

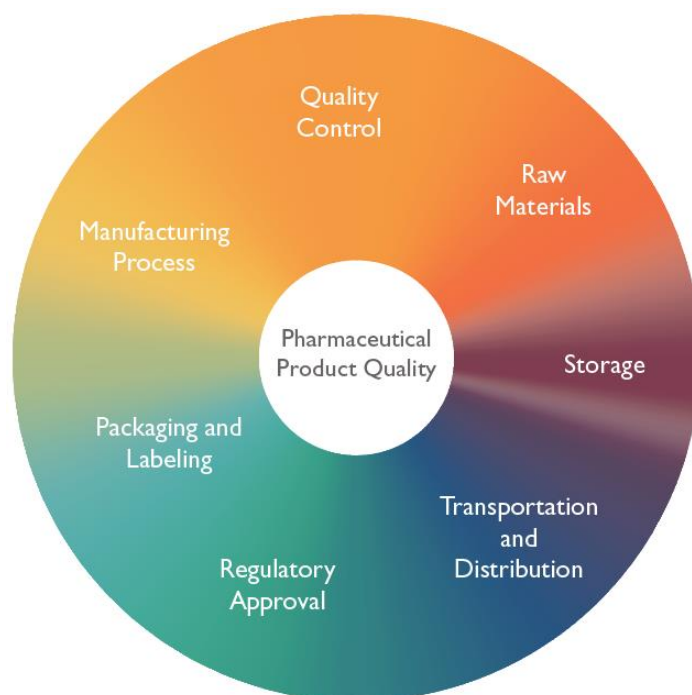
MODULE I
QUALITY ASSURANCE IN
PROCUREMENT

MODULE I

QUALITY ASSURANCE IN PROCUREMENT

Quality assurance (QA) is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates several factors and it is an integral part of all key activities in the product supply chain (Figure 1).

Figure 1: Determinants of pharmaceutical product quality in the supply chain



The determinants of pharmaceutical product quality in the supply chain and corresponding quality assurance approaches can be outlined as follows.

Raw materials

The quality of raw materials used to manufacture the product is critical in determining the quality of the finished pharmaceutical product. Therefore, sources and quality of the raw materials (active and inactive ingredients) must be assessed to ensure that they meet regulatory and international quality standards.

Quality control

The finished pharmaceutical product (FPP) must pass internal quality control testing performed by the manufacturer prior to submission for registration. Subsequently, once the product is approved, every lot released to the market must have a Certificate of Analysis (COA). In addition, once the manufacturer has been selected for procurement, the pharmaceutical product must pass the random pre- and post-shipment inspections conducted by the procurement agency through an independent inspecting agent using an independent WHO-prequalified or ISO:IEC 17025 certified quality control laboratory. Pre- and post-shipment testing assures the pharmaceutical product complies with the standards applied by the procurement agency and its regulatory requirements.

Manufacturing process

The manufacturing site and process used for the pharmaceutical product must comply with current Good Manufacturing Practice (cGMP) requirements, as evidenced by GMP certificate and/or inspection report issued by the WHO Prequalification Team: Medicines (PQTm), an SRA, a Pharmaceutical Inspection Co-operation Scheme (PIC/S) member inspectorate, or a recognized NMRA or regional registration harmonization initiative.

Packaging and labeling

The packaging components should be suitable with respect to safety of materials, compatibility of the materials with the finished product, and protection from moisture and light, to ensure product quality during transportation and storage. Labels and product information for health care providers and end users should be provided in the appropriate format and comply with the regulatory requirements of the country where the product will be used. Labels should contain information on cold storage if the product is heat-sensitive.

Regulatory approval

The pharmaceutical product should obtain regulatory approvals from the NMRA in the country of origin and the country where it will be used, proving that the product meets acceptable standards of safety, efficacy, and quality. Furthermore, regulatory approval from any SRA, WHO prequalification, and recommendation for procurement from ERP are good indicators that the pharmaceutical product is of assured quality, safety, and efficacy.

Transportation and distribution

The pharmaceutical product should be transported and distributed in a manner that will maintain the appropriate storage conditions (e.g., controlled temperature, protection from

the environment). The logistics system should support and ensure access and availability for these processes without compromising quality.

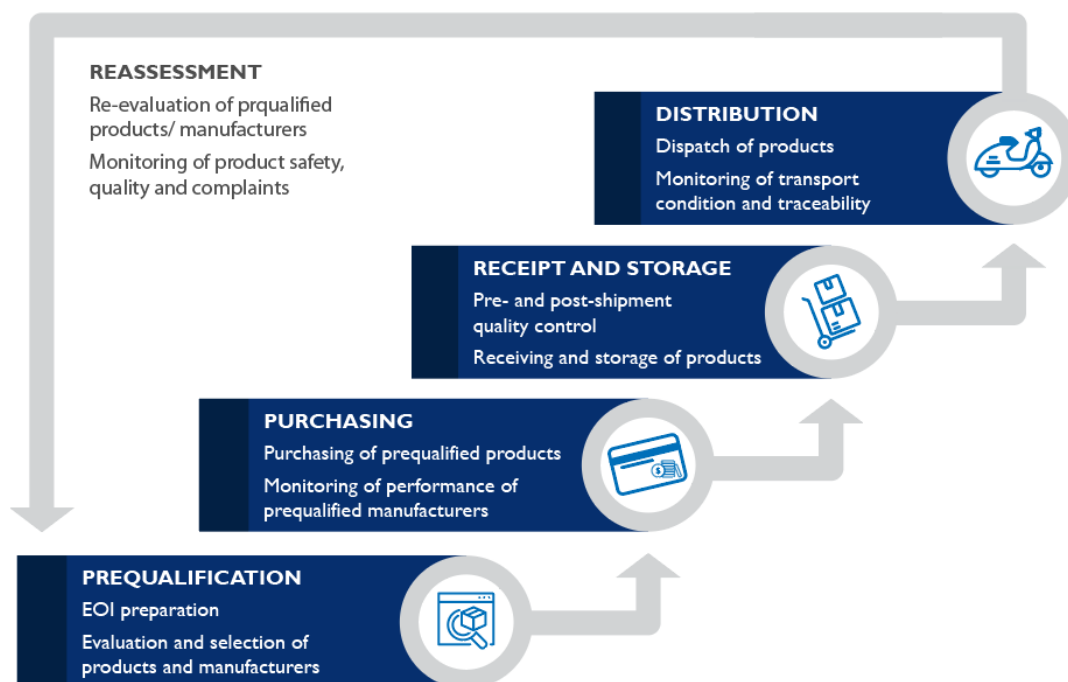
Storage

The pharmaceutical product needs to be stored under the appropriate conditions established based on the results of stability testing, in order to avoid changes in quality that may affect the safety and/or efficacy of the final product to be administered to/consumed by the public. Where special storage conditions are required (e.g., cold chain) these should be provided, checked, monitored, and records maintained.

According to WHO's MQAS, in the procurement of pharmaceutical products, quality assurance covers all steps in the provision of these products, as shown in Figure 2. The key objective of quality assurance during procurement is to ensure that only pharmaceutical products that are safe, effective, and of assured quality, and conform with internationally recognized standards for pharmaceutical products, are procured and *that their quality is maintained* until supplied to end users.

The quality assurance approaches for each step in the procurement of pharmaceutical products (as shown in Figure 2) will support procurement agencies in ensuring that procurement is carried out in accordance with the WHO MQAS. Ensuring an effective quality assurance system during procurement will reduce risks of sourcing substandard or falsified pharmaceutical products and reduce the risk of subsequent deterioration, thereby potentially reducing the incidence of product complaints and recalls, financial losses, and most important, the risk of harming patients' health.

Figure 2: Quality assurance framework for the procurement of pharmaceutical products



PREQUALIFICATION

Prequalification is one of the key elements in ensuring purchase and supply of quality-assured pharmaceutical products. Prequalification includes the activities undertaken in defining a product need, seeking expressions of interest (EOI) from manufacturers to supply the product, and assessing the product offered against the specifications, and assessing the facility where the product is manufactured against cGMP standards.

The list of prequalified products from a specific manufacturing site is identified following the product evaluation and manufacturing site inspection. Maintaining a list of prequalified products ensures that quality products are obtained from qualified sources.

The procurement agency should have trained and qualified personnel to perform prequalification activities as described in the WHO MQAS. The procurement agency should establish a document describing the policy and procedures for prequalification, including standards and criteria used in the evaluation of product information and manufacturing facilities. Prequalification requires a knowledge of QA principles, and the prequalification staff make decisions regarding quality.

Where prequalification activity is delegated to another organization (e.g., expert review panel, external evaluators, or quality control laboratory), a written agreement is required between the two parties. The contract giver should ensure that the contract acceptor meets the required qualifications. The written agreement for the performance of work and terms of reference for contracted evaluators should be in place before commencement of work.

Key Steps in the Prequalification Process

Figure 3 summarizes the key steps in the prequalification process. The quality assurance approaches for each step in the prequalification process are described below.

Figure 3: Prequalification process



STEP 01

**Solicit information**

Prepare expression of interest, including product specification
Establish submission procedures

✦ Develop a list of product specifications

The procurement agency should develop a list or catalog of products, described by International Nonproprietary Name (INN), that are identified for purchasing based on need, the national list of essential medicines, and the *WHO Model List of Essential Medicines*.¹ The unit or appointed person responsible for prequalification should establish technical specifications for the product(s) to be prequalified. The specifications should be detailed, clear, and unambiguous to avoid unnecessary submission and processing of documentation not relevant to the product to be sourced.

The product specifications should state, at a minimum:

- Name of the active pharmaceutical ingredient (API)/INN
- Strength per dose
- Dosage form (route of administration)
- Primary packaging materials
- Pack size
- Shelf life
- Labeling requirements

Recommended technical specifications for key MNCH products are provided in Module III of this manual.

Moreover, to be eligible for procurement and supply, the product also requires approval by the NMRA in both the country of origin and the country where it will be used.

✦ Establish quantification

All requests for products should include quantities. The personnel responsible for purchasing should establish quantification. Accurate quantification (forecast and supply plan) of needs is essential to avoid shortages or excess stocks. Quantities purchased should be based on a reliable estimate of actual need. The possible methods of product quantification include the consumption method, the morbidity method, and the adjusted or extrapolated consumption method, or better, a combination of several methods. Guidance on quantification of MNCH products should be consulted.^{2,3}

¹ World Health Organization. n.d. *WHO Model List of Essential Medicines*. Geneva: WHO. Available at <http://www.who.int/medicines/publications/essentialmedicines/en/>

² JSI and SIAPS. 2015. *Quantification of Health Commodities: RMNCH Supplement Forecasting Consumption of Select Reproductive, Maternal, Newborn and Child Health Commodities*. Updated January 2016. Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. Arlington, VA: Management Sciences for Health. Submitted to the United Nations Children's Fund by JSI. Arlington, VA: JSI Research & Training Institute, Inc. Available at <http://apps.who.int/medicinedocs/documents/s22288en/s22288en.pdf>

³ USAID | DELIVER PROJECT. 2014. *Quantification of Health Commodities: A Guide to Forecasting and Supply Planning for Procurement*. Arlington, VA: USAID | DELIVER PROJECT, Task Order 4. Available at <http://apps.who.int/medicinedocs/documents/s21547en/s21547en.pdf>

✦ Define procurement method

The procurement agency should apply the procurement method according to their policy and procedures. There are different methods of procurement. A brief description of each procurement method is provided below.

■ Restricted tender

In a restricted tender, also called a “closed bid” or “selective tender,” interested suppliers are approved in advance through a prequalification process. This type of procurement is often referred to as *limited international bidding* (LIB), which is an “invitation to competitive bids” conducted by direct invitation to all prequalified suppliers. Procurement agencies should use restricted tenders to invite bids from prequalified suppliers for all health products and services whenever possible.

■ Competitive negotiation

This method is also referred to as “international/national shopping.” The basis of this method is the comparison of price quotations obtained from several local or foreign suppliers. Usually, quotations are solicited from a minimum of three suppliers to ensure competitive prices. This method is appropriate for procuring small amounts of readily available products. However, its use should be explicitly justified, and approval should be obtained from senior management. Only prequalified products and suppliers should be used.

■ Direct procurement

In direct procurement, products are obtained directly from a single source without applying the requirements of a tender process or comparing price quotations. Normally, direct procurement is not recommended, but it may be used when there is only one prequalified source for the product to be procured. A history of “reasonable” prices for the product in question should be assessed to negotiate the price with the supplier.

■ Open tender

Open tender is the formal procedure by which all manufacturers, national and international, are invited to bid for the sale of goods. The term *international competitive bidding* (ICB), which is an open tender to all manufacturers, is often used. Open tendering is not appropriate for health products because it may be difficult to establish, before a contract is awarded, whether unknown bidders will be able to supply products of the required quality in the required quantities on a sustained basis.

✦ Establish procedure of submission and content of product information package

The unit or appointed person responsible for prequalification should establish the procedure for submitting product information package. The procedure should be written in clear, unambiguous language and should contain information detailing, at a minimum:

- The content (i.e., type of product information required) and format of submission (i.e., paper or electronic submission)
- The process of submission, including the focal point for the submission and address to which the documentation should be sent

The type of product information required for submission will depend on the registration status of products to be prequalified. According to the WHO MQAS, the product information package may be in three different formats:

- For products manufactured and registered in countries where regulatory requirements are in line with international regulations for assessment of safety, efficacy, and quality, the following information should be submitted:
 - A WHO-type certificate of pharmaceutical product (CPP) issued by a stringent regulatory authority, together with a Summary of Product Characteristics (SmPC), or proof of the official registration of the product.
 - If the product is different from the one registered by the SRA, arguments and/or data to support the application should be submitted. These may include differences in formulation, strength, or other specifications, such as packaging.
 - Products that are registered for export purposes only should be fully assessed unless these were approved or subject to a positive opinion under the Canada S.C. 2004, c. 23 (Bill C-9) procedure, or Article 58 of European Union Regulation (EC) No. 726/2004 or US Food and Drug Administration (US FDA) tentative approval.
- A standard product dossier as prepared for an NMRA should be submitted, provided it contains the appropriate information as required in the WHO guidelines (e.g., common technical document [CTD]). In such cases, the supplier should provide a covering letter that indicates where the required information can be found in the standard product dossier.
- A completed pharmaceutical product questionnaire with supporting information as listed in the annexes should be submitted. The interagency finished pharmaceutical product questionnaire is shown in Appendix 6 of the WHO MQAS.

It is apparent that, in the absence of WHO-prequalified or SRA-approved products, the procurement agency needs to review the product dossier or product questionnaires (options 2 or 3 above) submitted by the manufacturer to prequalify the product to be purchased. In reality, however, many procurement agencies have limited capacity or lack the technical expertise to do so. A pragmatic approach, using different assessment processes, documentation requirements, and quality control requirements, depending on the registration status of the product (e.g., WHO prequalification, SRA approval, ERP recommendation, recognized NMRA approval), is therefore suggested. Details can be found in [Module II](#).

Prepare and publish the invitation for EOI

Once the product specifications, quantification, procurement method, content of product information package, and procedure for submission are established, the invitation for EOI can be published widely to the manufacturers. The information in the EOI should include, at a minimum:

- Purpose of the invitation
- List of products, including specifications for each product
- Information on quantities required
- Details of the information to be submitted
- Procedure for submission, including information on details to be submitted, on the focal point for submission and on the format for submission

- Contact details (name, address, telephone number, fax, email, and postal address) for submission
- The closing date for receipt of the information by the procurement agency

An sample EOI is provided in Appendix 5 of the [WHO MQAS](#).

STEP 02



Receive product information

Identify, mark, and record the received files and samples
Allocate the unique reference number

The procurement agency should have the necessary infrastructure to receive and process the product information package submitted by manufacturers. It will require personnel for processing the documentation; written procedures for receiving, identifying, and marking files, containers, and samples; and sufficient space for unpacking and storage.

Each product should be allocated a unique reference number to ensure traceability of the product information package. A record of all the information received from each manufacturer should be maintained.

STEP 03



Screen product information

Check completeness of the product information package received and put in record
Inform the manufacturer the screening results and/or request for missing information

Each product information package submitted by the manufacturer should be screened for completeness. The screening should be done in accordance with a written procedure. A screening form should be used to ensure consistency of screening. There should be a written record of the screening of each product information package. Information to be recorded should include:

- Date of receipt
- Product number
- Name of product
- Name of the applicant (i.e., supplier)
- Name and address of manufacturer
- Outcome of screening

An example of a standard operating procedure (SOP) for screening, including a sample screening form, is shown in Appendix 7 of the [WHO MQAS](#).

Only product information packages that meet the requirements of the screening procedure should be retained for full evaluation. Incomplete product information packages should be excluded from the evaluation procedure and inspection process. The manufacturer should be informed of an incomplete information package and requested to supply the missing information within a specified period. If this request is not complied with, the application should be rejected on grounds of incompleteness.

STEP 04



Step 4: Evaluate product information

Abbreviated assessment for products with WHO prequalification, SRA approval, ERP recommendation, or recognized NMRA approval
Otherwise, full assessment

The personnel responsible for evaluation of the product information package should have relevant qualifications and experience, which may include a background in pharmaceuticals, pharmaceutical chemistry, or pharmacology. Ideally, they should be from a pharmaceutical regulatory background or have regulatory experience.

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.

Different assessment approaches may be used, depending on the registration status of products to be prequalified. For example, full assessment may not be required, and an abridged assessment may be used instead, when products are already prequalified by the WHO PQTm, approved by an SRA, or recommended for use by the ERP. Details are given in Module II of this manual.

Time frames should be set for evaluation of the product information package. A written procedure for evaluation should be followed. A sample SOP for evaluating the product information package is shown in Appendix 7 of the WHO MQAS. The person responsible for evaluation should monitor the process to ensure that each product information package is evaluated in compliance with these requirements.

Each evaluator should prepare a formal evaluation report for each product, including a recommendation for acceptance or rejection. The evaluation report should be communicated to the manufacturer.

A response should be invited from the manufacturer in cases where data and information are found to be incomplete or do not meet the guidelines. A reasonable period should be allowed for submission of additional data and information. This additional information should be assessed, and the final outcome of the evaluation should be communicated to the manufacturer.

The evaluation report should be filed with the product evaluation documentation for reference purposes and follow-up where relevant.

Samples may be analyzed—if deemed necessary based on risk assessment—in accordance with the finished product specification. If deemed necessary, samples should be randomly selected for analysis. Certificates of analysis of product samples should be made available to the procurement agency.

The procurement agency should have access to a quality control laboratory to perform analyses. Alternatively, a laboratory may be contracted to perform the analyses. In either case, the procurement agency should ensure that the laboratory complies with cGMP and Good Laboratory Practices (GLP).⁴ The use of a WHO-prequalified quality control

⁴ World Health Organization. 2010. "WHO Good Practices for Pharmaceutical Control Laboratories." Annex 1 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 44th Report. WHO Technical Report Series, No. 957. Geneva: WHO. Available at <http://apps.who.int/medicinedocs/documents/s18681en/s18681en.pdf>

laboratory or an ISO:IEC 17025 accredited laboratory is therefore recommended. The list of WHO-prequalified quality control laboratories can be found at <https://extranet.who.int/prequal/content/medicines-quality-control-laboratories-list>.

The procurement agency is responsible for ensuring access to raw data. The procurement agency should have a procedure for investigating, handling, and reporting out-of-specification results when these are obtained from laboratories. If a sample fails to meet the specifications, the procurement agency should investigate the problem and communicate the outcome to the manufacturer.

STEP 05



Step 5: Perform inspection

Desk review of GMP evidences from the WHO PQP, an SRA, a PIC/S member inspectorate, or a competent NMRA
Perform GMP inspection if deemed necessary

The need for an inspection may be waived where there is evidence that the site was inspected and approved by the WHO PQTm, an SRA, a PIC/S member inspectorate, a recognized NMRA, or regional registration harmonization initiative, if the following conditions apply:

- All aspects of cGMP for the relevant product(s) have been covered.
- The approval was within the last 36 months.
- There is a statement from the manufacturer that no major changes have been made to the premises, equipment, or key personnel since the inspection by the WHO PQTm, SRA, PIC/S member inspectorate, recognized NMRA, or regional registration harmonization initiative.

In addition to the GMP certificate, a copy of the inspection report, corrective and preventive action (CAPA) reports, and the most recently completed product quality review report from the manufacturer may be requested to verify the cGMP compliance status of the manufacturing site as part of the prequalification procedure.

However, GMP inspection may be warranted under certain circumstances—for example, report of incidents with the product and/or manufacturer. Inspections should be performed in accordance with a written procedure.

Information submitted in relation to the supply of the API, formulation of the product, manufacturing method, and stability data should be verified during the inspection. The inspection should cover the evaluation and assessment of the manufacturing documentation, premises, equipment, utilities, and materials. It should also cover verification of data and documentation, such as results, batch records, compliance with an SOP, as well as information submitted on the manufacturing method, equipment. Inspection should further include (but not be limited to) validation of the manufacturing process, validation of utilities and support systems, and validation of equipment.

Personnel responsible for inspecting manufacturing sites should have relevant qualifications and experience in pharmaceutical manufacturing, quality assurance, cGMP and GDP, performing inspections and audits, chemistry, and quality control. Ideally, they should have an inspection background from working with a pharmaceutical regulatory authority or experience in managing manufacturing sites. A sufficient number of inspectors should be appointed to carry out inspections within predetermined time frames. External inspectors

may be appointed, provided there is no conflict of interest and confidentiality undertakings are agreed upon and maintained.

The inspector or inspection team should prepare a formal inspection report for each manufacturing site inspected, and make a recommendation on the status of the manufacturer in relation to compliance with cGMP. The inspection report should be communicated to the manufacturer. Where non-compliance was observed, corrective actions and timelines for completing them should be suggested. A response with supporting documentation should be invited from the manufacturer. If any additional information is required, or if corrective action is necessary, a final recommendation as to the acceptability of the product and manufacturer should be made only after such information has been evaluated or the corrective action has been verified.

STEP 06

Step 6: Finalize the assessment process



Summarize the assessment outcomes and inform the manufacturer
Prepare a list of prequalified products and manufacturers

The outcomes of the evaluation of product information package, cGMP compliance, and laboratory results for samples analyzed, if applicable, should be collated and used as the grounds for making the decision to accept or reject a product and/or manufacturer. The procurement agency should inform the manufacturer in writing of the outcome of the prequalification of each product manufactured at each specified site.

The unit or appointed person responsible for prequalification should record the outcome of the prequalification process in a list of prequalified products and manufacturers. The list should be product- and manufacturing-site specific. The list may be published in the public domain.

The procurement agency should have an agreement with the supplier to ensure compliance with the prequalification principles and that the products supplied are the same products as were prequalified (e.g., they are manufactured at the same site and the same processes are adhered to).

The list should be reviewed and updated at regular intervals. Newly prequalified manufacturers should be added to the list as they become qualified, and non-compliant manufacturers should be removed from the list as soon as they are recognized as such.



Procurement should be done with the aim of purchasing effective, safe, and quality-assured products, and should not be focused on price alone. To be effective, the procurement agency should ensure that the following principles are applied in purchasing:

- Prequalified products are purchased from approved manufacturers or suppliers.
- Procurement and purchasing procedures are transparent.

- Activities follow formal written procedures throughout the process, including explicit criteria for awarding contracts.
- Independent contract review is ensured.
- Purchasing is based on the defined procurement policy of the procurement agency.
- Purchasing and tender documents list all pharmaceutical products by their INN or national generic names.
- Suppliers are selected and monitored through a process that takes into account product quality, service reliability and performance, delivery time, ethics, legal status, financial viability, and minimum order quantities.
- Intellectual property rights are respected in accordance with best practice and national law.

Purchasing should be done by personnel with appropriate qualifications and training. The personnel responsible for purchasing should be independent from those responsible for prequalification and quality assurance, and should sign confidentiality agreements and declarations of conflict of interest. The personnel should follow transparent, written procedures throughout the process of purchasing and should use explicit criteria for deciding to whom to award contracts. Procurement should be planned properly, and procurement performance should be monitored regularly.

The procurement process and products to be purchased need to comply with the destination country's legislation on registration and licensing status, quality standards, and intellectual property rights.

Whatever the procurement method, only prequalified products should be procured. Awards should be made to the manufacturer of the lowest acceptable offer for the prequalified product that meets the defined terms and conditions. The reference prices for MNCH products from key international procurers may be found in *the International Medical Products Price Guide*, available at <http://mshpriceguide.org/en/home/>.

Companies should be informed of the outcome. There should be an agreement with the supplier to ensure compliance with procurement principles and that products supplied are the same products as were prequalified (i.e., they are manufactured at the same site and the same processes are adhered to).

Monitor performance of manufacturers of prequalified products

There should be a procedure for continuous monitoring of the performance of manufacturers and suppliers. This may be a joint responsibility of the QA personnel and the purchasing group. If a decision is made to remove a product, manufacturer, or supplier from the list, the supplier or manufacturer should be notified and a mechanism should be in place to prevent purchasing from this supplier or manufacturer.

Monitoring may include:

- Review of quality control test results
- Verification that product batches supplied have been manufactured in compliance with standards and specifications accepted in the product dossier through inspection
- Pharmacovigilance (i.e., management of adverse event reporting)
- Review of rejected or failure batches

- Monitoring of complaints and recall
- Outcome of reinspection of manufacturing sites
- Outcome of reevaluation of product information
- Monitoring of direct and indirect product costs
- Monitoring of adherence to delivery schedules

Random samples of batches of pharmaceutical product(s) supplied by manufacturers of prequalified products, taken in accordance with a predefined sampling procedure (based on risk assessment), should be sent for independent testing at a reliable quality control laboratory (e.g., a WHO-prequalified laboratory) for compliance with final product specifications as part of the continuous monitoring program.

The monitoring process should include continuous commercial monitoring that includes tracking of lead time and monitoring for compliance with all contract terms and conditions.



The procurement agency should ensure that pharmaceutical products purchased are received and stored correctly and in compliance with Good Storage Practices (GSP) and GDP, as well as applicable legislation and regulations. Receipt and storage should be done in such a way that their quality and integrity is preserved, batch traceability is maintained, and stock can be rotated.

It is recommended that premises for storage are designed in such a manner that products will follow a unidirectional flow from receiving to dispatch to avoid any possible mix-ups. Effective measures should be in place to ensure the security of products.

Quality control during receipt and storage of products is important to ensure that the quality of products is satisfactory for their intended purpose before release for use. QA comprises pre-shipment and post-shipment quality control, as detailed below. The quality control unit will be in charge of quality control testing and release of received products for distribution. The analyses may be performed by a contracted laboratory, which must comply with cGMP and GLP for control laboratories. The use of a WHO-prequalified quality control laboratory or an accredited laboratory is recommended. The quality control laboratory must be capable of undertaking the full range of tests required.

Quality assurance approaches for receipt and storage of purchased products

Pre-shipment quality control

Pre-shipment is considered at the manufacturer level prior to sending the product(s) to the procurement agency or customer.

Each batch of pharmaceutical product should be tested by the manufacturer to determine that it conforms satisfactorily to its finished product specification, prior to supply. The batch

release is evidenced by the COA, which should follow the WHO model⁵ and include the results of all tests performed in comparison with the established acceptance criteria (limits), and a conclusion statement indicating the results are found to comply with product specifications.

The procurement agency may decide, using a risk-based approach, to test selected batches. It may not be necessary to do quality control testing for all products. One approach can be to limit quality control testing to those products that are not WHO-prequalified or that have no registration with an SRA. More details can be found in [Module II](#).

Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

Receipt of products

Incoming products should be cleared safely and promptly from the port of arrival. The procurement agency should ensure that all authorizations/permits or waivers necessary for the importation and customs clearance of products into the country of use are readily available prior to the delivery of the products. Specific arrangements may need to be made with local handling agents and customs to ensure speedy handling and clearance.

The person responsible for receiving the products should be independent of the person responsible for purchasing the products.

Receiving and dispatch bays should protect products from the weather. Receiving areas should be designed and equipped to allow containers of incoming products to be cleaned (de-dusting) if necessary before storage.

All incoming products should be quarantined immediately after receipt until they are released for use or distribution. Products should be quarantined until test results confirm that the products meet all of the requirements, specifications, and terms and conditions of the purchase order. Review of COAs is strongly recommended to confirm that products delivered adhere to what was ordered and are certified by the manufacturer to meet specifications.

Upon receipt, each incoming delivery should be checked for correspondence between the order, the delivery note, the supplier's labels and transport conditions (i.e., temperature and relative humidity as appropriate). The consignment should be examined for integrity of packages and seals, and uniformity of containers. Should the delivery consist of more than one batch, it should be subdivided according to supplier batch number.

Containers should be cleaned, where necessary, and labeled, if required, with the required data (i.e., label description, batch number, type, and quantity). Containers and products should be visually inspected for possible contamination, tampering and damage, expiry date, compliance with labeling and packaging instructions, and any suspect containers. If there is evidence of any irregularities, the entire delivery should be quarantined. Damage to containers and any other problem that might adversely affect the quality of the product should be recorded and investigated.

⁵ World Health Organization. 2002. "Model Certificate of Analysis." Annex 10 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 36th Report. WHO Technical Report Series, No. 902. Geneva: WHO. Available at <http://apps.who.int/medicinedocs/pdf/h3009e/h3009e.pdf>

Segregation must be provided for the storage of rejected, recalled, or returned materials or products. Such areas, materials, and products shall be suitably marked and secured. Access to these areas and materials shall be restricted.

Post-procurement quality control

Post-procurement quality control is considered at the procurement agency level or at the level of the customer. It is part of continuous monitoring of the performance of the manufacturers and suppliers.

The procedures for receipt of products should include random sampling for independent laboratory analysis by the procurement agency to ensure that pharmaceutical products meet the required standards. Sampling should be performed in accordance with a written procedure and with national legislation.

Products may also be randomly sampled at the end of the distribution chain and sent for independent analysis. Representative samples should be taken from containers in the consignment. Samples should be analyzed for compliance with the product specification.

Samples should be taken only by appropriately trained and qualified personnel and strictly in accordance with written sampling plans and sampling instructions based on a risk assessment.^{6,7,8} Containers from which samples have been taken should be labeled accordingly.

Stringent precautions should be taken to ensure that rejected products cannot be used. This can be achieved through separate storage or by means of a validated computerized system. Rejected products may await destruction or be returned to the supplier. They should be handled in accordance with a written procedure. Whatever action is taken should be approved by authorized personnel and recorded.

Storage of products

All staff should be trained to observe high levels of personal hygiene and sanitation. Personnel employed in storage areas should wear protective or working garments appropriate for the activities performed.

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of products, including space for segregation of rejected, expired, recalled or returned stock. Adequate ventilation should be in place to control temperature and relative humidity.

Highly hazardous, poisonous, and explosive materials such as narcotics, psychotropic drugs, and substances presenting potential risks of abuse, fire, or explosion must be stored in safe and secure areas. Adequate fire protection measures must be ensured in conformity with the rules of the concerned civic authority.

All products should be stored in an orderly fashion to permit batch segregation and stock rotation according to the first-to-expire-first-out rule. Stock should be stored off the floor

⁶ International Organization for Standardization (ISO). 1999. Sampling Procedures for Inspection by Attributes: Sampling Schemes Indexed by Acceptance Quality Limit for Lot-by-Lot Inspection. British Standard BS 6001-1:1999/International Organization for Standardization, ISO 2859-1:1999. Geneva: ISO.

⁷ American National Standards Institute (ANSI). n.d. Sampling Procedures and Tables for Inspection by Attributes. ANSI/ASQCZ1.4 and ANSI/ASQCZ1.9. Washington, DC: ANSI.

⁸ World Health Organization. 2005. "WHO Guidelines for Sampling of Pharmaceutical Products and Related Materials." Annex 4 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 39th Report. Technical Report Series, No. 929. Geneva: WHO. Available at <http://apps.who.int/medicinedocs/documents/s21440en/s21440en.pdf>

and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness and repair, and contents on pallets should be stacked in a manner that ensures there is no damage to containers on the lower level.

All products should be stored under the appropriate conditions as established by the manufacturer, which are based on the results of stability testing. Where special storage conditions are required (i.e., for temperature and humidity), these should be provided, checked, and monitored, and records maintained.

Temperature mapping of the facility should be well designed to support assurance of uniformity of the temperature across the storage facility. It is recommended that temperature monitors and relative humidity monitors (if required) be placed in the worst-case areas of the facility. Recorded monitoring data should be available for review.

Equipment used for continuous monitoring should be calibrated at suitable, predetermined intervals and results should be recorded, reviewed, and retained. Out-of-limit and out-of-trend results should be investigated in accordance with an SOP and appropriate action should be taken. All monitoring records should be kept for at least one year after the end of the shelf-life of the stored product, or as long as required by national legislation.

Cold rooms should be provided for storage of products requiring storage between 2°C and 8°C—for example, for oxytocin injection. Cold rooms should be qualified, which includes temperature mapping. The temperature should be controlled, monitored, and recorded, with results reviewed for compliance with the specified limits. Where electronic systems are used for data collection, provision should be made for backup of data at regular and defined intervals. Cold rooms should be fitted with alarm systems that will alert personnel to out-of-limit conditions.

Note: The use of the vaccine cold chain to store other products requiring storage between 2°C and 8°C may make it unnecessary to invest in maintaining multiple cold chain infrastructures.

Stock rotation and control is best maintained by the use of a validated stock control system. Care must be taken to select a system that can manage the rigid requirements for batch number control and expiry date, which are essential for handling pharmaceutical products.

Periodic stock reconciliation should be performed, comparing actual and recorded stock levels. All significant stock discrepancies should be subjected to investigation as a check against inadvertent mix-ups and/or incorrect issue. Records should be maintained.

Damaged containers should not be issued unless it is certain that the quality of the product inside is unaffected. Any damaged containers should be reported without delay to the person responsible for quality assurance. Any action taken should be in accordance with a written procedure and documented.

All stock should be checked regularly for obsolete and outdated products. All due precautions should be observed to prevent issue of outdated products. The handling of such materials should be subject to a written procedure.

Recalled products should be identified, recorded, reconciled, and stored separately in a secure area until a decision has been made regarding their disposition. The decision should be made as soon as possible, in coordination with the manufacturer. An assessment should be made by an appropriately qualified and experienced member of staff.

Returned goods should be handled in accordance with a written procedure. They should be placed in quarantine until a decision has been made regarding their disposition. Products returned from the customer should be destroyed in compliance with national requirements unless it is certain their quality is satisfactory. In that case, they may be considered for resale. The nature of the product, any special storage requirements, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. If any doubt arises over the quality of the product, it should not be considered suitable for reissue. Any action taken should be recorded.



The procurement agency should have a well-managed distribution system that achieves these objectives:

- Maintain a constant supply of medicines
- Keep medicines in good condition throughout the distribution process
- Ensure controlled transport conditions
- Minimize losses of medicines due to spoilage and expiry
- Maintain accurate inventory records
- Rationalize medicine storage points
- Use available transportation resources as efficiently as possible
- Reduce theft and fraud
- Provide information for forecasting medicine needs

Measures to ensure product integrity and quality during distribution

To ensure product integrity and quality during distribution, the principles established in the WHO *Guidelines for Good Trade and Distribution Practices for Pharmaceutical Starting Materials*⁹ should be followed.

Transport condition

Pharmaceutical products should be transported in such a way that the integrity of the product is not adversely affected and appropriate storage conditions are maintained. Where temperature excursions occur during transport, risk assessment should be done to ensure that an informed decision is made as to the fate of the products.

Every precaution should be taken to minimize the risk of theft and fraud. Different measures and strategies could be considered for preventing theft and fraud, including but not limited to: inventory control; using locked containers; shrink-wrapping entire pallets in plastic; using

⁹ World Health Organization. 2004. "Good Trade and Distribution Practices for Pharmaceutical Starting Materials." Annex 2 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 38th Report. WHO Technical Report Series, No. 917. Geneva: WHO. Available at <http://apps.who.int/medicinedocs/pdf/s4899e/s4899e.pdf>

unique identifiers (e.g., use uniquely identifiable and difficult-to-defeat tamper-indicating devices, imprint all containers and external packing with a unique seal or monogram, register batch numbers on all immediate containers and external packing and agree not to sell products from the same batch to any other buyer, use electronic tagging devices); imprinting containers and packaging; and batch number registration.

Cold chain

Special care should be exercised when using a cold chain. If pharmaceutical products are distributed under controlled cool or cold conditions, appropriate containers should be used. Containers should be packed following established SOPs to ensure that products are not negatively affected.

When a cooling agent, such as dry ice, is used in a cold chain, it is necessary to ensure that the product does not come in contact with the cooling agent as this may adversely affect the quality of the product, (e.g., as a result of freezing).

The process should be validated to cover the expected transport time, taking into account expected environmental conditions.

Temperature and relative humidity monitoring and records

Calibrated devices should be used to monitor conditions such as temperature and relative humidity (when it is required) during transportation. Records should be available for review.

Dispatch of products

Rules for dispatch procedures should be established according to the nature of the pharmaceutical products being dispatched and after taking into account any special precautions observed. Any special packaging requirements for movement of products must be met. Some products may require special protection before they can be shipped by sea or by air. All legislation that may affect these requirements must be complied with.

The outside container should offer adequate protection from all external influences and should be indelibly and clearly labeled. Products should be packed in such a way as to minimize the risk of theft (e.g., by using locked containers or by shrink-wrapping entire pallets in plastic).

Records for dispatch should be retained, stating at least the following: date of dispatch; customer's name and address; product description (e.g., name, dosage form and strength [if appropriate]), batch number and quantity); and transport and storage conditions.

Traceability

Distribution records should contain sufficient information to enable traceability of the product from the point of supply to the point of delivery. Traceability of products is crucial in case of the need for product recalls. It will also help to detect theft and fraud. Any discrepancies should be investigated and followed up by appropriate measures to tackle possible security breaches.

In addition to the distribution records, several technologies are available for the tracking of products from production to consumer; for example, the printing of 2D codes (like Datamatrix) on packages, the use of forensic inks packs, cryptographic signature, security seals, radiofrequency ID (RFID) labels, packaging with special materials, laser surface, or the combination of multiple technologies. These technologies allow more stringent control of the supply chain; however, their use could increase product cost.



The quality of all products procured should be continuously monitored. Requalification or reevaluation should occur at regular intervals to ensure that products procured continue to meet defined norms and standards.

Principles of routine and non-routine reevaluation of products and manufacturers

Reevaluation of products

Product information should be reviewed every five years or sooner if major changes occur in the meantime. The procurement agency should have a mechanism in place to ensure that manufacturers inform them of any contemplated changes to the product that may affect its safety, efficacy, or quality. With regard to the product, manufacturers should report the following:

- Change of manufacturing process, site or equipment relating to the product
- Change of contract manufacturers
- Change of pharmaceutical product release control laboratories
- Change of manufacturers of API or container or closure
- Changes to the formulation or composition of the product
- New analytical method in the testing of API, intermediate or finished product
- Change of specifications
- Change in shelf life

Based on the information submitted, the person responsible for prequalification should decide whether to approve the changes or whether to request additional data, and should inform the purchasing group about the changes and the result of the evaluation of such changes.

Non-routine reevaluation of products should be done in the following cases:

- If there is any omission by the manufacturer in the initial evaluation procedure, or evidence of omission during follow-up activities in relation to the requirements, including compliance with quality system standards and failure-to-notify complaints
- If any batch or batches of supplied product(s) are documented by the procurement agency as not being in compliance with the agreed specifications of the product or as revealing failure(s) regarding safety, performance or quality of the product
- If the investigation of a complaint leads to the conclusion that the quality and/or safety of the product is in question

- If any fraud or misconduct by the manufacturer is evident
- If any batch or batches of product(s) was supplied and is considered not to be in compliance with the agreed specification of the product
- If a complaint considered to be serious in nature has been received by the organization
- If, in the opinion of the organization, changes made in the sourcing of the API, formulation, manufacturing method, facility or other production aspects require a reassessment be made
- If supply has been suspended for one year or longer

In cases of changes or variations to products, the *WHO publication Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: A Manual for Medicines Regulatory Authorities¹⁰ (13)* provides guidance on when to proceed with which type of reevaluation

The procurement agency should suspend or withdraw a prequalified product and its manufacturing facility from the requalification list if there is evidence of non-compliance with the requirements for prequalification.

Reevaluation of manufacturers

Reinspection of manufacturers should take place at regular intervals based on a risk assessment, but no less often than every five years. Procurement agencies should have a mechanism in place that ensures that manufacturers inform them immediately of any changes to the manufacturing site, manufacturing process, or equipment that may have an impact on its prequalification. Non-routine requalification may be required in the following situations:

- If any information was omitted in the initial assessment
- If false or misleading information is suspected during the follow-up assessment
- If changes are implemented that may impact the prequalification of the manufacturing site, such as changes to key personnel or organizational structure, changes to equipment, apparatus or the manufacturing process, or the renovation or addition of facilities requiring validation, commissioning, or reinspection
- If a complaint considered to be serious in nature has been received

The procurement agency should suspend or withdraw a prequalified product and its manufacturing facility from the requalification list if there is evidence of non-compliance with the requirements for prequalification.

Monitoring of product quality and complaints

Random samples of batches of prequalified pharmaceutical product(s), taken in accordance with a predefined sampling procedure (based on risk assessment), should be sent for independent testing at a reliable quality control laboratory (e.g., a WHO-prequalified

¹⁰ World Health Organization. 2011. *Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: A Manual for National Medicines Regulatory Authorities (NMRAs)*. 2nd ed. Geneva: WHO. Available at http://apps.who.int/iris/bitstream/handle/10665/44576/9789241501453_eng.pdf;jsessionid=49861414B7761E8954861D6069D3A9DB?sequence=1

laboratory) for compliance with final product specifications as part of the continuous monitoring program.

Complaints should be handled in accordance with a written procedure. Any complaint concerning a pharmaceutical product or batch of products supplied should be thoroughly investigated and include a root cause analysis, risk assessment, and effective CAPA to avoid recurrence.

A written report of the complaint, investigation, effective implementation of the CAPA, and outcome should be available. The nature of the complaint should be communicated to the manufacturer. The outcome of the investigation should be communicated to the complainant.