

Manual for Procurement & Supply of Quality-Assured Maternal, Newborn and Child Health Commodities

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INTRODUCTION

The *Quality Assurance Manual for Procurement and Supply of Quality-Assured Maternal, Newborn and Child Health Commodities* is intended to assist national government procurement agencies in establishing a quality assurance system for procurement of maternal, newborn and child health (MNCH) products. It provides comprehensive information on specific quality requirements which must be met to ensure the quality, safety and efficacy of the MNCH products across the full supply chain up to the point of use by patients.

Procurement of quality-assured products is one of the most important steps in safeguarding patients' safety. The national government procurement agencies should develop and maintain a quality assurance system in accordance with the World Health Organization's (WHO) *Model Quality Assurance System for Procurement Agencies* (MQAS).^{1,2}

The quality of any pharmaceutical product should be assessed against international norms and standards. In an ideal world, national government procurement agencies would want to rely on the WHO Prequalification (WHO PQ), Stringent Regulatory Authority (SRA) approval, or WHO's Expert Review Panel (ERP) recommendation to assure the quality of pharmaceutical products they procure. In reality, however, many MNCH products are not covered by the WHO PQ or ERP mechanism. While there may be SRA-approved MNCH products, many of these are only available in developed countries or be offered at uncompetitive price internationally.

Additionally, national medicine regulatory agencies (NMRAs) should have the capacity to ensure the quality, safety and efficacy of medicines however in some contexts, this can be challenging to achieve. Recognizing the need for standard system to support regulatory strengthening, WHO developed the Global Benchmarking Tool (GBT). The GBT is designed to assess regulatory frameworks and functions of a national regulatory system through standard indicators and scores the system in terms of maturity level, ranging from one to four. Maturity level 3 indicates a well-functioning regulatory system however in the absence or insufficiency of this standard, national government procurement agencies have two options to qualify the pharmaceutical products they want to procure:

- Relying on the evaluation conducted by the NMRA that does not meet a maturity level 3 on the GBT, which could be an indicator that the medicine regulation system operates below a standard level of stringency;

¹ World Health Organization. 2014. "Model Quality Assurance System for Procurement Agencies." Annex 3 in *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 48th Report. WHO Technical Report Series, No. 986. Geneva: WHO. Available at <http://apps.who.int/medicinedocs/documents/s21492en/s21492en.pdf>

² World Health Organization. 2014. "Assessment Tool Based on the Model Quality Assurance System for Procurement Agencies: Aide-Memoire for Inspection." Annex 4 in *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 48th Report. WHO Technical Report Series, No. 986. Geneva: WHO. Available at <http://apps.who.int/medicinedocs/documents/s21468en/s21468en.pdf>

- Setting up their own assessment procedures in line with international standards, which requires a level of resources and capacity that is unlikely to be available in low- and middle-income countries.

A pragmatic approach to assure the quality of MNCH products procured by resource-limited national government procurement agencies is therefore necessary to optimize overall yield of existing mechanisms (WHO PQ, SRA approval, ERP recommendation, NMRA approval, internal assessment).³ This involves using abridged assessment, including only recognized NMRAs, and applying different quality control requirements at pre-, post-shipment, and post marketing surveillance. This should allow the resource-limited national government procurement agencies to access additional quality MCH products, beyond the WHO PQ, SRA, or ERP coverage.

In the long run, the goal should be building the capacity of national government procurement agencies in low- and middle-income countries to be able to prequalify the products they want to procure according to stringent standards. The NMRAs should also strengthen their own capacity and move toward the long-term goal of achieving GBT maturity level 3 status.

This manual is divided into 3 modules:

- **Module I** describes the general quality assurance for procurement as per the MQAS, including prequalification (selection) of pharmaceutical products and manufacturers; purchase of prequalified products; receipt and storage of purchased products; distribution of received products; and reassessment (monitoring) of pharmaceutical products and manufacturers.
- **Module II** sets out a pragmatic approach to assuring the quality of MNCH products that resource-limited national government procurement agencies may implement when assessing the products for prequalification and procurement.
- **Module III** provides useful technical information of life-saving MNCH products, including those listed by the UN Commission on Life-Saving Commodities for Women's and Children's Health (UNCoLSC), that national government procurement agencies can use to establish technical specifications for the product(s) to be prequalified.

³ Moore, T., D. Lee, N. Konduri, and L. Kasonde. 2012. *Assuring the Quality of Essential Medicines Procured with Donor Funds*. Health. Nutrition and Population (HNP) discussion paper. Washington, DC: World Bank. World Health Organization. n.d

GLOSSARY

The definitions below apply to the terms used in this manual. They may have different meanings in other contexts.

ACTIVE PHARMACEUTICAL INGREDIENT (API): A substance or compound intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

BATCH RELEASE: The process performed by the manufacturer's quality assurance unit of releasing a batch or lot of active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) to the market based on a review of all manufacturing and control records to determine compliance with all established approved written procedures and specifications.

CERTIFICATE OF ANALYSIS (COA): The list of test procedures applied to a particular sample with the results obtained and the acceptance criteria applied. It indicates whether the sample complies with the specification.

CERTIFICATE OF PHARMACEUTICAL PRODUCT (CPP): A certificate issued for a single product in the format recommended by WHO, which establishes the status of the pharmaceutical product and that of the applicant for the certificate in the exporting country. It is issued by the competent authority in the exporting country in accordance with the requirements of the competent authority of the importing country.

COMMON TECHNICAL DOCUMENT (CTD): A common format for the submission of quality, safety, and efficacy information to regulatory authorities used in member countries of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and being adopted by other, non-member countries. The CTD is organized into five modules. Module 1 is region-specific, and Modules 2–5 are intended to be common for all regions. Module 1 is for administrative information and prescribing information. Module 2 contains the CTD summaries, including the overall summary of quality information, the non-clinical overview and summary, and the clinical overview and summary. As a foundation for the CTD summaries, Module 3 contains detailed information on quality topics, Module 4 contains the non-clinical study reports, and Module 5 contains the clinical study reports.

COMPARATOR PRODUCT: A pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product, for which efficacy, safety, and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle as described in Guidance on the Selection of Comparator Pharmaceutical Products Equivalence Assessment of Interchangeable Multisource (Generic) Products (WHO Technical Report Series, No. 992, Annex 8 [2015]) should be used to identify a suitable alternative comparator product.

COMPLAINT HANDLING: A process of receiving, recording, investigating, and implementing appropriate corrective and preventive actions for any complaints and other information concerning potentially defective products received by a company according to GMP.

CONTRACT MANUFACTURER: A manufacturer performing some aspect of manufacturing on behalf of the primary manufacturer.

DISTRIBUTION: The procuring, purchasing, holding, storing, selling, supplying, import, export, or movement of pharmaceutical products, with the exception of the dispensing or provision of pharmaceutical products directly to a patient or his or her agent.

EXPERT REVIEW PANEL (ERP): The ERP is an independent advisory body of technical experts, coordinated by WHO. The ERP is a service to procurement or funding agencies. The ERP assesses the quality risks of pharmaceutical products that do not yet meet all stringent quality requirements, and based on transparent science-based criteria, provides advice for the purpose of aiding decisions regarding time-limited procurement.

FALSIFIED MEDICINES: Pharmaceutical products that deliberately/fraudulently misrepresent their identity, composition, or source.

FINISHED PHARMACEUTICAL PRODUCT (FPP): A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labeling.

GOOD DISTRIBUTION PRACTICES (GDP): That part of quality assurance that ensures that the quality of a pharmaceutical product is maintained by means of adequate control of the numerous activities that occur during distribution as well as providing a tool to secure the distribution system from counterfeits, unapproved, illegally imported, stolen, counterfeit, substandard, adulterated, and/or misbranded pharmaceutical products.

GOOD MANUFACTURING PRACTICES (GMP, ALSO REFERRED TO AS cGMP, OR CURRENT GOOD MANUFACTURING PRACTICE): That part of quality assurance that ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization.

GOOD STORAGE PRACTICES (GSP): That part of quality assurance that ensures that the quality of pharmaceutical products is maintained by means of adequate control throughout the storage.

INNOVATOR PRODUCT: Generally, the pharmaceutical product that was first authorized for marketing (typically as a patented product) on the basis of documentation of efficacy, safety, and quality.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH): An initiative involving regulatory bodies and pharmaceutical industry experts in the United States, Europe, and Japan that was established to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration to ensure that safe, effective, and quality-assured medicines are developed and registered in the most resource-efficient manner.

INVITATION FOR EXPRESSION OF INTEREST (EOI): Invitation calling upon interested parties (e.g., manufacturers or other suppliers) to submit an expression of interest (EOI) to the procurement agency by a specified deadline, for the purpose of participating in the prequalification procedure for specified product(s). An EOI should be accompanied by the required information on the relevant product(s).

MANUFACTURE: All operations of purchase of materials and products for production, quality control, release, storage, and distribution of pharmaceutical products, as well as the related controls.

MANUFACTURER: A company that carries out operations such as production, packaging, repackaging, labeling, and re-labeling of pharmaceuticals.

MARKETING AUTHORIZATION: Also referred to as product license or registration certificate. A legal document issued by a medicines regulatory authority that authorizes the marketing or free distribution of a medical product in the respective country after evaluation of its safety, efficacy, and quality. In terms of quality, it establishes the detailed composition and formulation of the medical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labeling, storage conditions, shelf-life, and approved conditions of use.

NATIONAL MEDICINE REGULATORY AUTHORITY (NMRA): A national body that administers the full spectrum of medicine regulatory activities, including, at a minimum, all of the following functions, in conformity with national medicine legislation:

- Marketing authorization of new products and variations of existing products
- Good Manufacturing Practices (GMP) inspection
- Inspection and licensing of manufacturers, wholesalers, and distributors
- Quality control laboratory testing
- Monitoring of adverse drug events (pharmacovigilance)
- Control of clinical trials
- Post-marketing surveillance of medical products' quality
- Provision of information on medicines and promotion of rational use of medicines
- Enforcement operations

PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S): A non-binding, informal cooperative arrangement between regulatory authorities in the field of Good Manufacturing Practices (GMP) for medicinal products for human or veterinary use. It is open to any authority having a rigorous GMP inspection system. PIC/S aims at harmonizing inspection procedures worldwide by developing common standards in the field of GMP and providing training opportunities to inspectors. It also aims at facilitating co-operation and networking between competent authorities and regional and international organizations, thus enhancing mutual confidence.

PHARMACEUTICAL PRODUCT: Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in humans, or with a view to making a medical diagnosis in humans, or to restoring, correcting, or modifying physiological functions in human.

PHARMACOVIGILANCE: The science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.

PREQUALIFICATION: The activities undertaken in defining a product or service need, seeking expressions of interest from enterprises to supply the product or service, and examining the product or service offered against the specification and the facility where the product or service is prepared against common standards of Good Manufacturing Practices (GMP). The inspection of the product or service and of the facility where it is manufactured is performed by trained and qualified inspectors according to common accepted standards. Once the product is approved, and the facility is approved for the delivery of the specified product or service, other procurement agencies are informed of the decision. Prequalification is required for all pharmaceutical products to be procured, regardless of their composition and place of manufacture/registration, but the extent and type of information requested from the supplier for assessment by the procurement agency may differ.

PROCUREMENT: The process of purchasing or otherwise acquiring any pharmaceutical product. For the purpose of this manual, *procurement* means the preselection of products and manufacturers through a procedure of qualification, including *prequalification* (see above) and continuous monitoring of these thereafter, purchase of the prequalified products from prequalified manufacturers (linked to the specific product) through defined purchasing mechanisms, storage and distribution.

PROCUREMENT AGENCY: A procurement agency, in the context of this manual, is defined as any organization, including national government procurement agency, purchasing pharmaceutical products or otherwise involved in their *prequalification* (see above), purchasing, storage, and distribution of pharmaceutical products.

PRODUCT INFORMATION PACKAGE: Information on pharmaceutical products submitted by manufacturers or suppliers in any of the formats specified in the procurement agency's guidelines to obtain prequalification for the products.

PRODUCT QUALITY REVIEW: Regular periodic or rolling quality reviews of all authorized medicinal products, including export-only products, which is conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify needed product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews. Product quality review is a GMP requirement listed under Chapter I, Pharmaceutical Quality System, of the Pharmaceutical Inspection Cooperation Scheme (PIC/S) GMP Guideline.

PRODUCT RECALL: A process for withdrawing or removing a pharmaceutical product from the pharmaceutical distribution chain because of defects in the product, complaints of serious adverse events related to the product, and/or concerns that the product is or may be falsified. The recall might be initiated by the manufacturer, importer, wholesaler, distributor, or a responsible agency.

QUALITY ASSURANCE: Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

QUALITY CONTROL: Quality control is concerned with sampling, specifications, and testing, and with the procurement agency's documentation and acceptance/rejection procedures that ensure that the necessary and relevant tests are carried out and that starting materials, intermediates, and finished products are not accepted for use, sale, or supply until their quality has been judged satisfactory.

RECALL: A process for withdrawing or removing a pharmaceutical material from the distribution chain because of defects in the materials or complaints of a serious nature. The recall may be initiated by the manufacturer/importer/distributor or a responsible agency.

SHELF LIFE: The period of time during which a pharmaceutical product, if stored as indicated on the label, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf life is used to establish the expiry date of each batch.

SPECIFICATIONS: A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the product described. It establishes the set of criteria to which a material must conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

STRINGENT REGULATORY AUTHORITY (SRA): A regulatory authority that is one of the following:

- a) A member of the International Conference on Harmonisation (ICH) effective prior to October 23, 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan, including its Pharmaceuticals and Medical Devices Agency
- b) An ICH observer effective prior to October 23, 2015, namely: the European Free Trade Association, as represented by Swissmedic, and Health Canada
- c) A regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement effective prior to October 23, 2015, namely: Australia, Iceland, Liechtenstein, and Norway

SUBSTANDARD MEDICINES: Substandard medicines are pharmaceutical products that fail to meet either their quality standards or their specifications, or both. Each pharmaceutical product that a manufacturer produces must comply with quality assurance standards and specifications, at release and throughout its shelf life, according to the requirements of the territory of use. Normally, these standards and specifications are reviewed, assessed, and approved by the applicable national or regional medicines regulatory authority before the product is authorized for marketing.

SUPPLIER: A person or entity providing pharmaceutical products and materials on request. Suppliers may be agents, brokers, distributors, manufacturers, or traders. Where possible, suppliers should be authorized by a competent authority.

UNREGISTERED MEDICINES: Pharmaceutical products that have not undergone evaluation and/or approval by the national or regional medicine regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

VARIATION: A change to any aspect of a pharmaceutical product, including but not limited to: the change of use of a starting material; a change to formulation, method, or site of manufacture; or change to specifications for the finished product and ingredients, container, and container labeling and product information. Variations can be classified as follows:

- Major variations are changes that could have major effects on the overall safety, efficacy, and quality of the finished pharmaceutical product (FPP). Manufacturers must submit the supporting data requiring the changes to the regulatory authority. Prior acceptance by the regulatory authority is required before the changes can be implemented.
- Minor variations are changes that may have minor effects on the overall safety, efficacy, and quality of the FPP. Manufacturers must meet all of the prescribed conditions for the change and submit the required documentation to the regulatory authority. Such minor variations can be implemented if no objection letter has been issued within a time period indicated by the regulatory authority. Should questions arise during the specified period, the change can only be implemented on receipt of a letter of acceptance from the regulatory authority.
- Notifications are changes that could have minimal or no adverse effects on the overall safety, efficacy, and quality of the FPP. Such notifications do not require prior acceptance but must be documented in notification to the regulatory authority immediately after implementation (immediate notification), or within 12 months following implementation (annual notification), depending on the types of changes, as indicated by the regulatory authority.