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Annex 6

Guidelines on the requalification of prequalified dossiers

1. Introduction

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 5 years from the date of prequalification of the product, or when requested to do so by WHO Prequalification (whichever date is earlier).

Section 12 of the above-mentioned guidelines states that:

> WHO will furthermore arrange for the products and manufacturing sites included in the list to be re-evaluated at regular intervals. If, as a result of this re-evaluation, it is found that a product and/or specified manufacturing site no longer complies with the WHO-recommended standards, such products and manufacturing sites will be removed from the list. Failure of a manufacturer or applicant to participate in the re-evaluation procedure will also lead to removal from the list.
>
> Re-evaluation, including re-inspections of manufacturing sites and contract research organizations (CROs), will be done at regular intervals, based on risk assessment, but at least once every 5 years.
>
> Re-evaluation, including re-inspections, shall also be performed:

[1] Procedure for prequalification of pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report.* Geneva, World Health Organization, 2009, Annex 4 (WHO Technical Report Series, No. 953) (http://www.who.int/medicines/publications/pharmprep/pdf_trs953.pdf#page=145).

- if any fraud or omissions by the applicant, manufacturer(s) of a finished pharmaceutical product (FPP) or active pharmaceutical ingredient (API), or CROs in the initial assessment procedure or during the follow-up activities, becomes evident; and
- if WHO or any United Nations agency considers that a batch or batches of supplied prequalified pharmaceutical products are not in compliance with the specifications which were found to be applicable upon prequalification.

Requalification will be applicable to multisource FPPs (generics) where the full dossiers have been submitted, assessed and prequalified by WHO. Renewal of marketing authorization for products that have been listed by WHO based on approval by a stringent regulatory agency[2] (SRA) remains the responsibility of the relevant SRA.

2. Requalification of prequalified dossiers

The objective of this quality review submission is to enable WHO to requalify the product based on an assessment of the data and information submitted by the holder of a prequalified product, which includes verification of the acceptability of the product and its conformity to current norms and standards, and assessment of consistency of the quality of the prequalified FPPs, and its manufacturing process(es) over the identified period.

The holder of a prequalified product should submit the following documents electronically (in pdf format and in also in WinWord where indicated):

- A covering letter, which should contain a clear statement by the responsible person submitting the quality review, indicating that the information submitted is true and correct.
- Summary of key product information (as per Appendix 1).
- Variations to the product (as per Appendix 2).
- A pharmaceutical quality information form (PQIF)[3], completed in WinWord format. It should reflect the requirements of current prequalification guidelines and should also take into account technical and

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[2] Stringent regulatory authority (SRA): a regulatory authority which is:
a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org); or
an ICH observer, being the European Free Trade Association (EFTA), as represented by Swiss Medic, Health Canada and World Health Organization (WHO) (as may be updated from time to time); or
a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

[3] Presentation of pharmaceutical quality information. In: *Guidance for submission of documentation for prequalification of multi-source (generic) finished pharmaceutical products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis*. Annex 8 (http://apps.who.int/prequal/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_ANNEX8.doc).

scientific progress. The API and FPP specifications should be provided in tabulated format, comparing the specifications at prequalification and at the time of the requalification submission.

- Copies of the current API and FPP specifications, duly signed and dated, including the test methods. The specifications should indicate the reference number, version number, effective date and change history if any.

A product quality review may be submitted as supportive documentation. It may also be requested by WHO.

Appendix 1

Summary of key product information

This section compares key information on the FPP at the time of prequalification and at the time of the submission for requalification. Table A1.1 should be completed by the holder of the prequalified product. Include remarks as a footnote to Table A1.1, where deemed necessary, to clarify the information provided.

Table A1.1
Summary of key product information

Item	Prequalified dossier	Current data[a]
Product number (e.g. HA001)		
INN, strength and pharmaceutical form		
Applicant (name, physical address and contact numbers)		
Manufacturing site(s) of FPP, with physical address (including unit and block numbers) and contact numbers (list separately if different steps are performed by different sites, e.g. packaging, quality control)		
Batch size(s) of FPP		
Product description (visual appearance)		
Primary and secondary packaging material(s) and pack size(s)		
Storage conditions of FPP		
Shelf-life of FPP		
FPP specification(s) reference number and/or version[b]		
Manufacturer(s) of API(s), with physical address (including unit and block numbers) and contact numbers (list each API separately)		
Number/version of each APIMF associated with the FPP		
Storage conditions of API		
Retest period of API(s)		
API specification(s) reference number and/or version (for each API)[b]		
All commitments and their outcomes		

INN, international nonproprietary name; FPP, finished pharmaceutical product; API, active pharmaceutical ingredient; APIMF, active pharmaceutical ingredient master file.

[a] If there has been no update of the dossier then indicate "N/A" (not applicable).

[b] According to the latest editions of *The International Pharmacopoeia* (Ph.Int.), the European Pharmacopoeia (Ph.Eur), the British Pharmacopoeia (BP) and/or the United States Pharmacopeia (USP). Where in-house specifications have been approved and there is now a monograph in any of the internationally-recognized pharmacopoeias (Ph.Int., Ph.Eur, BP, or USP), the specifications should be updated to comply with the new monograph or demonstrated to be at least equivalent. In the case that no compendial monograph exists, the applicant should ensure that the approved in-house specifications are updated, through the variation process, to reflect the requirements of current prequalification guidelines and to take into account technical and scientific progress (e.g. current ICH guidelines, general chapters of the Ph.Int.). Each new version of the documents should allow traceability to the prequalified dossier and approved variations.

Appendix 2

Variations to the product

The holder of the prequalified product should submit a review, in tabular format, of any minor and/or major changes (including those pending) to the initially prequalified product or to the terms of the initially prequalified dossier. Table A2.1 should be completed by the holder of the prequalified product.

Table A2.1

Information on variations to the prequalified product

Reference no.	Date of submission	Date of approval/ rejection and reference number of the letter	Date of implementation
Major changes			
Description of the change, e.g. change in the primary packaging site of a sterile product			
Minor changes			
Description of the change according to the PQ variation guide			

Add as many rows as necessary.

Note. Requests for variations should have been submitted in accordance with WHO's Guidance on variations to a prequalified product dossier[4].

[4] WHO Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 6 (WHO Technical Report Series, No. 943) (http://apps.who.int/prequal/info_general/documents/TRS943/TRS943.pdf#page=121).