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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

*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 Solubility study

i. Please describe method and conditions (e.g. shake flask method at 37±1ºC)
ii. Please attach the solubility study protocol, analytical method validation and solubility report. Kindly indicate location in the documentation.

2.4 Solubility study date

Dates of study protocol, study conductance and study report

Study information	Date
Study protocol	
Study conductance	
Study report	

2.5 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 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Intermediate pHs	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
pH 4.5	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Intermediate pHs	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
pH 6.8	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		
Other intermediate pH values (e.g. pKa, pKa-1, pKa+1)	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3	Experiment 1 Experiment 2 Experiment 3		

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.

3.3 Supportive studies

i. Summarize results of all studies found in the literature regarding in vivo or in situ intestinal perfusion animal models or in vitro permeation across a monolayer of cultured epithelial cells (e.g. Caco-2) with a positive and negative control.
ii. Please enclose a copy of the references.

4. Test product

4.1 Information of the biowaiver batch

i. Attach the certificate of analysis (COA) of biowaiver batch.

ii. Attach the formulation page and manufacturing process summary in the batch manufacturing records (BMRs) of biowaiver batch.

iii. Biowaiver batches should be at least of pilot scale

a. (≥100 000s @ 1/10 X full production scale, whichever greater. In case of production batch smaller than
100 000s, a full production batch will be required)

Batch number for test product batch	
Batch size	
Date of manufacture	
Expiry date	
Potency (Assayed content)	

Unit dose composition and batch manufacturing formula		
Ingredients	Unit Dose (mg)	Test Product Batch (kg)

5. Comparator product information

5.1 Comparator product (should be the same as Malaysia comparator product)

i. Please indicate location in the documentation of the following documents that should be enclosed:

ii. A copy of the prescribing information sheet (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate.

iii. A copy of the outer packaging of the comparator product. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.

iv. This information should be cross-referenced to the location of the Certificate of Analysis in this biowaiver submission.

5.2 Name and manufacturer of the comparator product and official address

5.3 Qualitative (and quantitative, if available) information on the composition of the comparator product

Please tabulate the composition of the comparator product based on available information and state the source of this information.

Batch number of comparator product	
Expiry date	
Potency (Assayed content)	
Source of information	

Composition of comparator product used in dissolution studies	
Ingredients	Unit Dose (mg)

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 test and comparator product

i. 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.
ii. 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.

7.4 Summarize conclusion taken from dissolution study

Please provide a summary statement of the studies performed.

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 supporting documents (for example assessment report from stringent regulatory authorities, SRAs) to show that this product has been registered via BCS biowaiver route and its active ingredient has been granted BCS class I.

9.0 COMMENTS FROM REVIEW– NPRA USE ONLY

10.0 CONCLUSIONS AND RECOMMENDATIONS – NPRA USE ONLY