Application for a Biowaiver:

Biopharmaceutics Classification System (BCS)

This application form is designed to facilitate information exchange between the applicant and the WHO Prequalification Team: medicines (PQT/MED) if the applicant seeks to waive bioequivalence studies based on the Biopharmaceutics Classification System (BCS). For further information, please see the ICH M9 guideline and WHO PQT/MED annotations document. This form is not to be used if a biowaiver is requested for additional strength(s) of a submitted product(s), in which case a separate *Biowaiver Additional Strength: Application Form* should be used.

PQT/MED has identified some active pharmaceutical ingredients (APIs) that are eligible for a BCS-based biowaiver application. For those APIs, it may not be necessary to provide absorption/permeability data to support the BCS classification of the respective API(s) in the application.

General instructions:

* Please review all the instructions thoroughly and carefully prior to completing the current Application Form.
* Provide as much detailed, accurate, and final information as possible.
* Please enclose the required documentation in full and state in the relevant sections of the application form the exact location (annex number) of the appended documents. For example, in section 2.5 indicate in which annex the Certificate of Analysis can be found.
* Please provide the document as an MS Word file.
* Please do not paste snapshots into the document.
* The appended electronic documents should be clearly identifiable by their file names, which should include the product name and annex number.
* Before submitting the completed application form, kindly check that you have provided all requested information and enclosed all requested documents.
* Should you have any questions regarding this procedure, please contact the PQT/MED via e-mail prequalassessment@who.int.

**Although the present application is for a BCS-based biowaiver, Module 2.7 of the dossier should include the following information if available:**

1. A list of all bioequivalence studies, including pilot studies, conducted with the proposed product *i.e*., same formulation and manufacturing process as that submitted for prequalification, regardless of the comparator (reference) product employed and regardless of the study outcome. Complete study synopses should be provided for all listed studies, in accordance with Annex I of ICH Guideline E3: *Structure and Content of Clinical Study Reports*.
2. A list of all bioequivalence or comparative bioavailability studies, including pilot studies, conducted during pharmaceutical development (development of formulation and/or manufacturing processes) of the product, regardless of the comparator (reference) product employed and regardless of the study outcome. Complete study synopses should be provided for all listed studies, in accordance with Annex I of ICH Guideline E3: *Structure and Content of Clinical Study Reports*.

Full study reports for all listed studies should be available upon request.Administrative data

**1. International Nonproprietary Name of active ingredient(s)**

*<< Enter information here >>*

**2. Dosage form and strength**

*<<Enter information here >>*

**3. Product WHO Reference number** *(if product dossier has been accepted for PQTm assessment)*

*<<Enter information here >>*

**4. Name of applicant and official address**

*<<Enter information here >>*

**5. Name of manufacturer of finished product and official address**

*<<Enter information here >>*

**6. Name and address of the laboratory or contract research organization(s) where the BCS-based biowaiver solubility and dissolution studies were conducted**

*<<Enter information here >>*

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

Signed on behalf of

<***company***>

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

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (Name and title)

# Justification for a BCS Biowaiver

## Active pharmaceutical ingredient (API)

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

*<<Enter information here >>*

## Therapeutic index of the API

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

*<< Enter information here >>*

## Pharmacokinetic properties of the API

Describe the pharmacokinetic properties (PK) of the API, particularly with respect to linearity. Enclose a copy of the literature references employed to document the PK properties (PK linearity or reasons for non-linearity).

*<< Enter information here >>*

## Dosage form

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

*<< Enter information here >>*

1.5 COMMENTS FROM REVIEW OF SECTION 1 – *WHO USE ONLY*

# Solubility

## Maximum therapeutic dose of the API

Enclose a copy of the labelling of the comparator product to document the maximum single dose that can be administered in a single administration (e.g. two tablets together).

*<< Enter information here >>*

## Stability of the drug in the physiological pH range

Discuss stability of the API in the pH range from 1.2 to 6.8 and in the gastrointestinal tract. Summarize studies conducted to demonstrate adequate stability and identify location of study report(s) in the dossier.

Discuss the ability of the analytical method to distinguish the API from its degradation products.

*<< Enter information here >>*

## 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.

*<< Enter information here >>*

## Method of solubility determination

Describe method and conditions (e.g., shake flask method at 37±1ºC)

Indicate location of the solubility study protocol.

*<< Enter information here >>*

## Solubility study dates

Indicate dates of study protocol, study conduct, and study report

*<< Enter information here >>*

## Analytical method validation

Summarize the results and indicate location in the documentation.

*<< Enter information here >>*

## Results

Indicate location of the solubility study report.

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 |  |  |

## Plot the solubility – pH profile

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

*<< Enter information here >>*

2.9 COMMENTS FROM REVIEW OF SECTION 2 – *WHO USE ONLY*

# Absorption / Permeability (Completion of this section is not necessary if the absorption/permeability classification of the API(s) is reported in appendix 1 of the PQT/MED document *PQT/MED-specific annotations for the ICH M9 Guideline for Biopharmaceutics Classification System (BCS)-based Biowaiver Applications*.)

## Human mass balance studies

Summarize results of studies conducted and indicate location of full study reports in the dossier.

Summarize results of all studies found in the literature.

Enclose a copy of the references describing human mass balance studies of the API.

*<< Enter information here >>*

## Human absolute bioavailability studies

Summarize results of studies conducted and indicate location of full study reports in the dossier.

Summarize results of all studies found in the literature.

Enclose a copy of the references describing human absolute bioavailability of the API.

*<< Enter information here >>*

## In vitro permeability methods (Caco-2 cell studies)

Summarize results of studies conducted and indicate location of full study reports in the dossier.

Summarize results of all studies found in the literature regarding in vitro permeation across a monolayer of cultured epithelial cells (e.g., Caco-2) with a positive and negative control.

Enclose a copy of the references.

*<< Enter information here >>*

## Supportive studies

Summarize results of all studies found in the literature regarding in vivo or in situ intestinal perfusion animal models.

Enclose a copy of the references.

*<< Enter information here >>*

3.5 COMMENTS FROM REVIEW OF SECTION 3 – *WHO USE ONLY*

# Test product

## Tabulation of the composition of the formulation(s) proposed for marketing and those used for comparative dissolution studies

* State the location of the master formulae in the quality part of the submission.
* Tabulate the composition of each product strength using the table below.
* For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of a capsule. A copy of the table should be filled in for the film coating/hard capsule, if any.
* Biowaiver batches should be at least of pilot scale (10% of production scale or 100,000 capsules or tablets whichever is greater) and manufacturing method should be the same as for production scale.

Please note: If the formulation proposed for marketing and those used for comparative dissolution studies are not identical, copies of this table should be filled in for each formulation with clear identification in which study the respective formulation was used

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Composition of the batches used for comparative dissolution studies | | | | |
| Batch number |  | | | |
| Batch size (number of unit doses) |  | | | |
| Date of manufacture |  | | | |
| Comments, if any | | | | |
| Comparison of unit dose compositions and of clinical FPP batches  (duplicate this table for each strength, if compositions are different) | | | | |
| Ingredients (Quality standard) | Unit dose (mg) | Unit dose (%) | Biobatch (kg) | Biobatch (%) |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| Equivalence of the compositions or justified differences |  | | | |

## Potency (measured content) of test product as a percentage of label claim as per validated assay method

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

*<< Enter information here >>*

4.3 COMMENTS FROM REVIEW OF SECTION 4 – *WHO USE ONLY*

# Comparator product

## Comparator product

Indicate location in the documentation of the following documents that should be enclosed:

A copy of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate.

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

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

*<< Enter information here >>*

## Name and manufacturer of the comparator product and official address

*<< Enter information here >>*

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

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

|  |  |  |
| --- | --- | --- |
| Composition of the comparator product used in dissolution studies | | |
| Batch number |  | |
| Expiry date |  | |
| Comments, if any | | |
| Ingredients | Unit dose (mg) | Unit dose (%) |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

## Identify the source of the comparator product (where it was purchased), the method of shipment, and storage conditions of the comparator product from the time of purchase until completion of the comparative dissolution studies

Attach relevant copies of the following documents proving the stated conditions:

A copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.

Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.

*<< Enter information here >>*

## Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory under the same conditions as the test product.

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

*<< Enter information here >>*

5.6 COMMENTS FROM REVIEW OF SECTION 5 – *WHO USE ONLY*

# Comparison of test and comparator formulations

## 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.

*<< Enter information here >>*

## 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.

*<< Enter information here >>*

## 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

*<< Enter information here >>*

6.4 COMMENTS FROM REVIEW OF SECTION 6 – *WHO USE ONLY*

# Comparative in vitro dissolution

## Comparative in vitro dissolution

Information regarding the comparative dissolution studies should be included below to provide adequate evidence supporting the biowaiver request. Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.

**Provide copies of the following documents as appendices to the biowaiver application form:**

* the dissolution study protocol(s) in this biowaiver application
* the dissolution study report(s) in this biowaiver application
* the analytical method validation report in this biowaiver application

**These appendices should be provided with the MS Word copy of this application form in Module 1.4 or 1.5 of the application.**

*<< Confirm that the three appendices are present in the CTD dossier >>*

## Dissolution study dates

Please indicate dates of study protocol, study conduct, and study report

*<< Enter information here >>*

## Summary of the dissolution conditions and method described in the study report(s)

Summary provided below should include the composition, temperature, volume, and method of de-aeration of the dissolution media, the type of apparatus employed, the agitation speed(s) employed, the number of units employed, the method of sample collection including sampling times, method of filtration, sample handling, and storage. Deviations from the sampling protocol should also be reported.

### Dissolution media: Composition, temperature, volume, and method of de-aeration

*<< Enter information here >>*

### Type of apparatus and agitation speed(s) employed

*<< Enter information here >>*

### Number of units employed

*<< Enter information here >>*

### Sample collection: method of collection, sampling times, sample handling, method and timing of filtration, and storage

*<< Enter information here >>*

### Deviations from sampling protocol

*<< Enter information here >>*

## Summarize the results of the dissolution study(s)

Provide a tabulated summary of individual and mean results with %CV, graphic summary, and any calculations used to determine the similarity of profiles **for each set of experimental conditions**.

*<< Enter information here >>*

## Summarize conclusions taken from dissolution study(s)

Provide a summary statement of the studies performed.

*<< Enter information here >>*

## Dissolution specifications

Provide proposed dissolution specifications and discuss them in relation to the results obtained in the BCS biowaiver

*<< Enter information here >>*

7.7 COMMENTS FROM REVIEW OF SECTION 7 – *WHO USE ONLY*

# Quality assurance

## Internal quality assurance methods

State location in this biowaiver application where internal quality assurance methods, including qualification of the dissolution apparatus(es), and results are described for each of the study sites.

*<< Enter information here >>*

## Auditing and inspections

Provide a list of all auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in this biowaiver application of the respective reports for each of the study sites, e.g. analytical laboratory, laboratory where dissolution studies were performed.

*<< Enter information here >>*

8.3 COMMENTS FROM REVIEW OF SECTION 8 – *WHO USE ONLY*

# ADDITIONAL SUPPORTING DATA

## 9.1 List of all bioequivalence studies conducted with proposed product and studies conducted during product development

*(Module 2.7 of the dossier should include the following information:*

1. *A list of all bioequivalence studies, including pilot studies, conducted with the proposed product, i.e. same formulation and manufacturing process as that submitted for prequalification, regardless of the comparator (reference) product employed and regardless of the study outcome. Complete study synopses should be provided for all listed studies, in accordance with Annex I of ICH Guideline E3: Structure and Content of Clinical Study Reports.*
2. *A list of all bioequivalence or comparative bioavailability studies, including pilot studies, conducted during pharmaceutical development (development of formulation and/or manufacturing processes) of the product, regardless of the comparator (reference) product employed and regardless of the study outcome. Complete study synopses should be provided for all listed studies, in accordance with Annex I of ICH Guideline E3: Structure and Content of Clinical Study Reports.*

*Full study reports for all listed studies should be available upon request.*

***Confirm below that the list of studies is provided as required. If no studies have been conducted, please so indicate here.****)*

*<< Enter information here >>*

CONCLUSIONS AND RECOMMENDATIONS – *WHO USE ONLY*