

MODULE II

PRAGMATIC APPROACH TO ASSURE QUALITY OF MNCH PRODUCTS

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Pharmaceutical products that have achieved SRA approval, have been prequalified by the WHO PQTm, or have a positive ERP recommendation are considered high-quality and therefore widely recommended for procurement. However, many MNCH products are not covered by the WHO PQTm, ERP, or an SRA. Moreover, procurement agencies have limited capacity and often are not able to assess the product information package and manufacturing site in the way that those stringent bodies do. A pragmatic approach is therefore necessary for procurement agencies with limited capacity, in order to support their procurement QA system and allow timely access to additional quality MNCH products beyond the WHO PQTm, SRA, or ERP coverage, to serve patient needs.

All pharmaceutical products must be approved by the NMRA in the country where they will be used. And, in addition, products should be only be procured if the product meets the following criteria:

1. The products are WHO prequalified by the WHO PQTm OR are approved by a stringent regulatory authority (soon to be replaced by WHO Listed-authorities).
OR
2. In the absence of either WHO-prequalified or SRA-approved, on an interim basis, they are approved by a qualified Expert Review Panel, convened by WHO
OR
3. In the absence of WHO-prequalified or SRA-approved or qualified by an ERP, products should be procured through accredited sources such as wholesalers which are recognized/accredited (i.e., GDP, ISO certified) by established entities as meeting a minimum level of product testing by a WHO PQP Control Laboratory, which would determine whether the product is substandard or falsified.

As with ERP, this does not ensure the products's quality, but provides a high level of confidence that the product is not substandard or falsified.

When it is necessary to adopt this process, such procurement approvals should be limited to 12 months.

Quality assurance of these products requires several components:

- Accordance with international standards of manufacturing quality (i.e., ICH or WHO), assessed independently by qualified experts
- Assured compliance with international cGMP (i.e., ICH or WHO) after site inspection by independent experts
- Assessment by an organization that can impose significant consequences for non-compliance

This module describes different assessment processes, documentation requirements, and quality control requirements, based on the registration status of the product to be prequalified, that should be considered to assure the quality of MNCH products during the prequalification and procurement.

ASSESSMENT PROCESS

There are two possible assessment approaches, abridged assessment or full assessment, as discussed below.

Abridged Assessment

Abridged assessment can be done for products already prequalified by the WHO PQTm, approved by an SRA, positively assessed by ERP, or registered by the NMRA of the country of use or other recognized NMRAs. The procurement agency can recognize the scientific evaluation of pharmaceutical products that has been conducted by those parties to facilitate and accelerate the prequalification process, and optimize use of procurement agency's and manufacturers' resources.

Under the abridged assessment procedure, the manufacturer shares evidence of previous regulatory approval with the procurement agency such as the WHO prequalification approval letter, marketing authorization or CPP issued by the SRA or recognized NMRA, the ERP letter indicating recommendation for use, and other documents as indicated in this module's Section 2, Documentation Requirements. The procurement agency then bases its decision to prequalify the product on the basis of this information to avoid repeating the comprehensive assessment.

Note: The validity period of the ERP recommendation is usually limited to a maximum duration of 12–18 months from the time of the ERP recommendation, depending on the quality assurance policy of the procurement agency that commissioned the ERP review. Therefore, the procurement agency that wishes to adopt the ERP recommendation needs to verify its validity at that point in time and undertake a risk analysis for the limited-time procurement.

Full Assessment

When the procurement agency needs to procure a product that has no WHO prequalification, regulatory approval from the SRA or other recognized NMRAs or ERP recommendation, a full assessment of the documents demonstrating quality, safety, and efficacy of the product, as indicated under Section 2(c) below, should be carried out. The procurement agency, through its technical

experts or appointed qualified external evaluators, has to assess the quality risks of the product to make a decision regarding time-limited procurement, during which time the manufacturer is expected to progress along the NMRA registration process or waiving the registration requirement.

Risk assessment is applied to the following major product attributes for the submitted product:

- GMP status of the manufacturing site
- FPP manufacture and controls
- Stability and shelf life
- API sources and quality
- Evidence of therapeutic equivalence

The following deficiencies should be considered as “objection to procurement”:

- Evidence of GMP compliance is insufficient.
- FPP specification or analytical validation for a critical test parameter are unacceptable; for sterile products, the manufacturing process is not adequately validated.
- The available stability data do not allow any assignment of product shelf life.
- Efficacy and safety data have not submitted, or are unsatisfactory (e.g., several major deficiencies).
- API specification is not acceptable for a critical test parameter such as impurities.

For the product that has deficiencies listed below, procurement may be considered only when there are no alternatives, and provided the benefit outweighs the risk of procuring a product that lacks full quality assurance. These deficiencies include:

- The FPP specification is acceptable but analytical methods are not sufficiently validated.
- Shelf life is supported by insufficient stability data (e.g., submission of data on only one batch of a product with potential stability problems).
- Bioequivalence data have not been submitted, but for orally administered products, multimedia dissolution data show similarity (i.e., for non-oral products other in vitro data, as applicable, indicate similarity), AND/OR the comparator is a generic product not prequalified or SRA-authorized.
- The API has acceptable specifications but GMP issues have been identified.

Samples should be analyzed for a product that does not possess regulatory approval from the NMRA of country of use or other recognized NMRAs or when the quality is in doubt, to ensure compliance with the finished product specification. The procurement agency should ensure that the testing laboratory complies with cGMP and GLP. The use of a WHO-prequalified quality control laboratory or an ISO:IEC 17025 accredited laboratory is, therefore, recommended.

DOCUMENTATION REQUIREMENTS

The type of product information package required for submission during the prequalification process will depend on the registration status of products to be prequalified, as reviewed below.

A. Products prequalified by the WHO PQTm, approved by an SRA, or positively assessed by the ERP

The products already prequalified by the WHO PQTm, approved by an SRA, or positively assessed by the ERP are considered quality-assured and therefore recommended for prequalification and procurement.

The procurement agency should stipulate that the submitted product be the same as the products approved under WHO PQTm or SRA or ERP in terms of all the technical characteristics, including:

- Same composition for both API and excipients
- Same API and excipient sources
- Same manufacturing facility/line/equipment/building
- Same specifications for the API
- Same specifications for the FPP
- Same type of packaging material

Any differences should be declared and justified by the manufacturers as not having any impact on altering the safety, efficacy, and quality of the FPP.

Abridged assessment can be carried out since the product has already passed the stringent evaluation of quality, safety, and efficacy. The following information/documents should be included in the product information package to be submitted to the procurement agency for abridged assessment during the prequalification process:

- A statement confirming that the FPP, including but not limited to composition/formulation, strength, manufacturing process, specifications, packaging, and product information, will, at the time of submission and after prequalification, in all respects be the same as the product prequalified by WHO PQTm, registered with the reference SRA, or recommended for use by the ERP
- A copy of the WHO prequalification approval letter, marketing authorization issued by the reference SRA, or the ERP letter indicating recommendation for procurement, or the equivalent thereof, to demonstrate that the product is already prequalified by the WHO PQTm, approved by SRAs, or reviewed and recommended for use by the ERP
- The approved product information (i.e., Summary of Product Characteristics or an equivalent thereof; the patient information leaflet or equivalent thereof; and the labeling)
- Samples of the same product for which prequalification is requested, to enable visual examination with respective COA

The product must be authorized by the NMRA in the country of use before it can be procured and supplied to the country. The procurement agency should work closely with the NMRA to ensure that expedited registration process is applied to accelerate an access to the product. The NMRA is encouraged to recognize the WHO prequalification approval letter, marketing authorization issued by the reference SRA, and the ERP letter indicating recommendation for procurement, to avoid duplication of assessment

B. Products approved by the NMRA in the country of use or other recognized NMRAs:

The NMRA is responsible for the quality assurance of medicines, including evaluation of the quality, safety, and efficacy data of the finished pharmaceutical products and inspection of the corresponding manufacturing facilities according to current international norms and standards. However, some NMRAs may not maintain their regulatory requirements or evaluation systems in line with the current international norms and standards. Therefore, the procurement agency should consult with the NMRA and WHO to determine whose regulatory approval can be recognized and an abridged assessment can be carried out.

The procurement agency should require that the submitted product be the same as the products approved by the NMRA, in the country of use or other recognized NMRAs, in terms of all the technical characteristics including:

- Same composition for both API and excipients
- Same API and excipient sources
- Same manufacturing facility/line/equipment/building
- Same specifications for the API
- Same specifications for the FPP
- Same type of packaging material

Any differences should be declared and justified by the manufacturers as not having any impact on the safety, efficacy and quality of the FPP.

Abridged assessment can be carried out since the product has already passed the evaluation of quality, safety, and efficacy according to international norms and standards. The following information/documents should be included in the product information package submitted to the procurement agency for abridged assessment during the prequalification process:

- A statement confirming that the FPP, including but not limited to composition/formulation, strength, manufacturing process, specifications, packaging, and product information, will, at the time of submission and after prequalification, in all respects be the same as the product approved by the NMRA in the country of use or other recognized NMRAs
- A copy of the marketing authorization or current CPP issued by the NMRA in the country of use
- Evidence of GMP compliance such as GMP certificate, inspection report issued by the recognized NMRA, or regional registration harmonization initiatives
- The approved product information (e.g., SmPC or an equivalent thereof, PIL or equivalent thereof, and the labeling)
- Samples of the same product for which prequalification is requested, to enable visual examination with respective COA

C. When the conditions established in A. and B. are not met, or there is a need to reassess the product quality

When the registered products may not meet the previous criteria set by the procurement agency or when there are not enough registered products available, the procurement agency may need to obtain the products from unregistered sources. The procurement agency should request the manufacturers to:

- Register the products with the NMRA in the country of intended use

OR

- Apply for a waiver, if they are able to meet the conditions for waiving the registration requirements as indicated by the NMRA in the country of intended use

The procurement agency should work closely with the NMRA to ensure that mechanisms or regulations are in place to fast-track registration or to waive the registration requirements, in order to facilitate government tenders.

To assure the quality of the product, full assessment should be carried out. The manufacturers should be requested to provide the following information/documents in the product information package for the procurement agency to review during the prequalification process:

- A copy of the marketing authorization, current CPP, or manufacturing authorization (certifying that the firm is allowed to manufacture the submitted product) issued by the NMRA in the country of origin
- Registration status in other countries, including all information on where the product has been withdrawn from the market, or on where application has been rejected, deferred or withdrawn
- Evidence of GMP compliance such as GMP certificate, inspection report issued by the competent NMRA
- Product quality review
- FPP manufacturing process
- API and FPP specifications in compliance with recognized standards from internationally recognized pharmacopoeia (e.g. United States, British, European or International Pharmacopoeias)
- Stability testing data (both accelerated and real time studies) as per ICH and/or WHO guidelines
- Evidence of safety and efficacy (e.g., bioequivalence data, data to support bio-waiver)
- The approved product information (e.g., Summary of Product Characteristics or an equivalent thereof, product information leaflet or equivalent thereof, and the labeling).
- Samples of the product with sufficient number of dosage form units to perform full laboratory analysis, including the respective COA

Technical experts of the procurement agency should review and perform a risk assessment of the information obtained to reach a conclusion as to the potential acceptability of the limited-time procurement. This assessment mechanism is a temporary solution to pursue while the product undergoes registration or a waiver for registration requirement is in process with the NMRA.

Suitably qualified external evaluators may be appointed, subject to compliance with the policy of the procurement agency regarding aspects such as confidentiality, conflicts of interest, and financial resources.

QUALITY CONTROL REQUIREMENTS

Quality controls consist of pre-shipment quality control at manufacturer level prior to sending the product to the procurement agency, post-shipment quality control at the procurement agency level, and postmarketing surveillance to ensure that the products are properly stored and always meet the

desired quality for use by the patient. The quality control requirements will depend on the registration status of products to be prequalified, as reviewed below.

A. Products prequalified by the WHO PQTm, approved by an SRA, or positively assessed by the ERP

Pre-shipment quality control:

- Pre-shipment quality control is required at manufacturer level prior to sending the product to the procurement agency.
- The procurement agency should check the COA issued by the manufacturer to confirm that the product delivered is the same that was prequalified and ordered and is certified to meet FPP specification.

Post-shipment quality control including import control (inspection and quality control testing on importation and arrival at the distribution/storage warehouse):

- Post-shipment quality control may be considered at the procurement agency level.
- Products may be randomly sampled and sent for independent laboratory analysis. Testing should be done to assess compliance with the product specifications. Use of a laboratory compliant with international standards (e.g., WHO-prequalified or ISO:IEC 17025 accredited) is recommended to ensure the accuracy of results.

Post-marketing surveillance:

- The products should be regularly sampled and tested as part of a risk-based post-marketing strategy to ensure that products are properly stored and always meet the desired quality for use by the patient. This will also help to identify substandard and falsified medicines that may have been smuggled into the supply chain.

B. Products approved by the NMRA in the country of use or other recognized NMRAs

Pre-shipment quality control:

- Pre-shipment quality control is required at the manufacturer level prior to sending the product to the procurement agency.
- The procurement agency should conduct pre-shipment inspections on randomly selected shipments through an independent inspection agent. The independent inspection agency is in charge of collecting the samples and forwarding them to a laboratory compliant with international standards (e.g., WHO-prequalified or ISO:IEC 17025 accredited) for quality control testing. This process is in addition to the manufacturer's own quality control testing.

Post-shipment quality control including import control (inspection and quality control testing on importation and arrival at the distribution/storage warehouse):

- Post-shipment quality control may be considered at the procurement agency level.
- Products may be randomly sampled and sent for independent laboratory analysis. Testing should be done to assess compliance with the product specifications. Use of a laboratory compliant with international standards (e.g., WHO-prequalified or ISO:IEC 17025 accredited) is recommended to ensure the accuracy of the results.

Post-marketing surveillance:

- The products should be regularly sampled and tested as part of a risk-based post-marketing strategy to ensure that the products are properly stored and always meet the desired quality for use by the patient. This will also help to identify substandard and falsified medicines that may have been smuggled into the supply chain.

C. When the conditions established in A. and B. are not met, or there is a need to reassess the product quality

Pre-shipment quality control:

- Pre-shipment quality control is required at the manufacturer level prior the product is forwarded to the procurement agency.
- The procurement agency should conduct pre-shipment inspections on each shipment through an independent inspection agent. The independent inspection agency is in charge of collecting the samples that are sent to a WHO-prequalified or ISO:IEC 17025 accredited quality control laboratory for testing. This process is in addition to the manufacturer's own quality control testing.

Post-shipment quality control including import control (inspection and quality control testing on importation and arrival at the distribution/storage warehouse):

- Post-shipment quality control is required at the procurement agency level.
- Products should be randomly sampled and sent for independent laboratory analysis. Use of a WHO-prequalified or a ISO:IEC 17025 accredited quality control laboratory is required to ensure the accuracy of the results. The samples should be analyzed for compliance with the product specifications.

Post-marketing surveillance:

- The products should be regularly sampled and tested as part of a risk-based post-marketing strategy to ensure that the products are properly stored and always meet the desired quality for use by the patient. This will also help to identify substandard and falsified medicines that may have been smuggled into the supply chain.