PQT/MED reliance on the work of national regulatory agencies and regional regulatory systems – new pathways

Introduction

PQT/MED has two pathways for prequalification of medicinal products - the abridged assessment pathway for innovator/generic/biosimilar products approved by a stringent regulatory authority (SRA[1]) and the full assessment pathway for generic/biosimilar products. The abridged pathway is a recognition mechanism (full reliance), while the full assessment pathway incorporates possibilities for partial reliance on the work of an SRA as needed.

WHO has taken the initiative to publicly designate regulatory authorities as WHO listed authorities (WLA). At the same time, various partners have expressed a desire that PQT/MED expand to new therapeutic areas, possibly including new chemical entities (NCEs) not previously approved by an SRA. In this context, PQT/MED is considering how to expand collaborations and reliance mechanisms for prequalification. Expanded reliance mechanisms may facilitate a shift of PQT/MED resources to the handling of more complex products and, possibly, certain NCEs developed with a focus on public health priorities.

This document describes PQT/MED's intention to expand the existing prequalification pathways by strengthening collaborations with national and regional regulatory authorities (NRAs) that have achieved a WLA[2], ML3 or ML4[3] status as assessed by WHO.[4]

Considerations for expansion of the prequalification pathways:

[1] Definition of SRA: https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf . All SRAs are being transitioned to the WHO Listed Authorities (WLA) list based on abbreviated performance evaluation such that the term SRA is replaced with WLA.

[2] WLAs are NRAs or regional regulatory systems (RRS) that have successfully completed assessment via the WHO Global Benchmarking Tool (GBT) and undergone the performance evaluation phase for publicly designating regulatory authorities as a WHO Listed Authority. (https://www.who.int/publications/m/item/list-of-who-listed-authorities-wlas)

[3] ML3 or ML4 NRAs are NRAs or regional regulatory systems included in the WHO list of NRAs operating at maturity level 3 or 4 as benchmarked against the GBT assessment tool https://www.who.int/publications/m/item/list-of-nras-operating-at-ml3-and-ml4

[4] Since *"the ultimate responsibility and decision for use of the list resides with the users (e.g. regulatory authorities, WHO Prequalification Programme, procurement agencies) and depends on the specific context of its intended use"(* https://iris.who.int/bitstream/handle/10665/341749/9789240023444-eng.pdf?sequence=1), this guidance note clarifies how PQT/MED intends to utilize the WLA, ML3 and ML4 listings and expand its collaborations.

The following points are considered when defining appropriate pathways for prequalification of products approved by WLAs, ML3 or ML4 NRAs.

- PQT/MED plays a critical role in ensuring that priority public health products meet a harmonized acceptable quality standard, thereby allowing harmonized and efficient procurement decisions[5] and national registrations. It is essential that procurers and recipient countries are assured that all prequalified products meet a harmonized international standard regardless of the basis of prequalification.
- In implementing their quality assurance (QA) policies, procurers may find it more efficient to deal with a product meeting a single common standard prequalified and registered in multiple counties rather than dealing with a product approved by multiple WLAs and thus potentially supplied according to various standards for example in terms of product specifications.
- Manufacturers find it more feasible to be able to manufacture and control a given product to a common internationally accepted single standard

Collaborations with WLAs, ML3 and ML4 NRAs to establish confidence

Collaboration with, and support of, NRAs by PQT/MED has been a foundational principle of PQT/MED's assessment activities and an intrinsic aspect of prequalification of medicines since its inception in 2001. Indeed, PQT/MED has been instrumental in the maturation of many NRAs.

In the light of the intention to increase reliance on the work of NRAs, and in keeping with established international best practice, confidence building measures are necessary between PQT/MED and partner NRAs. Such interactions serve not only to understand how an NRA approaches decision-making, but equally important to understand the numerous practical aspects of their procedures, documentation, style of reporting, limitations, and strengths so that PQT/MED procedures can make use of the shared information in the most efficient way.

PQT/MED will seek to strengthen collaboration with NRAs as they achieve WLA/ML3/ML4 status for example in identifying potential differences in requirements and approaches and agree on harmonization to the extent possible, thereby establishing mutual confidence for continued collaboration.

Beyond establishing the necessary memoranda of understanding regarding obligations, processes and confidentiality, collaboration may include:

- joint assessments and inspections

[5] The lists of prequalified products serve as "a one-stop shop" for procurers, providing them with quality-assured key public health products.
PQT/MED also engages with the various international procurers, including agencies funding procurement, as partners, to provide regulatory advice to support their procurement decisions including for products currently not invited to prequalification.

- staff exchange and identifying focal points
- participation of WLA staff in PQT/MED assessments and inspections,
- regarding obligations, processes, and confidentiality
- partial or full reliance on the work of the NRAs
- channeling selected applications proposed for prequalification to the NRAs such that prequalification will be based on partial or full reliance on the assessment outcome and approval decision of the NRAs
- ongoing engagements with the NRA regarding products submitted for prequalification based on the work of the NRA
- periodic meetings with NRAs that have supported the work of prequalification to exchange updates and experience
- co-development of new guidelines or co-participation in updating of existing guidelines as needed.
- acknowledging the WLA markets as acceptable sources for comparator products used in BE studies/comparability/similarity exercise for biosimilars.

These arrangements will foster common understanding and build confidence. For ML3 or ML4 NRAs these collaborations will contribute towards the NRA's effort in achieving a WLA status and pave the way for further collaboration in terms of additional reliance arrangements.

As part of the collaborations described above, PQT/MED could rely on the work of NRAs as follows:

A. Collaboration with WLAs in the context of the abridged procedure for prequalification

- PQT/MED will make use of marketing authorization decision issued by the WLA (hereinafter referred to as the reference WLA), utilizing the associated unredacted assessment and inspection reports, as a basis for prequalification of eligible products via the abridged pathway according to the guideline for prequalification of SRA approved products[6] and the associated practices.

- In this abridged pathway, PQT/MED will undertake a review of the unredacted FPP assessment reports, API assessment reports (if a DMF/APIMF is used) and inspection reports provided by the reference WLA to ensure compliance to PQT/MED requirements

[6] WHO Technical Report Series, No. 986, Annex 5 https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/prequalification/trs986-annex5.pdf?sfvrsn=8aae767d_2

and standards. In doing so, PQT/MED will engage with the reference WLA to seek clarifications where needed.

- Documents required for submission from the applicant will mainly be based on the list of documents described in the guideline for prequalification of SRA approved products. A complete CTD dossier will not be required normally; however, PQT/MED reserves the right to ask for a copy of the CTD dossier submitted to the reference WLA as needed.

- A prequalification decision or first action will be made within 60 calendar days of receiving a complete submission from the applicant, including the unredacted assessment and inspection reports from the WLA. If additional information is required from the applicant or the WLA, the WHO PQT/MED clock will be stopped until the information is provided. Once the additional information is received, the WHO PQT/MED clock will resume, with a target of an additional 30 calendar days to reach a decision based on the information provided. If PQT/MED cannot prequalify the product by the end of the 30-day period, the application will be cancelled. The application may also be cancelled if PQT/INS determines that an onsite inspection of the manufacturing sites or the CRO is necessary after reviewing the available information.

- PQT/MED may prepare a summary assessment report for any additional considerations including PQT/MED specific programmatic suitability considerations but will not write a complete assessment report[7].

Following prequalification of at least 5 products according to this pathway and provided common understanding has been established, PQT/MED will consider whether it can continue to rely on the work of the WLA *without* a need for review of unredacted assessment reports from the WLA.

Products approved by WLAs/SRAs that have so far supported prequalification of a significant number of products over a long time period based on the abridged procedure (i.e., BfArM, EMA, Health Canada, MHRA, MPA, CBG/MEB, Swissmedic, TGA, FAMHP or

[7] The WLA's unredacted assessment and inspection reports, together with relevant PQT/MED summary assessment reports may be shared with countries to facilitate national registration via the collaborative registration procedure (CRP) for prequalified products. The WLA should therefore agree to further sharing of its unredacted reports with countries in the context of CRP.

USFDA) may continue to be prequalified *without* submission of the corresponding unredacted assessment or inspection reports[8].

B. Collaborations with ML3 and ML4 NRAs in the context of a facilitated full PQT/MED assessment procedure[9] [10]

- PQT/MED may make use of marketing authorization decision issued by an ML3 or ML4 NRA, along with the associated unredacted assessment and inspection reports, as a basis for prequalification of eligible products via a facilitated full assessment and inspection procedure.[11]

- Such reliance could be partial, for example with respect to the quality assessment only or the safety/efficacy assessment only, or complete and cover all aspects of the dossier. In any case, the applicant needs to provide the complete CTD dossier as submitted to the reference NRA (updated/supplemented as per PQT/MED submission guidelines). With respect to the assessment of API information, the application may refer to a Prequalified API or APIMF already held by PQT/MED or provide the NRA assessment reports and associated APIMFs referenced in the NRA application to PQT/MED. For inspections, the applicant needs to provide complete set of information required for desk review.

- PQT/MED aims to complete its first action for the assessment and desk review of inspection reports and associated information within 120 calendar days of receipt of a

[8] This does not exclude the possibility of submission of unredacted assessment reports from these agencies to PQT/MED to support assessment of the suitability of the product for use in populations, settings or regions relevant for prequalified products or for further sharing with NRAs to facilitate national registration of the product via CRP as a prequalified product according to a separate procedure (https://extranet.who.int/prequal/sites/default/files/document_files/Procedure%20to%20enable%20national%20registration%20of%20products%20prequalified%20%20based%20on%20SRA%20approval%20through%20CRP-18-March-2025_0.pdf)

[9] Initially as a pilot procedure

[10] As part of this collaboration, PQT/MED aims to understand the NRAs procedures and approaches and to provide feedback, as needed. Specifically, the following needs to be clarified, among other aspects,
- the NRA's review processes,
- limitations, or exceptions that may exist within the NRA processes,
- use of recognition in the NRA processes,
- the NRA's APIMF/DMF processes and functions,
- how NRA reviews and inspections are undertaken,
- the link between GMP determinations and quality reviews,
- the quality of the NRA reports and their usefulness,
- how the NRA reports are compiled and where information is located,
- the report writing style

[11] Assessment and, if available, inspection reports may also facilitate prequalification of the associated APIs.

complete submission, including the unredacted NRA assessment and inspection reports. If further information is needed from the applicant or the authorizing NRA, the WHO PQT/MED clock will be stopped until the information is provided. Once received, the WHO PQT/MED clock will restart with a target of 60 further calendar days to decision based on the additional information. If at the end of the 60-day period, PQT/MED cannot reach a positive assessment decision or PQT/INS, following a desk review, requires an onsite inspection of the manufacturing site(s) or the CRO, the application will no longer be considered as submitted via the pilot facilitated full assessment procedure. Assessment may however continue via the regular full assessment and inspections procedure[12].

- At the time of prequalification, PQT/MED will acknowledge the work of the reference NRA in the associated prequalification announcements and in the WHOPAR and WHOPIR.

- PQT/MED may use the PQT/MED assessment and inspection reports in the Collaborative Registration Procedure (CRP) when requested.

- Variations to the prequalified products will be submitted to PQT/MED directly. Any prior assessments and approvals by the reference NRA may be submitted to facilitate the variation review by PQT/MED.

- OOS results and recalls initiated by the applicant are to be immediately reported to PQT/MED and the reference NRA. PQT/MED will collaborate with the reference NRA in handling these cases.

- Product quality complaints raised by procurers, countries and other stakeholders should be reported to PQT/MED and the reference NRA. PQT/MED will handle the review of such complaints in collaboration with the NRA.

- Once greater experience is gained from this pilot, further refinements to the described process may be considered

Eligibility criteria for applications submitted for prequalification via the above-described pathways

- The product (FPP/BTP/API) must be invited to prequalification

[12] https://extranet.who.int/prequal/medicines/full-assessment-multisource-generic-fpps

- For products approved by ML3/ML4 NRAs, the product must have received marketing authorization from the reference NRA after the date the NRA achieved the ML3/ML4 status
- For products approved by WLAs, the product must have received marketing authorization from the reference NRA since the three years prior to designation of the NRA as a WLA[13].
- The NRA status as WLA includes at a minimum the marketing authorization and registration (MA), licensing of establishments (LI), regulatory inspection (RI-GMP/GDP/GCP), market surveillance and control (MC), laboratory access and testing (LT) and vigilance (VL) functions for Medicines. [14] [15]

Pre-submission meetings

Applicants interested to make a prequalification application according to the above-described procedures are requested to contact PQT for a pre-submission meetings.

[13] Does not apply for products approved by BfArM, EMA, Health Canada, MHRA, MPA, CBG/MEB, Swissmedic, TGA, FAMHP or USFDA
[14] For innovative products, the WLA status should also include the clinical trial (CT) function
[15] Note: the designation of NRAs as ML3/ML4 by WHO requires achievement of ML3/ML4 indicators for all regulatory functions