical to those used in the Singapore reference product, with the exception of minor excipients that are unlikely to affect the bioavailability of the product (e.g. colourants and inks);

(d) The drug substance does not have a narrow therapeutic range or safety margin – e.g. does not require careful dosage titration or patient monitoring; and

(e) The BE reference product

  (i) contains the same nominal quantity of active ingredient as the Singapore reference product; and

  (ii) exhibits similarity in comparative dissolution profiles with the Singapore reference product.

In addition, the applicant should provide a comparative table that lists the qualitative compositions of both the BE and Singapore reference products, and comparative dissolution profile data as mentioned in Section 3.

2.4 Study Conduct – Fasting/Fed Conditions

2.4.1 Immediate-Release Products

In general, a single-dose BE study conducted in accordance with the recommendations as stated in the package insert of the Singapore reference product should be submitted (refer to table below).

Singapore Reference Product Package Insert Recommendations	Fasted/Fed BE Study
"Take with food"	1. Single-dose fed study, **OR**
"Take without regard to meals" **OR** "take on an empty stomach"	1. Single-dose fasting study

2.4.2 Delayed-Release Products (e.g. enteric-coated)

In general, single-dose BE studies under both fasting and fed conditions should be submitted regardless of the recommendations stated in the package insert of the Singapore reference product (refer to table below).

Singapore Reference Product Package Insert Recommendations	Fasted/Fed BE Study

Not applicable	1. Single-dose fed study, **AND**
	2. Single-dose fasting study

2.4.3 Prolonged/Extended/Sustained-Release Products

In general, single-dose BE studies under both fasting and fed conditions should be submitted. In addition, a multiple-dose study conducted in accordance with the recommendations as stated in the package insert of the Singapore reference product should be submitted (refer to table below).

Singapore Reference Product Package Insert Recommendations	**Fasted/Fed BE Study**
"Take with food"	1. Single-dose fasting, **AND** 2. Single-dose fed, **AND** 3. Multiple-dose fed
"Take without regard to meals" **OR** "take on an empty stomach"	1. Single-dose fasting, **AND** 2. Single-dose fed, **AND** 3. Multiple-dose, fasting

Applicants are advised to be familiar with the relevant guidelines from EMA CHMP and *ASEAN Guideline for the Conduct of Bioequivalence Studies* for more information on meal requirements for BE studies, as well as information on design and conduct of BE studies in general.

3 COMPARATIVE DISSOLUTION PROFILE

A dissolution test is used as a tool to identify formulation factors that may influence and have a critical effect on the BA of the product. Apart from supporting product interchangeability, a dissolution test is also used in quality control to ensure batch-to-batch consistency of production batches and to check that the dissolution profiles of production batches remain similar to the pivotal clinical trial batch(es).

Dissolution profiles should be determined in at least three dissolution media within the physiological range, such as 0.1 N HCl, a pH 4.5 buffer and a pH 6.8 buffer. In addition, dissolution profiles should also be determined in the product release medium, if it is different from the three dissolution media.

For comparative dissolution profile testing, the following data should be submitted:

(a) Individual dissolution data in each of the pH media;

(b) Mean, range and relative standard deviation (RSD) of dissolution data from 12 units in three different pH media; and

(c) Statistical comparison using a procedure described in relevant international guidelines, e.g. f_2 calculations.

3.1 Comparative Dissolution Profile Data Requirements for POM in Oral Solid Dosage Forms

The following comparative dissolution profile data should be submitted:

- Between the generic product and the Singapore reference product;
- Between the BE test and reference products (where applicable); and
- Between the BE and Singapore reference products (where applicable).

Examples of the specific comparative dissolution profiles to be submitted in support of a GDA submission for the following scenarios are illustrated in Figure 8:

(a) When the BE reference product is the Singapore reference product: comparative dissolution profile A

(b) Same scenario as (a) but with multiple strengths of generic product: comparative dissolution profiles A and B

(c) When the BE reference product is not the Singapore reference product: comparative dissolution profiles A, C and D

(d) Same scenario as (c) but with multiple strengths of generic product: comparative dissolution profiles A, B, C and D.

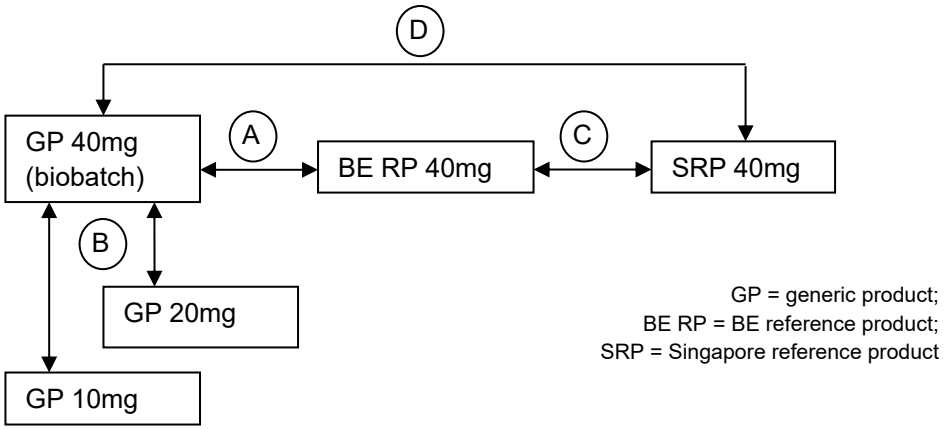


Figure 8 Comparative dissolution profile data required for different scenarios (POM)

Note:

Comparative dissolution profile A: only one medium (product release medium) is required

Comparative dissolution profile B, C and D: at least three dissolution media (including product release medium if applicable) are required

3.2 Comparative Dissolution Profile Data Requirements for P and GSL in Oral Solid Dosage Forms (Modified-Release)

Comparative dissolution profile data between the generic product and the Singapore reference product should be submitted.

If multiple strengths of the generic product are submitted, comparative dissolution profile data should be provided between the generic product and the Singapore reference product for each strength (see Figure 9).

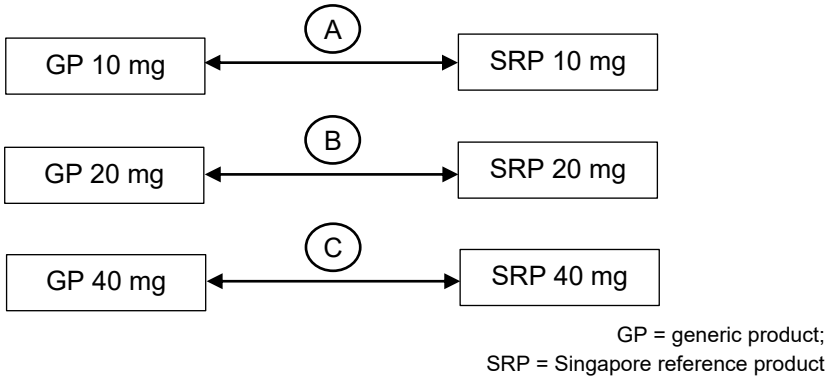


Figure 9 Examples of Comparative dissolution profile data required for P and GSL modified-release products

Note:

Comparative dissolution profile A, B, C: at least three dissolution media (including product release medium if applicable) are required

For more information on the conduct and reporting of comparative dissolution profile testing, applicants are advised to refer to the ASEAN Guideline for the Conduct of Bioequivalence Studies and other relevant international guidelines, as appropriate.

4 BIOWAIVER REQUESTS

The results from bioequivalence studies should be provided in support of the safety and efficacy of each proposed generic product and proposed strength included in a GDA submission. However, bioequivalence studies may be waived under certain circumstances, as explained in this section. In such cases, justifications supporting the biowaiver should be provided for each product and strength unless otherwise stated.

4.1 Biowaivers for Certain Dosage Forms

In general, BE data or justification(s) for not providing such data are not required for the following products:

(a) Simple or complex solutions that do not contain any ingredient which can be regarded as a pharmacologically active substance;

(b) Haemodialysis and peritoneal dialysis solutions;

(c) Simple aqueous solutions intended for intravenous injection or infusion containing the same active substance(s) in the same concentration as currently registered products. Simple solutions do not include complex solutions such as micellar or liposomal solutions;

(d) Solutions for injection that contain the same active ingredients and excipients in the same concentrations and which are administered by the same route(s) as currently registered products;

(e) Powders for reconstitution administered as solutions and where the solution meets either criterion (c) or (d) above;

(f) Oral solutions containing the same active ingredient(s) in the same concentration as a currently registered oral solution and which does not contain excipients that may significantly affect the gastric passage or absorption of the active ingredient(s);

(g) Products for topical use, provided that the product is intended to act without systemic absorption when applied locally;

(h) Products containing substances which are not systemically or locally absorbed and which do not contribute to a therapeutic effect (e.g. barium sulphate enemas, powders in which no ingredient is absorbed). If there is doubt as to whether absorption occurs, a study or justification may be required;

(i) Gas for inhalation; and

(j) Otic or ophthalmic products prepared as aqueous solutions and containing the same drug substance(s) in the same concentration as currently registered products.

For all other cases, justifications for requesting a biowaiver of BE studies is required.

4.2 General Biowaiver Criteria for Multiple Strengths

When a generic product is to be marketed in several strengths, the BE study should in general be conducted at the highest strength. For immediate-release oral solid

dosage forms, the results of a single BE study may be extrapolated to all strengths in the series, i.e. *in vivo* BE studies for the other strength(s) may be waived, provided that the applicant submits scientific justifications addressing the following general requirements:

(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 the 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 in 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 (refer to Figure 8). Failure to demonstrate similarity may require additional comparative dissolution profile testing with the respective strength of the Singapore reference product. In addition, comparative dissolution

profile testing demonstrating similar profiles at the same dose (e.g. two 5 mg tablets versus one 10 mg tablet) may be required.

(e) in addition, the applicant should address the pharmacokinetic linearity of the active ingredient(s) over the therapeutic dose range in accordance with international guidelines, e.g. ASEAN, EU CHMP.

If the justification is not considered adequate, the applicant will be required to provide relevant biopharmaceutic data (e.g. BE study).

Additional considerations apply to modified-release oral solid dosage forms. Applicants are advised to be familiar with the relevant international guidelines e.g. from EMA CHMP or US FDA concerning the strength(s) to be studied for modified release oral solid dosage forms.

4.3 BCS-based Biowaiver

The Biopharmaceutics Classification System (BCS) is a scientific framework that categorises drug substances into four groups, according to their solubility and permeability properties.

BCS-based biowaivers are applicable for an oral immediate release tablet or capsule if the criteria specified in paragraph [I] or [II] below are fulfilled:

I. the drug substance has been proven to exhibit high solubility and high permeability (BCS class I) and

- the generic product has either a very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) *in vitro* dissolution profile with respect to the Singapore reference product and
- excipients that might affect bioavailability (e.g. mannitol, sorbitol) are qualitatively the same and quantitatively similar in the generic product and the Singapore reference product. In general, the use of the same excipients in similar amounts is preferred.

II. the drug substance has been proven to exhibit high solubility and limited permeability (BCS class III) and

- the generic product and the Singapore reference product have very rapid (> 85 % within 15 min) *in vitro* dissolution profiles and
- all excipients should be qualitatively the same and quantitatively similar in the generic product and the Singapore reference product (except for film coating or capsule shell excipients).

Other important criteria for eligibility of BCS-based biowaivers include:

- Therapeutic range of the active ingredient – narrow therapeutic index drugs are not eligible for BCS-based biowaivers;
- Dosage form - BCS-based biowaivers are applicable for immediate-release oral solid dosage forms with systemic action but not for sublingual, buccal and modified-release formulations; and
- Active ingredient – generic products containing a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance from that of the reference product are not eligible for BCS-based biowaivers. Generic products containing a different salt may be eligible for BCS-based biowaivers provided that both generic and reference products contain salts belonging to BCS class I (high solubility and complete absorption).

The documents to support a BCS-based biowaiver should include:

- Supportive information for the proposed BCS classification of the drug substance, e.g. complete solubility study report(s) and the corresponding study protocol(s), literature review of absolute bioavailability;
- Complete dissolution report on comparative dissolution profile testing conducted between the generic product and Singapore reference product;
- Certificates of analysis of the generic product and the Singapore reference product; and

- Comparative table that lists the qualitative and quantitative compositions of both the generic product and Singapore reference product, including justifications for any differences in the excipient(s) used.

If a generic product is to be marketed in several strengths and the submission is based on a BCS-based biowaiver approach, a complete set of the abovementioned documents is required for each strength (i.e. each application), as each strength is evaluated independently. A biowaiver for multiple strengths cannot be applied simultaneously with a BCS-based biowaiver.

If the documentation is not considered adequate, the biowaiver request may not be granted and the applicant will be required to provide a relevant BE study.

Applicants are advised to be familiar with the ICH M9 guideline concerning BCS-based biowaivers.

This document reflects the current thinking of HSA on the minimum data necessary for evaluation. HSA reserves the right to request for additional information if deemed appropriate.
