



EVALUATIONS AND REGISTRATION DIVISION

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS) BASED BIOWAIVER INFORMATION FORM

This form is designed to facilitate information exchange between the Applicant and the MCAZ if the Applicant seeks a waiver from bioequivalence studies, based on the Biopharmaceutics Classification System (BCS).

The list of APIs eligible for a BCS-based biowaiver is in Appendix I of the ***“Guideline on waiver of in vivo bioequivalence requirements for immediate-release solid oral dosage forms”***. It is, therefore, not necessary to provide data to support the BCS classification of the respective API(s) in the application i.e. data supporting the drug substance solubility or permeability class

General Instructions:

- 1.1 Please review all the instructions thoroughly and carefully prior to completing the Form.
- 2.1 Provide as much detailed and accurate information as possible.
- 3.1 Please enter the data and information directly following the shaded areas.
- 4.1 Please enclose the required documentation in full and state in the relevant sections of the 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.
- 5.1 The appended electronic documents should be clearly identified with their file names, which should include the product name and Annex number.
- 6.1 Before submitting the completed Form, ensure that you have provided all requested information and enclosed all requested documents.

The signed paper version of this Biowaiver Information Form together with Annexes (and their electronic copies in Microsoft Word) should be included to the Module 1 of the CTD part of the submitted dossier.

Administrative data

1. International Non-proprietary Name of active ingredient(s)
2. Dosage form and strength
3. Application number
4. Name of applicant and official address
5. Name and address of manufacturer (s) of finished product
6. Name and address of the laboratory or Contract Research Organisation(s) where the BCS-based biowaiver dissolution studies were conducted.

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

Signed on behalf of

_____ Name and title

----- Signature

----- Date

1.0 Justification for a 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 reference.

1.2. Therapeutic Index of the API

Please enclose a copy of the reference product labelling and literature references employed to support that the drug does not exhibit a narrow therapeutic index for all authorised indications

1.3. Pharmacokinetic properties of the API

Please enclose a copy of the literature references employed to document the 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

1.5 COMMENTS FROM REVIEW OF SECTION 1 – MCAZ USE ONLY

2.0 Solubility

(Completion of this section is not necessary if the API(s) are included on the list of biowaiver-eligible APIs in the “*Guideline on waiver of in vivo bioequivalence requirements for immediate-release solid oral dosage forms*”.)

2.1. Maximum therapeutic dose of the API

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

<< Please enter information here >>

2.2. Stability of the drug in the physiological pH range

Please discuss stability of the API in the pH range from 1.2 to 6.8 and in the gastrointestinal tract.

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

<< Please enter information here >>

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.

<< Please enter information here >>

2.4. Method of solubility determination

Describe the method and conditions (e.g., shake flask at 37 +/- 1°C

Indicate location of the solubility study protocol

<< Please enter information here >>

2.5. Solubility study dates

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

<< Please enter information here >>

2.6. Analytical method validation

Summarize the results and indicate location in the documentation.

<< Please enter information here >>

2.7. Results

Please indicate location of the solubility study report.

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	Experiment 1	Experiment 1	Experiment 1 Experiment 2		

pH values (e.g. pKa, pKa-1, pKa+1)	Experiment 2 Experiment 3	Experiment 2 Experiment 3	Experiment 3		
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2.8. Plot the Solubility – pH profile

Please attach the plot of the pH-solubility profile based on the above data

<< Please enter information here >>

2.9 COMMENTS FROM REVIEW OF SECTION 2 – MCAZ USE ONLY

3.0 Absorption / Permeability

(Completion of this section is not necessary if the API(s) are included on the list of biowaiver-eligible APIs in the “Guideline on waiver of in vivo bioequivalence requirements for immediate-release solid oral dosage forms”.

The API, Amlodipine, is included on the list of biowaiver-eligible APIs in the MCAZ guideline on BCS biowaiver and hence this section has not been completed.

3.1. Human mass balance studies

Summarise results of all studies found in the literature.

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

<< Please enter information here >>

3.2. Human absolute bioavailability studies

Summarise results of all studies found in the literature.

Please enclose a copy of the references describing human absolute bioavailability of the API.

<< Please enter information here >>

3.3. Supportive studies

Summarise 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. Please enclose a copy of the references.

<< Please enter information here >>

3.4 COMMENTS FROM REVIEW OF SECTION 3 – MCAZ USE ONLY

4.0 Test product

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

- Please 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 (%)
Amlodipine Besilate (BP)				
Dibasic Calcium Phosphate (BP)				
Sodium starch glycolate (BP)				
Colloidal Silicone Dioxide (BP)				
Microcrystalline Cellulose (BP)				

Magnesium stearate (BP)				
Equivalence of the compositions or justified differences				

4.2 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 (CoA) in this biowaiver submission.

4.3 COMMENTS FROM REVIEW OF SECTION 4 – MCAZ USE ONLY

5.0 Comparator (Reference) product

5.1. Comparator (Reference) product

Please 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 reference 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 (CoA) in this biowaiver submission.

5.2. Name and manufacturer of the comparator (reference) product and official address

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

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

Composition of the reference product used in dissolution studies	
Batch number	
Expiry date	
Comments, if any	

Ingredients	Unit dose (mg)	Unit dose (%)
Calcium hydrogen phosphate anhydrous		
Magnesium stearate		
Microcrystalline cellulose		
Sodium starch glycolate		

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

Please attach relevant copies of the following documents proving the stated conditions:

A copy of the invoice from the distributor or company from which the reference 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 reference product from the time of purchase to the time of study initiation.

5.5. Potency (measured content) of the reference 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 (CoA) in this biowaiver submission.

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5.6 COMMENTS FROM REVIEW OF SECTION 5 – MCAZ USE ONLY

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6.0 Comparison of test and reference 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 reference products

The data obtained and methods used for the determination of the quantitative composition of the reference 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 reference products with respect to drug release and *in vivo* absorption

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

7.0 Comparative in vitro dissolution

7.1. Comparative in vitro dissolution

Information regarding the comparative dissolution studies should be included below to provide adequate evidence supporting the biowaiver request.

Please state the location of:

- 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

7.2. Dissolution study dates

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

7.3. 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, sample handling, filtration and storage. Deviations from the sampling protocol should also be reported.

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

7.3.2. Type of apparatus and agitation speed(s) employed

7.3.3. Number of units employed

7.3.4. Sample collection: method of collection, sampling times, sample handling, filtration and storage

7.3.5. Deviations from sampling protocol

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7.4. Summarize the results of the dissolution study(s)

Please 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**.

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7.5. Summarize conclusions taken from dissolution study(s)

Please provide a summary statement of the studies performed.

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7.6. Dissolution specifications

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

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7.7 COMMENTS FROM REVIEW OF SECTION 7 – MCAZ USE ONLY

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8.0 Quality Assurance

8.1. Internal quality assurance methods

Please state location in this biowaiver application where internal quality assurance methods and results are described for each of the study sites.

8.2. 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.

8.3 COMMENTS FROM REVIEW OF SECTION 8 – MCAZ USE ONLY

8.4 CONCLUSIONS AND RECOMMENDATIONS – MCAZ USE ONLY

9.0 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 >>

9.2 CONCLUSIONS AND RECOMMENDATIONS – MCAZ USE ONLY