Procedure to enable prequalification of products approved by SRAs for use outside the SRA region[1]

Introduction

According to WHO's *Procedure for prequalification of pharmaceutical products* (TRS 961, Annex 10) the role of the PQ programme is to provide "United Nations agencies with advice on the acceptability, in principle, of pharmaceutical products for procurement by such agencies… The pharmaceutical products found to meet the WHO-recommended quality standards are included in the list of medicines, as manufactured at the specified manufacturing sites, which are considered to be acceptable, in principle, for procurement by United Nations agencies." TRS 961, Annex 10 furthermore states that "WHO recognizes the evaluation of relevant products by Stringent Regulatory Authorities (SRAs)[2] which apply standards for quality equivalent to those recommended by WHO."

The current requirements for prequalification via the abridged route are outlined in WHO's *Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities*[3] (SRA guideline). The SRA guideline currently excludes the prequalification of products that have received a positive opinion or tentative approval but are for export only and not intended to be marketed in the SRA's country/region. The guideline also excludes products that have received full SRA marketing authorization but are not yet marketed in the SRA country/region.

Based on the experience gained in using the above-mentioned guideline and comments received from stakeholders, PQT/MED intends to pilot a procedure that would allow for prequalification of products approved by SRAs for export only purposes. This will be based on the existing abridged prequalification procedure for products approved by SRAs with full marketing authorizations and on the market of the SRA country/region. Products prequalified via this pilot procedure will also be eligible for national registrations through WHO's Collaborative Registration Procedure (CRP) for prequalified products.

Scope

According to this pilot, certain SRA approved products or those that received a positive opinion or tentative approval from an SRA will be eligible for prequalification via the abridged procedure and subsequently eligible for collaborative registration by NRAs as a prequalified product, irrespective whether

[1] includes products approved by SRAs for marketing in the SRA region but are yet to be marketed in the SRA region.

[2] All SRAs are being transited to the WHO Listed Authorities (WLA) list based on abbreviated performance evaluation such that the term SRA is replaced with WLA.

[3] WHO Technical Report Series No. 986, Annex 5, 2014. All SRAs are being transited to the WHO Listed Authorities (WLA) list based on abbreviated performance evaluation such that the term SRA is replaced with WLA.

- the product has been approved by the reference SRA for marketing in the country/region of the reference SRA but is yet to be placed on the market of the SRA[4] or

- the product has received a positive opinion / tentative approval from EMA (i.e., EU-M4all), USFDA (Tentative approvals) or Swissmedic (MAGHP).

The pilot is applicable only to products that have been approved or received a positive opinion / tentative approval by the reference SRA since the beginning of 2012[5].

The intended pilot procedure

As noted above, this pilot opens the possibility to prequalify certain eligible SRA approved products via the abridged procedure, as well as subsequent collaborative registration by NRAs as a prequalified product[6].

It is acknowledged that the prequalification of products that are approved by an SRA for export only or have not yet been placed on the SRA market may pose additional risks compared to products that are marketed in the SRA's country/region due to potentially limited post-marketing oversight by the SRA, for instance:

- Lack of GMP compliance due to limited SRA inspections. The SRA may prioritise inspections in the SRA-region as per a risk-based approach where products destined only for markets outside the SRA's country/region may be classified as low risk. Furthermore, even if the manufacturing site may be inspected by the reference SRA and found to be GMP compliant, the production line and quality system associated with manufacturing of such products may not be inspected as thoroughly as products marketed in the SRA region.

- Variations may not have been promptly communicated to or approved by the reference SRA for a non-marketed product.

To mitigate such risks in this pilot procedure, PQT/MED will require certain conditions and information additional to those required by the current *Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities* (SRA guideline)[1].

[4] Applicable only for products approved by SRAs/WLAs that have supported prequalification of products over a long time based on the abridged procedure (i.e., EMA, BfArM, MHRA, MPA, CBG/MEB, Swissmedic, TGA, FAMHP and USFDA). A draft guidance regarding prequalification of products approved by other WLAs is to be published.

[5] 2012 is the year during when WHO's Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (full assessment route) have been published and implemented. This will ensure that the dossier format and assessment requirements of the different SRAs and WHO PQT/MED can be regarded as current and sufficiently similar.

[6] This option does not replace the alternative listing procedure discussed at https://extranet.who.int/prequal/medicines/general-information-who-list-prequalified-medicinal-productbut should be seen as a new option for products that have received an SRA positive opinion / tentative approval.

The following conditions would apply:

i. The reference SRA agrees to share its unredacted assessment and inspection reports including variation reports with PQT/MED for possible review but primarily for further sharing to countries via the WHO CRP mechanism to facilitate national registration of the product as an SRA approved and prequalified product. The assessment reports must be either written in or translated to English. The reference SRA provides assurance to PQT/MED that the product will be subjected to routine regulatory oversight throughout its life cycle including periodic inspections of manufacturing sites and variation reviews as for products approved for marketing in the SRA country. The SRA may issue a one-time generic letter to PQT/MED applicable to all such products.

ii. The manufacturer commits to exercise its regulatory responsibility in reporting changes to the product, product quality complaints and out of specification results to the reference SRA as for products marketed in the SRA country.

iii. The product was approved by the SRA since 2012 onwards as noted above.

Provided that the above conditions are met, the product will be eligible for submission according to the abridged prequalification procedure, based on submission of the following:

1. A cover letter, which should include:

   a) a statement indicating that the information submitted is true and correct;
   b) a statement indicating the applicant's intention to participate in the CRP;
   c) a declaration confirming that for WHO prequalification, the API manufacturer(s) and the FPP manufacturer's API specifications for the API(s) used in the manufacture of the FPP are as currently approved by the reference SRA;
   d) a declaration confirming that for WHO prequalification, the FPP – including but not limited to composition, manufacturing and sites of manufacture, specifications, packaging, product information – will, at the time of submission and after prequalification, in all respects be the same as the product that received a positive opinion / tentative approval from the reference SRA;
   e) a statement confirming that Applicant agrees to the publishing of WHO PQT/MED *Clinical and Preclinical Information* additional to the SRA accepted product information in accordance with the *Note with respect to WHO PQT/MED Recommended Clinical and Preclinical Information additional to the SRA Approved Product Information for Products Prequalified via the Abridged (SRA) Route*[7]*;*
   f) a commitment to provide periodic safety update reports (PSURs) or periodic adverse drug experience reports (PADERs) for the product directly to WHO PQT/MED.

2. A copy of the positive opinion / tentative approval issued by the reference SRA to demonstrate that the product has been accepted in accordance with the reference SRA requirements.

[7] At: https://extranet.who.int/prequal/

3. A copy of the current WHO-type certificate of a pharmaceutical product issued and fully completed, including answers to each question, by the reference SRA.

4. The latest SRA approved product / prescribing information (summary of product characteristics (SmPC), or an equivalent thereof, the patient information leaflet (PIL), or equivalent thereof, and the labelling). A web link to the SRA-approved product information, preferably on the website of the SRA itself, should be provided if available.

5. If available, a public assessment report, such as the Scientific Discussion of the European Public Assessment Report (EPAR), issued by the reference SRA.

6. A sample of the product, one per pack type. This should be provided with the submission to enable visual inspection thereof and for publishing of an image on WHOPAR part 2 and on the product's listing information (once the product is prequalified). The respective certificate of analysis should be attached.

7. A copy of the currently SRA approved FPP specifications (release and shelf-life), dated and signed or certified by authorised personnel, with the analytical test procedures.

8. The quality information summary (QIS-SRA_MED-crp). The QIS-SRA_MED-crp template, available on the WHO PQT/MED website, should be fully completed and submitted with the application. It should contain the latest information approved by the reference SRA.

9. A list of variations allowed by the reference SRA post approval, with provision of the regulatory approval letters as well as a detailed discussion of the approved changes. Any variations allowed by the reference SRA while the application is under assessment should be submitted to PQT/MED on a rolling basis, as part of a response submission. Information on pending variations should be provided.

10. A letter from the reference SRA addressing condition i above. WHO PQT/MED will then request the unredacted assessment and inspection reports directly from the reference SRA.

11. A letter from the applicant addressing condition ii above.

12. Reassurance from the applicant that the manufacturing site and the production lines dedicated to the product to be prequalified are regularly GMP inspected by the SRA (e.g., GMP certificate released by the SRA, GMP inspections report extracts, GMP-related communication to and from the SRA). The evidence will need to be assessed by WHO PQT/MED together with PQT Inspection Services in order to evaluate any risk associated with possible lack of GMP compliance. WHO inspections of the relevant manufacturing or clinical facilities may be conducted, if considered necessary based on information submitted by the manufacturer.

13. A list of country(s) where the product is currently on the market.

14. stability data according to the *Request to submit stability data with the submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities* (stability guidance) to enable WHO PQT/MED to assign a WHO recommended storage condition, with shelf-life, for the product when distributed in regions with harsh climatic conditions, such as zone IVb.

The submission must be in English, and should include certified English translations of the product information and other official documents, if applicable. These documents should be made available electronically. The English language version of the product information, in the case of English translations, should be submitted as MS Word files. Portable document format (pdf) files should be text searchable.

Furthermore, WHO may request additional data, when considered necessary, for the use of the product in populations, settings or regions relevant for prequalified products. If necessary, this additional information will be included in the WHO public assessment report (WHOPAR). The SRA-approved product information will not be changed by WHO. WHO would not normally inspect the manufacturing site(s) or clinical testing site(s) of an SRA-approved product; however, there may be circumstances under which WHO will conduct an inspection in collaboration with the reference SRA. Such inspections may occur as part of the prequalification application/assessment process or after prequalification of the product.

Variations to a product or renewal of the positive opinion / tentative approval of a product remain the responsibility of the reference SRA. WHO PQT/MED should be notified immediately by the applicant of any variations approved by the reference SRA, with supportive approval information issued by the reference SRA, to ensure that the prequalified product remains the same as accepted by the reference SRA. If applicable, the revised QIS-SRA_MED-crp (in MS Word format) should accompany the notification showing the changes thereto in tracked format, as well as other information held by WHO PQT/MED. Visit the WHO PQT/MED website for the submission procedures. WHO PQT/MED will contact the reference SRA to request the corresponding unredacted assessment reports written by the SRA.

WHO PQT/MED should be informed by the applicant immediately in case of withdrawal of the product, any regulatory action taken by the reference SRA or of any critical safety or quality-related issues reported for batches on the market.

When a product that received a positive opinion / tentative approval only for marketing outside the country or region of the SRA is prequalified via this pilot, it will be listed under ‘Prequalification – Abridged – WHO CRP - B’.

Collaborative registration procedure (CRP)

The national registration of a product that has been prequalified via this abridged procedure can be facilitated according to WHO's

> *Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines*[8]

For this purpose, WHO will provide the NRA with the SRA's unredacted assessment reports, a list of variations accepted by the SRA and the relevant PQT/MED summary assessment reports.

[8] WHO Technical Report Series No. 996, Annex 8, 2016