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 WHO 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 Non-proprietary 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 PQT/MED 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, permeability (if applicable), 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, including enantiomeric purity, or identify differences (e.g., salt form).

*<< Enter information her >>*

## 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 and indicate the location in the submitted dossier of the appended documents >>*

## Pharmacokinetic properties of the API

Describe the pharmacokinetic properties (PK) of the API, particularly with respect to the active moiety (parent drug and/or metabolite), the compound that is absorbed (active drug/prodrug/active metabolite), and the extent of absorption. Enclose a copy of the literature references employed to document the PK properties.

*<< Enter description here and indicate the location in the submitted dossier of the appended document >>*

## Dosage form

Confirm that:

* the dosage form (solid or suspension) is an immediate release product for systemic action.
* the posology is limited to oral administration (with intestinal and no buccal/sublingual absorption).
* the administration without water is not included in the proposed posology of the test product or the authorised posology of the comparator.

*<< 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 therapeutic dose that can be administered in a single administration (e.g., two tablets together).

*<< Enter information here and indicate the location in the submitted dossier of the appended labelling >>*

## Polymorphism

The same polymorphic form should be employed in the test and comparator products. If differences exist, high solubility must be demonstrated for both polymorphs.

Indicate location of the report demonstrating the polymorphic forms of the API of test and comparator products.

*<< Enter information here and indicate location in the submitted dossier of the appended documents >>*

## Method of solubility determination

Describe method and conditions (e.g., shake flask method at 37±1ºC) and justify the selected alternative if different from the shake flask method. In the case that equilibrium solubility experiments are not conducted, justify why they are not feasible (e.g., the high amount of API required for the experiment, or the pH of the medium cannot be maintained with pharmacopoeial buffers).

Indicate location of the solubility study protocol.

*<< Enter information here and indicate the location of the solubility study protocol >>*

## Stability of the drug during the solubility experiments

Discuss stability of the API in the pH range from 1.2 to 6.8 at 37 (±1) ºC during the solubility experiments and the ability of the analytical method to distinguish the API from its degradation products. Summarize studies conducted to demonstrate adequate stability.

Indicate location of the stability study report and protocol in the dossier.

*<< Enter information here and indicate the location in the submitted dossier of the appended documents >>*

Confirm that the precipitate in the equilibrium solubility experiments is the same compound that was added as starting material in the solubility experiment. Summarize studies conducted to demonstrate that the compound and polymorph of the starting material and the final precipitate are the same. Indicate location of the corresponding report and protocol in the dossier.

*<< Enter information here and indicate the location in the submitted dossier of the appended documents >>*

## Analytical method validation

Summarize the results and indicate location in the documentation.

*<< Enter information here and indicate the location in the submitted dossier of the appended documents >>*

## Solubility study dates

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

*<< Enter information here >>*

## Results

Indicate location of the solubility study report.

*<< Indicate here the location in the submission dossier of the appended documents >>*

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 | Mean conc. (CV(%) | Amount that can be dissolved in 250 ml |
| pH 1.2 | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Mean Cs (CV%) | A mL |
| Intermediate pHs | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Mean Cs (CV%) | B mL |
| pH 4.5 | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Mean Cs (CV%) | C mL |
| Intermediate pHs | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Mean Cs (CV%) | D mL |
| pH 6.8 | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Mean Cs (CV%) | E mL |
| Other intermediate pH values (e.g., pKa, pKa-1, pKa+1) | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Experiment 1Experiment 2Experiment 3 | Mean Cs (CV%) | F mL |

## Plot the solubility – pH profile

Attach the plot of the solubility – pH profile based on the above data and identify the pH of minimum solubility. Discuss this profile based on the pKa(s) of the molecule.

*<< Enter the solubility – pH plot here, identify the pH of minimum solubility and discuss the solubility profile of the drug depending on the pKa(s)>>*

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 WHO Guideline for Biopharmaceutics Classification System (BCS)-based Biowaiver Applications*.)

## Human mass balance studies

Summarize results of human mass balance studies (conducted or found in the literature).

Indicate location of full study reports in the dossier or enclose a copy of the references describing human mass balance studies of the API.

*<< Enter information here and indicate location in the dossier of the appended documents >>*

## Human absolute bioavailability studies

Summarize results of human absolute bioavailability studies (conducted or found in the literature).

Indicate location of full study reports in the dossier or enclose a copy of the references describing human absolute bioavailability of the API.

*<< Enter information here and indicate location in the dossier of the appended documents >>*

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

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

*<< Enter information here and indicate location in the dossier of the appended documents >>*

## Supportive studies

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, and in vivo or in situ intestinal perfusion animal models.

Enclose a copy of the references as attachments to this application form in separate PDF files.

*<< Enter information here and indicate location in the dossier of the appended references >>*

## Stability of the drug in the physiological pH range

Discuss the stability of the API for 1 hour in gastric fluid and 3 hours in intestinal fluid at 37 (±1) ºC in those cases where the permeability is addressed with mass balance studies, unless ≥ 85% of the dose is recovered as an unchanged drug in urine, or by Caco-2 cells studies, and the ability of the analytical method to distinguish the API from its degradation products.

Summarize studies conducted to demonstrate adequate stability. Indicate location of the stability study report and protocol.

*<< Enter information here and indicate the location in the submitted dossier of the appended documents >>*

3.6 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.

*<< Indicate here the location of the master formulae in the module 3 >>*

* 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 and indicate the location in the dossier of the CoA>>*

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 authorised 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.

*<< Enter information here on the location in the dossier of the labelling and carton box >>*

## Name and Marketing Authorisation Holder of the comparator product and official address

*<< Enter information here >>*

## Qualitative (and quantitative, if available) information on the composition of the comparator product used for comparative dissolution studies

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 (%) |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

*<< Enter information here on the source of this information >>*

## 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 from the distributor to the site where dissolution studies were conducted and storage conditions of the comparator product from the time of purchase to the time of study initiation (i.e., shipment and storage in site where dissolution studies were conducted).

*<< Indicate the location in the submitted dossier of the appended documents >>*

## 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 the submitted dossier.

*<< Enter information here and indicate the location in the submitted dossier of the CoA of the comparator >>*

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

# Comparison of test and comparator formulations

## Identify the processes involved in the absorption of the API

A literature-based summary of the mechanism by which the drug is absorbed (e.g., transcellular or paracellular passive transport, active uptake or efflux transporters involved) should be included.

*<< Enter information here and indicate the location in the dossier of references appended >>*

## Identify qualitative (and quantitative, if available) differences between the excipient 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.

Indicate the total core weight or content of the proposed product (e.g. capsule or sachet) as percentage of the total core weight or content of the comparator.

*<< Enter information hereon the methods used for determination of quantitative composition of the comparator and total core weight of the test as percentage of the comparator >>*

|  |  |
| --- | --- |
| Composition of the core content of test and comparator products | Comparisons |
|  | TEST PRODUCT | COMPARATOR PRODUCT | Differences between amounts | Difference between % in each product |
| Ingredients  | Amount (mg) | Amount (%) | Amount (mg) | Amount (%) | % of the amount in comparator | Difference (%) |
| Filler A | a mg | X % | b mg | Y% | ⎮a - b⎮ / b \* 100 | ⎮X - Y⎮ |
| Filler B |  |  |  |  |  |  |
| Disintegrant |  |  |  |  |  |  |
| Binder |  |  |  |  |  |  |
| Lubricant |  |  |  |  |  |  |
| Glidant |  |  |  |  |  |  |
| Other excipients |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Total weight | T | 100% | R | 100% |  |  |

X = a/T\*100 and Y = b/R\*100

## Identify any excipients present in either product that may affect absorption because they 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 on the excipients that may affect absorption and indicate the location in the dossier of references >>*

## Identify qualitative (and quantitative, if available) differences between test and comparator in excipients that may affect absorption

The quantitative differences in each of these excipients (e.g., mannitol, sorbitol, surfactants, PEG 400) should be expressed with respect to the amount of the same excipient in the comparator product. In addition, the cumulative difference for excipients that may affect absorption should be reported if more than one of these excipients are included in the test and comparator.

*<< Enter information here in line with the information on the table above >>*

## Identify qualitative (and quantitative, if available) differences between test and comparator in excipients that are not known to affect absorption

The quantitative differences in each of these excipients (e.g., fillers, disintegrants, binders, lubricants, glidant, etc.) should be expressed with respect to the percentage of these excipients in the tablet core or capsule content.

Each excipient should be classified according to its function in the dosage form (i.e., filler, disintegrant, binder, lubricant, glidant, etc.).

*<< Enter information here in line with the information in the table above >>*

## Provide a detailed justification on the impact of any differences between the compositions of the test and comparator products with respect to solubility, gastrointestinal motility, transit time and intestinal permeability, including transporter mechanisms

Assess mechanistically the impact of the qualitative and quantitative differences in excipients on the API absorption by considering the amount of excipient used, the mechanism by which the excipient may affect absorption and the absorption properties (rate, extent and mechanism of absorption) of the API.

*<< Enter information here. For example, if it is known that the API has high permeability due to active uptake, excipients that can inhibit uptake transporters are likely to be of concern. For BCS class I APIs that exhibit slow absorption, the potential for a given excipient to increase absorption rate should also be considered. >>*

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

# Comparative in vitro dissolution

For products with more than one strength, the BCS approach should be applied for each strength. It is required that test and comparator product dissolution profiles are compared at each strength.

## 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 and indicate their location>>*

## Dissolution study dates

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

Dissolution profiles for the test and comparator products should be generated in the same laboratory by the same staff at the same time using the same equipment. Compilation of historical data is not acceptable.

*<< 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: Compositions, temperature, volume, and method of de-aeration

Pharmacopeial buffer at pH 1.2, pH 4.5, and pH 6.8. as well as buffer at the pH of minimum solubility (if different) should be used.

*<< Enter information here >>*

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

Paddle apparatus at 50 rpm or basket apparatus at 100 rpm. When high variability or coning is observed in the paddle apparatus at 50 rpm for both comparator and test products, the use of the basket apparatus at 100 rpm is recommended. Alternative methods (such as the use of sinkers or other appropriately justified approaches) may be considered to overcome issues such as coning, if scientifically substantiated

*<< Enter information here and justifications in case of deviations from the usual agitations speed >>*

### Number of units employed

At least 12 units of comparator and test product should be used for each dissolution profile determination

*<< Enter information here >>*

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

Filters should be employed in line, at the end of the sampling probe, or both during sample collection

*<< 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 SD and %CV, graphic summary, and any calculations used to determine the similarity of profiles **for each set of experimental conditions**, i.e., based on f2 similarity factor comparison where dissolution is not complete in 15 min for both test and comparator.

When the variability is too high, the bootstrap 90% confidence interval of expected f2 should be employed.

*<< 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 on the location in the submission of the appended documents >>*

## 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 the submitted dossier of the respective reports for each of the study sites, e.g., analytical laboratory, laboratory where dissolution studies were performed.

*<< Enter information here on the location in the submission of the appended documents >>*

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 on the location in the submitted dossier of the appended documents or confirm if no in vivo study has been conducted with the applied product or during its pharmaceutical development regardless of the study outcome or comparator >>*

CONCLUSIONS AND RECOMMENDATIONS – *WHO USE ONLY*