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In reply please refer to:

Your reference:

<date>

Dear <contact person>,

WHO Prequalification Team – Medicines REQUALIFICATION OF PREQUALIFIED DOSSIERS

In accordance with the provisions set out in section 12 (Maintenance of prequalification status) of the *Procedure for prequalification of pharmaceutical products*¹, holders of WHO-prequalified products should submit a quality review after five years from the date of prequalification of the product, or when requested to do so by the WHO Prequalification Team – Medicines (whichever date is earlier). This procedure forms part of the maintenance of the prequalified product and is called Requalification.

The objective of this quality review submission is to enable the Prequalification Team - Medicines (PQTm) to confirm the prequalification status of the product based on an audit process for review of the data and information submitted by the holder of a prequalified product. Review of a dossier selected for audit under this process generally includes verification of the acceptability of the product in meeting current norms and standards, and an assessment of consistency of the quality of the prequalified Finished Pharmaceutical Product (FPP), and its manufacturing process(es) over the identified period.

The review also takes into consideration recently published guidelines: *Guidelines on submission of documentation for a multisource (generic) finished product. General format: preparation of product dossiers in common technical document format*² and *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*³. These guidelines have been developed in line with the ICH CTD structure. Accordingly, the previously used PQIF template has been replaced with the CTD Quality Overall Summary – Product Dossier (QOS-PD) template and Quality Information Summary (QIS), which is a condensed version of the QOS-PD.

Although it is mandatory for new dossiers to have completed QOS-PD and QIS templates, **only the QIS should be submitted for requalification** for capturing of the key, prequalified quality information about the product.

¹ World Health Organization. 2011. WHO Technical Report Series, No. 961, Annex 10:

http://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS961_Annex10.pdf

²http://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesSubmissionDocumentationMultisourceGenericGeneralFormatTRS961Annex15.pdf?ua=1

³ http://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex4TRS-970.pdf?ua=1

An important consideration during the requalification process is the acceptability of the source of API. WHO PQTm encourages applicants currently using the full dossier route to consider switching to the use of a Prequalified API (CPQ), CEP or APIMF for the accepted API source, since such an option may now be available. Applicants may choose to continue supporting their FPP using the full dossier route, but should note that they may be requested to provide a complete module 3.2.S.2 following the outcome of the initial requalification review.

Your company's product:

- <...>

was prequalified on <...> and is now due for requalification.

You are requested to provide the following regarding this product for evaluation purposes:

- 1 Cover letter. The cover letter should contain a clear statement by the responsible person submitting the quality review, indicating that the information submitted is true and correct.
- 2 A sample(s) within expiration date of the product in all pack types (one pack size per pack type will suffice), as prequalified.
- 3 A review, in tabular format, of accepted changes to the initially prequalified product (see Appendix 1).
- 4 For a product where there is no published WHOPAR - the current Summary of Product Characteristics, Patient Information Leaflet and labeling (facsimile) in accordance with WHOPAR guidance: <https://extranet.who.int/prequal/content/contents-and-structure-whopar>
- 5 For a product for which a QIS existed by the time it was prequalified, the information on the latest QIS of the product should be transferred to the current QIS template, available on the PQTm website. Ensure that the information is correctly transferred. Include a declaration in the cover letter indicating that the information in the QIS has been correctly transferred from the latest QIS. **Also provide the latest QIS of the product from which the new QIS has been constructed.** Take note of the points listed under point 6 (a to g) below.
- 6 For a product where there is no existing QIS, the current QIS template should be completed in Word format and submitted. The QIS the template is available on the PQTm website. It should reflect the requirements of current prequalification guidelines following the CTD format and should also take into account technical and scientific progress and include or note the following, where applicable:
 - a) As much as possible you should use tabulated formats provided in the template without modification.
 - b) Study the listing information and WHOPAR parts 3, 4, 5 (only the quality related information, for example sections 1, 2, 3, 6 and 7 in part 4) of the product on the WHO PQTm website in relation to the information accepted by WHO PQTm. Indicate where corrections are needed to the listing information and/or the quality related information of any one or more of these WHOPAR parts. Otherwise, where applicable, provide a declaration that the information is correct.
 - c) For the submission or confirmation of API information, note that the option for Full Details in the Dossier is only acceptable where the FPP and API manufacturer is the same. In all other cases CPQ, CEP or APIMF options should be used. The use of Full Details in the Dossier is discouraged and a change to one of the other options is possible during requalification.
 - d) For section 2.3.S.2.1(a) - Whenever reference to use of CPQ, CEP or APIMF is made, you should provide a copy of the appropriate current confirmation of PQ, CEP or letter of access from the API manufacturer /source, with a declaration that it is current. For the full dossier submission option a signed declaration from the API manufacturer that they have provided to you all information pertaining to the manufacture, control and stability of the API, including confidential information and a declaration that they will inform you of all changes to the preparation, control and stability of the API should be included.
 - e) For section 2.3.S.4.1(a) – Confirm that the API supplier has been contacted and the current supplier specifications have been obtained, and that the FPP manufacturer's API specifications are reflecting those in the current CPQ, CEP or APIMF. If not indicate the difference(s) and

either provide a justification, which may be a reference to a variation accepted by WHO PQTm, or submit a variation in parallel to your requalification submission.

- f) Section 2.3.S.7: *Stability* - Note that if the retest period or shelf life (where applicable) was not previously assigned or stated on the CEP for the prequalified product, you may be requested to justify the proposed retest period/shelf-life.
 - g) For the excipients in *Section 2.3.P.1 Composition* table indicate the respective grades as well as trade names, if applicable.
- 7 A product quality review, covering the topics listed in Annex 1 attached to this letter, irrespective of whether or not batches were manufactured during the review period.

- 8 Copies of currently approved signed/dated specifications and test procedures for the API(s) and FPP(s). The specifications should indicate the reference number, version number, effective date and change history if any.

Documents should be made available electronically (**No paper copies, see Annex 2 for electronic document requirements**). Note that pdf files should as far as possible be text selectable. (see Annex 2)

You are requested to respond within two months of date of this letter. In case the timeline cannot be kept you may request WHO for further time, with the date of expected submission.

The product samples and CD/DVDs (in the format described in Annex 2) should be sent to the WHO Prequalification Team - Medicines at the following address with all packages/containers clearly marked as indicated below:

CONFIDENTIAL: REQUALIFICATION

Attention: Dr. Matthias Stahl
WHO Prequalification Team - Medicines
Product number: <number>
UNICEF Supply Division
Oceanvej 10-12,
2150 Nordhavn
Copenhagen
Denmark

The documentation may also be sent via a secure link to an online document repository. The link should be sent in an email to the following email address: FPPassessment@who.int. The Subject line of the emails should clearly indicate "Requalification submission" and the application number. The date of receipt will be the date the file is successfully downloaded.

WHO will arrange for the evaluation of the information submitted according to current norms and standards prevailing in the Prequalification of Medicines Programme (<https://extranet.who.int/prequal/>). Any matters that may arise as a result of the evaluation will be communicated to you for clarification.

As part of the requalification procedure WHO may separately conduct re-inspection of the relevant CRO, FPP and API manufacturing sites. If, as a result of this requalification process, the product and corresponding site(s) are found to meet the current WHO recommended standards, the product will remain on the list of prequalified products. However, if it is found that a product and/or specified CRO/manufacturing site(s) no longer complies with the WHO-recommended standards, the product may be removed from the list. Failure of a manufacturer or applicant to participate in the requalification procedure may also lead to removal of the product from the list.

For further information on this matter, please use the e-mail address – prequalassessment@who.int – and ensuring that the e-mail mentions the corresponding WHO product reference number. Kindly note that due to confidentiality and security reasons dossier information should not be submitted by e-mail.

Your cooperation is appreciated.

Yours sincerely,

Dr. Matthias Stahl
Group Leader – Medicines Assessment
Prequalification Team
Regulation of Medicines and other Health Technologies

Appendix 1
**Variations to the
product**

The holder of the prequalified product should submit a review, in tabular format, of any notifications, minor or major changes (only accepted changes) to the initially prequalified product. Table 1 should be completed and submitted in WinWord Format by the holder of the prequalified product.

Table 1. Information on variations to the prequalified product

Reference no.	Date of submission and WHO variation number (if available)	Date of approval/rejection and reference number of the letter	Date of implementation
Major changes (Vmaj)			
Description of the change according to the PQ variation guideline			
Minor changes (Vmin)			
Description of the change according to the PQ variation guide			
Notifications. Indicate whether Immediate notification (IN) or Annual notification (AN)			
Description of the change according to the PQ variation guide			

Add as many rows as necessary

Comment. Requests for variations should have been submitted in accordance with *the WHO guidelines on variations to a prequalified product*⁴

ANNEX 1 (to letter of Requalification)

PRODUCT QUALITY REVIEW

The product quality review report (PQR) should be presented based on the data and information derived from all the batches manufactured over the period of the last 12 months of the 5 year period. *(Note: If the number of all consecutive batches is less than 10 over the period of the last 12 months, then the PQR for the preceding two review periods should also be provided. Applicants are reminded that annual PQRs should be prepared as long as the product remains prequalified. This applies irrespective of whether or not batches were manufactured in a given review period.*

The report should include at least the following topics:

1. A table of reviewed batches with batch numbers, manufacturing dates and batch size. Any differences from the prequalified batch size should be clarified.
2. A review⁵ of starting materials (active pharmaceutical ingredients and excipients).
3. A review of primary packing materials used in the FPP, including reference to those from new sources.
4. A tabulation of batch analysis data (including in-process test results and finished product quality control results) together with statistical and trend analysis where appropriate. Batches that failed to meet prequalified specification(s) should be addressed in Topic 5.
5. A review of all out-of-specification and related investigations, with indication of batches that failed to meet specification(s).
6. A review of all deviations.
7. A review of variations to the prequalified product dossier including submitted/granted/refused variations.
8. A review of review of all changes not listed in topic 7.
9. A review of summary of the results of the stability-monitoring programme. Trend analysis should be presented and discussed.
10. A review of validation and stability commitments, if applicable.
11. A review of all quality-related returns, complaints and recalls.
12. A review of adequacy of any corrective actions.
13. A list of validated analytical and manufacturing procedures and the revalidation dates.

⁵ A review implies a summary of data and analysis/discussion thereof, with a conclusion.



ANNEX 2 (to letter of Requalification)

REQUALIFICATION - ELECTRONIC DOCUMENTATION REQUIREMENTS

Documents should only be submitted in electronic format.

All the electronic documents submitted for requalification should therefore,

- be preferably book-marked text selectable PDF documents that permit easy navigation between sections as well as copying of critical information. The QIS and Table 1 (see above) should however be in the WinWord format.
- include a table of contents with headings listed.
- be paginated throughout, but page numbers may be restarted for each section or subsection as required. Heading and sub-heading granularity must be respected.
- Be translated if non-English documents should are provided.

In addition in order to facilitate transfer from the CD/DVD into the WHO IT environment the following recommendations should be followed to avoid instances where the documents cannot be transferred successfully due to incompatibility.

- Avoid the submission of single documents that are excessively large (>50MB).
- The maximum permitted file or folder name should be no more than 64 characters.
- The maximum length of a path should be no more than 128 characters, including file name, and extension. The careful selection of document titles is encouraged to avoid this limit, but if necessary the use of abbreviated file or folder name is permitted.
- The use of special characters in folder or file names is to be avoided in order to prevent conflicts with certain software. Prohibited special characters include:
 - Tilde (~)
 - Number sign (#)
 - Percent (%)
 - Ampersand (&)
 - Asterisk (*)
 - Braces ({})
 - Backslash (\)
 - Colon (:)
 - Angle brackets (<>)
 - Question mark (?)
 - Forward slash (/)
 - Plus sign (+)
 - Pipe (|)
 - Quotation mark (")