GUIDANCE ON BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)-BASED BIOWAIVER

National Pharmaceutical Control Bureau,

Ministry Of Health Malaysia.

January 2013

Adopted and adapted mainly from the following:

1. Guideline On The Investigation Of Bioequivalence (European Medicines Agency, London, 20 January 2010, CPMP/EWP/QWP/1401/98 Rev. 1/Corr)

2. Annex 7: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (World Health Organization (WHO), Technical Report Series, No 937, 2006)

3. Annex 8: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms (World Health Organization (WHO), Technical Report Series, No 937, 2006)

to suit local requirements.

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1. INTRODUCTION

The Biopharmaceutics Classification System (BCS) is a scientific framework that is based on the aqueous solubility and intestinal permeability of the drug substance. It classifies the drug substance / active pharmaceutical ingredient (API) into four classes as below:

Class 1: High Solubility – High Permeability
Class 2: Low Solubility – High Permeability
Class 3: High Solubility – Low Permeability
Class 4: Low Solubility – Low Permeability

Combining the dissolution of the pharmaceutical product with these two properties of the drug substance/API, takes the three major factors that govern the rate and extent of drug absorption from immediate-release solid dosage forms into account. On the basis of their dissolution properties, immediate-release dosage forms can be categorized as having "very rapid", "rapid", or "not rapid" dissolution characteristics.

On the basis of solubility and permeability of the drug substance/API, and dissolution characteristics of the dosage form, the BCS approach provides an opportunity to waive *in vivo* pharmacokinetic bioequivalence testing for certain categories of immediate-release drug products.

For exemption from an *in vivo* pharmacokinetic bioequivalence study, an immediate-release generic product should exhibit very rapid or rapid *in vitro* dissolution characteristics, depending on the BCS properties of the drug substance/API. *In vitro* data should also demonstrate the similarity of dissolution profiles between the test and comparator products.

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, i.e., it may represent a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory in vitro data.

Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form. However, it is not applicable for sublingual, buccal, and modified release formulations. For orodispersible formulations the BCS-based biowaiver approach may only be applicable when absorption in the oral cavity can be excluded.

BCS-based biowaivers are intended to address the question of bioequivalence between specific test and reference products. The principles may be used to establish bioequivalence in applications for generic medicinal products, extensions of innovator products, variations that require bioequivalence testing, and between early clinical trial products and to-be-marketed products.

2. SUMMARY OF REQUIREMENTS

BCS-based biowaiver are applicable for an immediate release drug product if
• the drug substance has been proven to exhibit high solubility and complete absorption (BCS Class I; for details see section 3) and
• either very rapid (> 85 % within 15 min) or rapid (85 % within 30 min) in vitro dissolution characteristics of the test and reference product has been demonstrated considering specific requirements (see section 3.2.1) and
• excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred (see section 3.2.2).

Biowaiver should be considered only when there is an acceptable benefit – risk balance in terms of public health and risk to the individual patient.

C***urrently, biowaiver is considered for BCS Class I drug substances/active pharmaceutical ingredient (API) listed in section 4 only.***

3. DATA TO SUPPORT A REQUEST FOR BIOWAIVER

3.1 Drug Substance/ Active pharmaceutical ingredient (API)

Generally, sound peer-reviewed literature may be acceptable for known compounds to describe the drug substance characteristics of importance for the biowaiver concept.

Biowaiver may be applicable when the active substance(s) in test and reference products are identical.
Biowaiver may also be applicable if test and reference contain different salts provided that both belong to BCS-class I (high solubility and complete absorption; see sections *3.1.1 and 3.1.2*).
Biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active 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.

The drug substance should not belong to the group of ‘narrow therapeutic index’ drugs

3.1.1 Solubility

The pH-solubility profile of the drug substance should be determined and discussed. The drug substance is considered highly soluble if the highest single dose administered as immediate release formulation(s) is completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at 37±1 °C.
This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range. Replicate determinations at each pH condition may be necessary to achieve an unequivocal solubility classification (e.g. shake-flask method or other justified method). Solution pH should be verified prior and after addition of the drug substance to a buffer.

3.1.2 Absorption

The demonstration of complete absorption in humans is preferred for BCS-based biowaiver applications. For this purpose complete absorption is considered to be established where measured extent of absorption is ≥85 %. Complete absorption is generally related to high permeability.

Complete drug absorption should be justified based on reliable investigations in human. Data from

• absolute bioavailability or
• mass-balance studies

could be used to support this claim.

When data from mass balance studies are used to support complete absorption, it must be ensured that the metabolites taken into account in determination of fraction absorbed are formed after absorption.
Hence, when referring to total radioactivity excreted in urine, it should be ensured that there is no degradation or metabolism of the unchanged drug substance in the gastric or intestinal fluid. Phase 1 oxidative and Phase 2 conjugative metabolism can only occur after absorption (i.e. cannot occur in the gastric or intestinal fluid). Hence, data from mass balance studies support complete absorption if the sum of urinary recovery of parent compound and urinary and faecal recovery of Phase 1 oxidative and Phase 2 conjugative drug metabolites account for ≥ 85 % of the dose.

The more restrictive requirements will also apply for compounds proposed to be BCS class I but where complete absorption could not convincingly be demonstrated.

Reported bioequivalence between aqueous and solid formulations of a particular compound administered via the oral route may be supportive as it indicates that absorption limitations due to (immediate release) formulation characteristics may be considered negligible. Well performed

in vitro permeability investigations including reference standards may also be considered supportive to *in vivo* data.

3. 2 Drug Product

3.2.1 In vitro Dissolution

3.2.1.1 General aspects

Investigations related to the medicinal product should ensure immediate release properties and prove similarity between the investigative products, i.e. test and reference show similar *in vitro* dissolution under physiologically relevant experimental pH conditions. However, this does not establish an *in vitro*/*in vivo* correlation. *In vitro* dissolution should be investigated within the range of pH 1 – 6.8 (at least pH 1.2, 4.5, and 6.8). Additional investigations may be required at pH values in which the drug substance has minimum solubility. The use of any surfactant is not acceptable.

Test and reference products should meet requirements as outlined in ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies. In line with these requirements it is advisable to investigate more than one single batch of the test and reference products.

Comparative *in vitro* dissolution experiments should follow current compendial standards in the British Pharmacopeia or United States Pharmacopeia. Alternative methods can be considered when justified. However, thorough description of experimental settings and analytical methods including validation data should be provided. It is recommended to use 12 units of the product for each experiment to enable statistical evaluation.

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

3.2.1.2 Evaluation of in vitro dissolution results

Drug products are considered ‘very rapidly’ dissolving when more than 85 % of the labeled amount is dissolved within 15 min. In cases where this is ensured for the test and reference product the similarity of dissolution profiles may be accepted as demonstrated without any mathematical calculation.

Absence of relevant differences (similarity) should be demonstrated in cases where it takes more than 15 min but not more than 30 min to achieve almost complete (at least 85 % of labeled amount) dissolution. F_2-testing (see Appendix II of the ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies) or other suitable tests should be used to demonstrate profile similarity of test and reference. However, discussion of dissolution profile differences in

terms of their clinical/therapeutic relevance is considered inappropriate since the investigations do not reflect any in vitro/in vivo correlation.

3.2.2 Excipients

Although the impact of excipients in immediate release dosage forms on bioavailability of highly soluble and completely absorbable drug substances (i.e., BCS-class I) is considered rather unlikely, it cannot be completely excluded.
As a general rule, for BCS-class I drug substances, well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be considered and discussed. A description of the function of the excipients is required with a justification whether the amount of each excipient is within the normal range.
Excipients that might affect bioavailability, like e.g. sorbitol, mannitol, sodium lauryl sulfate or other surfactants, should be identified as well as their possible impact on

• gastrointestinal motility
• susceptibility of interactions with the drug substance (e.g. complexation)
• drug permeability
• interaction with membrane transporters

Excipients that might affect bioavailability should be qualitatively and quantitatively the same in the test product and the reference product.

3.3 Fixed Combinations (FCs)

BCS-based biowaiver are applicable for immediate release FC products if all active substances in the FC belong to BCS-class I and the excipients fulfil the requirements outlined in section 3.2.2. Otherwise in vivo bioequivalence testing is required.

NPCB reserves the right to request for any additional information not specifically described in this document in order to ensure safety, efficacy and quality of products

4. LIST OF DRUG SUBSTANCE/ ACTIVE PHARMACEUTICAL INGREDIENTS (API) THAT MAY BE CONSIDERED FOR BIOWAIVER

The list of drug substances/active pharmaceutical ingredients below is adopted from WHO Annex 8: Proposal to Waive In vivo Bioequivalence Requirements for WHO Model List of Essential Medicines Immediate-Release, Solid Oral Dosage Forms, 2006 and adapted to local requirements.

Note: This list is not exhaustive and will be reviewed from time to time according to the WHO Model List of Essential Medicines and upon scientific judgment and patient risk assessment by the national drug authority.

1. Allopurinol
2. Amiloride hydrochloride
3. Cyclophosphamide
4. Chloroquine phosphate or sulfate
5. Levonorgestrel
6. Norethisterone
7. Primaquine diphosphate
8. Proguanil hydrochloride
9. Promethazine hydrochloride
10. Propylthiouracil
11. Quinine bisulfate or sulfate

ABBREVIATIONS

API	Active pharmaceutical ingredient
ASEAN	Association of Southeast Asian Nations
BCS	Biopharmaceutics Classification System
FC	Fixed combination
WHO	World Health Organization