

**FOOD AND DRUGS AUTHORITY**

**APPLICATION FOR A BIOWAIVER:**

**ADDITIONAL STRENGTH**

**TO BE SUBMITTED AS ELECTRONIC COPIES**

CONFIDENTIAL

THE CHIEF EXECUTIVE OFFICER,

FOOD AND DRUGS AUTHORITY

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**Document No : FDA/DNC/AP-FOR-09**

**Date of First Adoption : 1st August 2017**

**Date of Issue : 8th January 2024**

**Version No : 01**

This application form is designed to facilitate information exchange between the applicant and FDA if a biowaiver is requested for additional strength(s) of the submitted product(s). This form is not to be used if the applicant seeks to waive bioequivalence studies, based on the Biopharmaceutics Classification System (BCS), in which case, a separate *Biowaiver Application Form: Biopharmaceutics Classification System (BCS)* should be used.

A request for a waiver from the requirement for conducting bioequivalence studies on additional strengths of the product submitted for assessment to FDA can be made based on the proportionality of the formulations of the series of strengths. If additional strengths are proposed and a biowaiver for these strengths is sought, the information requested from page 2 onwards of this document should be provided.

For further guidance, please consult:

* FDA guidelines for the registration of allopathic medicine and the bioequivalence guideline.

Employing the dissolution conditions described in the guidelines referenced above, in vitro dissolution data comparing the different strengths of the submitted product, one of which is the reference strength, must be provided.

The format of the dissolution study report(s) provided in support of this waiver request should be consistent with the format employed as a part of a BCS-based biowaiver application.

Final assessment of the proportionality of the proposed formulations and the acceptability of the comparative dissolution data will be made during evaluation of the Quality part of the dossier.

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 2.4, indicate in which annex the Certificate of Analysis can be found.
* The appended electronic documents should be clearly identifiable by their file names, which should include the product name and annex number.
* Please provide the application form as an MS Word file.
* Before submitting the completed application form, kindly check that you have provided all requested information and enclosed all requested documents.

Administrative data

|  |
| --- |
| **1. International Nonproprietary Name of active ingredient(s)***< Enter information here >* |

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| --- |
| **2. Dosage form and strengths***< Enter information here >* |

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| --- |
| **3. Product FDA application numbers** *(if available for any strengths of the product line, including the reference strength)**< Enter information here >* |

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| **4. Name of applicant and official address***< Enter information here >* |

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| **5. Name of manufacturer of finished product and official address***< Enter information here >* |

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| **6. Name and address of the laboratory or contract research organization(s) where the biowaiver dissolution studies were conducted** *(if applicable)**< 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)

# Test product

## Tabulation of the composition of formulation proposed for marketing

* State the location of the master formulae in the quality part of the submission.
* 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 or 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.

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| --- |
| Composition of the batch used for comparative dissolution studies |
| Batch number for biowaiver batch |  |
| Batch size (number of unit doses) |  |
| Date of manufacture |  |
| Expiry date |  |
| Comments, if any |
| **Unit dose compositions and FPP batch composition** |
| Ingredients (Quality standard) | Unit dose (mg) | Unit dose (%) | Biowaiverbatch (kg) | Biowaiverbatch (%) |
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## 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 >>*

## Pharmacokinetics

* State whether the drug displays linear or non-linear pharmacokinetics.
* Provide literature-based support for your response and append all references cited in the response and state the location of these references in the dossier.
* State concentrations at which non-linearity occurs and any known explanations. Particular attention should be paid to absorption and first-pass metabolism.

*<< Enter information here >>*

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| Comments from review of Section 1.1 - 1.3 – *FDA use only* |
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# Reference strength

## Reference strength

In this context, the reference strength is the strength of the FPP that was compared to the FDA Comparator product in an in vivo bioequivalence study.

## Tabulation of batch information for the reference strength

The biobatch of the reference strength (batch employed in the in vivo bioequivalence study) should be employed in the comparative dissolution studies.

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| Batch information for batch used for comparative dissolution studies |
| Batch number |  |
| Batch size (number of unit doses) |  |
| Date of manufacture |  |
| Expiry date |  |
| Comments, if any |
| **Unit dose compositions and FPP batch composition** |
| Ingredients (Quality standard) | Unit dose (mg) | Unit dose (%) | Batch (kg) | Batch (%) |
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## Batch confirmation

If the batch of reference strength employed in the comparative dissolution studies was not the biobatch of the reference strength (batch employed in the in vivo bioequivalence study), the following information should be provided:

* Batch number of biobatch.
* Justification for use of a batch other than the biobatch.
* Comparative dissolution data for batch employed vs. (historical data for) biobatch.
* As an appendix, executed batch manufacturing records (BMRs) for batch employed in dissolution studies.

*<< Enter information here >>*

## Potency (measured content) of reference 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 >>*

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| Comments from review of Section 2.1 – 2.4 – *FDA use only* |
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# Comparison of Test and Reference strengths

## Tabulation of batch information for the test and reference strengths

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 or hard capsule, if any.

|  |  |  |
| --- | --- | --- |
| Component and Quality Standard | Function | Strength (label claim) |
| XX mg | XX mg |
| Quantity per unit | % \* | Quantity per unit | %\* |
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| TOTAL |  |  |  |  |  |

\* Each ingredient expressed as a percentage of the total core.

## Confirmation of proportionality

The applicant should confirm that the test and reference strength formulations are directly proportional. Any deviations from direct proportionality should be identified and justified in detail.

*<< Enter information here >>*

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| Comments from review of Section 3.1 – 3.2 – *FDA use only* |
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# Comparative in vitro dissolution:Studies comparing different strengths of the test product

* **As per the FDA quality guideline: Quality Part, comparative dissolution studies should be conducted in pH 1.2, 4.5, and 6.8 media. If the proposed dissolution medium for release of the products differs from these media, comparative dissolution data in the proposed release medium should also be provided.**
* Summary information regarding the comparative dissolution studies should be included below to provide a complete summary of the data supporting the biowaiver request.

**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.**

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

## 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 sample storage. Deviations from the sampling protocol should also be reported.

### Dissolution study dates

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

*<< Enter information here >>*

### 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, timing and method of filtration, sample handling, 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 >>*

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| Comments from review of Section 4.1 – 4.3 – *FDA use only* |
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# Comparative *in vitro* dissolution: studies comparing each strength of the test product to equivalent strength of comparator product; only to be submitted in case in vitro dissolution data between different strengths of test product (see Section 4) are not similar

* This section is applicable in cases where, due to low solubility of the active pharmaceutical ingredient, similar comparative dissolution between differing strengths is difficult to achieve.
* Comparative dissolution data will be reviewed during the assessment of the Quality part of the dossier.
* **As per the FDA quality guideline *Finished Pharmaceutical Product (FPP): Quality Part*), comparative dissolution studies should be conducted in pH 1.2, 4.5, and 6.8 media. If the proposed dissolution medium for release of the products differs from these media, comparative dissolution data in the proposed release medium should also be provided.**
* Summary information regarding the comparative dissolution studies should be included below to provide a complete summary of the data supporting the biowaiver request.

## Purchase, shipment and storage of the comparator product

As per the documentation requirements for comparator products, attach relevant copies of documents (e.g. receipts) proving the stated conditions.

*<< 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 >>*

## State the location of:

* the dissolution study protocol(s) in the dossier
* the dissolution study report(s) in the dossier
* the analytical method validation report in the dossier.

*<< 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, sample handling, and sample 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, timing and method of filtration, sample handling and storage

*<< Enter information here >>*

### Deviations from sampling protocol

*<< Enter information here >>*

## 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**.

*<< Enter information here >>*

## Summarize conclusions taken from dissolution study(s)

Please provide a summary statement of the studies performed.

*<< Enter information here >>*

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| Comments from review of Section 5.1 – 5.6 – FDA use only |
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| CONCLUSIONS AND RECOMMENDATIONS – *FDA use only* |
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