



**Bahagian Regulatori Farmasi Negara (NPRA)**  
**National Pharmaceutical Regulatory Agency (NPRA)**  
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## CENTRE OF PRODUCT AND COSMETIC EVALUATION

### APPLICATION FOR BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS) BIOWAIVER

Adopted from the:

“WHO/PQT: medicines; Application for a Biowaiver: Additional Strength (Application from 01 May 2010)”.

With some adaptation for MALAYSIA application.

#### General Instructions

- Please review all the instructions thoroughly and carefully prior to completing the current application form.
- This form is not to be used other than Biopharmaceutics Classification System (BCS) biowaiver of the submitted product(s).
- Please submit this application form together with the relevant documents in QUEST 3+ system under section P9 for product screening and evaluation.
- Please provide / fill in as much detailed, accurate and final information as possible.
- All the appended documents should be clearly identifiable by their location and tagging of the file names. Kindly refer to the ‘Guide on how to upload the BE study report and other relevant documents in QUEST 3+ system under section P9’.
- Kindly check that you have signed on the checklist, provided all requested information and enclosed all requested documents.
- Should you have any questions regarding this procedure or the checklist, kindly contact Generic Medicine Section (Bioequivalence Evaluation) via e-mail [be\\_sug@npra.gov.my](mailto:be_sug@npra.gov.my)

\*Reminder:

- i. Please be informed that all data submitted to support the registration application for this product will be subjected to further evaluation
- ii. Please refrain from changing/removing all submitted data unless requested by NPRA or the data has been updated as per latest registration requirements.
- iii. Kindly be reminded that decision whether the dossier is allowed for registration will be subjected to full evaluation and the final decision by the Drug Control Authority (DCA).
- iv. Kindly also note that satisfactory and complete documentation must be submitted within 180 working days, after first evaluation remark is received to avoid rejection.

I, the undersigned, certify, that the information provided in this application and the attached documents is correct and true.

Signed on behalf of:

\_\_\_\_\_ (Product registration holder’s name and address)

\_\_\_\_\_ (Date)

\_\_\_\_\_ (Name & title)

## Administrative data

(Please fill in the following information)

1.	Product name	
2.	Active ingredient	
3.	Dosage form and strength	
4.	Name and full address of the drug substance manufacturing site	
5.	Name and full address of the finished product manufacturing site	
6.	Name and address of laboratory or contract research organization(s) where the biowaiver dissolution studies were conducted	

### 1. Justification For BCS Biowaiver

#### 1.1 Active Pharmaceutical Ingredient (API)

Please confirm that the proposed product contains the same active substance (e.g. salt, ester, ether, isomer) as the comparator (Malaysian comparator product).

#### 1.2 Therapeutic index of the API

Please enclose a copy of the comparator product labeling and literature references employed to support that the drug does not exhibit a narrow therapeutic index for all authorized indications.

### **1.3 Pharmacokinetic properties of the API**

Please enclose a copy of the literature references employed to document the pharmacokinetic (PK) properties (PK linearity or reasons for non-linearity).

### **1.4 Dosage form**

Please confirm that:

- the dosage form is an immediate release product for systemic action
- the posology is limited to oral administration
- the administration without water is not included in the proposed posology

## **2. Solubility**

### **2.1 Maximum therapeutic dose of the API**

Please enclose a copy of the labelling of the comparator product to document the maximum single dose that can be administered in a single administration

## 2.2 Stability of the drug in the physiological pH range

- i. Please discuss stability of the API in the pH range from 1.2 to 6.8 and in the gastrointestinal tract.
- ii. Please discuss the ability of the analytical method to distinguish the API from its degradation products

## 2.3 Polymorphism

The existence of polymorphism for the API should be reported here. If the API exists in multiple polymorphic forms, it should be demonstrated that the same polymorphic form is employed in the test and comparator products. If differences exist, high solubility must be demonstrated for both polymorphs.

## 2.4 Solubility study

- i. Please describe method and conditions (e.g. shake flask method at  $37\pm 1^\circ\text{C}$ )
- ii. Please attach the solubility study protocol, analytical method validation and solubility report. Kindly indicate location in the documentation.

## 2.5 Solubility study date

Dates of study protocol, study conductance and study report

Study information	Date
Study protocol	
Study conductance	
Study report	

## 2.6 Result

- i. Please indicate location of the solubility study report.
- ii. Please fill in the following table for the necessary pH values. Add as many rows as necessary to create a solubility – pH profile

Theoretical pH	Observed pH	Adjusted pH	Individual concentration at saturation (Cs) values	Cs (mean and CV (%))	Amount that can be dissolved in 250 ml
pH 1.2	Experiment 1	Experiment 1	Experiment 1		
	Experiment 2	Experiment 2	Experiment 2		
	Experiment 3	Experiment 3	Experiment 3		
Intermediate pHs	Experiment 1	Experiment 1	Experiment 1		
	Experiment 2	Experiment 2	Experiment 2		
	Experiment 3	Experiment 3	Experiment 3		
pH 4.5	Experiment 1	Experiment 1	Experiment 1		
	Experiment 2	Experiment 2	Experiment 2		
	Experiment 3	Experiment 3	Experiment 3		
Intermediate pHs	Experiment 1	Experiment 1	Experiment 1		
	Experiment 2	Experiment 2	Experiment 2		
	Experiment 3	Experiment 3	Experiment 3		
pH 6.8	Experiment 1	Experiment 1	Experiment 1		
	Experiment 2	Experiment 2	Experiment 2		
	Experiment 3	Experiment 3	Experiment 3		
Other intermediate pH	Experiment 1	Experiment 1	Experiment 1		

values (e.g. pKa, pKa-1, pKa+1)	Experiment 2	Experiment 2	Experiment 2		
	Experiment 3	Experiment 3	Experiment 3		

### 2.7 Plot the solubility – pH profile

Attach the plot of the pH-solubility profile based on the above data

## 3. Absorption / Permeability

### 3.1 Human mass balance studies

- i. Summarize results of all studies found in the literature.
- ii. Please enclose a copy of the references describing human mass balance studies of the API.

### 3.2 Human absolute bioavailability studies

- i. Summarize results of all studies found in the literature.
- ii. Please enclose a copy of the references describing human absolute bioavailability of the API.







## **6.0 Comparison of test and comparator formulations**

### **6.1 Identify any excipients present in either product that are known to impact in vivo absorption processes**

A literature-based summary of the mechanism by which these effects are known to occur should be included and relevant full discussion enclosed, if applicable.

### **6.2 Identify all qualitative (and quantitative, if available) differences between the compositions of the test and comparator products**

The data obtained and methods used for the determination of the quantitative composition of the comparator product as required by the guidance documents should be summarized here for assessment.

### **6.3 Provide a detailed comment on the impact of any differences between the compositions of the test and comparator products with respect to drug release and *in vivo* absorption**

**7.0 Comparative dissolution studies between i) test and comparator product** Comparative dissolution studies should be conducted in pH 1.2, 4.5 and 6.8 media. The proposed dissolution medium for release of the products should also be provided if it differs from the aforementioned pH media.

i. Please attach the dissolution study protocol, analytical validation method and dissolution study report.

**7.1 Dates of study protocol, study conductance and study report**

Study information	Date
Study protocol	
Study conductance	
Study report	

**7.2 Summary of the dissolution conditions and method**

Temperature of dissolution medium	
Volume of dissolution medium	
Type of apparatus	
Agitation	
Detection method	
Number of units employed	
Sampling collection (method of collection, sampling times, sample handling, filtration and storage)	

**7.3 Summarize the results of the dissolution study**

Please provide a tabulated summary of individual and mean results with %CV, graphic summary and any calculations used to determine the similarity of profiles.

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**7.4 Summarize conclusion taken from dissolution study**

Please provide a summary statement of the studies performed.

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### **7.5 Dissolution specification**

Please provide proposed dissolution specifications and discuss them in relation to the results obtained in the BCS biowaiver.

### **8.0 Supporting document**

Please attach relevant document (e.g regulatory references and scientific papers) to support the BCS based biowaiver for this active ingredient.

### **9.0 COMMENTS FROM REVIEW – NPRA USE ONLY**

### **10.0 CONCLUSIONS AND RECOMMENDATIONS – NPRA USE ONLY**