Variation to a Prequalified Finished Pharmaceutical Product (FPP)

Please complete each section of this application form electronically as a Word document and as a scanned signed PDF file. Submit in electronic format; no hard copies are required. When completing the template, the examples should be deleted.

# Application details

## Variation type: (tick all applicable options)

|  |  |
| --- | --- |
| Single variation | Major variation (Vmaj) |
| Minor variation (Vmin) |
| Grouped variations | Immediate notification (IN) |
| Annual notification (AN) |

## Associated finished pharmaceutical product (FPP) name /PQ ref. number(s):

*e.g. TB 173 -Isoniazid Tablets 100mg*

## Applicant details

Please note that the contact listed in the table below will be the primary contact in communications for this specific application.

|  |  |
| --- | --- |
| Applicant Company |  |
| **Primary contact person responsible for this application** | Title:  First name:  Family name: |
| **Contact person's job title** |  |
| **Contact person's postal address** | |
| **Unit** |  |
| **Building/PO Box Number** |  |
| **Road/Street** |  |
| **Plant/Zone** |  |
| **Village/Suburb** |  |
| **Town/City** |  |
| **District/Mandal** |  |
| **Province/State** |  |
| **Postal code** |  |
| **Country** |  |
| **Contact person's email address** |  |
| **Contact person's phone number** |  |

If there are other contacts who should be routinely copied into correspondence for this application, they should also be listed below. Reproduce this section for more contacts if applicable.

|  |  |
| --- | --- |
| Additional contact person | Title:  First name:  Family name: |
| **Contact person's job title** |  |
| **Contact person's postal address** | |
| **Unit** |  |
| **Building/PO Box Number** |  |
| **Road/Street** |  |
| **Plant/Zone** |  |
| **Village/Suburb** |  |
| **Town/City** |  |
| **District/Mandal** |  |
| **Province/State** |  |
| **Postal code** |  |
| **Country** |  |
| **Contact person's email address** |  |
| **Contact person's phone number** |  |

# Summary of proposed changes- for IN, Vmin and Vmaj

If there are no IN, Vmin or Vmaj changes please delete this section.

* For multiple changes (grouped variation), reproduce this section and provide separate summaries for each proposed change.
* The specific details of the change should be described in the table below, but a separate document should be provided discussing and justifying the change. A discussion on the relevant conditions and documentation as specified in the [Guidelines on variations to a prequalified product](http://apps.who.int/iris/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y#page=107&zoom=auto,-501,678) (copy of the relevant page(s) from the variation guideline for each change applied for) should also be provided.
* Please refer to [FAQ: Variation document](https://extranet.who.int/pqweb/key-resources/documents/frequently-asked-questions-faq-variaiton-prequalified-pharmaceutical" \t "_blank) regarding categorization of an unclassified variation.

## Variation title and number:

*e.g.*

* *Minor variation # 31b: Change in manufacturing process of the FPP.*

*Or,*

* *Immediate notification as agreed with PQT/MED #31u: Change in manufacturing process of the FPP (evidence of agreement with PQT/MED should be included in the submission)*

*Or,*

* *Unclassified Minor variation #31u: change in manufacturing process (A justification of why the change is considered to be unclassified in the variation guideline, and why it should not be considered as a major change by default should be included in the submission)*

*Or,*

* *Major change by default #31u: Change in manufacturing process*

## Summary of current and proposed details:

|  |  |
| --- | --- |
| Current details | Proposed details |
| e.g.  ***Mixing and Granulation***  *Additional Purified Water Addition Time: NMT 5mins*  *Total Granulation time not included*  ***Sifting and sizing of dried granules***  *Screening for final milling of rifampicin part dried granules is 1.5mm* | ***Mixing and Granulation***  *Additional Purified Water Addition Time: NMT 3 minutes*  *Total Granulation time: 8-13 minutes included*  ***Sifting and sizing of dried granules***  *Screening for final milling of rifampicin part dried granules is 1.0mm* |

*If the description of changes is extensive, it is possible to include an Annex to the application form (in Word or text-selectable PDF)*

## Reason for change:

## Date of implementation (for Immediate Notification only):

## If relevant to the variation, list the supporting active pharmaceutical ingredient master file number (APIMF or WHOAPI):

# Summary of proposed changes- for Annual notification only

If there are no AN changes please delete this section

* A change can only be submitted as Annual notification if it complies fully with the conditions and documentation requirements as specified in the [Guidelines on variations to a prequalified product](http://apps.who.int/iris/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y#page=107&zoom=auto,-501,678) (variation guideline) or in [FAQ: Variation document](https://extranet.who.int/pqweb/key-resources/documents/frequently-asked-questions-faq-variaiton-prequalified-pharmaceutical) (Appendix II). The variation number as laid down in the PQ variation guideline should be indicated, or reference made to the recommendations in FAQ document.
* If a change is not categorized in the variation guideline or FAQ, but annual notification has been agreed with PQ through classification request procedure (FAQ document, No. 8), the change number recommended by PQ should be indicated and recommendation from PQ (email communication) should be included in the submission.
* For changes that should be managed and documented within the pharmaceutical quality system (PQS) as per GMP change control (examples are given in FAQ document, Appendix III), variation applications are not required. Should you wish to include such changes in the annual notification to update the version numbers of documents listed in the QIS, e.g. Batch manufacturing records, Validation protocol, Analytical Procedures, etc., it should be clearly identified in the application form that the changes are made as per GMP change control (under the column of “Variation number and title”). It is your responsibility to ensure that the changes are made in compliance with WHO GMP requirements, and the overall quality of the product is not compromised by the changes. Relevant documentation (e.g. CAPAs, SOPs) will be subjected to review during a GMP inspection.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Summary of changes** | | | | |
| **Variation number and title** | **Pre-change details** | **Post-change details** | **Justification**  **(*Summary of studies performed to assess the effects of each change, if applicable*)** | **Date of implementation** |
| *e.g. 38c.1 - Change in the analytical procedures for the FPP involving: Modification or*  *replacement of analytical procedure* | ***Sample Preparation***  *Weigh 10 tablets and determine the average weight. Crush the tablets to a fine powder.*  *Weigh accurately and transfer the tablet powder equivalent to about*  *200 mg of Emtricitabine to a 250 mL volumetric flask. Add about 150 mL of*  *diluent and shake mechanically for 5 min and sonicate for 20 min with*  *intermittent shaking.*  *Allow to equilibrate to room temperature and dilute to volume with*  *diluent, mix. Centrifuge the solution for 5 min at 4000 rpm.*  *Filter the solution through 0.45 μm*  *PVDF (25 mm) filter (MDI or equivalent), discarding first 3 mL of the filtrate. Use the filtrate.* | ***Sample Preparation***  *Weigh 10 tablets and determine the average weight.*  *Transfer 10 intact tablets to a 2500 mL volumetric flask. Add about 300 mL of water, sonicate for 5 mins to disperse the tablets completely. Add 1400 mL of Methanol and sonicate for 30 min ·with intermittent vigorous shaking with interval of 5 mins.*  *Allow to equilibrate to room temperature and dilute to volume with diluent, mix. Centrifuge the solution for 5 min at 4000 rpm.*  *Filter the solution through 0.45 μm*  *PVDF (25 mm) filter (MDI or equivalent), discarding first 3 mL of the filtrate. Use the filtrate.* | *Sample preparation of assay test is modified by using intact tablets instead of crush tablets to overcome the variations observed in assay results.*  ***The below mentioned documents can be made available upon request***   1. *Validation of the revised method including repeatability, intermediate precision, robustness.* 2. *Comparative results of one batch by using the currently accepted and the proposed methods* | *21 August 2021* |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

*If the description of changes is extensive, it is possible to include an Annex to the application form (in Word or text-selectable PDF)*

*Note:*

* *For FPPs that have an agreed-upon Quality of Information Summary (QIS), the QIS should be revised and submitted with any revised sections highlighted (track change and clean version).*
* *Documentation for AN need not be submitted, but should be available immediately on request. When an annual notification involves a change in specifications or standard test procedures (STP) for an API or FPP, the signed and dated version of the revised specification and STPs should be submitted and should include a table of change history.*

# Documentation checklist

The following documents have been submitted together with this application form:

|  |  |
| --- | --- |
| Note: All relevant documents must be provided for this application to be valid. | |
| A summary document introducing, explaining and discussing the proposed changes in Word or text selectable PDF. | *Yes* |
| Supporting documentation  *A discussion on the relevant conditions and all supporting documents as stipulated for the change in the* [*Guidelines on variations to a prequalified product*](http://apps.who.int/iris/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y#page=107&zoom=auto,-501,678) *are included in this submission or are available on request (for AN only)* | *Yes*  *Not applicable* |
| When an annual notification involves a change in specifications or standard test procedures (STP) for an API or FPP, the signed and dated version of the revised specification and STPs are included in the submission, which includes a table of change history. | *Yes*  *Not applicable* |
| For the change which is not classified in the [Guidelines on variations to a prequalified product](http://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3TRS-981.pdf?ua=1), a justification of the proposed classification is provided together with supporting documentation. | *Yes*  *Not applicable* |
| Quality Information Summary (QIS)  *For FPPs that have an agreed upon QIS, the QIS should be revised. A revised QIS with track changes and clean version are submitted and the change history updated.* | *Yes*  *No agreed QIS*  *No change to QIS* |

# Declaration

*Please check all declarations that apply.*

I declare that:

All conditions specified for each change in the Guidance on Variations to a Prequalified Product or otherwise agreed with PQT/MED have been met.

There are no changes being made other than those applied for in this submission, except for possible editorial changes. Any other changes will be applied for separately.

The change has been assessed for the impact on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

The information submitted is true and correct.

Name: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date:\_\_\_\_\_\_\_\_\_\_\_\_\_