## WHO Global Malaria Programme

# Good procurement practices for artemisinin-based antimalarial medicines

World Health Organization

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# Abbreviations

| | |
|---|---|
| ACT | artemisinin-based combination therapy |
| AL | artemether–lumefantrine |
| API | active pharmaceutical ingredient |
| AQ | amodiaquine |
| AS | artesunate |
| DHA | dihydroartemisinin |
| EMEA | European Medicines Agency |
| FPP | finished pharmaceutical product |
| GFATM | Global Fund to Fight AIDS, Tuberculosis and Malaria |
| GMP | good manufacturing practice |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| INN | International Nonproprietary Name |
| ISO | International Organization for Standardization |
| MQ | mefloquine |
| N.B. | nota bene (note well) |
| PPQ | piperaquine |
| SP | sulfadoxine–pyrimethamine |
| SRA | stringent regulatory authority |
| TRIPS | trade-related aspects of intellectual property rights (World Trade Organization) |
| UNFPA | United Nations Population Fund |
| UNICEF | United Nations Childrens' Fund |
| UNITAID | international facility for the purchase of commodities for the prevention and control of HIV/AIDS, Tuberculosis and Malaria |
| WHO | World Health Organization |
| WHO PQP | WHO Prequalification Programme |

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The manual is based on the standards and guidelines cited at the end of the document.

# Glossary

**Accelerated stability testing:** studies designed to increase the rate of chemical degradation and physical change of an active pharmaceutical ingredient or finished pharmaceutical product (FPP) by using exaggerated storage conditions as part of the formal stability testing programme. The data thus obtained, in addition to those derived from long-term stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing are not always predictive of physical changes (*4*).

**Acceptance criteria:** measurable terms under which a test result will be considered acceptable. The terms can be numerical limits, ranges or other forms (*5*).

**Active pharmaceutical ingredient (API):** substance or compound intended for use in the manufacture of an FPP as a pharmacologically active compound (ingredient) (*1*).

**Affordability:** extent to which pharmaceutical products are available to the people who need them at a price they can pay (*1*).

**Artemisinin:** chemical compound (sesquiterpene lactone) extracted from the leaves of the plant *Artemisia annua* (sweet wormwood), also known as *qinghaosu*.

**Artemisinin-based antimalarial medicines:** for the purposes of this manual, artemisinin-based combination therapy and artemisinin-based suppositories and injectable products.

**Artemisinin-based combination therapy (ACT):** combination of artemisinin or an artemisinin derivative with one or more antimalarial agents of a different class.

**Artemisinin derivative:** active pharmaceutical ingredient derived from artemisinin. The commonest derivatives are artemether (methyl ether of dihydroartemisinin), artesunate (hemisuccinate ester of artemisinin), dihydroartemisinin (main active metabolite of artemisinin derivatives, also known as artenimol) and artemotil (ethyl ether of artemisinin, previously known as arteether).

**Authorization:** see *marketing authorization*.

**Batch:** defined quantity of pharmaceutical products manufactured in a single process or series of processes and therefore expected to be homogeneous (*6*).

**Batch number:** distinctive combination of numbers and/or letters, which uniquely identifies a batch; for example, on labels, batch records and corresponding certificates of analysis (*6*).

**Bilayered tablet:** tablet containing two different APIs in two separate layers, in order to minimize chemical or physical interaction between the two.

**Bioavailability:** rate and extent to which the API is absorbed from a pharmaceutical dose form and becomes available at the site(s) of action (*1*). Bioavailability is measured from the concentration/time curve of the API in the systemic circulation or by its excretion in urine (*3*).

**Bioequivalence:** two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailability, in terms of peak ($C_{max}$ and

$T_{max}$) and total exposure (area under the curve) after administration of the same molar dose under the same conditions, is similar to such a degree that their effects can be expected to be essentially the same (*7*).

**Biowaiver:** approval of the dossier (application) for a drug on the basis of evidence of equivalence other than by testing in vivo (*7*).

**Brand (proprietary) name:** registered trade name given to a pharmaceutical product by the manufacturer (as opposed to generic name).

**British approved name:** short, distinctive name selected in accordance with the guiding principles for substances, the systematic chemical or other scientific names of which are too complex for convenient general use. British approved names are devised or selected by the British Pharmacopoeia Commission and published by the Health Ministry on the recommendation of the Commission of Human Medicines to provide a list of names of substances or articles referred to in section 100 of the Medicines Act 1968 (*8*).

**Certificate of analysis (COA):** document listing the results of testing of a representative sample drawn from the batch to be delivered; should be equivalent to the WHO model certificate of analysis (*9*).

**Certificate of pharmaceutical product (CPP):** document in a standard format issued under the WHO certification scheme by the drug regulatory authority of the exporting country (see **Annex 1**); intended to confirm that a medicine is authorized for use in the country of origin (*10*).

**Co-blistered product:** combination product packed in a single blister pack containing two or more different medicines in separate blisters (adapted from *11*). In this manual, co-blistered products are denoted by '+', e.g. 'artesunate + amodiaquine'.

**Co-formulated product:** product containing two or more APIs in the same dosage form (such as a tablet, capsule, suspension or injection). Solid dosage forms that contain two active ingredients in separate layers are called bilayered tablets. In this manual, co-formulated APIs are denoted by '–', e.g. 'artemether–lumefantrine'.

**Common technical document:** standardized format of application for marketing authorization or registration of FPPs by a regulatory authority.

**Comparator:** an FPP with which a generic product is intended to be interchangeable in clinical practice; usually the innovator product for which efficacy, safety and quality have been established. The comparator product is usually selected at national level by the medicines regulatory authority (*7*).

**Consignment:** quantity of FPPs supplied at one time in response to a particular request or order; may comprise one or more packages or containers and may include material belonging to more than one batch (*6*).

**Container:** material used in the packaging of a pharmaceutical product; includes primary, secondary and transportation containers. Containers are referred to as 'primary' if they are intended to be in direct contact with the product and as 'secondary' if they are not intended to be in direct contact with the product (*6*).

**Contract:** business agreement for the supply of goods or performance of work on the basis of mutually agreed terms and conditions (adapted from *6*).

**Co-packaged:** product consisting of two or more separate pharmaceutical products in their final dosage form that are packaged together for distribution to patients in the same unit (*10*), including co-blistered products. In this manual, co-packaged products are denoted by '+', e.g. 'artesunate + mefloquine'.

**Counterfeit pharmaceutical product:** product with a false representation[1] of its identity[2] and/or source;[3] applies to the product, its container or other packaging or labelling information. Counterfeiting can apply to both branded and generic products. Counterfeits may be products with correct ingredients or components,[4] with wrong ingredients or components, without active ingredients, with incorrect amounts of active ingredients or with fake packaging. Counterfeiting of medical products is not the same as violations or disputes concerning patents. Medical products (whether generic or branded) that are not authorized for marketing in a given country but are authorized elsewhere are not considered counterfeit. Substandard batches, quality defects or noncompliance with good manufacturing practice (GMP) and good distribution practice in legitimate medical products should not be confused with counterfeiting (*12*). (See also **SUBSTANDARD PRODUCT.**)

**Dissolution test:** test designed to determine the amount of API(s) released from a solid oral dosage form, such as a tablet or a capsule, into a known volume of dissolution medium within a predetermined time (*13*).

**Dosage form:** form (e.g. tablet, capsule, injection) of an FPP (*3*).

**Drug master file (DMF):** detailed information on a specific facility, process or product submitted to a drug regulatory authority, intended for incorporation into the application for marketing authorization (*14*).

**Efficacy:** maximum ability of a medicine or treatment to produce a result regardless of dosage. A medicine passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. For example, in the procedure mandated by the United States Food and Drug Administration, Phase II clinical trials gauge efficacy and Phase III trials confirm efficacy (*3*).

**Essential medicines list (EML):** list of those medicines that satisfy the priorities among the health-care needs of a population, are selected for relevance to public health, for which there is evidence of efficacy and safety and are comparatively cost-effective .

**Excipient:** substance or compound, other than the API and packaging materials, intended or designated for use in the manufacture of an FPP and included in its final composition.

**Expert Review Panel:** independent panel of experts who advice which pharmaceutical products that are awaiting approval by a stringent regulatory authority or the WHO Prequalification Programme (WHO PQP) are eligible for procurement with funding from the GFATM for a limited period until they obtain such approval.

**Expiry date:** date on an individual container (usually on the label) of a product up to and including which the product is expected to meet specifications, if stored correctly. It is established for each batch by adding the shelf-life (as established by adequate stability studies) to the date of manufacture (*4*).

**Finished pharmaceutical product (FPP ):** product that has undergone all stages of production, including packaging in its final container and labelling; may contain one or more APIs (*10*).

**Fixed-dose combination (FDC):** combination of two or more APIs in a fixed ratio of doses (*10*). A combination of APIs may be administered as single entity, concurrently (co-packaged or co-blistered) or as an FPP (co-formulated). For the purposes of this manual, 'fixed-dose combination' refers to co-formulated FPPs.

[1] Counterfeiting is done fraudulently and deliberately. Criminal intent or careless behaviour shall be considered during the legal procedures for the purposes of sanctions imposed.

[2] Includes any misleading statement with respect to name, composition, strength or other element

[3] Includes any misleading statement with respect to manufacturer, country of manufacture, country of origin, marketing authorization holder or steps of distribution

[4] Refers to all components of a medical product

**Formulation:** composition of a dosage form, including the characteristics of its raw materials and the operations required to process it (*15*).

**Generic name:** approved or International Nonproprietary Name (INN) of a drug given by WHO (*3*).

**Generic product:** pharmaceutical product, usually intended to be interchangeable with an innovator product, which is usually manufactured without a license from the innovator company and marketed after expiry of the patent or other exclusivity rights. Such products may be marketed in dosage forms or strengths different from those of the innovator products. The term should not be confused with 'generic name'. Generic products may be marketed either under the approved INN or under a brand (proprietary) name (*1*).

**Good clinical practice (GCP):** standard for clinical studies, which encompasses design, conduct, monitoring, termination, audit, analysis, reporting and documentation and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented (*16*).

**Good distribution practice (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 comprise distribution (*6*).

**Good laboratory practice (GLP):** quality control system for the organization of and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported (*16*).

**Good manufacturing practice (GMP):** the part of quality assurance that ensures that products are consistently produced and controlled to the standards appropriate to their intended use and as required in the marketing authorization (*1*).

**Incoterm:** international commerce term, one of a series of international sales terms published by the International Chamber of Commerce and widely used in international commercial transactions; used to divide transaction costs and responsibilities between buyer and seller and reflect state-of-the-art transport practices (*17*).

**Innovator pharmaceutical product:** FPP first authorized for marketing (usually as a patented product) on the basis of documented efficacy, safety and quality according to requirements at the time of the authorization. When a substance has been available for many years, it may not be possible to identify the innovator pharmaceutical product (1).

**Interchangeable pharmaceutical product:** product that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice (*7*).

**International nonproprietary name (INN):** shortened scientific name based on the API. WHO is responsible for assigning INNs to pharmaceutical substances (*1*).

**Labelling:** identification of a pharmaceutical product, which includes the following information, as appropriate: name; API(s), type and amount; batch number; expiry date; special storage conditions or handling precautions; directions for use, warnings and precautions; names and addresses of the manufacturer and/or the supplier (*6*).

**Long-term stability study:** experiment on the physical, chemical, biological, biopharmaceutical or microbiological characteristics of an FPP (or API) during and beyond its expected shelf-life and storage period of samples retained under the labelled storage conditions expected in the intended place of use. The results are used to establish the shelf-life (or retest period), to confirm the projected shelf-life (or retest period) and to recommend storage conditions (*4*).

**Manufacture:** all operations of purchase of materials and products, production, quality control, release, of pharmaceutical products and related controls (*18*).

**Manufacturer:** company that produces, packages, repackages, labels and/or relabels pharmaceutical products (*1*).

**Marketing authorization:** official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (with INNs or national generic names when they exist), the shelf-life and storage conditions and packaging characteristics. It specifies the information on which authorization is based (e.g. "The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence."). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – a register – and is often said to be 'registered' or to 'have registration'. Market authorization is occasionally referred to as a 'license' or 'product license' (*1*).

**Metabolite:** intermediate or product of metabolism, the set of chemical reactions that occur in living organisms in order to maintain life.

**Monograph:** set of properly selected standardized texts with methods of analysis that can be used to assess the integrity of FPPs and starting materials. Such standards, when met, ensure the quality of a product with respect to identity, purity, strength, packaging, storage and labelling. Monographs are published in pharmacopoeias (*3*).

**Multisource pharmaceutical product:** see 'generic product'.

**Originator product:** see 'innovator pharmaceutical product'.

**Packaging:** any material, including printed material, used in the packaging of a pharmaceutical but excluding any outer packaging used for transport or shipment. Packaging materials are referred to as 'primary' or 'secondary' according to whether they are intended to be in direct contact with the product (*18*).

**Parenteral:** intended for administration outside the alimentary canal, i.e. by injection, infusion or implantation into the body (*13*).

**Pharmacopoeia:** book containing an official list of monographs and accepted standards for the potency, purity, quality, packaging and labelling of pharmaceutical products. The most widely used pharmacopoeias are the *International Pharmacopoeia*, the *United States Pharmacopeia*, the *British Pharmacopoeia*, the *Japanese Pharmacopoeia* and the *European Pharmacopoeia*. Other countries may have their own pharmacopoeias (*3*).

**Prequalification:** for the purposes of this manual, standardized quality assessment procedure of WHO to evaluate the acceptability, in principle, of pharmaceutical products for purchase by United Nations agencies. Agencies using information resulting from the prequalification procedure should perform additional steps of qualification before purchasing, such as ensuring the financial stability and standing of the supplier, the ability to supply the required quantities, the security of the supply chain, preshipment quality control and other aspects (*19*). At WHO, prequalification is undertaken by the WHO Prequalification Programme (WHO PQP, **http://www.who.int/prequal**).

**Procurement agency:** any organization that purchases or otherwise acquires any pharmaceutical product, vaccine or other medicine for human use (*1*); in the context of this manual, a specialized organization, usually a not-for-profit, nongovernmental or United Nations organization, that

purchases artemisinin-based antimalarial medicines or is otherwise involved in their prequalification, purchase, storage and distribution.

**Product:** for the purposes of this manual, an FPP.

**Quality assurance (QA):** wide-ranging concept covering all matters that individually or collectively influence the quality of a product; the totality of the arrangements made to ensure that pharmaceutical products are of the quality required for their intended use (*1*).

**Quality control (QC):** sampling, specifications and testing and the documentation and acceptance or rejection procedures of the procurement agency, which ensure that the necessary relevant tests are actually carried out and that the starting materials, intermediates and FPPs are not accepted for use, sale or supply until their quality has been judged to be satisfactory (*1*).

**Release:** release of a batch of API, an excipient or an FPP for sale or supply after certification by the authorized person(s) that it corresponds to the requirements of the marketing authorization (adapted from *18*).

**Residual solvent:** organic solvent used or produced in the manufacture of an API, an excipient or an FPP, which is not completely removed during manufacture.

**Reference substance:** chemical that is an authenticated, uniform material intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination and which is of adequate purity for its intended use (*20*).

**Registration:** any statutory system of approval required at national level as a precondition for introducing an FPP onto the market (*3*).

**Regulatory authority:** national body that administers the full spectrum of regulatory activities for medicines, including all the following functions, in conformity with national drug legislation:

- giving marketing authorization for new products and variations of existing products;
- laboratory testing for quality control;
- monitoring adverse drug reactions;
- providing drug information and promoting rational drug use;
- inspecting and licensing manufacturers, wholesalers and distribution channels to ensure GMP;
- enforcement operations; and
- monitoring drug use (*1*).

**Retest period:** period during which an API is expected to remain within its specifications and, therefore, can be used in the manufacture of a given FPP, provided that the API has been stored under the defined conditions. After this period, a batch of API destined for use in the manufacture of an FPP should be retested for compliance with the specification and then used immediately. A batch of API can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specifications. For most substances known to be labile, it is more appropriate to establish a shelf-life than a retest period (21).

**Safety:** a safe product is one that does not cause harm or injury, is associated with a low incidence of adverse reactions and significant side-effects when adequate instructions for use are followed and has little potential harm under conditions of widespread availability (*3*).

**Sampling:** operation to obtain a representative portion of a pharmaceutical product, on the basis of an appropriate statistical procedure, for a defined purpose, e.g. acceptance of consignments or batch release (*6*).

**Shelf-life:** period during which an API or FPP, if stored correctly, is expected to comply with the specifications determined in stability studies on a number of batches of the API or FPP. The shelf-life is used to establish the expiry date of each batch (*4*).

**Specifications (pharmaceutical):** list of tests, references to analytical procedures and appropriate acceptance criteria (numerical limits, ranges or other) for the tests described; they establish criteria to which an API or FPP should conform in order to be considered acceptable for its intended use (*4*).

**Stability:** ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf-life.

**Stability testing :** long-term accelerated (and intermediate) studies undertaken on batches according to a prescribed protocol to establish or confirm the retest period (or shelf-life) of an API or the shelf-life of an FPP (*4*).

**Standard treatment guidelines:** guidelines for the management of a specific health condition in a country or an institution, on the basis of available evidence and/or best practice.

**Starting material:** any substance of a defined quality used in the production of an API or an FPP, excluding packaging materials; includes APIs and pharmaceutical excipients (*18*).

**Stringent regulatory authority (SRA):** regulatory authority that has the expertise and capacity to fulfil all the functions of a medicines regulatory authority in such a manner as to ensure stringent medicines control. See **Annex 2** for a list of SRAs as defined in the harmonized quality assurance policy of funders and United Nations organizations on which this manual is based.

**Substandard pharmaceutical product:** a legal branded or generic pharmaceutical product that does not meet generally accepted national or international standards for quality, purity, strength or packaging (*3*).

**Supplier:** person or company providing APIs or FPPs on request; includes distributors, manufacturers and traders (*6*).

**Strength:** content of API(s) per dosage unit (e.g. one tablet, capsule or ampoule) of an FPP (adapted from *3*).

**Tamper-evident packaging:** packaging with a closure system sealed in such a manner that the contents cannot be used without destroying the seal, and with an indicator or barrier to entry, which, if breached or missing, can reasonably be expected to provide visible evidence that tampering (altering, pilfering or falsifying of the pharmaceutical product) has occurred.

**Therapeutic equivalence:** two FPPs are therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if, after administration at the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administrered to patients by the same route under the conditions specified on the label; can be demonstrated by appropriate bioequivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies (*7*).

**Validation:** proving and documenting that any process, procedure or method actually and consistently leads to the expected results (*22*).

**Zone IV:** climate zone defined by WHO for the purposes of stability testing of FPPs for hot and humid climates. Climate zone IVa refers to long-term testing at 30 °C and 65% relative humidity, and climate zone IVb refers to long-term testing at 30 °C and 75% relative humidity.

# Purpose, target audience and objectives

The aim of this manual is to provide support for the procurement of safe, effective, quality-assured artemisinin-based antimalarial medicines that meet stringent, internationally agreed quality standards. These standards are reflected in the harmonized quality criteria for these medicines agreed between the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), UNICEF, UNITAID, the United States President's Malaria Initiative, the World Bank and WHO, subject to their adoption as part of their respective procurement policies.

The target audience for this manual includes programme managers, procurement officers, health officers and supply chain managers in the public and private sectors who are responsible for procuring and distributing artemisinin-based antimalarial medicines (including artemisinin-based combination therapies and artemisinin-based suppositories and injectables).

This manual summarizes simple, practical information from publications related to the quality of medicines that are readily accessible only to specialized procurement agencies. Its aim is to improve understanding of the following aspects of procurement:

- medicines that are recommended in evidence-based treatment guidelines;
- common problems with the quality of artemisinin-based antimalarial products;
- elements of pharmaceutical product quality;
- model product specifications;
- documentation supplied to support pharmaceutical product quality; and
- role, principles and methods of quality control testing.

The manual does not cover the general aspects of procurement, which are dealt with extensively in other documents (*1*–*3*). The WHO document cited in reference (*1*) is the recognized guideline used by many donors and United Nations agencies.

## How this manual is organized

- A list of **abbreviations** and a **glossary** of technical terms are included in the introductory section.
- The **checklist** at the beginning of this manual lists **16 steps** in the procurement of quality-assured artemisinin-based antimalarial medicines and indicates the persons or entities usually responsible for each step.
- **Steps 1–16** are discussed in detail in the remaining sections of the manual, providing information on aspects of safety and efficacy (**STEP 1**), product specification (**STEP 4**) and pharmaceutical quality (**STEPS 6** and **8**).
- ***The text in italics and bold with arrow symbols*** (➔) suggests solutions to the challenges mentioned in the corresponding section.

- **Boxes** contain examples related to the text, and other noteworthy information (as N.B.). INTERNET SOURCES and recommendations for FURTHER READINGS are listed at the end of the corresponding section.
- SUGGESTED SEARCH TERMS for Internet are given where applicable; these can be entered into the search box provided by Google™ and other general search engines to find web pages, even if the site address has changed.
- Instructions to reader to consult specific sections of the manual are given in **BOLD CAPITALIZED FONT.**
- **References** are given as numbers in brackets (*x*) and are listed before the annexes. Internet addresses are given for documents available online.
- The **annexes** illustrate some conventions and formats used for quality assurance in pharmaceutical procurement.
- The manual ends with an **index**.

# Introduction

## Why the quality of artemisinin-based antimalarial medicines is important

Quality is one of the most important considerations in the manufacture and procurement of medicines. The aim of having quality assurance measures in place all along the supply chain is to ensure that each procured batch of a finished pharmaceutical product (FPP) meets approved manufacturing quality standards. Poor-quality medicines affect the health and lives of patients, damage the credibility of health-care programmes and increase the burden on the health-care system.

The quality of artemisinin-based antimalarial medicines is particularly important, as the use of ineffective or unsafe substandard products in the treatment of malaria may be harmful. If parasites are exposed to low levels of antimalarial medicines in the blood, resistant parasites will survive and multiply, favouring the emergence and spread of resistant strains.

Half of the world's population is at risk for malaria. Almost 250 million cases are estimated to occur each year. Malaria causes an estimated 860 000 deaths annually, and 85% of the fatalities are children (*23*). Artemisinin and its derivatives, a class of highly effective, well-tolerated antimalarial medicines, have transformed the treatment of malaria in recent years. The effectiveness of these medicines must be protected, as no new class of antimalarial medicines is expected to enter the market within at least the next decade (*24*).

The quality of artemisinin-based antimalarial products is therefore not negotiable and must be the first consideration in procurement. If artemisinin-based products are to retain their efficacy, safe and effective medicines must be selected, each batch must be quality-assured, from the starting materials through manufacture and distribution up to the point of dispensing, and patients must use the medicines correctly. Good-quality diagnostic materials are also important, as a wrong diagnosis can affect forecasting for antimalarial medicines, resulting in under- or overstocking, expired stock and wasted funds.

## Challenges in ensuring the quality of artemisinin-based antimalarial medicines

### *Extraction from raw plant materials*

Artemisinin is manufactured from *Artemisia annua* (sweet wormwood), a Chinese traditional medicinal plant, which takes at least 6–8 months to mature between planting and harvest. The raw plant materials vary greatly in quality, depending on the area and the practices used in cultivation (including exposure to pesticides) and the collection and storage of the plants, which must be kept in cool conditions. The planning and logistics of the manufacture of artemisinin-based antimalarial medicines is challenging and may be long.

➔ ***Artemisinin-based antimalarial medicines may not always be promptly available. The procurement cycle should therefore start at least 6–9 months before the medicines are received.***

### *Chemical instability*

Artemisinin and derived compounds – i.e. artemether, artesunate, dihydroartemisinin (artenimol) and artemotil (previously known as arteether) – are all chemically unstable. This is useful for their antimalarial activity but results in problems in the manufacture of some dosage forms, in particular co-formulated products. Bilayered tablets were therefore designed to separate APIs such as artesunate and amodiaquine from each other.

The instability of the artemisinins continues to pose challenges after manufacture, i.e. during their shelf-life, as the products are easily damaged by high temperatures and humidity.

➔ ***Artemisinin-based medicines are difficult to manufacture. Product documentation must therefore be assessed before FPPs are selected (see STEP 8).***

➔ ***The primary packaging should effectively protect the products from moisture and air. As packaging alone cannot protect medicines from high temperatures for a long time, the products must be transported and stored with care (see STEP 14).***

### *Documentation of quality*

Artemisinin-based products were first developed and marketed in China in the 1970s. Few regulatory authorities in countries with established pharmaceutical industries and stringent medicines control have experience with these compounds. WHO PQP has identified a number of issues in the quality of manufacturers' dossiers for antimalarial products.

➔ ***Procurement entities should request manufacturers to supply documentation demonstrating that their products comply with the standards of the WHO PQP or stringent regulatory authorities (SRAs) (see STEP 6).***

### *Good manufacturing practice (GMP)*

Not all manufacturers comply with GMP. Common problems include inadequate checks of buildings, equipment and operational methods and procedures before use, unvalidated methods of manufacture, cleaning and analytical testing, insufficient control of starting and packaging materials, resulting in possible contamination (e.g. during sampling, weighing, dispensing or storing materials), and inconsistent labelling.

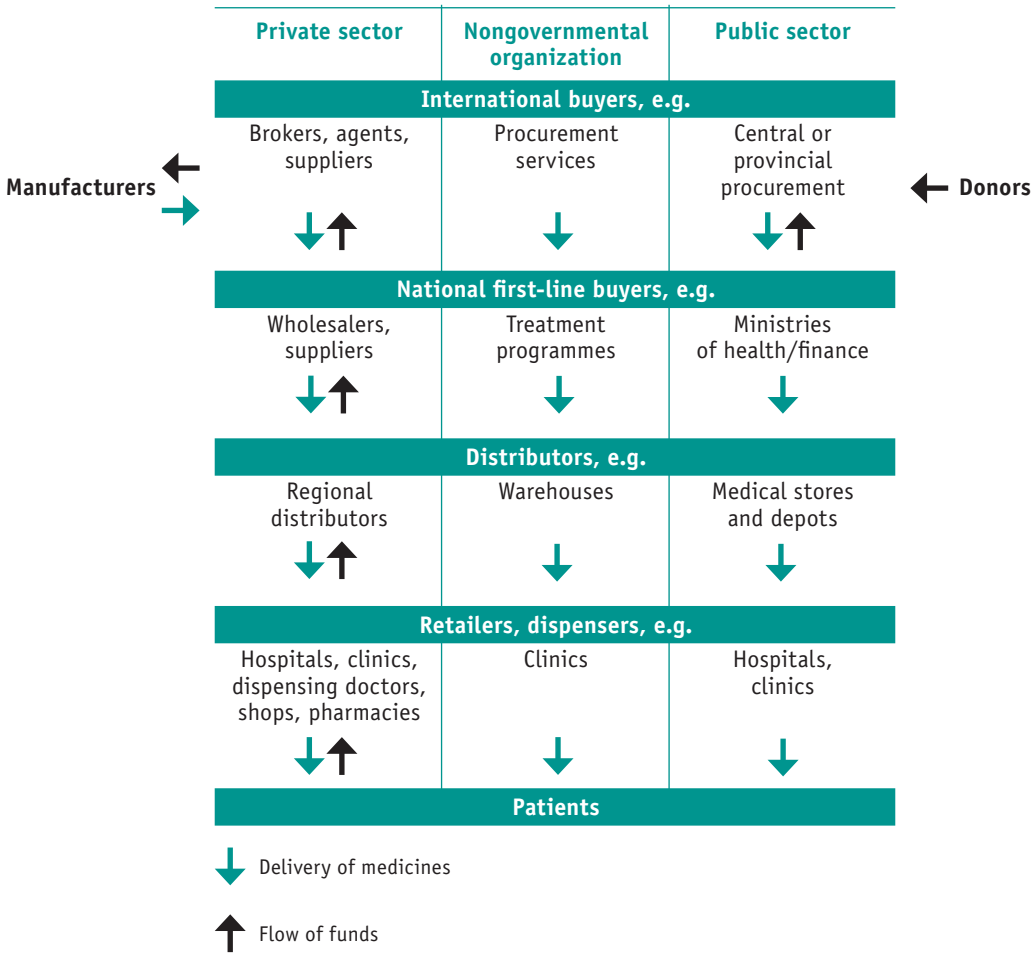
➔ ***GMP certification is an important consideration in procurement of artemisinin-based antimalarial medicines. Not all GMP certificates reflect the same standards of control of manufacturing processes and APIs (see STEP 8).***

### *Complex procurement channels*

The supply of antimalarial medicines is highly fragmented, with a huge private sector. Products are forwarded through various levels of procurement (see **FIGURE 1**), and national regulatory authorities have limited control over products circulating on the market, especially in the private sector.

➔ ***Procurement entities can help to ensure the quality of the products they procure. They should understand the elements of quality and specifications and should monitor and evaluate quality at each of the 16 steps of procurement described in this manual.***

**Figure 1. Levels of procurement of artemisinin-based antimalarial medicines**




## *Substandard products and counterfeiting*

Quality assurance relies on good product design and on strict control of all the ingredients of a pharmaceutical product and all processes, transport and tests that it undergoes during and after its manufacture. Substandard products are a consequence of flaws in the manufacturing process. In a globalized market, with increasing competition and increasing demand, it is more and more difficult for manufacturers to control all aspects of manufacture.

Counterfeits are a specific type of substandard product, which are deliberately and fraudulently mislabelled with respect to source and content for profit-making purposes. Both branded and generic products may be counterfeited. Artemisinin-based products are likely targets for counterfeiting for several reasons: they are widely used in countries where regulatory controls tend to be weak; they are distributed globally through a wide variety of channels, which can be difficult to control; and large quantities of these relatively expensive products are in circulation, increasing the potential profits of counterfeiters. Surveys have suggested that 38–53% of shop-bought artesunates in mainland South-East Asia are counterfeit (*26*); counterfeit artemisinin derivatives and ACTs in Africa have also been reported. WHO's International Medical Products Anti-Counterfeiting Taskforce (IMPACT) works with governments, industry and international organizations to combat the counterfeiting of medicines (*12*).

The two basic approaches for guarding against procurement of substandard products are:

- verification of the quality assurance measures applied to a product during its lifetime, as reflected in the product documentation (see **Annex 3** for an example of how such documentation can be requested for assessment); and
- quality control testing (see **steps 11** and **13**), an additional safeguard that allows the detection of substandard products, which can then be returned or recalled.

➔ ***Good procurement and distribution practices can help ensure that patients have access to affordable, good-quality antimalarial medicines.***

### *Funding*

As artemisinin-based antimalarial medicines are expensive, it is important to ensure successful procurement. They are often financed from donor funds, available from a wide range of organizations.

➔ ***Different donors may have different procedures, timelines and requirements for funding, which must be coordinated and observed for procurement.***

## Procurement checklist

The checklist below gives the key steps in procuring quality-assured artemisinin-based antimalarial medicines. More detailed information on each step is given in the remaining sections of this manual. While the steps are shown sequentially, they do not necessarily take place one after the other in practice, nor will all the steps have to be repeated for each tender.

### STEP 1.

| Selecting safe, effective antimalarial medicines | *Responsible entity* |
|---|---|
| • Select medicines in accordance with WHO *Guidelines for the Treatment of Malaria*, national standard treatment guidelines and programme needs. | Ministry of health, managers of national malaria control programme |

### STEP 2.

| Estimating requirements | *Responsible entity* |
|---|---|
| • Investigate opportunities for joint quantification.<br>• Quantify national need for treatment courses, based on consumption or morbidity data.<br>• Forecast the numbers of packages needed, based on available funding.<br>• Prepare delivery schedules on the basis of shelf-lives and storage and distribution capacities. | Programme managers, procurement management unit in collaboration with e.g. health information system managers and finance officers of the government |

### STEP 3.

| Securing funding | *Responsible entity* |
|---|---|
| • Calculate the expected total cost of procuring and distributing the required quantities of products (determined in **step 2**).<br>• Identify and secure funding (national budget, subsidies, donor funding). | Programme managers, in consultation with ministry of health |

## STEP 4.

| Defining product specification | *Responsible entity* |
|---|---|
| • List required product formulations (see **STEP 1**).<br>• List required quality specifications and the documentation to be submitted in support of compliance. | Technical experts (pharmaceutical), who provide input to **STEP 5** |

## STEP 5.

| Selecting procurement method and preparing tender documents | *Responsible entity* |
|---|---|
| • Decide on tender format and scope.<br>• Prepare tender documentation with invitation to bid, instructions to bidders, conditions including technical specifications and schedule of requirements. | Procurement management unit<br>Coordination with technical experts performing **STEP 4** |

## STEP 6.

| Inviting tenders | *Responsible entity* |
|---|---|
| • In a fair, transparent process, identify and contact potential suppliers of stringently assessed products (approved by WHO PQP or an SRA).<br>• If not enough such products are available on the market, identify potential suppliers of equivalent alternative products and communicate the call for tender among these suppliers fairly and transparently. | Procurement management unit in consultation with regulatory and pharmaceutical experts |

## STEP 7.

| Investigating bid responses and validity | *Responsible entity* |
|---|---|
| • Conduct a preliminary evaluation of offers on the basis of predetermined criteria.<br>• Examine suppliers' records, administrative information and licensing status. | Procurement management unit |

## STEP 8.

| Evaluating product quality | *Responsible entity* |
|---|---|
| • Identify offers that comply fully with the technical specifications. | Quality assurance officers (pharmacists, pharmaceutical specialists) |

## STEP 9.

| Evaluating bids commercially | *Responsible entity* |
|---|---|
| • From those bids that are recommended on the basis of technical evaluation, select that which offers optimal value in terms of service and financial and logistic conditions.<br>• Tender evaluations should be based on criteria spelt out in the tender documents (see **STEP 4**). | Procurement management unit |

## STEP 10.

| Contracts | *Responsible entity* |
|---|---|
| • On the basis of tender documentation (see **STEP 5**) and the results of bid evaluation, prepare contracts with the selected supplier(s).<br>• Include any additional or specific requirements, such as language or packaging for the country of use.<br>*Note:* Avoid long-term contracts for products that are not WHO-prequalified or SRA-authorized in order to have more opportunities for review of quality. | Procurement management unit, on behalf of ministry of health, and supplier, based on a memorandum of understanding |

## STEP 11.

| Preshipment inspection and quality control | *Responsible entity* |
|---|---|
| • Identify opportunities for joint quality control testing.<br>• Contract a qualified laboratory (preferably WHO-prequalified or ISO-17025-accredited) in a competitive process.<br>• Ensure sampling, testing of batches, handling of results and reporting as per agreed procedures and funders' requirements. | Procurement management unit (managing contract) and quality assurance department (technical input) |

## STEP 12.

| Port clearance and receipt | *Responsible entity* |
|---|---|
| • For international procurement, liaise with the supplier, the consignee and staff at the port of entry before each shipment.<br>• On receipt, check products against orders and specifications.<br>• Report procurement outcomes as required by programme and funders. | Relevant department of procurement unit in charge of logistics, receipt, stock control and reporting |

## STEP 13.

| Post-shipment quality control | *Responsible entity* |
|---|---|
| • Identify opportunities for joint quality control testing.<br>• Contract a qualified laboratory (preferably WHO-prequalified or ISO-17025-accredited) in a competitive process.<br>• Ensure sampling, testing of batches, handling of results and reporting as per agreed procedures and funders' requirements. | Procurement officers and quality assurance department, collaboration with national regulatory authority |

## STEP 14.

| Storage and distribution | *Responsible entity* |
|---|---|
| • Liaise with stock control officers or warehouse staff responsible for storage and distribution of medicines in accordance with good practice. | Staff performing the technical evaluation (see STEP **8**) should alert storage personnel to any special storage requirements. |

## STEP 15.

| Monitoring supplier performance | *Responsible entity* |
|---|---|
| • Check that deliveries match orders over time.<br>• Keep a record of lead times and other procurement outcomes. | Quality assurance department, reporting to procurement department<br>Warehousing |

## STEP 16.

| Monitoring variations | *Responsible entity* |
|---|---|
| • Ensure continuing compliance with contractual specifications.<br>• Handle any changes as contractually agreed. | Procurement management unit |

# STEP 1.

# Selecting safe, effective antimalarial medicines

Effective treatment is the cornerstone of malaria control. The choice of antimalarial medicines should be based on the best available clinical evidence. Research indicates the following:

- Widespread resistance to all well-established antimalarial medicines (such as chloroquine and sulfadoxine + pyrimethamine) has been observed in most endemic regions in the past few decades.
- Artemisinin-based combination therapies (ACTs) are at present the only remaining effective treatment for uncomplicated malaria.
- Wrong combinations, wrong dosages and monotherapy promote resistance, so that the medicines will become useless.

➔ ***For malaria control and to minimize new resistance, treatment programme staff should select safe, effective medicines and promote their appropriate use as recommended in WHO and national guidelines.***

## 1.1 WHO guidelines

WHO has drawn up standard treatment guidelines (*27*) and lists of essential medicines (*28*) to guide countries in setting national treatment policies. The WHO standard treatment guidelines for malaria are drawn up and reviewed by health professionals with a wide range of expertise and are updated approximately every 2 years. The antimalarial medicines recommended are those for which there is adequate current evidence of efficacy and safety and which are likely to remain effective for the next 3–5 years. The guidelines provide simple, straightforward recommendations that can be adapted and applied effectively in most settings. Future editions will take into account the cost-effectiveness of various treatment options on the basis of changes in the market for ACTs.

Medicines recommended in the WHO guidelines are reflected in the WHO model essential medicines list (*28*). In October 2007, a model essential medicines list for children (*29*) became available. Essential medicines satisfy the priorities among the health-care needs of the population and should be available in functioning health systems at all times, in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price that the individual and the community can afford.

Antimalarial medicines currently recommended by WHO are listed in **Table 1**. Dihydroartemisinin–piperaquine has been shown to be safe and effective in large trials in Asia and Africa and has been added to the list of recommended ACTs. WHO recommends use of this formulation to address emerging artemisinin resistance on the Thailand–Cambodia border (*30*). Quinine is used as an alternative medicine for the treatment of severe malaria, and for the management of treatment failure.

To contain the development of resistance, the artemisinin derivatives and other medicines in ACTs should not be made available singly, except in rectal and parenteral formulations for the management of severe malaria. Oral artemisinin-based monotherapies should be removed from the market. ACTs should be procured and distributed in a packaging designed to improve patients' adherence to treatment as well as rational medicines use. Fixed-dose combinations are preferred.

ACTs are also effective schizonticidal medicines against other species, i.e. *P. vivax*, *P. malariae* and *P. ovale*. ACTs do not prevent relapses of *P. vivax* and *P. ovale* malaria, and for radical treatment of *P. vivax* malaria, ACTs should be given in combination with primaquine. Artesunate + sulfadoxine–pyrimethamine is not effective against *P. vivax* malaria in many places. Severe cases of *P. vivax* malaria should be treated in the same way as severe and complicated falciparum malaria.

Countries can adapt the WHO standard treatment guideline and essential medicines list for their own use, with appropriate implementation and scale-up strategies. The latest version should always be consulted.

➔ ***WHO Guidelines for the treatment of malaria (27), the essential medicines list (28) and the essential medicines list for children (29) reflect the available scientific evidence. They should guide countries' selection of antimalarial medicines.***

INTERNET SOURCES

- WHO. *Guidelines for the treatment of malaria*
  http://www.who.int/malaria/publications/atoz/9241546948/en/index.html
  Search: **"malaria treatment guidelines"**
- WHO. Model lists of essential medicines
  http://www.who.int/medicines/publications/essentialmedicines/en/
  Search: **"model list of essential medicines"**

**Table 1. WHO-recommended medicines for the treatment of malaria**

| Active pharmaceutical ingredient(s) in available formulation(s) | Uncomplicated falciparum malaria | Treatment failure | Severe malaria |
|---|---|---|---|
| Artemether–lumefantrine oral | ✓ | ✓* | |
| Artesunate +– amodiaquine oral[a] | ✓ | | |
| Artesunate + mefloquine oral | ✓ | ✓* | |
| Artesunate + sulfadoxine–pyrimethamine oral[a] | ✓ | | |
| Dihydroartemisinin–piperaquine oral | ✓ | ✓* | |
| Artesunate (or quinine) combined with tetracycline or doxycycline or clindamycin, oral | | ✓ | |
| Artesunate, intravenous or intramuscular | | | ✓ |
| Artemether, intramuscular | | | ✓ |
| Quinine, intravenous or intramuscular | | | ✓ |
| Artemotil, intramuscular | | | ✓** |
| Artesunate, rectal | | | ✓*** |
| Artemisinin, rectal | | | ✓*** |

From reference *27*
+ co-packaged products;
– co-formulated products;
+– co-packaged FPPs also available as co-formulated tablets, since some API–API incompatibilities have been resolved;
* only if not used as first-line treatment;
** used if no alternative is available, as few clinical trials have been conducted;
*** for patients with severe malaria before referral to a facility where complete parenteral treatment with artesunate, quinine or artemether can be administered.
[a] For areas where amodiaquine or sulfadoxine–pyrimethamine cure rate ≥ 80%.

## 1.2 National guidelines

National treatment guidelines reflect national policies on malaria treatment. In most cases, they are adapted from the WHO *Guidelines for the treatment of malaria* (*27*), with account taken of factors such as the level of resistance to the medicine in the combination and patient acceptability.

According to WHO's global antimalarial drug policy database in February 2009, 80 countries had adopted ACTs for first-line treatment of uncomplicated *P. falciparum* malaria. In some countries, national treatment guidelines have been adapted. For example, dihydroartemisinin and piperaquine are being used in Cambodia, China and Viet Nam.

➔ ***National standard treatment guidelines reflect national policies and should be respected in procurement.***

INTERNET SOURCE

- WHO. Global antimalarial drug policies database
  http://www.who.int/malaria/am_drug_policies_by_region_afro/en/index.html
  Search: **"Country antimalarial drug policies"**

## 1.3 Special situations

In, for example, cases of drug-resistant malaria, an antimalarial agent may be needed that is not included in the current standard treatment guidelines. The safety and efficacy of that medicine will then have to be evaluated on the basis of the available data by a group of experts with appropriate medical and regulatory expertise. For instance, the GFATM has a Technical Review Panel, which verifies situations in which the selection of medicines procured with grant funds is not in line with the WHO *Guidelines for the treatment of malaria*.

At national level, a treatment programme committee will make this assessment. If procurement is funded by donors, other international bodies might have to approve the choice of these medicines. In emergency situations, such as epidemics or ACT supply shortages, when large populations are at risk for illness or death, approval must be accelerated.

➔ ***Special situations might require the procurement of antimalarial medicines not listed in the standard treatment guidelines or the essential medicines list. The decision to procure such medicines should be made by medical experts.***

## 1.4 Safe, effective antimalarial medicines and preferred presentations

The information given on the previous pages indicates that the following rules should be followed in selecting antimalarial medicines for procurement:

- Antimalarial formulations included in the WHO *Guidelines for the treatment of malaria* and in national malaria treatment guidelines can be considered safe and effective and are therefore suitable for procurement.
- For antimalarial medicines that are listed in only one of the two above-mentioned sets of guidelines, the selection should be clearly justified.
- National and possibly international expert committees should decide on the procurement of any other antimalarial medicines for use in special situations.

To ensure patient adherence and to promote rational medicines use, co-formulated fixed-dose combinations should be selected. If these are not available, easy-to-use co-blistered (co-packaged) presentations should be selected. Preferred product presentations are listed in **Table 2**. Depending

on the setting of use, additional aspects of, for example packaging, labelling and instructions for use, should be considered to ensure that the medicines are suitable for the intended purpose (see model specification under **STEP 4)**.

**Table 2. Preferred antimalarial product presentations (as of September 2009)**

| **ARTEMETHER–LUMEFANTRINE** co-formulated tablet | **Recommended regimen by weight and age group (not recommended during the first trimester of pregnancy or for children weighing < 5 kg)** | | | |
|---|---|---|---|---|
| | **5–14 kg (< 3 years)** | **15–24 kg (≥ 3–8 years)** | **25–34 kg (≥ 9–14 years)** | **> 34 kg (> 14 years)** |
| | 20 mg/120 mg twice daily for 3 days | 40 mg/240 mg twice daily for 3 days | 60 mg/360 mg twice daily for 3 days | 80 mg/480 mg twice daily for 3 days |
| | Pack size | | | |
| 20 mg/120 mg | 6 | 12 | 18 | 24 |
| 40 mg/240 mg | – | 6 | – | 12 |
| 60 mg/360 mg | – | – | 6 | – |
| 80 mg/480 mg | – | – | – | 6 |

| **ARTESUNATE–AMODIAQUINE (BASE)** co-formulated tablets (bilayered) | **Recommended regimen by weight and age group** | | | |
|---|---|---|---|---|
| | **4.5 to < 9 kg (2–11 months)** | **9 to< 18 kg (1–5 years)** | **18 to < 36 kg (6–13 years)** | **≥ 36 kg (≥ 14 years)** |
| | 25 mg AS (base)/ 67.5 mg AQ (base) once daily for 3 days | 50 mg AS (base)/ 135 mg AQ (base) once daily for 3 days | 100 mg AS (base)/ 270 mg AQ (base) once daily for 3 days | 200 mg AS (base)/ 540 mg AQ (base) once daily for 3 days |
| | Pack size | | | |
| 25 mg/67.5 mg (base) | 3 | – | – | – |
| 50 mg/135 mg (base) | – | 3 | – | – |
| 100 mg/270 mg (base) | – | | 3 | 6 |

| **ARTESUNATE + AMODIAQUINE (BASE)** co-formulated tablets (preferable); co-blistered tablets | **Recommended regimen by age group** | | | |
|---|---|---|---|---|
| | **5–11 months** | **≥ 1–6 years** | **≥ 7–13 years** | **> 13 years** |
| | 25 mg AS + 76.5 mg AQ (base) once daily for 3 days | 50 mg AS + 153 mg AQ (base) once daily for 3 days | 100 mg AS + 306 mg AQ (base) once daily for 3 days | 200 mg AS + 512 mg AQ (base) once daily for 3 days |
| | Co-packs (if co-blistered) | | | |
| 25 mg + 76.5 mg (base) | 3 + 3 | – | – | – |
| 50 mg + 153 mg (base) | – | 3 + 3 | 6 + 6 | 12 + 12 |
| 100 mg + 306 mg (base) | – | – | 3 + 3 | 6 + 6 |

**Table 2.** ***continued***

| **ARTESUNATE TABLETS + MEFLOQUINE (BASE)** co-blistered tablets | Recommended regimen by age group | | | |
|---|---|---|---|---|
| **Day** | **5–11 months** | **≥ 1–6 years** | **≥ 7–13 years** | **> 13 years** |
| Day 1 | 25 mg AS | 50 mg AS | 100 mg AS | 200 mg AS |
| Day 2 | 25 mg AS + 125 mg MQ (base) | 50 mg AS + 250 mg MQ (base) | 100 mg AS + 500 mg MQ (base) | 200 mg AS + 1000 mg MQ (base) |
| Day 3 | 25 mg AS | 50 mg AS | 100 mg AS + 250 mg MQ (base) | 200 mg AS + 500 mg MQ (base) |
| | Co-packs | | | |
| 25 mg + 125 mg (base) | 3 + 1 | | | |
| 50 mg + 250 mg (base) | – | 3 + 1 | 6 + 3 | – |
| 100 mg + 250 mg (base) | – | – | 3 + 3 | 6 + 6 |

| **ARTESUNATE + SULFADOXINE–PYRIMETHAMINE** co-blistered tablets | Recommended regimen by age group | | | |
|---|---|---|---|---|
| **Day** | **5–11 months** | **≥ 1–6 years** | **≥ 7–13 years** | **> 13 years** |
| Day 1 | 25 mg AS + 250/12.5 mg SP | 50 mg AS + 500/25 mg SP | 100 mg AS + 1000/50 mg SP | 200 mg AS + 1500/75 mg SP |
| Day 2 | 25 mg AS | 50 mg AS | 100 mg AS | 200 mg AS |
| Day 3 | 25 mg AS | 50 mg AS | 100 mg AS | 200 mg AS |
| | Co-packs | | | |
| 25 mg + 250/12.5 mg | 3 + 1 | | | |
| 50 mg + 500/25 mg | | 3 + 1 | 6 + 2 | – |
| 100 mg + 500/25 mg | – | – | 3 + 1 | 6 + 3 |

| **DIHYDROARTEMISININ–PIPERAQUINE** co-formulated tablets | Recommended regimen by weight and age group* | | | |
|---|---|---|---|---|
| | **5–9.9 kg (< 2 years)** | **10–19.9 kg (≥ 2–9 years)** | **20–39.9 kg (≥ 10–14 years)** | **≥ 40 kg (≥ 15 years)** |
| | 20 mg DHA/ 160 mg PPQ once daily for 3 days | 40 mg DHA/ 320 mg PPQ once daily for 3 days | 80 mg DHA/ 720 mg PPQ once daily for 3 days | 120 mg DHA/ 960 mg PPQ once daily for 3 days |
| | Pack size | | | |
| 20 mg + 160 mg | 3 | | | |
| 40 mg + 320 mg | – | 3 | 6 | 9 |

* Based on weight per age correlations for Asian populations

| **ARTEMETHER** oily injection | |
|---|---|
| • Paediatric: 20 mg; 40 mg/ml<br>• Adult: 80 mg/ml; 100 mg/ml | Only for management of severe malaria<br>0.5-ml ampoules, 1-ml ampoules; 2-ml ampoules |

| **ARTESUNATE** powder for injection | |
|---|---|
| • Ampoules or vials containing 60 mg anhydrous artesunate | Only for management of severe malaria<br>Co-packed with a separate ampoule of 5% sodium bicarbonate solution and 5% dextrose or isotonic saline |

| **ARTESUNATE** rectal preparations (suppositories) | |
|---|---|
| • 50 mg; 100 mg; 200 mg; 400 mg | Only for initial management of severe malaria until parenteral treatment can be started at a higher level of the health system |

# STEP 2.
# Estimating requirements

Four steps must be taken before artemisinin-based products can be supplied to buyers: cultivation of plants, production of the raw material in powder form, processing by API suppliers and manufacturing of FPPs. The total production cycle of several ACTs exceeds 14 months. Although initiatives are under way to provide incentives to farmers, a continuous supply of plant material is not ensured.

Experience has shown the instability of the supply of artemisinin-based products in the absence of reliable forecasts. In 2004, there was a scarcity and a rise in price due to a rapid increase in the demand for ACTs, and in 2008 and 2009 agricultural production was reduced in response to overproduction in 2006 and 2007 with a consequent fall in prices (*31*). Reliable estimates of demand can stabilize the demand and reduce the risk for suppliers. Two approaches can be used for this purpose:

- conclusion of long-term, extendable agreements with suppliers, with careful monitoring of supplier performance and ongoing product quality (see **STEPS 15** and **16**); and
- pooled procurement, ranging from informed buying (when purchasers share information on prices and suppliers but purchase individually) to central contracting and purchasing through a global procurement agent (*32*).

Organizations that have pooled the procurement of other pharmaceutical products have confirmed that forecasting of demand is important. The quantities of antimalarial medicines required in a specific area for a specific population are generally estimated annually or semi-annually.

➔ ***Reliable estimates must be made of the required quantities of antimalarial medicines in order to avoid shortages, price increases, stock-outs and wasting of resources due to oversupply and expiry of products.***

➔ ***Estimates are made in two phases: quantification of the treatments needed and forecasting of actual amounts to be ordered.***

➔ ***A realistic work plan should be followed, with coordination by a responsible person.***

➔ ***If collaboration in procurement with other entities is envisaged, they should be approached and involved from this step onwards.***

## 2.1 Quantification

Quantification involves the determination of the number of antimalarial treatments expected to be needed during a defined period. It is usually undertaken at national level on the basis of information from all geographical areas and all levels of the health-care system. Collection of such information in decentralized systems can be challenging.

There are two main methods of quantification:

- In the *consumption method*, requirements are estimated on the basis of the amounts consumed in the past. Adjustments are made for stock-outs, seasonal patterns and any other foreseeable changes. This method is preferred when reliable records of past consumption are available and no major changes in prescribing practices are anticipated.
- In the *morbidity method*, requirements are estimated on the basis of the estimated numbers of children, pregnant women and other adults who will need treatment of uncomplicated or severe malaria at health facilities within the target area, in line with standard treatment guidelines for each of these groups. This method is appropriate when past consumption would give an unrealistic picture of the amount of antimalarial medicines required; for instance, if records are unreliable, previous budgets were too low, prescribing patterns require improvement, facilities are expanding or new treatments are being introduced. For example, in some areas where large amounts of ACTs are used and vector control interventions are successful (e.g. Rwanda, Senegal and Zanzibar, United Republic of Tanzania), the consumption of ACTs has decreased over time, requiring adjustments in quantification.

Quantification estimates should be updated quarterly, jointly with relevant partners.

## 2.2 Forecasting

Forecasting involves planning demand on the basis of allocated funds and actual needs. To determine the actual number of packs of each medicine required at each level of the supply chain, account must be taken of the results of quantification, pack sizes, stocks on hand, safety stock required and anticipated losses. Some systems base their forecasts on losses as high as 10%, as artemisinin-based antimalarial medicines are vulnerable to high temperatures and humidity and to theft.

In long-term agreements, some flexibility may be needed, requiring manufacturers to hold and rotate a stock of sufficient APIs and packaging materials, for production and shipment of defined minimum quantities of products at short notice (e.g. within 2 weeks of receipt of an order).

Most artemisinin-based antimalarial FPPs have a short shelf-life of 24 months or less. Storage capacity at the points of delivery is often limited, and lead times may be long.

➔ ***Owing to the short shelf-lives of artemisinin-based antimalarial medicines and the varied uptake rates of the different products, annual or semi-annual forecasts may have to be replaced by shorter cycles.***

➔ ***Staggered schedules for deliveries during the forecasting cycle should be worked out to ensure that products can be stored and used up before they expire.***

FURTHER READING

- WHO. *A model quality assurance system for procurement agencies* (*1*), pp. 28–29.
- Quick JD et al. *Managing drug supply* (*2*), pp. 184–206.
- United States Pharmacopeial Convention. *Ensuring the quality of medicines in low-income countries. An operational guide* (3), pp. 63–64.
- WHO. Global Malaria Programme. *Malaria case management: operations manual* (33), pp. 31–40.

## STEP 3.

# Securing funding

Realistic financial guarantees are important in order to share the risk between the manufacturer and the buyer (*32*). Artemisinin-based antimalarial medicines are much more expensive than other such medicines.

Financial planning is based on accurate forecasting (see **STEP 2**) and a realistic assessment of the total cost of procurement, including the cost of the products, transport and handling fees, duties and taxes, and allowances for price increases and fluctuating exchange rates.

## 3.1 National funding

National governments have adopted ACTs as the first-line treatment for malaria and are making available adequate funding, although administrative challenges persist.

➔ ***Governments should include a budget line for ACTs.***

## 3.2 Donor funding

Significant, increasing funding is being made available for these medicines by government development banks, multilateral and bilateral agencies and nongovernmental organizations. Outside the health sector, funds can be accessed through schemes such as poverty-reduction support credit programmes and the 'heavily indebted poor country' initiative (**http://www.imf.org/external/np/exr/facts/hipc.htm**).

The provision of assistance by donors varies, such as for training, laboratory support and quality control testing. They also have varying requirements, such as quality criteria, preshipment quality control testing and reporting of procurement outcomes in a publicly available database.

➔ ***Procurement managers should calculate the total anticipated cost of procurement and compare it with their available funding, so that any shortfall can be addressed.***

➔ ***Applications for funding should be based on realistic estimates of the costs to be covered (see STEP 9).***

➔ ***The special requirements of funders must be taken into account in tender documents (see STEP 5) and contracts (see STEP 10).***

➔ ***Disbursement timelines, costing and budget plans must be well managed to avoid stockouts.***

Information on the scope of assistance and requirements for funding by different organizations can be found on their web sites. Major funders of antimalarial medicines include:

- Affordable Medicines Facility – malaria (AMFm): **http://www.theglobalfund.org/en/amfm/**
  Search: **"affordable medicines facility malaria"**
- Global Fund, information on grant applications: **http://www.theglobalfund.org/en/applying/**
  Search: **"global fund" applying grants**
- UNITAID: **http://www.unitaid.eu/en/**
  Search: **unitaid**
- United States President's Malaria Initiative: **http://www.fightingmalaria.gov/**
  Search: **"president's malaria initiative" "malaria communities program"**
- World Bank's malaria booster programme: **http://go.worldbank.org/6FBVYVI050**
  Search: **"world bank" malaria "booster program"**

## STEP 4.

# Defining product specifications

A specification is a detailed, unambiguous statement of the buyer's requirements in terms of the attributes and features of the product, with a description of the means by which compliance with those requirements can be verified. The specification is generally attached to the bidding documents and forms part of the supply contract.

The model specification shown in **TABLE 3** lists the technical requirements for artemisinin-based antimalarial medicines, on the basis of the stringent norms and standards of safety, efficacy, quality, packaging and labelling, as applied by WHO PQP and SRAs. It can serve as a general technical guide for procurement officers preparing tenders for procurement.

Indications on how to assess compliance with each requirement are shown next to the specifications. For products that have marketing authorization from an SRA or which are WHO-prequalified, bioequivalence need not usually be evaluated.

**Table 3. Model specification for a pharmaceutical product**

| Aspect | Requirement (include or adapt as appropriate) | Proof of compliance | Body responsible for assessment |
|---|---|---|---|
| **1. FINISHED PHARMACEUTICAL PRODUCT (FPP)** | | | |
| **1.1 Product identification and description** | | | |
| Formulation | Products of the following formulation(s), as recommended in the WHO standard treatment guidelines and national guidelines in the country of use, should be supplied:<br>Specify INN(s), strength of all APIs, dosage form and route of administration.<br>Submissions should state the form of each API: salt, base or ester. | Description of product, specifying form of APIs (salt, base or ester); reference to standard treatment guidelines and essential medicines list | Technical assistant, on basis of medicines selected by medical experts (see **STEP 1**) |
| Co-formulations/ co-packs of combination therapies | Combination therapies should be either co-packed (co-blistered) or, preferably, co-formulated (fixed-dose combination) to facilitate patient adherence to recommended regimens.<br>Specify recommended co- formulations and/or co-packs (see **STEP 1**, list under 1.4) | Description of packaging, samples (see packaging and labelling below) | Technical assistant, taking into account setting of use of the medicines ('fit-for'purpose' requirements) |
| Score lines (break marks) | If tablets are scored for flexible dosing, the uniformity of content must be sufficient to guarantee equal distribution of APIs in each fraction of the tablet, especially in the case of fixed-dose combinations. | Certificate of analysis for FPP<br>Product sample | Technical expert (pharmaceutical) |
| **1.2 Packaging** | | | |
| Protective function | All packaging must be designed to protect the dosage form and to render it suitable for the intended use throughout the stated shelf-life. | Stability report, container-closure system (sample) | Technical expert (pharmaceutical) |

**Table 3.** ***continued***

| Aspect | Requirement (include or adapt as appropriate) | Proof of compliance | Body responsible for assessment |
|---|---|---|---|
| Course-of-therapy packaging | ACTs should be prepackaged into course-of-therapy pack sizes, containing all the doses of a treatment course in a well-designed blister pack, with the individual doses in easily recognizable subunits.<br>Parenteral dosage forms should be packed in units that will facilitate course-of-therapy use, together with any diluents. | Packaging sample | Technical assistant |
| Climate conditions | All packaging must be suitable for delivery and use in zone IV climate conditions as established in stability studies (for primary and secondary packaging, see below) and ISO norms (for outer packaging). | Stability report<br>Packaging sample | Technical expert (pharmaceutical)<br>Technical assistant |
| Tamper-evidence | All packaging must be tamper-evident. | Packaging sample | Technical assistant |
| Same packaging | Products must be supplied in the same primary and secondary packaging in terms of material and size and with the same container or closure system as that approved (or submitted for approval) by an SRA or WHO PQP and evaluated in stability studies. State and justify any exceptions. | Supplier's undertaking | Verification by buyer (see STEP **16**) |
| 1.2.1 *Primary packaging (in direct contact with the dosage form)* | | | |
| Packaging materials | Primary packaging materials must be considered safe for use with the dosage form and for the intended route of administration. Containers must not interact with contents or have been adversely affected by manufacturing processes such as sterilization.<br>For parenteral products, components that will at any stage come into contact with any part of the product must comply with requirements specified by the British, European or United States pharmacopoeia. | Manufacturer's packaging specifications<br>Reference to pharmacopoeial monographs | Technical assistant<br>Technical expert (pharmaceutical) |
| Co-blister packs (adapt as appropriate for the treatment course) | Good-quality material must be used for the lidding material, e.g. aluminium foil.<br>The forming film should be transparent to ensure that tablets and capsules are visually identifiable by size, colour and/or shape.[a]<br>If light-sensitive, the product must be protected from light by the film coating or the secondary packaging material (store in carton).<br>Information on seal integrity should be provided as part of stability studies. | Manufacturer's packaging specifications, packaging sample<br>Stability report | Technical assistant<br>Technical expert (pharmaceutical) |
| Glass ampoules | Glass ampoules should have single-ended, break-off necks. | As above | |
| Glass containers | Glass containers should not exceed a volume of 250 ml. | As above | |
| Rectal dosage forms (suppositories) | Rectal dosage forms should be individually sealed in tear-off packaging to facilitate detachment of each suppository before it is opened for use. (See also **Labelling**, instructions for use) | Product sample | Technical assistant |
| Marking | Primary packs should be marked as follows: (specify). Specify any required marking, e.g. "government use only – not for sale". | Undertaking of supplier verification | Technical assistant, buyer |

**Table 3. *continued***

| Aspect | Requirement (include or adapt as appropriate) | Proof of compliance | Body responsible for assessment |
|---|---|---|---|
| 1.2.2 *Other packaging* | | | |
| Protection | Parenteral dosage forms must be packed in rigid boxes, strong enough to resist crushing during transport and storage.<br>Glass bottles must be separated by criss-cross partitions or be packed individually in cartons. | Description | Logistics officer |
| Batch segregation | Each unit of packaging should contain products from no more than one batch of pharmaceuticals.[b] | Undertaking of supplier, checked at preshipment inspection or on receipt | Technical assistant<br>Buyer |
| **1.3 Labelling** | | | |
| Label content (▲ denotes items required by the WHO Good Manufacturing Practices) | All FPPs must be labelled as required by national legislation in the country of use. The following label information is required on all unit packs: | Product sample or copy of label artwork | Technical assistant |
| ▲ API(s); name | The International Nonproprietary Name (INN), generic name or acceptable equivalent nonproprietary name must be clearly legible. If a brand name is included, it must not be so prominent as to mask the appearance and readability of the nonproprietary name of the product.<br>The use of brand names on packages, labels and package inserts is subject to the buyer's approval. | As above | As above |
| ▲ Strength | Amount of each API per dosage unit, per unit of volume or per unit of weight, as appropriate | As above | As above |
| ▲ Dosage form | Pharmaceutical dosage form (e.g. tablet, capsule) | As above | As above |
| Excipients | For oral preparations, list any excipient contained in the product known to have a recognized action or effect (as included in guideline on Excipients in the label and package leaflet of medicinal products for human use[c]).<br>For parenteral preparations, list names and amounts of all excipients of medical and/or pharmaceutical relevance e.g. "contains 10% ethanol" (other examples of excipients include gluten, metabisulfites, parabens and tartrazine). | As above | As above |
| Pharmacopoeial standard | Pharmacopoeial standard as described in the International, United States or British pharmacopoeia, if available. The current edition should always apply. | As above, with reference to pharmacopoeia, edition and year of issue | As above |
| Quantity | Net quantity per unit pack labelled on that unit pack (primary, secondary, tertiary) | As above; compare with package insert | As above |
| ▲ Storage instructions | Storage instructions and any special storage or handling precautions<br>Storage conditions stated on the label must correspond to those determined in stability studies. | As above, stability report | As above |
| Storage conditions during transport | Recommended temperature and humidity conditions during transport (see also '**Stability**') | As above | As above |

**Table 3. *continued***

| Aspect | Requirement (include or adapt as appropriate) | Proof of compliance | Body responsible for assessment |
|---|---|---|---|
| ▲ Instructions for use | Instructions for use and warnings and precautions that may be necessary (e.g. "to be swallowed whole – do not chew")<br>The label on suppositories must caution that the product is intended for rectal use only. | Product sample or copy of label artwork<br>Note | As above<br>Must correspond to package insert and scientific summary of product characteristics |
| ▲ Batch number | Batch number assigned by the manufacturer | As above | As above |
| Manufacture date | Manufacture date in an uncoded form | As above | As above |
| ▲ Expiry date | Expiry date in an uncoded form, preferably in the format MM/YYYY. Four digits must be used for the year. | As above | As above |
| ▲ Instructions for storage after opening | Limited shelf-life after the primary package is opened and/or reconstituted, if applicable | As above, stability report | As above<br>Technical expert (pharmaceutical) |
| ▲ Details of supplier or holder of marketing authorization | Name and address of manufacturer or company or person responsible for placing the product on the market<br>The names of the marketing authorization holders in the source and the recipient country should be stated.<br>When the manufacturer is distinct from the supplier, both should be clearly specified, e.g. "Manufactured by company 'A' for company 'B'". | Product sample or copy of label artwork | Technical assistant |
| Label language | Labels should be in (specify language(s)) Certified translations into applicable languages must be supplied for verification before supply of products. | As above, and/or undertaking of supplier | Technical assistant |
| Special marking | Labels should carry the following marking: (specify, e.g. 'For Government use only') | | |
| Label formats | The design of the secondary label (and, when applicable, the primary label) must allow for the addition of dispensing information, without covering important information on the manufacturer's label. | Product sample or copy of label artwork | Technical assistant |
| Product names | Preferably only the INN or generic name of the product should be written on all labels. If a brand name is included, it must not mask the appearance and readability of the INN of the product.<br>Specify any naming formats.[d] | Product sample or copy of label artwork | Technical assistant |
| Labelling materials | Self-adhesive labels should consist of pharmaceutical defiberized paper (80 g/m2) that are film- or UV-coated for protection against humidity and firmly affixed to be tamper-evident and to prevent detachment in tropical climates. | Manufacturer's label specifications | Technical assistant |
| Label printing | Type should be applied preferably by lithography directly onto the container or packaging. Print should be easily legible, preferably black on white. | As above | Technical assistant |
| **1.4 Product information** | | | |
| Patient information leaflet (package insert) | A detailed insert or patient information leaflet must be included within the secondary package or attached to the primary pack. The manufacturer's name and licence number must be indicated on the package insert. | Copy of package insert | Technical assistant |

**Table 3. *continued***

| Aspect | Requirement (include or adapt as appropriate) | Proof of compliance | Body responsible for assessment |
|---|---|---|---|
| Accuracy of information | Information on the use and safety of the product must conform to WHO *Guidelines for the treatment of malaria* and approved product information on safety and efficacy. | Package insert checked against summary of information on product safety, efficacy and use | Medical officer |
| Wording of information | Patient information must be complete, unambiguous and easy to understand. | Copy of package insert | Technical assistant |
| Storage conditions | Recommended temperature and humidity during transport, storage and use, as determined in stability studies, must be stated on the package insert, giving both lower and upper limits, when applicable. | Package insert, checked against stability report | Technical expert (pharmaceutical) |
| Language | Package inserts should be provided in (specify language). A certified translation into a suitable language, e.g. English, should be provided for evaluation. | Package insert and/or undertaking by supplier | Technical assistant |
| Excipients | A list of the excipients (stated qualitatively, whether or not present) should be included.[e] | List of excipients | Technical expert (pharmaceutical) |
| **1.5 Quality control standards and compliance with specifications** | | | |
| Pharmacopoeial monograph | The product must comply with specific monographs of the International, British or United States pharmacopoeia, when available.<br>Any additional specifications (e.g. dissolution, syringeability) must be provided. | Reference to pharmacopoeia edition and year of issue, manufacturers' specifications | Technical expert (pharmaceutical) |
| In-house specifications and analytical methods | If no pharmacopoeial monograph is available, a copy of the applicable specification, a description of all analytical tests, with validation data when appropriate, and limits for results for the API and excipients must be supplied. | Manufacturer's specifications, signed by person responsible for quality assurance | Technical expert (pharmaceutical) |
| General requirements | The product must comply with general requirements for dosage forms (tablets, capsules, parenteral preparations, rectal preparations, oral liquids, oral powders) as stated in the International, European, British or United States pharmacopoeia. | Reference to pharmacopoeia, volume and year of issue | Technical expert (pharmaceutical) |
| Batch certificate, and certificate of analysis | A WHO-type batch certificate, with an attached WHO-type certificate of analysis must accompany each shipment. The certificate of analysis must be original, signed by the quality assurance expert of the manufacturer and dated, or its authenticity must otherwise be assured. | Batch certificates with certificate of analysis of last three batches | Technical expert (pharmaceutical) |
| **1.6 Stability, shelf-life and storage conditions** | | | |
| Stability in zone IV | Supporting data should be submitted to demonstrate the stability of the product in (specify climate zone or country as appropriate)[f] | Stability report | Technical expert (pharmaceutical) |
| Additional stability data | Stability under the expected conditions during transport should be demonstrated if this was not part of regulatory stability testing. | Report on additional stability testing | Technical expert (pharmaceutical) |
| Ongoing stability; same product and packaging | All product supplied should have the same formula, have been manufactured at the same site and packed in the same packaging material with the same container or closure system(s) as those assessed during stability testing.<br>The supplier is responsible for giving the buyer the results of ongoing stability studies. | Stability report, ongoing stability testing results, undertaking by supplier | Technical expert (pharmaceutical)<br>Verification by buyer |

**Table 3.** ***continued***

| Aspect | Requirement (include or adapt as appropriate) | Proof of compliance | Body responsible for assessment |
|---|---|---|---|
| Storage conditions | The recommended storage conditions should reflect the outcome of the stability studies performed by the manufacturer and must correspond to the storage conditions stated on the label and package insert.<br>Storage instructions must comply with WHO recommendations. | Stability report | Technical expert (pharmaceutical) |
| Shelf-life | Unless the buyer has given specific authorization in writing, products must have a remaining shelf-life that is at least 75% of that established at the time of delivery.[g]<br>For products with 2 years' shelf-life or less, stability data should be submitted showing that the shelf-life cannot be extended. | Stability report, undertaking by supplier, certificate of analysis accompanying products delivered | Technical expert (pharmaceutical)<br>Verification by buyer |
| **1.7 Therapeutic equivalence (for generic products)** | | | |
| In vivo bioequivalence studies | For generic products, a report on demonstration of bioequivalence in vivo must be submitted. | Bioequivalence testing report | Technical expert (pharmaceutical) |
| Same product | All product batches supplied must be equivalent to the test batch used in the bioequivalence study in terms of starting materials and suppliers thereof, formula, manufacturing line and manufacturing methods. | Undertaking by supplier | Verification by buyer (see STEP **15**) |
| **1.8 Regulatory situation (licensing status)** | | | |
| Country of production | Medicines must be authorized for use in the destination country.<br>Proof of the regulatory situation of the product should be provided by a WHO-type certificate (*24*) no more than 24 months old. | Certificate of pharmaceutical product or equivalent certification | Technical assistant |
| Other countries | If the product is authorized for use and currently marketed in other countries, registration numbers and countries must be listed. | List of countries and registration numbers | Technical assistant |
| WHO PQP or authorization by an SRA | Products should be either WHO-prequalified or have marketing authorization for use (not for export only) in a country participating in the ICH (or, for products used exclusively outside the ICH region, have obtained a positive opinion by EMEA under the European Union Article 58 scheme).<br>Such products will be preferred, in principle.<br>Note: Inclusion of this requirement is strongly recommended | WHO prequalification number<br>or<br>certificate of pharmaceutical product issued by an SRA<br>or<br>positive opinion under European Union Article 58 | Technical assistant |
| Interim advice for procurement by an expert group | Alternatively, products should have a current advice for procurement by an expert group. Procurement of such products should be considered only to ensure the availability of necessary products. The selection should revert to WHO-prequalified or SRA-authorized products as soon as these become available.<br>*Note:* inclusion of this requirement is strongly recommended. | Proof of expert assessment<br>or<br>procurement entity's own assessment | Technical assistant to verify (e.g. expert review panel advice for procurement, see STEP **6**)<br>Pharmaceutical experts |

**Table 3.** ***continued***

| Aspect | Requirement (include or adapt as appropriate) | Proof of compliance | Body responsible for assessment |
|---|---|---|---|
| **1.9 Samples** | | | |
| Number and description | (State number) non-returnable samples must be submitted for each product in their final status with packaging, labelling and package insert as intended to be supplied on purchase orders.<br>N.B. Commercial and marketing samples are not acceptable.<br>For large pack sizes, specify a reduced number of dosage units to be included, if applicable. | Product sample | For visual and organoleptic inspection by technical assistant and analysis by quality control laboratory |
| Expiry | Each preshipment sample submitted should not expire within 12 months. Samples submitted as part of the bid evaluation may have an expiry date of less than 12 months. | As above | Technical assistant |
| Certificate of analysis | A certificate of analysis should be submitted with the sample. | Certificate of analysis for sample | Technical expert (pharmaceutical) |
| **2. MANUFACTURING SITE** | | | |
| Manufacturer(s) and licensing status | All manufacturing sites at which any aspect of manufacture of the FPP occurs must be stated for each product (including production, sterilization, packaging, quality control and any other manufacturing activity performed).<br>All contract manufacturers and sites of contract manufacture must be listed.<br>All sites involved in the manufacture of each product must be licensed by the relevant authority for the activity being undertaken. | List of FPP manufacturers, activities and license numbers | Technical assistant |
| GMP compliance of manufacturing site | A GMP certificate or inspection report issued after inspection by WHO PQP, an SRA or a member of a pharmaceutical inspection cooperation scheme authority should be provided for the specific site and production line where the product is manufactured. | GMP certificate for FPP manufacturing site | Technical assistant |
| Same site | All product supplied must be manufactured at the site and on the production line for which the GMP certificate was submitted as part of this tender.<br>The manufacturing site should be explicitly stated with each delivery of products. | Undertaking by supplier | Verification by buyer (see STEP **15**) |
| **3. ACTIVE PHARMACEUTICAL INGREDIENT (API)** | | | |
| API manufacturers | Site(s) of manufacture of APIs as well as any alternative manufacturers should be listed.<br>The activities of the API manufacturer(s) should be stated, together with countries, license numbers and validity of each license. | List of API manufacturers and licence numbers | Technical assistant |
| GMP | A GMP certificate should be supplied for each source site of APIs. | GMP certificate for API manufacturing site(s) | Technical assistant |
| Certification | API(s) must be authorized for use in pharmaceutical products with marketing authorization in the country of manufacture. All alternative sources should be listed. | Certificate of suitability, drug master file | Technical expert (pharmaceutical) |

**Table 3.** ***continued***

| Aspect | Requirement (include or adapt as appropriate) | Proof of compliance | Body responsible for assessment |
|---|---|---|---|
| Pharmacopoeial standard | When relevant monographs exist, API(s) and excipients should, as a minimum, comply with the current requirements of the International, European, British or United States pharmacopoeia. | Reference to pharmacopoeia, volume, year | Technical expert (pharmaceutical) |
| In-house standard | When API(s) are not described in a pharmacopoeia, a copy of the supplier's specifications, including a description of the tests and limits for results for the API, must be supplied. | Manufacturers' specifications, signed by the person responsible for quality assurance | Technical expert (pharmaceutical) |
| Certificate of analysis | A confirmatory certificate of analysis from the manufacturer of the FPP should be available at least for the duration of the shelf-life of all batches of the FPP in which the API and excipients are used. The certificate should be satisfactory, as defined in WHO guidelines.<br>A certificate of analysis from the API manufacturer should be available at least for validation of the product. | Certificate of analysis for each API, from FPP manufacturer | Technical expert (pharmaceutical) |



Adapted from specifications used in draft UNICEF tender documents, 2008–2009

[a] This may not apply to particular combinations.

[b] This will apply in particular to large-volume procurement.

[c] *The rules governing medicinal products in the European Union*, Volume 3B; available at: http://www.emea.europa.eu/htms/human/humanguidelines/ efficacy.htm

[d] See example in **STEP 8** under 'Labelling'.

[e] This information is also important for contract laboratories: in the case of liquid dosage forms and artemisinin solids, it is needed for preparing an analytical placebo to identify placebo artefacts by high-performance liquid chromatography

[f] Many products on the market may not be stable in zone IV; this requirement should be reinforced for new products. A list of storage conditions for long-term stability studies in different countries is given in **STEP 8**, under 'Stability'.

[g] This requirement may be difficult to fulfil, and negotiations will be needed during procurement. A continuous supply of medicines to treatment programmes should be assured as a priority.

## STEP 5.

# Selecting the procurement method and preparing tender documents

### 5.1 Procurement method

The aim of procurement is to secure the lowest possible purchase price for quality-assured products, to ensure the reliability of suppliers in terms of both quality and service, to maintain transparency and to minimize opportunities for illicit influences on procurement. Four procurement methods can be distinguished (*2*).

- *Open tender*: any supplier can submit offers. This is not recommended, as medicines must meet complex quality criteria, which should be assessed by regulatory and/or pharmaceutical experts before the procurement cycle (see **STEP 4**).
- *Restricted tender*: prequalified suppliers can submit offers. As described in **STEP 4**, approval by WHO PQP or an SRA is a suitable criterion for product prequalification by procurement entities. If few or no suppliers can offer such products, suppliers of other products should be identified for competitive bidding.
- *Competitive bidding*: only a few prequalified suppliers are approached for negotiations.
- *Direct procurement*: purchase is made directly from a single supplier at the quoted price. This option is not desirable, as dependence on a single supplier may not guarantee a sustained supply of needed products at affordable prices in the long term.

To avoid dependence on a single supplier, some procurement entities award the bid for a proportion of the required quantities to two or more suppliers. Such 'split tender' systems minimize the risk for supplier default but are likely to raise prices.

In some countries, preference is given to local manufacturers, at least for public procurement. Local manufacturers must be able to supply FPPs that meet the requirements described in the specification (see **STEP 4**) if they are to be considered for bidding.

➔ ***Procurement entities should obtain bids from several suppliers who are able to supply FPPs that meet the required specifications.***

➔ ***Procurement requires considerable expertise and resources. Some buyers, including most national governments, have an experienced procurement unit. Those that do not should consider using an international procurement agency.***

### 5.2 Tender documentation

Tender documentation includes the technical specification (see **STEP 4**) and other requirements that define the commercial and logistic framework for procurement. The following aspects should be covered:

- required product formulations (see **STEP 1**);
- required technical specifications and documentation to be submitted in support of compliance (see **STEP 4**);

- requirements for outer packaging and shipping, which include compliance with ISO norms, dimensions, volumes, stacking requirements, materials, crush resistance, padding and external marking;
- required quantities and delivery schedules (see **STEP 2**), required delivery terms (e.g. Incoterms: 'free carrier', nearest main sea- or airport) and ordering procedures;
- applicable terms and conditions that will form the basis for selection;
- time frames for submitting bids and for orders and delivery (Bidders should be alerted to any anticipated delays, for example if medicines still have to be authorized for use in the destination country.);
- procedures for awarding tenders;
- any special conditions in adjudicating tenders, such as preference for products approved by WHO PQP or an SRA, disqualification of suppliers of monotherapies;[1]
- request to applicants to state their administrative and legal details, their link with the product and commitment to ongoing quality; and
- standardized proposal form, stating delivery lead times, expected delivery date, gross weight of the order, personnel involved and contact details, and a quotation for the total amount, including any discounts.



Most funders have their own format for bidding documents. Information and guidance on procurement are available on the web sites of many funding organizations (see **STEP 3**). An example is the toolkit for procurement of antimalarial medicines under the Malaria Control Booster Program (*34*).

Tender documentation spells out the technical requirements and the criteria for awarding bids.

Tender documentation is the basis for any future contracts (see **STEP 10**). Subsequent changes can cause additional costs and delays and may appear unjustified to contract partners, especially if they are unexpected.

➔ ***Procedures must be consistent, to make the tender process fair and transparent.***

➔ ***Technical requirements must be well planned to minimize avoidable changes. Any anticipated adaptations (such as specific language or packaging requirements for specific settings of use) should be mentioned in the tender documentation.***

FURTHER READING

- WHO. *A model quality assurance system for procurement agencies* (*1*).
- Quick JD et al., eds. *Managing drug supply* (*2*).

[1] Updated information on manufacturers' positions on marketing of artemisinin-based monotherapies can be found on the web site of the WHO Global Malaria Programme:
**http://www.who.int/malaria/monotherapy_manufacturers.pdf**

Search: **manufacturers "oral artemisinin-based monotherapies" site:who.int**

## STEP 6.

# Inviting tenders

A significant portion of the global supply of artemisinin-based antimalarial medicines comes from countries with new, fast-growing pharmaceutical industries, notably China, India, Pakistan and Viet Nam and, more recently, countries in Africa including Ghana, Kenya, Nigeria, Togo, Uganda and the United Republic of Tanzania. The regulatory systems in the countries of production have varying capacities, requirements and policies.

Authorization of medicines in the country of use is a legal requirement. In many countries, registration is a prerequisite for public sector procurement. Local registration is intended to ensure that products are safe, effective and of good quality. Most national regulatory authorities in malaria-endemic countries, however, lack resources and capacity. Two types of approval provide reasonable assurance that FPPs meet acceptable standards of quality, safety and efficacy: WHO PQP and SRAs. Major funding and United Nations agencies have agreed to define SRAs as countries that participate in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (see **Annex 2**).

➔ ***Information from WHO PQP or SRAs can be used to accelerate registration in the destination country.***

**EXAMPLE: GFATM RECOMMENDATIONS ON ACCELERATED REGISTRATION**

To avoid any limitation to the competition among quality-assured FPPs, it is recommended that national regulatory authorities accelerate product registration by accepting the following information:

- For WHO-prequalified FPPs, the prequalification approval letter and supporting documentation, including the WHO prequalification report and the manufacturer's summary of information on the quality, safety and efficacy of the FPP, together with all the information necessary for quality control testing of products and reference standards.
- For SRA-authorized FPPs, the executive summary of the "Common technical document for the registration of pharmaceutical products for human use" (common technical document) or sections of that document relating to the quality, safety and efficacy of the FPP, together with all necessary attachments.

## 6.1 WHO Prequalification Programme (WHO PQP)

Generic products improve access to affordable antimalarial treatment. As regulatory capacity is limited in many countries, WHO PQP assesses products according to a standardized procedure (*19*), which includes review of product dossiers and inspection of manufacturing sites to ensure that all aspects related to products comply with GMP (*18*) and supplementary guidelines (*5*,*22*,*35*,*36*). WHO PQP recognizes the findings of SRAs.

WHO PQP also inspects contract research organizations that perform bioequivalence studies for compliance with WHO good clinical practices and good laboratory practice (*37*).

Manufacturers are invited to submit 'expressions of interest' for producing FPPs that are considered priorities for evaluation by WHO, in consultation with UNICEF, UNAIDS and UNFPA. In 2007, UNICEF and WHO decided that manufacturers participating in joint UNICEF/WHO tenders for ACTs must submit dossiers to WHO PQP. In 2008 and 2009, 11 ACTs were WHO-prequalified.

On receipt of applications, WHO PQP screens the documentation for completeness and acceptability for assessment. If it meets the requirements, the manufacturer is sent an acceptance letter with a WHO PQP reference number and the date on which the submission was received. Once WHO prequalification is completed, WHO PQP uses formal procedures to deal with reassessment, complaints and maintenance of the prequalification status by manufacturers (see **STEP 16**).

➤ ***The following information on WHO-prequalified antimalarial medicines is publicly available on WHO PQP's web site:***

- list of FPPs, with reference number, product description, name of manufacturer, manufacturing site, packaging and date of prequalification;
- for dossier assessment, public assessment reports, WHO public assessment reports (parts 1–8: abstract, presentation, product information leaflet, summary of product characteristics, labelling, discussion, steps before prequalification and steps following prequalification) and notices of suspension; and
- for inspections, public inspection reports, WHO public inspection reports (summaries of GMP inspection reports on manufacturing sites for APIs, FPPs, contract research organizations and quality control laboratories) and notices of concern.

The web site also includes a list of the formulations that are under assessment, showing the status of dossier evaluation, without identifying the manufacturers. WHO PQP works with national regulatory authorities to ensure uniform, stringent standards of safety, efficacy and quality. The Programme's web site also provides information on training seminars, workshops and meetings, some of which are specific to antimalarial medicines.

N.B. WHO PREQUALIFICATION

- An acceptance letter from WHO PQP does **not** mean that a product is WHO-prequalified. It means that the submission has been received and will be reviewed.
- For WHO-prequalified FPPs, all product details must correspond exactly to those on the WHO PQP list. For example, the same FPP manufactured by the same manufacturer at a different, unlisted manufacturing site is not considered to be WHO-prequalified.

INTERNET SOURCE

- WHO PQP (list of prequalified products for malaria) **http://www.who.int/prequal**
  Search: **Prequalification programme malaria**

## 6.2 Stringent regulatory authorities (SRAs)

Regulatory authorities grant marketing authorization for FPPs only after review and acceptance of product dossiers on safety and efficacy and GMP inspection of the production site to assess the manufacturing processes and compliance with specifications. A first registration is often limited to a period determined by the issuing authority, after which there is a reassessment. If the result is acceptable, the product may be given marketing authorization for an unlimited period.

Authorization by an SRA (as defined in **Annex 2**) provides reasonable assurance that a product is safe, effective and of good quality. For manufacturing facilities located outside countries participating in the ICH or the Pharmaceutical Inspection Cooperation Scheme, authorization should include a physical GMP inspection to the standards of WHO, the ICH or the Pharmaceutical Inspection Cooperation Scheme. Ideally, the inspection should cover all facilities relevant to the production line on which the product is manufactured, although inspections are not always conducted in this way in practice.

Proof of regulatory status is usually delivered in the form of a 'certificate of pharmaceutical product', which is a document in a standard format recommended by the WHO Certification Scheme (*38*) (see **Annex 1**). It is issued by the national regulatory authority of the exporting country to confirm that an FPP is authorized for use in that country.

To strengthen this scheme, it has been suggested (*39*) that the certificate include information on batch release site, that it be issued only for products actually authorized for marketing and manufactured in the issuing country (not those that are exported from a third, transit country), and that it be issued in a fake-deterrent format.

➔ ***Although no comprehensive list of SRA-authorized artemisinin-based antimalarial medicines is publicly available, some organizations maintain and share their product lists, which include such FPPs (see section 6.4).***

N.B. REGULATORY STATUS, CERTIFICATE OF PHARMACEUTICAL PRODUCT

- A WHO-type certificate of pharmaceutical product does not imply WHO approval of the product. It means that the certificate is in the document format recommended by WHO.
- The certificate of pharmaceutical product should be either an original or a copy certified to be genuine.
- If the national regulatory authority in the country of production does not issue WHO-type certificates, an equivalent document should be supplied, which clearly states whether the product is registered in the country of production.
- The registration must apply to the correct product. For example, for a co-formulated product, registration of each of the two products is not sufficient.
- Marketing authorization by an SRA should refer to sale in that country (not 'for export only'). Medicines for export are often regulated less strictly than those for domestic use, for example in terms of GMP and quality control (*40*).

### *6.2.1 Special stringent regulatory schemes for exported products*

As malaria is not endemic in the ICH region, few artemisinin-based antimalarial medicines are registered by an SRA. Manufacturing sites located in countries with SRAs may produce for export only, which often means that they are subject to less stringent inspection and quality control requirements (*29*), because in many cases registration 'for export only' is not designed to guarantee the safety and efficacy of a medicine for use.

Approval under the regulatory schemes of EMEA, Health Canada and the United States Food and Drug Administration is possible for medicines that are marketed exclusively outside the ICH region.

➔ ***Under European Union Article 58 (41), EMEA's Committee for Medicinal Products for Human Use gives scientific opinions, in cooperation with WHO, on medicinal products for human use. This is recognized as a stringent assessment of antimalarial medicines.***

The other two schemes, the Canadian Bill C-9 (*42*) and United States Food and Drug Administration tentative approval (*43*), apply to the provision of antiretroviral drugs and HIV-related medicines only.

INTERNET SOURCE

- EMEA. Scheme to assess medicines used outside the ICH region.
  http://www.emea.europa.eu/htms/human/non_eu_epar/background.htm
  Search: **emea "article 58" opinions "human medicines"**

## 6.3 Risk assessment of finished pharmaceutical products not approved by the WHO Prequalification Programme or a stringent regulatory authority



Certain formulations may not be available on the market as WHO-prequalified or SRA-authorized products, as was the case for injectable artesunate at the time this manual was written. In such cases, procurement entities have to consider other products, until stringently assessed FPPs become available.

FPPs that have not been approved should undergo a technical evaluation in order to weigh the risks and benefits of procuring them. The risks include those for public health, such as ineffective treatment, unexpected adverse drug reactions and drug resistance. The type of such assessments depends on the requirements of funders (see the example of the GFATM below) and countries. At national level, expert groups might be formed of staff in charge of technical evaluation of tenders and national regulatory authority staff.

An example of a technical submission, including the required documentation, is given in **Annex 3**. Screening of submissions for completeness and subsequent evaluation require considerable regulatory and pharmaceutical experience and expertise.

➔ ***Technical assessment of products not approved by WHO PQP or an SRA can take several months. If possible, assessment should be performed before the procurement cycle is under way.***

➔ ***Some of the documentation used in the assessment might allow acceleration of authorization in the country (see the example at the beginning of STEP 6).***

➔ ***The quality of such FPPs must be monitored continuously. Products that are WHO-prequalified or SRA-authorized should be procured as soon as feasible, given the constraints of quantification, shipment, distribution and use of the medicines in treatment programmes. Long-term contracts (more than 1 year) should be avoided.***

### EXAMPLE: GFATM'S EXPERT REVIEW PANEL

Requirements for funding of antiretroviral, antituberculosis or antimalarial medicines by the GFATM (as of 1 July 2009):

- In principle, the GFATM will finance safe, effective FPPs only if they are approved by WHO PQP or an SRA.
- If fewer than two such FPPs can be supplied in sufficient quantities within 90 days from order (or longer if this is acceptable to buyers), GFATM resources can be used to buy FPPs eligible for procurement based on the advice of the Expert Review Panel. The Panel consists of specialists with experience and expertise in the medical, pharmaceutical and regulatory fields.
- The GFATM invites expressions of interest for review by the Panel from manufacturers of required product formulations. The only products that are eligible are those for which a submission to WHO PQP or an SRA has already been accepted for assessment and which are manufactured at a site compliant with all applicable aspects of GMP, as certified after an inspection to WHO, ICH or Pharmaceutical Inspection Cooperation Scheme standards.
- Manufacturers should submit a product questionnaire (see **Annex 3**) with attached certificates and reports to support the quality of the product. After review of these data, the Expert Review Panel will decide whether to consider the FPP eligible for procurement. The advice is valid for up to 12 months. If the product is not approved by WHO PQP or an SRA within that time, the GFATM can ask the Expert Review Panel to consider extending its advice in justified cases.
- Of the 26 FPPs eligible for procurement based on advice of the Expert Review Panel with effect from 1 July 2009, three were ACTs.

INTERNET SOURCE

- GFATM. Quality assurance Information (contains a link to the list of products eligible for procurement by the Expert Review Panel)
  http://www.theglobalfund.org/en/procurement/quality/
  Search: **global fund procurement quality assurance information**

## 6.4 Sources of quality-assured antimalarial finished pharmaceutical products

**Table 4** lists the web sites on which products that have been approved by WHO PQP, an SRA or an expert group are listed.

➔ ***WHO-prequalified products or those approved by an SRA (see Annex 2) are the preferred options for procurement (see sections 6.1 and 6.2).***

➔ ***Buyers should have a strategy to minimize the risks for poor quality associated with other products (see section 6.3).***

➔ ***Regardless of registration status or WHO prequalification status, all suppliers should be asked to furnish evidence to support the equivalence of the FPPs to be supplied under a particular bid with products that have been prequalified.***

| Table 4. Quality-assured antimalarial finished pharmaceutical products (FPPs) | | | |
|---|---|---|---|
| **Organization and web site** | **WHO-PQP** | **SRAs** | **Other** |
| WHO-PQP (list of prequalified products for malaria)<br>**http://www.who.int/prequal**<br>Search: **prequalification programme malaria** | ✓ | * | – |
| Global Fund. List of malaria pharmaceutical products classified according to the Global Fund quality assurance policy (for information only; procurement entities must verify the registration status of the products listed)<br>**http://www.theglobalfund.org/documents/psm/list_malaria.pdf**<br>Search: **"global fund" list malaria** | ✓ | Some | Expert Review Panel |
| Global Fund. List of products eligible for procurement based on advice of Expert Review Panel<br>**http://www.theglobalfund.org/documents/psm/expert review_panel_recommended_products_2009.xls**<br>Accessible from link on page on "quality assurance information"<br>**http://www.theglobalfund.org/en/procurement/quality/**<br>Search: **global fund procurement quality assurance information** | – | – | Expert Review Panel |
| WHO Global Malaria Programme. Antimalarial medicines available for procurement by WHO<br>**http://www.who.int/malaria/medicines.pdf**<br>Search: **antimalarial medicines procurement WHO** | ✓ | Some | |
| UNICEF vendor list<br>Internet access restricted, not publicly available<br>For general information on the UNICEF supply division, see<br>**http://www.unicef.org/supply/index_about.html**<br>Search: **unicef supply division procurement** | ✓ | Some | UNICEF technical experts |

* The WHO-PQP list includes all FPPs with tentative approval by the United States Food and Drug Administration (antiretrovirals) and will include FPPs with a positive opinion from the EMEA under European Union Article 58.

## STEP 7.

# Investigating bid responses and validity

According to the recommended principles for purchasing pharmaceutical products (*1*), suppliers should be prequalified by an assessment of their products and manufacturing sites, as described in STEP **6**, before the procurement cycle begins.

Once bids have been received, a number of supplier- and product-related criteria should be fulfilled before the offers are considered further.

## 7.1 Supplier criteria

- financial stability and standing,
- valid authorization to trade in pharmaceuticals,
- a responsible pharmacist,
- a quality assurance system,
- compliance with WHO good distribution practice standards (*6*) and
- implementation of the WHO model quality assurance system for procurement agencies (*1*).

## 7.2 Product criteria

- compliance with minimum requirements stated in the tender documentation;
- registration status (authorization in the destination country can cause costs and delays);
- disclosure of sources in the case of brokers (who can be protected by a non-circumvention agreement);
- supplier's ability to trace the origin of the supplied products from the starting materials throughout manufacture and distribution; and
- supplier's ability to supply the required quantities.

Artemisinin-based antimalarial medicines are not always procured directly from the manufacturer, and the complex procurement channels used for these medicines are a challenge for quality assurance. In many regions of the world, national regulatory authorities struggle to ensure the quality of the medicines that are marketed in their countries and have little capacity to monitor those that are passing through their territory for marketing elsewhere.

➔ ***Purchasers should take the responsibility to ensure that suppliers, international brokers and agents fulfil these basic requirements.***

# STEP 8.
# Evaluating product quality

This section of the manual gives information on the quality of pharmaceuticals and the documentation to be provided by manufacturers to support it (see **STEP 4**). Although some documentation should be assessed by pharmaceutical experts, technical staff involved in the procurement of pharmaceuticals can use the information as a reference for quality-related aspects when evaluating bids.

## 8.1 Elements of product quality

### *8.1.1 Clinical safety and efficacy*

The therapeutic action and adverse effects of FPPs in the human body are evaluated as part of regulatory assessment for marketing authorization. Procedures differ according to the regulatory assessment that the product underwent initially (see **SECTION 8.2**).

➔ ***In a functioning regulatory environment, procurement entities should not have to duplicate this assessment, nor do they have the capacity to do so.***



### *8.1.2 Quality of FPPs*

The quality of an FPP is judged on the basis of the following criteria:

- *compliance with product specifications*, showing for instance that the product contains APIs of the correct identity, content and purity and that the amounts of impurities and degradation products do not exceed the defined limits at the time of batch release and during shelf-life; other parameters, such as dissolution, clarity of solution and sterility of injections, are also part of the specifications, depending on the dosage form.
- *stability*, ensuring that the FPP in its supplied packaging and stored according to the manufacturer's instructions will continue to comply with specifications and will retain its bioavailability throughout the specified shelf-life;
- *bioavailability*, i.e. the extent to which a dose of a therapeutically active drug reaches its site of action; and
- *complete and correct labelling and product information*, to ensure that the FPP will be prescribed and used correctly.

The manufacturing processes, specifications, analytical methods and shelf-life of an FPP are approved at the stage of regulatory assessment. The compliance of each batch with these criteria is tested routinely by the manufacturer before each batch is released. The quality of the FPP remains the responsibility of the manufacturer during its shelf-life, provided it is stored and transported according to instructions.

➔ ***Procurement entities must verify the quality of FPPs on the market before purchase.***

## 8.2 Types of pharmaceutical products

Three types of pharmaceutical products can be distinguished with regard to development and regulatory assessement: innovator products, generic equivalents of innovator products and new formulations or combinations of well-known APIs. Each type is briefly discussed below. **Annex 4** lists the elements of product quality and the levels at which they are assessed for each of these three product types.

### *8.2.1 Innovator products*

In order to support a marketing application for a product containing a new chemical entity, innovator companies must submit detailed accounts of its properties and its therapeutic and adverse effects. This information is based on extensive research carried out over the many years of drug development, including:

- pharmaceutical trials: data on chemistry (e.g. structure, physical properties, synthesis, specification, impurities and stability characteristics);
- preclinical trials: data on pharmacological properties (in animals and humans), toxicology (short- and long-term studies in animals, including carcinogenicity studies), reproductive and teratological studies in animals; and
- clinical trials in humans: premarketing studies, including Phase I (safety), Phase II (safety and efficacy) and Phase III (safety and efficacy studies in multiple centres).

Phases I–III studies are conducted with limited numbers of healthy volunteers, for limited periods and do not necessarily detect all the long-term effects of a product. Therefore, postmarketing studies and pharmacovigilance are conducted after registration of the product to monitor its safety and efficacy in the long term.

To ensure product quality, manufacturers must ensure that each batch meets the requirements for identity, strength, dissolution, purity and stability by implementing strict standards of GMP.

### *8.2.2 Pharmaceutical equivalents or alternatives*

Pharmaceutically equivalent products may be marketed when patent protection for the innovator product has expired or when it does not apply (see **step 9**). Generic equivalents are products containing the same amount(s) of API(s) in the same dosage form (for example a tablet); pharmaceutical alternatives also contain the same amount(s) of API(s), but the dosage form differs (for example, an immediate-release capsule or a suspension instead of a tablet), although the route of administration and the intended rate of release of the API into the body must be the same. For example, a suppository or a slow-release capsule would not be a generic alternative for an immediate-release tablet.

For registration of generic products, investigation of clinical efficacy and safety in clinical trials need not be repeated. Instead, manufacturers of generic products must demonstrate that their products are 'good-quality copies' of the innovator product. For products that have been on the market for a long time, it may not be possible to identify the innovator product. Generic products are then assessed against a comparator product.

- In terms of safety and efficacy, generics must be shown to be therapeutically equivalent to the innovator product. This is done by bioequivalence studies, which show that the product is released into the body at the same rate and to the same extent as the comparator (for more details, see **section 8.3**).

- Generic products must have the same or comparable manufacturing quality as the innovator products: they must meet the same batch requirements for identity, strength, dissolution, purity and stability and must be manufactured under the same strict standards of GMP.

### 8.2.3 New combinations or dosage forms

Some FPPs contain well-known APIs in dosage forms or combinations that are different from those of the comparator. Safety and efficacy are demonstrated in different ways, depending on the situation.

- If the API(s) and their amount(s) are the same but the route of administration is different (for example, a suppository instead of a tablet), direct evidence of safety and efficacy is required. This includes published data from clinical trials of other preparations in which the same APIs were administered by the same route, or information from clinical trials performed with the proposed product itself.
- If the new product contains a new combination of APIs, the situation may be more complex, and WHO's guidelines for registration of fixed-dose combination medicinal products (*10*) should be consulted. The guidelines describe four scenarios, each with its own requirements for demonstrating safety and efficacy.

Compliance with manufacturing quality standards must be demonstrated in the same way as for innovator and generic products.

### 8.2.4 Artemisinin-based antimalarial medicines

Few artemisinin-based antimalarial medicines have been approved as innovator products by an SRA, because there has been no market for these products in countries with SRAs. As information on the clinical safety and efficacy of these compounds is now well documented in the literature (*44–46*), equally few generic ACT formulations are modelled on stringently assessed innovators.

Many artemisinin-based antimalarial medicines are new formulations (for example bilayer tablets) or new combinations (such as the fixed-dose combination of artesunate + amodiaquine). Others are generic copies of these new formulations.

➔ ***Artemisinin-based antimalarial medicines are difficult to assess in the regulatory framework.***

➔ ***Procurement entities can use the information in Annex 4 to verify that all aspects have been assessed by a national regulatory authority before considering a product for selection. Relevant committees that are empowered to take decisions under special circumstances in the interests of public health may also be consulted.***

## 8.3 Bioavailability and bioequivalence

### 8.3.1 Bioavailability

Bioavailability is the rate and extent of absorption, distribution and elimination of an API after administration of the medicine containing it. If a product intended for systemic action is not bioavailable, it cannot have the desired effect in the body.

While aqueous solutions for injection and most oral solutions are absorbed into the body almost immediately (depending on how easily the API can cross cell membranes), bioavailability must be established for other dosage forms, such as tablets, capsules, transdermal products, certain parenteral products and certain oral solutions. APIs in the last type of product will be absorbed at different rates and to different extents, depending on their solubility and permeability (classified in the biopharmaceutics classification system (*7*)), the release rate from the dosage form, the

excipients and coatings used in the formulation, drug particle size and, for poorly soluble APIs, crystal form (polymorphism).

Absolute and relative bioavailability are distinguished:

- The *absolute bioavailability* of a given dosage form (for example a tablet) is the fraction of the administered dose absorbed intact into the systemic circulation when compared with the amount of the same dose of API absorbed after intravenous injection (which is considered to be 100% bioavailable).
- The *relative bioavailability* is the fraction of the administered dose absorbed from a dosage form (for example a tablet) into the systemic circulation when compared with another dosage form containing the same API (for example a capsule). Hence, relative bioavailability can be used to determine the effects of differences in formulation on the systemic bioavailability of a given drug. Bioequivalence (see below) is an extension of this concept, in which the bioavailability of a particular API in a generic product is compared with that in an innovator product.

➔ ***The bioavailability of new APIs is assessed by national regulatory authorities before FPPs are registered.***

### *8.3.2 Bioequivalence*

Bioequivalence studies are conducted as part of the regulatory assessment of generic products in order to demonstrate that the APIs are released into the body at a similar rate and extent as from a comparator product. If so, it is assumed that efficacy and adverse events will be essentially the same (provided that the impurities in the generic product are comparable to those in the comparator).

➔ ***Bioequivalence indicates whether a generic FPP is a 'good copy' of an innovator or comparator product.***

#### a) Choice of comparator

Bioequivalence testing is possible only if there is a suitable comparator product. For many artemisinin-based combination products, however, neither is there a stringently registered combination product nor is the therapeutic use of the individual APIs clinically established. WHO maintains an online list of acceptable comparators for antimalarial medicines.

INTERNET SOURCE

■ 'Living' list of recommended comparator products published on WHO PQP's web site.
**http://apps.who.int/prequal/info_applicants/info_for_applicants_bioequivalence_comparator.htm**.
Look for list of recommended comparator products for antimalarial medicines.
Search: **prequalification programme comparator applicants**

#### b) Methods of demonstrating bioequivalence

Methods of demonstrating bioequivalence for regulatory purposes depend on the type of product (*7*). Testing of bioequivalence in vivo in human volunteers is required for the following types of products (covering most artemisinin-based antimalarial medicines):

- oral immediate-release pharmaceutical products with systemic action when one or more of the following criteria apply:
  - critical use medicine;
  - narrow therapeutic range (when the minimum effective dose and the maximum safe dose are close), steep dose–response curve (when a small increase in dose causes a big difference in response);
  - documented evidence of problematic bioavailability or bioequivalence for the API or its formulations (unrelated to dissolution problems); and
  - scientific evidence suggesting that differences in the polymorphs, the excipients or the manufacturing processes could affect bioequivalence.
- non-oral, non-parenteral pharmaceutical products designed to act systemically (such as suppositories);
- fixed-dose combination products with systemic action, in which at least one API must be studied in vivo; and
- oral modified-release pharmaceutical products (delayed release and extended release).

Depending on the type of product to be assessed, different types of studies may be necessary to show bioequivalence.

Studies of pharmacokinetics, investigating drug concentrations over time, are the simplest and most frequently conducted type. The variable most commonly assessed is the total amount of drug absorbed, i.e. the area under the curve, although the maximum concentration ($C_{max}$) and the time until $C_{max}$ is reached ($T_{max}$) are also important. Studies of pharmacokinetics are adequate to



N.B. CONCLUSIONS AND REPORTS OF STUDIES OF PHARMACOKINETICS FOR BIOEQUIVALENCE IN VIVO

- The report of a bioequivalence study should include the name and address of the contract research organization and responsible investigators who performed the study and complete documentation of the study protocol, conduct and evaluation, in compliance with good clinical practice (*47*) and good laboratory practice (*48*).
- Samples should ideally be taken from industrial-scale or pilot-scale batches not smaller than 10% of the expected full production batches or 100 000 units, whichever is higher (unless otherwise justified). Samples must be produced with equipment, machinery and process similar to those used for the products that will be supplied.
- The comparator product should preferably be the innovator pharmaceutical product. Generic products should be used as comparators only if no innovator product is available. Otherwise, a 'bio-creep' phenomenon is observed, in which the similarity with the innovator product becomes progressively less, until products can no longer be considered interchangeable with the innovator. For fixed-dose combinations, the individual components should be used as comparators, unless an equivalent comparator fixed-dose combination exists which has been studied extensively in clinical trials. For such a product, there would be direct evidence of efficacy and safety, and it would be a suitable comparator.
- The number of study participants recruited should be justified by statistical tests. It should not usually be fewer than 12; in most studies, 18–24 participants will be needed.
- Bioequivalence is demonstrated if the 90% confidence interval around the geometric (log-transformed) mean area under the curve ratio (the bioavailability relative to that of the innovator product) lies between 80% and 125%. Dissolution profiles for the test product and for the reference product in vitro should also be provided.

demonstrate the bioequivalence of generic products to a comparator product and of fixed-dose combinations, which can be assessed either against a corresponding innovator product or against the single components of innovator products if no clinical trials have been conducted with the combination. Such studies can also provide a measure of pharmaceutical quality in vivo.

When studies of pharmacokinetics are not possible, for example for drugs that are not absorbed into the systemic circulation but are designed to act locally, comparative studies of pharmacodynamics can be carried out to establish bioequivalence. Such studies provide a measure of a pharmacological or therapeutic effect that is relevant to the claims of efficacy or safety. This method is not usually used for artemisinin-based antimalarial medicines, which are designed to act in the bloodstream.

➔ ***For artemisinin-based antimalarial medicines for which there is a suitable comparator, studies of pharmacokinetics in vivo for bioequivalence are the method of choice for assessing clinical safety and efficacy indirectly.***

### c) Biowaivers

Bioequivalence testing in vivo is not necessary for certain types of drugs. The requirement can thus be waived ('biowaiver'), and bioequivalence can be established in vitro in dissolution tests instead. National regulatory authorities are still establishing clear guidelines for assessing products with a biowaiver. WHO has compiled a list of oral dosage forms on its essential medicines list and their eligibility for biowaivers on the basis of solubility, permeability and potential risks (*16*). **None of the artemisinin-based antimalarial medicines discussed in this manual qualifies for a biowaiver**.

### d) Bioequivalence testing in vitro

Once extreme strengths have been tested in vivo, in-vitro methods (dissolution testing) can be used to evaluate additional strengths of a medicine, provided that the pharmacokinetics are linear and allow interpolation and provided that the different strengths are of proportional composition (e.g. common blend).

Dissolution test conditions for evaluating bioequivalence are more comprehensive than those for dissolution tests used in quality control testing. The quantity of drug dissolved ($Q$) over time ($t$) should be tested in at least 12 units in three media (at pH 1.2, 4.5 and 6.8), with samples collected at short intervals, e.g. 10, 15, 20, 30, 45 and 60 min. For details of various dissolution testing requirements, consult WHO's guidelines on registration requirements to establish the interchangeability of multisource (generic) pharmaceutical products (*36*).

FURTHER READING

- WHO guidelines on establishing interchangeability for multi-source products (*36*), performing bioequivalence studies in vivo (*49*) and biowaivers (*37*)

## 8.4 Product stability

Stability is the ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf-life. Pharmaceutical products can degrade chemically or change physically as a result of exposure to light, high temperatures, humidity and of reactions with excipients or other APIs in fixed-dose combination products. Some of the consequences are:

- decrease or increase in the content of API (increase in solutions due to solvent loss);
- formation of potentially toxic degradation products;
- change in appearance, which may affect patient acceptability;
- functional modification, e.g. changed dissolution rate or profile or changed bioavailability;
- degraded microbiological status (for example, growth of bacteria); and
- loss of package integrity, label quality and product quality.

Artemisinin compounds are prone to instability. While APIs are relatively stable, most FPPs have a short shelf-life of 24 months owing to the instability of APIs within the product, especially in combination products (*31*).

➔ ***The stability of artemisinin-based antimalarial medicines is a challenge and must be addressed repeatedly during the procurement cycle.***

### 8.4.1 Stability testing

Stability is tested by storing products at defined temperatures and relative humidity for defined periods and testing them at different times to evaluate any changes. Testing should address those attributes that are likely to change during storage and are likely to influence quality, safety or efficacy. The analytical methods used must be validated to show that they actually indicate product stability. For example, tests for related substances or degradation products should be validated to demonstrate that they are specific and sensitive enough to detect the substances likely to occur in the product being examined.

It is important to test the FPPs in the same packaging in which they will be marketed and stored.

For products that are to be diluted or reconstituted before administration, stability 'in use' must be determined in order to define the optimal storage time and conditions for the product once it has been prepared for administration.

### 8.4.2 Determination of shelf-life and storage conditions

Formal studies of stability are required as part of regulatory measures in order to determine the shelf-life during which a product is likely to remain in compliance with its specifications, provided it is stored as indicated on the label.

The studies should be conducted under both long-term conditions (i.e. those of the intended storage conditions) and accelerated conditions (i.e. when the product is exposed to temperatures and humidity exceeding the anticipated requirements for subsequent storage). Although the results of accelerated testing are not always predictive of physical changes, they can be used to determine a provisional shelf-life and to evaluate the effect of short-term excursions outside the label storage conditions, such as might occur during shipping.

For most artemisinin-based antimalarial products, a provisional shelf-life of 24 months is granted at registration if the results of accelerated studies (minimum, 6 months) and limited long-term studies (12 months) support it. The shelf-life is then confirmed by long-term studies covering the full shelf-life. These studies are usually conducted on the first three production batches, preferably with APIs from different batches. Follow-up stability testing is performed on one batch per year after registration, and the results are reviewed as part of inspection programmes for compliance with GMP.

Given the short shelf-lives of artemisinin-based FPPs, it is important to know the start date for their shelf-life. According to EMEA regulations (*50*), the date of release is the relevant date; how-

ever, if release testing was conducted more than 30 days after the production date, the production date (the date of the first step in which the API is combined with other ingredients) should be taken as the start of the shelf-life.

### 8.4.3 Climate zones

Storage conditions for stability testing have been defined for four climate zones, numbered I–IV. The stability of antimalarial medicines should ideally be evaluated for zone IV (hot, humid conditions or global market), which is subdivided into zones IVa and Ivb (*21*). The conditions for zone IV testing, as defined in WHO guidelines (*4*) are as follows:

**Table 5. Conditions for zone IV texting as per WHO guidelines**

| Type of testing | Temperature (°C) | Relative humidity (%) | Time covered at submission (months) |
|---|---|---|---|
| Accelerated | 40 ± 2 | 75 ± 5 | Minimum, 6 |
| Long-term (zone IVa) | 30 ± 2 | 65 ± 5 | 6 or 12 * |
| Long-term (zone IVb) | 30 ± 2 | 75 ± 5 | 6 or 12 * |

* 6 months for stable APIs, 12 months for artemisinin derivatives, which are not stable

The required conditions for long-term stability studies have been established for WHO Member States (**Annex 5**).

➔ ***The procurement entity should verify that the claims regarding the stability of FPPs on the label match the requirements in the country of use.***

### 8.4.4 Storage instructions

Storage instructions derived from the outcomes of the stability studies must conform with the WHO recommendations shown below.

**Table 6. Storage instructions as per WHO recommendations**

| Instruction on label | Interpretation |
|---|---|
| Do not store above 30 °C | Store from +2 °C to +30 °C |
| Do not store above 25 °C | Store from +2 °C to +25 °C |
| Store in refrigerator | Store from +2 °C to +8 °C |
| Store in freezer | Store from –15 °C to –25 °C |
| Do not refrigerate | In addition to 'Do not store above 30 °C (25 °C)', mainly for semisolid or liquid preparations that should not be stored in a refrigerator |
| Do not freeze | In addition to 'Store in refrigerator', mainly for semisolid or liquid preparations that should not be frozen |
| Protect from moisture | Store at no more than 60% relative humidity under normal storage conditions; to be given to patients in a moisture-resistant container |
| Protect from light | To be given to patients in a light-resistant container |

### 8.4.5 Additional stability testing

For products tested under storage conditions for zones I and II only (as recommended in ICH guidelines), additional testing should be performed to confirm stability in zone IVb (hot and humid climate or for global distribution). Stability under special transport and climate conditions outside storage conditions should be supported by additional data as appropriate. Confirmed long-term stability testing conditions for countries can be found in **Annex 5**.

N.B. CONCLUSIONS AND REPORTS OF STABILITY TESTING

Stability reports should support the claim that a product is stable for the defined shelf-life if it is stored in the defined conditions. They should include detailed information on packaging and container or closure systems, which should be the same as those of the FPP that will be supplied subsequently.

Stability studies are considered positive if the following criteria are met:

- at least three batches of production batch size or pilot batches with a batch size of at least 10% of the production batch size tested;
- testing at least every 3 months during the first year, every 6 months in the second year and annually thereafter for long-term stability studies and at least three times for accelerated studies;
- content changed by no more than 5% from the initial assay value or meets the acceptability criteria for potency in biological or immunological procedures;
- degradation products and microbial contaminants within acceptable limits;
- acceptability criteria for appearance, physical attributes and functionality tests are met (e.g. colour, hardness, friability, phase separation, pH); and
- solid oral dosage forms comply with dissolution acceptability criteria for 12 dosage units. These criteria must be the same as for release testing.

Reports should describe the specifications and methods used. Specific methods such as high-performance liquid chromatography or gas chromatography should be used for the assay and for determination of degradation products of artemisinin-based antimalarial products. The procedures used for testing the stability of FPPs should have been validated or verified, and both the accuracy and the precision (standard deviations) of the validation should be recorded.

Reports should include trend graphs of relevant parameters, analyses, discussion of results and conclusions on shelf-life and storage conditions if a trend is evident. Numerical results, rather than only the word 'complies' or 'conforms', should be given when applicable.

Reports must be signed by the responsible person.

New data on stability are required if there is any change to the FPP that may affect its stability, such as changes in single steps or the entire route of synthesis of an API, in the composition of the FPP or in its immediate packaging (see STEP **16**).



FURTHER READING


- WHO. *Guidelines for stability testing of pharmaceutical products containing well established APIs in conventional dosage forms* (*4*)
- Kindermans JM et al. Ensuring sustained ACT production and reliable artemisinin supply. *Malaria Journal*, 2007, 6:125. doi:10.1186/1475-2875-6-125 (*31*)


## 8.5 Pharmaceutical specifications and analytical methods

Pharmaceutical specifications and valid analytical methods form the basis of quality control for APIs and FPPs.

### *8.5.1 Pharmaceutical specifications*

During drug development, the properties of a pharmaceutical product are designed and described in detail, together with the methods for testing each attribute. Properties commonly tested include appearance, identity, content, related substances (impurities), as well as dissolution or disintegra-

tion (for solid dosage forms), uniformity of content or weight variation (for solid dosage forms), pH (for liquids), microbial limits, and sterility and bacterial endotoxins (for injectables).

➔ ***Pharmaceutical specifications provide the means for an independent check of the quality of a product at any time during its shelf-life.***

➔ ***The outcomes of testing with validated analytical methods are reflected on batch certificates and certificates of analysis (see below).***

### *8.5.2 Analytical methods*

#### a) Identity tests

Identity tests are used to demonstrate that products contain the correct API(s), usually by comparing a property of the sample (e.g. spectrum, chromatographic behaviour, chemical reactivity) with that of a reference standard. For artemisinin-based antimalarial medicines, identity can be tested by photometry in the infrared region. If no infrared spectrophotometer is available, thin-layer chromatography can be used in combination with other reactive tests.

#### b) Assays

The potency of a substance or product, i.e. the content per unit, is tested by assays. For FPPs, the result must lie within a defined percentage range of the label claim. Assay methods used for artemisinin-based antimalarial medicines should include high-performance liquid chromatography or spectrophotometry in the visible and ultraviolet regions.

#### c) Tests for related substances

Related substances (impurities) that may result from API synthesis or from degradation are detected by chromatographic methods, which may be the same as the assay methods. Pharmacopoeial methods have limitations in this regard, as many were designed to detect the substances that are likely to occur during the route of synthesis used for the innovator product. If a different route of synthesis was used for the API, these methods will not necessarily detect impurities. Premarketing quality control testing must therefore be supplemented by other methods if necessary, and postmarketing surveillance is increasingly important.

#### d) Dissolution and disintegration testing

Dissolution testing allows measurement of the rate of release of drugs into solution from tablet or capsule formulations under controlled conditions. Assays are used to determine the concentrations of API in the dissolution medium at one or more time.

Over the past three decades, dissolution testing has become a powerful tool for characterizing the quality of oral pharmaceutical products.

- When applied at one or more defined times in a defined medium, under defined conditions (apparatus, rotation speed and temperature), dissolution testing is used to monitor batch-to-batch consistency of the manufacturing process and the subsequent consistency of the release characteristics of products during storage. The acceptance criteria should be stringent enough to identify a difference in release properties.
- As dissolution rates depend on the characteristics of the dosage form, such as particle size distribution and crystal form (polymorphism or solvates), of the API(s) and mechanical properties such as FPP water content and resistance to crushing force, dissolution testing can indicate any changes occurring during manufacture and storage.

- Dissolution profiles can be used to test for similarity in vitro. For this purpose, dissolution rates are determined at multiple times in different media corresponding to physiological conditions in the gastrointestinal tract. The dissolution profiles of test drugs and comparator drugs should be included in the documentation submitted with the reports of in-vivo bioequivalence studies.

If dissolution is not tested, the time it takes tablets or capsules to disintegrate in an immersion fluid without leaving a residue is tested. If the result is within acceptable limits, it will be concluded that the APIs are released into the body as intended. For APIs clasified in the biopharmaceutics classification system as being poorly soluble, such as the artemisinins, dissolution testing is recommended.

#### e) Tests for uniformity of content and uniformity of mass

The aim of tests for uniformity of content is to determine whether APIs and excipients have been mixed adequately during manufacture. This is important for fixed-dose combinations and for scored (breakable) tablets, to ensure that each unit or part of a unit contains the quantity of API required for the recommended treatment regimen. The pharmacopoeias and WHO's guideline on fixed-dose combinations (*10*) should be consulted to determine when uniformity of content should be tested (usually when the tablet contains less than 25 mg or less than 25% of the API).

If uniformity of content is not tested (for tablets or capsules that contain only one API that constitutes more than 25 mg per tablet or makes up more than 25% of the tablet weight), uniformity of mass is tested. If the weight of the units is uniform within acceptable limits, it can be concluded that each unit contains the required amount of API(s).



#### f) Other tests

Other tests include checks of appearance, pH and microbial limits for liquid dosage forms. Sterility and bacterial endotoxins are tested when appropriate, e.g. for injections.

### *8.5.3 Standards for specifications*

Different standards are used to test the compliance of APIs and FPPs with pharmaceutical specifications. They differ in the way in which they were designed, validated and used over time, and should be used in the following order of preference:

- pharmacopoeial standards;
- innovator manufacturer's standards (if no pharmacopoeial monograph has been published in one of the pharmacopoeias);
- generic manufacturer's standards (if no equivalent innovator product exists, if the innovator's standards are not available or if the standards of such a product cannot be applied to the generic product); and
- standards and analytical methods prepared by an independent laboratory (if manufacturers do not release their in-house methods).

#### a) Pharmacopoeial standards and reference substances

Pharmacopoeias are national, legally-binding publications containing specifications and analytical methods for testing, called monographs, for APIs and dosage forms (FPPs). General requirements on quality-related subjects, such as microbiological purity, dissolution testing, tablet friability or stability, are also given. Many pharmacopoeial monographs are based on specifica-

tions set by the manufacturers of innovator products. These monographs are the preferred basis for quality control of products, as they have been validated and standardized during their preparation and use by many quality control laboratories.

A 'reference substance' is an authenticated, uniform material for use in specified chemical and physical tests, in which its properties are compared with those of a product under examination and which has adequate purity for its intended use (*20*). Primary chemical reference substances are established by pharmacopoeial authorities with the respective monographs. On this basis, national and regional collections of secondary chemical reference substances have been established. In case of doubtful results or dispute over secondary chemical reference substances, tests will be repeated with the pharmacopoeial standard.

The *International Pharmacopoeia*, maintained by WHO (*13*), gives priority to essential medicines. It has a wide, expanding collection of monographs for artemisinin-based antimalarial medicines. Specifications are prepared independently in an international consultation. The needs of developing countries are taken into account. Classical analytical procedures are used, with robust alternative methods when complex methods are suggested. Available international chemical reference substances for tests are listed in relevant WHO guidelines (*51*). Orders can be directed by email to **qsm@who.int** or to **icdra@who.int**.

➔ ***The pharmacopoeias generally recognized in procurement include the British, International, European and United States pharmacopoeias (for APIs and excipients only).***

### b) Pharmacopoeial monographs for artemisinin-based antimalarial medicines

Available *International Pharmacopoeia* monographs on artemisinin-based antimalarial medicines as of January 2009 and general requirements for dosage forms, are listed in **Table 7**. At the end of 2008, monographs on artemisinin, its derivatives and their associated medicines were under accelerated revision, particularly with respect to chromatographic tests for related substances, assays and sample preparation.

The *United States Pharmacopeia* contains monographs on antimalarial medicines manufactured or sold in the United States. In addition, it provides standards for antimalarial medicines legally marketed outside the United States (*52*). As of 15 January 2009, draft monographs were available on the *United States Pharmacopeia* web site for mefloquine hydrochloride tablets, artemether, lumefantrine and artemether–lumefantrine tablets.

➔ ***Current editions of pharmacopoeias should always be used. International Pharmacopoeia monographs are publicly available on the Internet.***

INTERNET SOURCES

- WHO. *International Pharmacopoeia* (*13*) **http://apps.who.int/phint/**
  Search: **ph int site:who.int**
- List of monographs on antimalarial medicines available in the *International Pharmacopoeia*
  **http://www.who.int/medicines/publications/pharmacopoeia/mon_mal/en/index.html**
  Search: **"International Pharmacopoeia" antimalarial monographs**
- *United States Pharmacopeia*. About USP – An overview. **http://www.usp.org/aboutUSP/**
  Search: **US pharmacopeia**
- *British Pharmacopoeia*. Setting standards for medicine. **http://www.pharmacopoeia.co.uk/**
  Search: **British pharmacopoeia**

### c) General pharmacopoeial requirements for artemisinin-based antimalarial medicines

The FPPs procured should comply not only with specific monographs or sets of specifications but also with the general pharmacopoeial requirements for tablets, capsules, suppositories or injectables (**Table 7**).

**Table 7. General pharmacopoeial requirements for dosage forms**

| Dosage form | *International Pharmacopoeia* | *British Pharmacopoeia* | *European Pharmacopoeia* monograph number | *United States Pharmacopeia* |
|---|---|---|---|---|
| All | • General notice<br>• General requirements or respective dosage forms | • General notices<br>• General monograph for respective dosage form | | • General information<br>• Pharmaceutical dosage forms |
| Tablets | ✓<br>+ Dissolution test for solid oral dosage forms | ✓ | 0478 | ✓ |
| Capsules | | ✓ | 0016 | ✓ |
| Parenteral preparations | ✓ | ✓ | 0520 | ✓<br>+ General requirements for injections |
| Suppositories | ✓ | ✓ | 1145 | ✓ |
| Oral liquids | General requirements for liquid preparations for oral use | ✓ | 0672 | ✓ |
| Oral powders | | ✓ | 1165 | ✓ |

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### d) Manufacturers' specifications

Specifications for new APIs and FPPs are defined by the manufacturer as part of product development. When an innovator product is launched, the competent national regulatory authorities evaluate the manufacturer's quality specifications by rigorous scientific assessment in conjunction with the results of preclinical and clinical safety and efficacy tests. Manufacturers use the specifications to confirm product quality during manufacture and when each batch is released. The specifications also have a predictive value, to support the responsibility of the manufacturer for the product during its entire shelf-life.

After pharmacopoeial monographs have been published, manufacturers may continue to use their own specifications. Manufacturers' release specifications must be compatible (demonstrated to be at least of the same scientific level) with any published pharmacopoeial specifications but can differ in certain respects. They may be more exacting than the corresponding pharmacopoeial requirements, or they may be based on analytical methods other than those described in the pharmacopoeia. Some requirements of the pharmacopoeia may already be met during development or manufacture of the product, e.g. by in-process controls and manufacturing process validation studies.

If an FPP is WHO-prequalified, WHO PQP has information on the manufacturer's validated methods. Procedures for information-sharing are described in **STEP 16**.

Procurement entities should encourage manufacturers to submit their pharmaceutical specifications to pharmacopoeia for possible inclusion.

➔ ***Manufacturers do not always provide detailed information on analytical methods and reference materials. Procurement entities should insist on obtaining this information. This requirement should be built into tender documents and contracts, with a confidentiality agreement.***

N.B. MANUFACTURERS' SPECIFICATIONS AND ANALYTICAL METHODS

Specifications should contain all the chemical and physicochemical attributes of the product and the analytical procedures to verify them.

For each analytical procedure, the manufacturer should:

- describe it in detail so that adequately trained analysts can carry it out reliably
- justify it in comparison with other possible approaches, and
- give validation data showing that it actually gives the required results.

The specifications should be signed by the person responsible for quality assurance.

### *8.5.4 Analytical method validation*

Specific analytical methods are designed to test specific APIs and FPPs. These methods must be validated to ensure that they give true results. This is usually done by testing samples with known variations and verifying whether the results are within a defined range of the expected result. Analytical methods should be revalidated after any change in the synthesis of API, the composition of the FPP or the analytical procedure itself.

Analytical methods must fulfill certain requirements. For example, they should be specific (detect only the substance of interest), accurate (give unbiased results), precise (give similar results every time) and robust (perform well under different circumstances). All these requirements are not equally important for all types of tests. WHO (*22*) and ICH guidelines (*53*) summarize the requirements for analytical methods (see **Table 8**) and provide terminology and validation methods.

Challenges in testing artemisinin-based antimalarial medicines include interactions between APIs, APIs and excipients and known or new degradation products. Chromatographic procedures used in assays and tests for impurities should be selective enough to distinguish between related molecules (e.g. in the case of a test for artesunate-related substances, the method should be able to distinguish artemisinin and dihydroartemisinin (artenimol), which are its precursors). For fixed-dose combinations, one or more methods should quantify, accurately and precisely,

**Table 8. Requirements for analytical methods**

| Characteristic | Type of test | | | |
|---|---|---|---|---|
| | | Test for impurities | | Assay<br>• content/potency<br>• dissolution (measurement only) |
| | Identity test | Quantitative | Limit | |
| Accuracy | – | + | | + |
| Precision | | | | |
| – repeatability | – | + | – | + |
| – intermediate precision[a] | – | + | – | + |
| Specificity (selectivity) | + | + | + | + |
| Limit of detection | – | – [b] | + | – |
| Limit of quantification | – | + | – | – |
| Linearity and range | – | + | – | + |
| Robustness | + | + | + | + |

+ Characteristics that should usually be evaluated.
– Characteristics that are not usually evaluated.
[a] When a reproducibility study has been performed, intermediate precision is not needed.
[b] May be needed in some cases.

each API and should discriminate between each of the different APIs and their respective impurities or degradants and any incompatibility products. Dissolution testing of these compounds is complicated by the poor solubility and the instability of artemisinin-based compounds; for example, artesunate decomposes to dihydroartemisinin at low pH values.

N.B. VALIDATION REPORTS OF ANALYTICAL METHODS

Analytical method validation is normally verified as part of GMP.

The report should provide the results of validation studies, with statistical proof that the different methods are capable of detecting and quantifying APIs and relevant impurities and degradation products.

The report should be recent enough to reflect the latest developments and changes in materials and manufacturing processes.

The report should be signed by the person responsible for quality assurance at the manufacturer's.

#### (a) Method transfer

Method transfer is a form of method validation, performed when an analytical method for a specific product is to be used for the first time at a laboratory different from that in which it was designed or validated. The aim of method transfer is to ensure that a test still gives valid results when it is carried out at the new laboratory by new operators with the instruments of that laboratory. In practice, method transfer is performed by carrying out replicate tests of the same samples at both laboratories and comparing the results statistically.

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FURTHER READING

- WHO. *Supplementary guidelines on good manufacturing practices: validation* (*22*).
- ICH guideline Q2R1. *Validation of analytical procedures* (*53*).
- ICH guideline Q6A. *Specifications: test procedures and acceptance criteria for new APIs and new FPPs: chemical substances* (*54*).

### *8.5.5 Certification of compliance with specifications*

#### a) Batch certificate and certificate of analysis

A batch certificate for a pharmaceutical product is issued by the manufacturer and should be supplied as part of the tender and procurement documentation. It is an attestation of the quality and expiry date of a specific batch or consignment of a pharmaceutical product. It includes the specifications of the final product at the time of batch release and the results of a full quality control analysis, as documented in an attached certificate of analysis, which states the results of quality control testing. A model batch certificate for a pharmaceutical product is one of three types of certificate delivered in the WHO certification scheme (*38*).

### N.B. BATCH CERTIFICATES

A batch certificate should contain at least the following information:

- name and dosage form of the product;
- batch number and, where appropriate, the manufacturer or supplier;
- references to relevant specifications and testing procedures;
- test results, including observations and calculations, and reference to any specifications (limits);
- date and reference numbers of testing;
- initials of persons who performed the testing;
- date and initials of persons who verified the testing and the calculations, when appropriate; and
- a clear statement of release or rejection (or other status decision) and a dated signature of the designated person responsible for quality assurance at the manufacturer. The signature of laboratory staff only is not sufficient.

A certificate of analysis is a document listing the results of testing of a representative sample drawn from the batch to be delivered.

### N.B. CERTIFICATES OF ANALYSIS

Analysis records for APIs and FPPs should include at least the following:

- name and address of the laboratory performing the tests;
- registration number of the certificate of analysis;
- name, description (i.e. grade, quantity received, type of container) and number (used by the original manufacturer and repacker or trader) of the batch for which the certificate is issued, the date of manufacture and the expiry date (or retest date);
- date on which the batch for which the certificate is issued was received;
- reference to the test procedure used, including the acceptance criteria (limits);
- results of all tests performed on the batch for which the certificate is issued (in numerical form, where applicable) and a comparison with the established acceptance criteria (limits);
- any additional test results obtained for samples of the batch as part of a periodic, statistically based testing programme;
- a statement indicating whether the results were found to comply with the requirements;
- date(s) on which the test(s) was (were) performed;
- signature of the head of the laboratory or another authorized person;
- name, address and telephone and fax numbers of the original manufacturer. If supplied by repackers or traders, the certificate should show the name, address and telephone and fax numbers of the repacker or trader and a reference to the original manufacturer.
- a statement of the expected conditions of shipping, packaging, storage and distribution, deviation from which would invalidate the certificate; and
- a copy of the certificate from the original manufacturer, if the sample is supplied by a repacker or trader.

Model formats for these certificates are found in the following WHO guidelines:

INTERNET SOURCES

- WHO-type model batch certificate of a pharmaceutical product (*38*).
  http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/en/
- WHO-type model certificate of analysis (*55*).
  http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf

## 8.6 Control of active pharmaceutical ingredients

Control of starting materials, including APIs and excipients, is an important part of GMP. WHO provides guidance on the manufacture of excipients (*14*).

In the procurement of artemisinin-based antimalarial medicines, the excipients do not present major risks for quality, and their control is essentially left to national regulatory authorities and WHO PQP. APIs contained in artemisinin-based products, however, must be controlled continually for impurities, as they degrade readily. The artemisinin molecule contains a reactive functional group, which is fundamental for its antimalarial activity but which makes it unstable. Artesunate readily degrades into dihydroartemisinin (artenimol). As this is itself an API with antimalarial efficacy, its degradation is not of serious safety concern; however, dihydroartemisinin is also unstable, and secondary degradation products may form. Various types of residual solvents may be present in APIs, depending on the manufacturing process.



### *8.6.1 Control by manufacturers of FPPs*

As part of GMP, FPP manufacturers should control the quality of all the starting materials used. They should ensure that the source site(s) operate to GMP standards. They should also request specifications and analytical methods for the APIs and should sample and test APIs before use in manufacturing. In lieu of testing, they may accept a certificate of analysis, provided that they verify the API manufacturers' test results and assess their capacity periodically.

It is important that the FPP manufacturer knows the process by which the API is manufactured and incorporates appropriate testing for residual solvents.

### *8.6.2 Verification by procurement entities*

To establish the quality of the API(s) used in the manufacture of the FPPs, procurement entities can request documentation on the source sites and the materials themselves. For WHO-prequalified products, WHO PQP has information on API sources. Procedures are under way to make some of this information publicly available (see STEP **16**).

In procurement, the type of standard used to verify API quality depends on the degree of confidence in the FPP manufacturer's compliance with GMP with regard to API sources.

### EXAMPLE: ARTEMISININ USED AS A STARTING MATERIAL FOR FPPs CONTAINING ARTEMETHER OR ARTESUNATE

If the FPP has been approved by WHO PQP or an SRA, the artemisinin starting material does not need to comply with the *International Pharmacopoeia monograph*. The API manufacturer's specifications for artemisinin should be sufficient and acceptable for manufacture of the FPP.

If the FPP has not been approved by the WHO PQP or an SRA, the approving procurement agency of the FPP should ensure that the artemisinin starting material meets international standards that are appropriate for starting materials used in the production of APIs.

### N.B. DOCUMENTATION OF THE QUALITY OF APIs

Documentation for sites:

- GMP certificates for the source site(s) of each API
- Not all GMP certificates reflect equally stringent standards or scope of inspections (see SECTION **8.7**).

Documentation for APIs, in order of preference:

- a certificate of suitability delivered by the *European Pharmacopoeia* or
- the open part of a drug master file accepted in an ICH country, or
- a technical file that summarizes the synthesis route and the characteristics.

WHO has proposed guidelines and a certification scheme for the control of starting materials. Some elements of this scheme may be implemented in national law. The aim is to establish and maintain close collaboration between manufacturers, national regulatory authorities and buyers throughout the distribution and trade chain.

### FURTHER READING

- WHO procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (*56*).
- WHO good trading and distribution practices for starting materials (*9*).
- WHO pharmaceutical starting materials certification scheme (SMACS) (*57*).

## 8.7 Good manufacturing practice (GMP)

GMP is "that part of quality control which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization" (*18*). The purpose of GMP is to ensure that products are manufactured consistently in accordance with validated processes. GMP covers all areas of manufacture, including premises, equipment, materials, cleaning, personnel, documentation and quality control testing.

Guidelines for pharmaceutical GMP include the WHO Global Malaria Programme text (*18*), the guidelines of the Pharmaceutical Inspection Cooperation Scheme (*58*), those of the Association of South East Asian Nations and national GMP legislation, applied by national regulatory authorities during site inspections to assess and license manufacturing sites. The rules, interpretation and stringency of these inspections vary.

A more general method for ensuring product quality is use of a quality management system such as ISO 9001:2000 (*59*). Such a system can be used in any type of company. It provides mechanisms

and checks in production, shipping and distribution, so that the company can consistently produce products that satisfy customers' expectations.

N.B. GMP CERTIFICATES

Not all GMP certificates reflect the same stringent standard and scope of inspection.

WHO has recommended a model format (*60*) for GMP certificates issued by national regulatory authorities (see **Annex 6**). This is often submitted by manufacturers as a 'WHO certificate'; however, it is only as good as the issuing authority and does not mean that inspections were necessarily performed to WHO standards.

WHO PQP performs stringent site inspections of all product-related aspects as part of WHO prequalification.

WHO PQP does *not* issue GMP certificates. Instead, public inspection reports (WHO-PI) are posted on the Internet.

For FPPs that are not WHO-prequalified, GMP certificates should be issued by an SRA (see **Annex 2**) or a Pharmaceutical Inspection Cooperation Scheme member.

Inspections should ideally be product-specific, i.e. take into account all aspects of GMP that are relevant to the production line on which the FPP is manufactured. Not all SRAs, however, perform product-specific inspections.

Certificates should be current. If no date of validity is stated, they should not be older than 3–5 years (the routine reassessment frequency of many SRAs and WHO PQP).

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FURTHER READING

- WHO. *Guidelines on good manufacturing practices* (*18*).
- WHO PQP public inspection reports http://www.who.int/prequal

## 8.8 Packaging

Packaging can be considered an integral part of a pharmaceutical product. It must protect the dosage form against external influences, such as moisture, light, oxygen, biological contamination and physical damage, as far as possible. Packaging alone cannot protect a product from high temperatures, which must be controlled during storage and distribution (see **step 14**). Packaging must be compatible with the dosage form and must not interact with it in any way. It must carry the correct information and identification of the product.

Pharmaceutical packaging materials and systems must be subject, in principle, to the same quality assurance and good manufacturing requirements as pharmaceutical starting materials and finished dosage forms. Detailed packaging specifications for materials in direct contact with the product must be included in tenders, supplied by the manufacturer and used for subsequent monitoring of compliance with approved standards.

Information on packaging must match that on the label and on package inserts (see **section 8.10** for examples of discrepancies).

For ACTs, the packaging design should be 'user-friendly'. Blister packs should contain individual doses in easily recognizable subunits, so that patients understand how to take their prescribed treatment. Some packaging specifications might have to be designed or adapted after tenders are awarded, to suit country needs. Procurement entities can accept undertakings by manufacturers that they will comply with these specifications. Any changes to packaging in the country of use should be treated as a variation (see **step 16**).

N.B. PACKAGING

Primary packaging (that in direct contact with the dosage form) must conform to pharmacopoeial standards.

Secondary and other packaging must provide protection during shipment and during storage and distribution in malaria-endemic countries. Useful packaging standards include those of the ISO.

Packaging of all supplied product must be consistent with that investigated in stability studies.

ACTs should be prepackaged into course-of-therapy pack sizes, containing all the doses of a treatment course in a well-designed blister pack, with individual doses in easily recognizable subunits.

Injectable products should be co-packaged with appropriate diluents.

Oral liquids should be co-packed with dose-measuring devices

Packaging should be tamper-evident.

FURTHER READING

- WHO consultation on specifications for prepacking antimalarial medicines (*11*).
- WHO guidelines on packaging for pharmaceutical products (*61*).

## 8.9 Labelling

Labelling and marking are essential to ensure product identification and traceability throughout its history. Like packaging, labelling is an important aspect of GMP. Information on the label must match that on the packaging and on package inserts (see **SECTION 8.10** for examples of discrepancies).

### EXAMPLE: SPECIFICATIONS FOR NAMING AND LABELLING (ADAPTED FROM UNICEF TENDER DOCUMENTATION, 2009)

Manufacture dates specified in the format dd/mm/yyyy, e.g. 08/07/2009

Expiry date in a format that can be easily understood: the preferred format is dd/mm/yyyy, with the year of expiry as four digits

Co-formulated FPPs denoted with a '–' sign, e.g. 'artemether–lumefantrine 20 mg/120 mg' tablets

Co-packaged FPPs denoted with a '+' sign, e.g. 'artesunate 50 mg tablets + amodiaquine 153 mg (as hydrochloride) tablets'

INNs or generic names of products not abbreviated anywhere, including on labels and package

Strength of each API appears next to its name in co-blistered products, e.g. 'artesunate 50 mg tablets + amodiaquine 153 mg (as hydrochloride) tablets', and after the names of the APIs for co-formulated products, indicating the respective dosage strength separated by '–', e.g. 'artemether–lumefantrine 20 mg/120 mg tablets'

If the API is a salt (e.g. hydrochloride), the label can indicate the strength of both the salt and the base, e.g. 'amodiaquine hydrochloride 200 mg (equivalent to amodiaquine 153 mg base)'.[1]

[1] Shorter formats are in use to denote product strength, for example: 'amodiaquine 153 base (as hydrochloride)'. For clinical and pharmaceutical reasons, however, product labels should have the full information for both, as shown in the above example.

Requirements with regard to label content and materials for artemisinin-based antimalarial medicines are included in the model specification (see **STEP 4**). Some aspects, such as language or special marking, should be customized to suit the intended use of the FPP. Naming formats are important, and procurement entities should specify these precisely to suit their requirements.

## 8.10 Product information and users

A safe, effective medicine can be useless or even dangerous if it is used in the wrong way. Prescribing information, a summary of data on clinical safety and efficacy, is needed to ensure proper use of the product in accordance with the findings of clinical trials and standard treatment guidelines. For generic products, the information on use must necessarily be the same as for the corresponding innovator products.

Correct medicine use concerns prescribers as well as patients. The manufacturer should therefore include information for safe use of FPPs in two versions: a scientific version for health-care professionals and a package insert (also called a 'package leaflet' or 'patient information leaflet') for patients (see **TABLE 9**).

### *8.10.1 Verifying product information and user aspects*

National regulatory authorities verify the prescribing information for correctness, completeness and consistency on the basis of available clinical evidence and technical information before they authorize a product for marketing. SRAs place increasing emphasis on the patient version. For example, the United States Food and Drug Administration requires that patient counselling information be provided.

When procurement entities intend to purchase antimalarial products, they must check the product information provided. Information can be checked against parts 3 and 4 of the WHO public assessment reports for WHO-prequalified products or against that provided in the WHO *Model formulary*.

INTERNET SOURCES

- WHO PQP. Public assessment report; Part 3: Product information leaflet; Part 4: Summary of product characteristics
  http://apps.who.int/prequal/whopar/whoparproducts/whopar_index.htm
  Search: **whopar overview malaria site:who.int**
- WHO. Model formulary (based on WHO Model list of essential medicines)
  http://apps.who.int/emlib/modellist.aspx?/language=en&mdtype=formulary
  Search: **model formulary**

Specific requirements may be added for package inserts to ensure that they are user-friendly, acceptable to patients and easy to understand. Requirements may be specified, for example, with regard to naming conventions (see the example in **SECTION 8.9**), size, format, language and wording. As blister packs are too bulky to fit into dispensing envelopes, it is difficult to include written information.

➔ ***Product information provided on labelling, packaging, package inserts and information for prescribers must match. The information must be clear, correct and consistent.***

**Table 9. Information on use for prescribers and patients**

| Information for prescribers (main headings and content) | Patient information leaflet (main headings and wording) Important information to be included (*34*) |
|---|---|
| Therapeutic indications (specific, as investigated in clinical trials; e.g. for use in uncomplicated or complicated malaria, species of *Plasmodium*) | What the medicine is and what it is used for<br>Malaria is a curable disease.<br>The earlier you treat it with the right medicine the better.<br>Malaria is caused by a parasite.<br>The longer the parasite is in the body, the greater the chance that it can kill.<br>Other diseases may coexist with malaria, or the parasite may be resistant to the medicine |
| Instructions to promote adherence | Completing the whole course of treatment is important.<br>If you do not complete the treatment, the malaria is not cured.<br>The full treatment is needed to kill all the parasites; if the treatment is not completed, malaria will come back. |
| Dosage and route of administration (for each indication and age group, maximum doses and duration of use, need for dosage adjustments, food restrictions) | How to take or use the medicine:<br>– make sure you complete the prescribed course even if you feel better.<br>– if you forget to take the medicine …<br>– effects when treatment with the medicine is stopped …<br>People have to use the right dosage for their age and weight.<br>Bigger and older children require higher doses.<br>If a child vomits, give the unit dose to replace the one that is lost. |
| Contraindications | Before you take or use the medicine:<br>Do not take/use the medicine if … |
| Special warnings and special precautions for use | Take special care with the medicine…<br>Taking or using the medicine with food and drink … |
| Interaction with other medicinal products and other form of interactions | Taking or using other medicines … |
| Safety in pregnancy and lactation | Pregnancy …<br>Breastfeeding … |
| Effects on ability to drive and use machines | Driving and using machines … |
| Undesirable effects | Like all medicines, this one can have side effects.<br>Tell your doctor if you notice any of the following: …<br>If you become sicker during or after completion of the treatment, see a trained health worker. |
| Treatment of overdose | If you take or use more of the medicine than you should … |
| Pharmacological properties (pharmacokinetics, pharmacodynamics, preclinical safety data) | Important information about some of the ingredients … |

**EXAMPLE:**

In technical assessments of products, UNICEF has found inconsistent or confusing information, for example on age groups ('4–12 years', '7–14 years', 'child', 'toddler', 'baby'), weight ranges and indications for treatment.

### *8.10.2 Updating product information*

The correctness and completeness of product information must be safeguarded at every step of procurement and distribution, perhaps involving repackaging, relabelling or addition of information e.g. in other languages. The information must be kept up to date, especially on safety issues, as these might emerge only after the product has been used for a long time.

Any variation in the approved information (including translation) must be brought to the attention of the original supplier and approved by the regulatory authority in the country of origin (see also STEP **16**).

## STEP 9.

# Evaluating bids commercially

### 9.1 Pricing information

Transparency in pricing of ACTs will assist procurement entities in selecting suppliers and can contribute to keeping the cost of treatment at affordable levels. WHO has published information on sources and prices for antimalarial medicines (*62*).

Various online mechanisms in the public domain exist to provide information on prices of medicines. The information must be interpreted with caution: prices are not necessarily representative because reporting is often voluntary. Not all the information is complete or reliable, especially if data are entered on line directly by procurement officers from all over the world. Because a few very high or very low prices could affect the average price, many databases indicate a median price (such that 50% of quoted prices are below it, the other 50% above it) to give a better indication.

Examples of online sources of pricing information for antimalarial medicines are:

INTERNET SOURCES

- WHO. Global price reporting mechanism, AMDS database (transaction prices reported by various large procuring entities)
  http://www.who.int/hiv/amds/gprm/en/
  Search: **"global price reporting mechanism"**
- International drug price Indicator guide (Management Sciences for Health)
  http://erc.msh.org/dmpguide/index.cfm?search_cat=yes&display=yes&module=dmp
  Search: **"international drug price indicator guide"**
- Health Action International. Global database (prices of originator brands, most-sold generics, lowest-price generics, including a few prices for antimalarials as of December 2008)
  http://www.haiweb.org/globaldatabase/main.htm
  Search: **Health Action International pricing database**
- GFATM. Price and quality reporting mechanism (products procured with Global Fund resources only)
  http://pqr.theglobalfund.org
  Search: **price and quality reporting site: theglobalfund.org**

➔ ***When comparing prices, purchasers should carefully consider how information is collected in each price reporting mechanism and to what extent the prices for a given treatment are comparable, for example, how freight and insurance are accounted for, how different pack sizes are reflected or whether the product has been customized for a certain country or project.***

## 9.2 Operational costs

When comparing bids, it is important to obtain details and to conduct negotiations on the various elements that will affect the final treatment cost per patient, including:

- size and weight of deliveries, which affect transport and storage requirements. Most ACTs are supplied in blisters containing a full treatment course. Blister packs are bulky, and the choice of the pack size (number of treatment courses per box or dispenser) can substantially affect the total volume and chargeable weight.
- cost of transport options to the agreed point of delivery as specified by Incoterms (Rules at the core of world trade: http://www.iccwbo.org/Incoterms) by airfreight or seafreight in refrigerated containers; who pays for insurance, handling fees and port clearance. For example, a price quoted on the premises of a manufacturer will be lower than that quoted for delivery of the same items to the buyer's shop.
- cost and effectiveness of security measures in transit;
- cost of any customization of products before they can be used in a specific country or programme;
- product registration status, as a requirement for authorization in the destination country can cause delays (SEE STEP 6 on accelerated authorization);
- guaranteed delays between receipt of order and availability of goods for dispatch and between dispatch and arrival at the point of delivery. Delays can incur indirect costs, for example if emergency supplies have to be procured.
- effect of the choice of a particular product on programme support costs, such as administrative costs.

➔ ***Product quality, rather than the cost of the products, should be the first criterion in evaluating bids (see STEP 8).***

➔ ***For products of acceptable quality, the total cost of the operation, rather than the cost of the products alone, should be compared.***



## 9.3 Patents

A patent gives a legal right to prevent or exclude others from manufacturing, marketing or importing an invention (which may include an API or FPP) that has been granted patent rights by a State for a fixed period. The procedure for granting patents, the requirements placed on the patentee and the extent of the exclusive rights vary widely among countries according to national laws and international agreements.

Patent protection granted for medicines under national law should be respected in procurement. To purchase necessary health products at an affordable cost, countries can make use of the safeguards allowed under the agreement on trade-related aspects of intellectual property rights (TRIPS), under which compulsory or voluntary licences can be granted for generic equivalents of patented products in the interests of public health (*63*).

There are two types of patents: product patents are for specific products, while process patents are for the process by which the product is manufactured. Because artemisinin-based compounds are derived from a plant, process patents usually apply to these medicines. Product patents may apply to the non-artemisinin-based partner medicines in ACTs.

Although information on patents pending or granted in countries is theoretically in the public domain, it is often difficult to locate or is outdated. To obtain updated information on intellectual

property rights, procurement entities can try to obtain information from innovator manufacturers on patents granted and on any countries in which they have waived their patent rights or have provided immunity from suit, but this information is not easy to obtain.

Patents do not currently limit access to artemisinin-based antimalarial medicines. According to the United States procurement toolkit (*34*), the only ACT patented in some endemic countries in 2006 was artemether–lumefantrine by Novartis under the names Coartem™ and Riamet™.

➔ ***Patents might pose problems for artemisinin-based antimalarials when new products come onto the market or when companies start enforcing patent rights in countries. Technical assistance (including legal assistance) should be sought when lack of information and ambiguity lead to difficulties in procuring essential health products at the lowest possible price.***

FURTHER READING

- Médecins Sans Frontières. Drug patents under the spotlight (*64*). **http://www.who.int/3by5/en/patents_2003.pdf**

## STEP 10

# Contracts

Contract conditions provide the basis for monitoring and evaluating product quality and supplier performance. Buyers are obliged to ensure that contracts and procurement documents protect their interests.

The supplier should be committed to work with the buyer to minimize potential public health risks. They should be obliged to:

- supply only batches of product with quality characteristics identical to those for which WHO prequalification, stringent marketing authorization or assessment by an expert group has been granted;
- actively recall defective products and replace goods within defined times, either in kind or by covering the direct and related costs;
- notify the buyer and obtain his or her approval before shipment, in the case of any changes in the contractually agreed product's status or specifications; and
- report any serious quality or safety concerns related to the manufacture, control or use of their product, including suspension or cancellation of marketing authorizations.

Contracts are also shaped by the requirements of funders who finance procurement of the products. If applicable, procurement entities should have the right to:

- access manufacturing sites for inspection, preshipment sampling and quality testing (quality control testing does not relieve the supplier of any obligation to ensure ongoing product quality);
- disclose prices, lead times and results of quality control testing; and
- terminate the contract and request compensation of funding as a penalty if the supplier does not fulfil his or her contractual obligations.

➔ ***Procurement entities should ensure that what they accept to purchase is exactly what has been WHO prequalified or SRA-authorized: FPPs must be manufactured at the same site, from the same starting materials and by the same processes (see STEP 16).***

➔ ***Contracts should oblige the buyer to report any changes to contractually agreed specifications. An expert representing the procurement entity can then decide at what level the change should be handled (see STEP 16).***

➔ ***Contracts should include a reference to standard trade definitions, such as Incoterms, to define the conditions of delivery.***

➔ ***Shelf-life is a major issue for artemisinin-based antimalarial medicines. Contracts should state that products with the longest documented shelf-lives should be supplied. Subsequent reduction will have to be handled as a major variation (see STEP 16), which could result in supply interruptions.***

➔ ***All contracts should specify that liability for the product remains with the manufacturer or the marketing authorization holder with whom the contract is established.***

## STEP 11.

# Preshipment inspection and quality control

Quality control involves sampling, specifications and testing, with the procurement agency's documentation and acceptance or rejection procedures, which ensure that the necessary relevant tests are actually carried out and that starting materials, intermediates and FPPs are not accepted for use, sale or supply until their quality has been judged to be satisfactory.

➔ ***Quality control testing of batches is essential to complement quality assurance in manufacture and procurement.***

## 11.1 Role of preshipment inspection and quality control

Quality control testing at the manufacturing site before shipment complements quality control testing of the manufacturer. Its aim is to confirm that each batch of FPP conforms to the specifications agreed in the purchasing contract and documented in the certificate of analysis that accompanies the batch certificate.

Preshipment quality control may not be required in all cases. It does not apply to locally produced products. For imported products, some organizations conduct preshipment quality control testing only if the products are not WHO-prequalified or SRA-authorized.

Preshipment inspection of goods is required in certain cases, usually if the shipment is destined for countries with import certification schemes. This check serves to verify the goods against contractual specifications in terms of number, description and quality, as far as this can be verified by inspection, and to assess import duties and taxes correctly according to fair and uniform application of import and customs regulations.

## 11.2 Contracting a laboratory

Some procurement entities have their own quality control laboratories, which sample products at the manufacturing sites and test them before shipment. Others contract a laboratory to do such testing on their behalf. The laboratory should be selected in a competitive process. It is strongly recommended that the laboratory be WHO-prequalified or ISO-17025-accredited. It should be capable of carrying out full pharmacopoeial testing.

An agreement should be concluded with the selected laboratory, covering (see **STEP 8** for background information):

- standards and reference materials to be used;
- tests to be conducted;
- cost of method development, validation and/or transfer;
- cost of testing (first batch, subsequent batches);
- sample size; and
- handling of results that are not in conformity.

➔ ***Although procurement entities can usually rely on the selected quality control laboratory to specify and handle these aspects competently, they should understand the issues involved and should retain control of the quality control.***

## 11.3 Shared arrangements

Testing a large number of samples at the same time can have several advantages. It reduces the amount of expensive reference standards required for testing. It saves the expense of setting up analytical systems, which can reduce the cost of analysis per sample significantly. The laboratory will have a central record of sampled batches, so that unnecessary duplicate testing of samples from the same batch can be avoided. Lastly, the test results will be directly comparable, as they were obtained with the same methods and equipment.

➔ ***Quality control testing of large numbers of batches at the same time should be considered, for instance by arranging for quality control testing with other buyers.***

## 11.4 Preparation for sampling

Coordination is important to avoid delays in sampling and transport. The manufacturer and the laboratory should exchange the following information before each shipment:

- list of batch numbers in the consignment;
- expected shipment date and sampling date;
- location of the sampling venue and contact details of the responsible persons;
- practical arrangements, such as directions and access to the sampling area; and
- a list of all documentation needed for transport or export of samples (e.g. copy of manufacturer's licence).

## 11.5 Sampling for preshipment quality control

The frequency of preshipment quality control depends on the type of product. To increase cost–effectiveness and to minimize delays in delivery, quality control testing should focus on products with the highest risk. Some procurement entities test each batch; others test each of the first three to five batches supplied and then one in every 10 or 20 batches randomly thereafter, with testing becoming more frequent if any problems are reported. The Expert Review Panel's product advice for procurement with GFATM resources include advice on preshipment quality control testing.

The WHO guideline on sampling (*65*) proposes use of defined sampling standards, such as BS 6001-1, ISO 2859 or ANSI/ASQCZ 1.4 1993, and lists the steps to be followed in sampling. Sufficient samples should be taken for testing and for future reference in case of disputes (retention samples) in accordance with standard operating procedures and regulations. Batches selected for quality control testing should be held until the outcome of the testing is known.

Batches can be considered uniform. Once a product has passed quality control testing, there is no need to test other samples of the same batch, unless there are reasons for doing so, such as complaints about product quality.

➔ ***A record of batches tested should be kept to minimize duplicate testing.***

## 11.6 Interpretation of results

Any doubtful or unexpected result obtained in quality control testing should be investigated according to a predefined standard operating procedure. If the results are confirmed as 'out of specification', the products should be quarantined and the results should be confirmed before any further steps are taken.

If a sample is noncompliant and the manufacturer objects to the results, the retention sample kept by the manufacturer should be analysed in the presence of the manufacturer's specialist. The second sample kept at the laboratory for replicate tests will be analysed in case of dispute (*66*).

A system should be in place to decide what to do if single batches of a consignment fail quality control testing. For example, UNICEF and GFATM reject failed batch(es) and test additional batches according to a predefined protocol.

- ***Product batches selected for quality control testing should be released only once the results have been found to be acceptable. Noncompliant batches should be rejected in accordance with agreed procedures.***
- ***National regulatory authorities, SRAs or WHO PQP should be informed if any batches approved by these bodies fail quality control testing after batch release by the manufacturer.***

FURTHER READING

- WHO. *Guidelines for sampling of pharmaceutical products and related materials* (*65*).
- WHO. *Good practices for national pharmaceutical quality control laboratories* (*66*).

# STEP 12.
# Port clearance and receipt

## 12.1 Before receipt of each shipment

Enough storage space must be available at the port of entry, even if clearance will be delayed. The information that should be exchanged between the sender and the receiver includes:

- a detailed list of all documentation and forms required in the destination country (e.g. invoice, packing list, certificates of analysis, airway bill, procurement or custom waivers and other documentation);
- language requirements for documentation; and
- date and details of shipment, with expected date of arrival.

Procurement officers should liaise with customs officials about expected consignments and their status, to ensure prompt clearance.

## 12.2 On receipt of each shipment

Receiving staff should be independent from purchasing staff. If possible, more than one person should be present when supplies are received.

Received products should be handled in a secure receiving area according to batch segregation principles. Received batches should be quarantined until they are accepted into stock or distributed further.

The purpose of postshipment inspections and receiving procedures is to check products and packaging to verify that what was delivered is what was ordered and that the products are certified by the manufacturer to meet specifications. Specifically, consignments should be checked for:

- the total number of received packages or items;
- any signs of damage to packaging or seals;
- expiry dates of certification or authorization;
- remaining shelf-life (2 years or at least 75% of the established shelf-life, whichever is higher); and
- complete, current and consistent labels, markings, delivery note, order and certificate of analysis.

Any discrepancies must be handled as contractually agreed (see STEP 10).

## 12.3 After receipt of each shipment

Procurement outcomes, such as prices and lead times, must be documented and reported, in line with the requirements of the procurement system or funders.

Records of each delivery should be kept for the period required by national regulations, or for at least 1 year after expiry of all goods included in the delivery.

FURTHER READING

- WHO. A model quality assurance system for procurement agencies (*1*).
- Quick JD et al. (eds). *Managing drug supply* (*2*).

# STEP 13.
# Postshipment quality control

When products arrive in a country, they have already been tested by the manufacturer and perhaps also before shipment (see **STEP 11**). The main role of postshipment quality control is to determine any damage to the products during transport and storage.

Quality control testing is expensive, but so are the return and replacement of substandard products. Quality assurance measures taken along the supply chain, such as verification of documentation, use of temperature and humidity monitors during transport and storage and protection against fraud, should be taken to minimize the chance of quality deficiencies.

## 13.1 Extent of testing

Postshipment quality control is a regulatory requirement in some countries. As full-scale pharmacopoeial testing is expensive, the national authority may decide to focus on identifying substandard products and damage from heat and humidity by identity tests and assays (*67*), although damage to the products' shelf-life can be detected only by another round of accelerated stability testing.

- ***The extent of postshipment quality control should be justified by legal requirements or the potential risks of not testing the products.***
- ***As in preshipment testing (see* STEP 11*), shared arrangements with other buyers can reduce costs and minimize duplicate testing of the same batches.***

## 13.2 Selection of laboratory

Quality control of procured products in the destination country should be carried out at the national quality control laboratory or by laboratories that are recognized by the national regulatory authority (contract laboratories). The laboratories should be either approved by WHO PQP[1] or accredited in accordance with ISO17025. Some funders will finance capacity-building for national regulatory authorities and control laboratories. Suppliers frequently contest test results, and this often delays procurement. Inclusion of specific requirements for quality control testing and the consequences of substandard results in the tender documentation may help avoid or limit potential litigation with suppliers.

**EXAMPLE:**

The GFATM encourages buyers to work with national regulatory authorities to strengthen national quality assurance systems and to include funds for items such as buildings, equipment, staff costs and training in their grant applications.

[1] In June 2009, 10 laboratories were prequalified, in: Algeria, France, India, Kenya (*2*), Morocco, Singapore, South Africa (*2*) and Viet Nam. An updated list of prequalified laboratories, with their areas of expertise, is given at http://www.who.int/prequal/lists/pq_qclabslist.pdf.

## 13.3 Interpretation of results

Results should be handled according to the principles described in **STEP 11**. The supplier remains liable for any damage to the product up to the contractually agreed point of delivery (as specified by Incoterms). Until the end of the shelf-life, the quality of the FPP remains the responsibility of the manufacturer, provided the product is stored and transported according to instructions.

- ***If it is confirmed that the product does not comply with specifications, one or more of the measures agreed in the contract, such as recall of product, replacement at the expense of the manufacturer or publication of outcome, should be instituted.***
- ***Rejected batches should be disposed of safely, to ensure that they do not re-enter circulation. The record of disposal is part of the product history, which should be traceable throughout all steps.***

## 13.4 Reporting the results of quality control

Deficiencies in the quality of antimalarial medicines circulating on the market have been reported (*68*). The results of quality control, including negative results, have been made publicly available by some organizations.

**EXAMPLE:**

As part of its revised quality assurance policy for pharmaceutical procurement, effective from 1 July 2009, the GFATM is implementing online price and quality reporting, which will include the results of pre- and postshipment quality testing of ACTs. If the reporting is reliable and consistent, this database will be a valuable addition to quality assurance systems for procurement.

FURTHER READING

- WHO. *Guidelines for sampling pharmaceutical products and related materials* (*65*).
- WHO. *Good practices for national pharmaceutical quality control laboratories* (*66*).

# STEP 14.
# Storage and distribution

Artemisinin-based antimalarial medicines are expensive, have short shelf-lives and are easily damaged by heat and moisture. They must therefore be stored and distributed with great care. Detailed guidance is given in other documents (see **'Further reading'**), but some important points are listed below.

## 14.1 Temperature monitoring and control

To protect the products from heat and moisture, refrigerated transport should be considered. Monitoring devices can be included to detect any breaches.

Lead times can be very long especially in landlocked countries, so that transport by air may be preferred. Care should be taken that capsules do not freeze in baggage holds, as sub-zero temperatures may cause them to disintegrate.

## 14.2 Stock control

Requirements for storage space, personnel, environmental control and inventory control described in other publications should be followed. Expiry dates should be checked at frequent intervals. Procedures should be in place to deal with expired products.

At larger warehouses, batch samples might have to be kept of all issued supplies for control purposes.

## 14.3 Security and control of access

To prevent fraud, theft and diversion, strict control of access to stores and security measures in transit should be enforced.

## 14.4 Batch traceability and recalls

The traceability of batches is important, if products have to be recalled because of problems with quality. It can also be helpful for detecting fraud or theft. Records of distribution should contain sufficient information to allow the product to be traced from the point of supply to the user. Any anomalies should be investigated and followed up by appropriate measures in order to close any breaches.

FURTHER READING


- WHO. *A model quality assurance system for procurement agencies* (*1*).
- Quick JD et al. (eds). *Managing drug supply* (*2*).
- United States Pharmacopeial Convention. Ensuring the quality of medicines in low-income countries (*3*).
- WHO. *Guide to good storage practices for pharmaceuticals* (*69*).
- WHO. *Good distribution practices for pharmaceutical products* (*6*).

## STEP 15.

# Monitoring supplier performance

As described in other documents (*1*,*2*), procurement organizations should monitor supplier performance and maintain their own lists of qualified suppliers.

Depending on the buyer's capacity and level in the supply system, artemisinin-based antimalarial medicines may be sourced directly from manufacturers or from national or international suppliers who handle all or part of the bidding, contracting or distribution. WHO's model quality assurance system for procurement agencies (*1*) gives the general principles. Specific indicators for monitoring and evaluating procurement of antimalarial medicines at the different levels have been suggested (*34*). Examples of outcomes that could be monitored include:

- *prequalification*: presence of a system, methods used;
- *bidding*: methods and time frames for preparation and evaluation of bids, number and outcomes of protests, procurement lead time;
- *contract management*: percentage increase in final contract amount due to changes, number of late payments;
- *quality of supplied products*: number of batches that failed quality control testing, number of variations from agreed specifications; and
- *supplier*: lead time, back orders, correctness and completeness of product-related documentation and responsiveness to queries.

➔ ***As in tender management (see STEP 5), competitive procurement based on prequalification of at least two suppliers of good-quality FPPs is desirable. Dependence on a single supplier is unlikely to result in a sustainable supply at competitive prices in the long term.***

FURTHER READING

- WHO. *A model quality assurance system for procurement agencies* (*1*).
- Quick JD et al. (eds). *Managing drug supply* (*2*).
- World Bank Procurement Policy and Services Group. Malaria booster control program. Procurement and supply management toolkit (*34*).

# STEP 16.
# Monitoring variations

Although contracts oblige the supplier to supply only batches of FPPs that meet the agreed specifications (see STEP **10**), buyers should reinforce this commitment throughout the duration of the contract.

> **EXAMPLE:**
>
> For every order placed, Médecins Sans Frontières asks suppliers to sign a summary sheet in the dossier, listing the specifications, sources of APIs and excipients, and manufacturing sites of the FPP.

Changes to the processes for manufacturing FPPs are, however, inevitable in a competitive environment, and such changes are often intended to improve quality (e.g. stability, batch-to-batch consistency, analytical method) or product information (e.g. safety updates) (*15*).

Not all variations occur during manufacture at the site of origin. For example, antimalarial medicines may be repackaged or relabelled for distribution at some point along the procurement chain in order to meet requirements of language or pack size. Such variations must be brought to the attention of the original supplier and handled as variations (see SECTION **16.2**).

## 16.1 Detecting variations

### *16.1.1 Reliance on WHO PQP and SRAs*

The mechanisms of WHO PQP and SRAs for reassessment (typically every 3–5 years) and handling of complaints can support procurement entities in verifying the ongoing quality of products.

WHO PQP regularly conducts verification inspections at short notice, focusing for example on manufacturing sites with high production volumes and potentially frequent changes in the APIs used. Since 2008, WHO PQP has published 'notices of concern' (when manufacturers fail to take corrective action) and 'notices of suspension' (removal from the list) on its web site.

➔ ***On request, WHO PQP will help buyers to verify ongoing compliance with contractual specifications for specific batches (such as API specifications shown in batch manufacturing records) during its verification inspections.***

### *16.1.2 Own inspections*

Some procurement entities have their own processes for requalifying certain aspects of product quality. If they have sufficient expertise and capacity, they may wish to inspect manufacturing sites, at least for FPPs that have not yet been approved by WHO PQP or an SRA or that have been associated with recent problems of quality. If they do so, they should work with national regulatory authorities.

Procurement officers, recipients of goods and other entities involved in any step along the supply chain should be alert to any signs of quality variations that are not brought to their attention by suppliers. Apart from actual complaints and deficiencies found on visual checks or quality testing of products (see **STEPS 11** and **13**), such signs include:

- uncharacteristic results on certificates of analysis for batches procured, e.g. with respect to dissolution testing;
- deviations from usual routines, such as unusual batch number formats, which could indicate manufacture at a different site; and
- information on changes in products or approval status of manufacturing sites from independent sources, such as professional electronic fora or web-based reporting mechanisms.

### *16.1.3 Information-sharing*

Procurement entities cannot always ascertain what has been approved by the authority that made the initial assessment. The technical information submitted on a questionnaire during bidding (see **ANNEX 3** for an example) might not match that lodged with WHO PQP or the SRA, and the same applies to subsequent changes.

➔ ***Information-sharing among procurement entities will benefit other buyers.***

> **EXAMPLE:**
>
> The product questionnaire shown in Annex 3 contains a provision for information-sharing between agencies (see **SECTION 1**, point 3: 'Note for the applicant').

➔ ***WHO PQP has mechanisms for sharing product information, subject to the protection of commercially sensitive information (19):***

- Information-sharing with national regulatory authorities of WHO Member States has been introduced; information-sharing with nongovernmental organizations is possible if the manufacturer gives consent in writing.
- Part 8 of WHO PQP's online WHO public assessment reports (see **STEP 6**) contains information on steps to be taken following prequalification. In July 2009, assessment reports were available for seven antimalarial medicines, although Part 8 had not yet been completed because the dates of WHO prequalification were recent.
- WHO PQP is planning to publish the letters of prequalification, which include information about the FPP, on its web site (linked to the name of the prequalified FPPs).

## 16.2 Handling variations

WHO PQP and SRAs have formal procedures for handling variations, depending on the impact on product quality. The WHO PQP procedure handles changes at three levels (*70*):

- Minor variations, which have no impact on the functional characteristics of the pharmaceutical product (such as shelf-life extension) or on its use (such as pack size, but not type, which must correspond to recommended regimens), can be approved by the purchaser after a technical review of documentation.

- For major changes, such as changes in the process for manufacturing the API, the composition of the FPP or the primary packaging in direct contact with the dosage form, manufacturers should provide documentation to prove that the change will not affect the agreed quality of the product.

Critical changes, such as replacement, addition, changed dosage or removal of an API, changes to the pharmaceutical form or dosage form and changes in the route of administration, require a new application for stringent marketing authorization or WHO prequalification.

➔ ***Quality control should be stepped up in cases of suspected or reported quality variations, unless they have been fully justified, as described above.***

➔ ***Any major or critical variation in quality that is not justified in a formal variation procedure should be reported to the bodies that approved the product (national regulatory authorities, SRAs or WHO PQP).***

FURTHER READING

- WHO. *Procedure for prequalification of pharmaceutical products* (Section 12, Maintenance of prequalification status) (*19*).
- WHO. *Guidance on variations to a prequalified product dossier* (*70*).

STEP 16

# References[1]


1. *A model quality assurance system for procurement agencies (Recommendations for quality assurance systems focusing on prequalification of products and manufacturers, purchasing, storage and distribution of pharmaceutical products)*. Geneva, World Health Organization, 2007 (WHO/PSM/PAR/2007.3). **http://www.who.int/medicines/publications/ModelQualityAssurance.pdf**
2. Quick JD et al., eds. *Managing drug supply*. 2nd ed. Hartford, Connecticut, Kumarian Press, 1997.
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# Annexes

## ANNEX 1.

# WHO model certificate for a pharmaceutical product

*This model certificate is available on the WHO web site at:*

**http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/modelcertificate/en/**

### Certificate for a pharmaceutical product[1]

*This certificate conforms to the format recommended by the World Health Organization.*

No. of certificate: .....

Exporting (certifying country): .....

Importing (requesting country): .....

1. Name and dosage form of the product: .....

1.1 Active ingredient(s)[2] and amount(s) per unit dose:[3] .....

For complete composition, including excipients, see attached:[4] .....

1.2 Is this product licensed to be placed on the market for use in the exporting country?[5]
☐ Yes ☐ No

1.3 Is this product actually on the market in the exporting country? .....

*If the answer to 1.2 is yes, continue with section 2A and omit section 2B.*

*If the answer to 1.2 is no, omit section 2A and continue with section 2B.*[6]

2.A.1 Number of product licence[7] and date of issue: .....

2.A.2 Product licence holder (name and address): .....

2.A.3 Status of product licence holder:[8] (Key in appropriate category as defined in note 8)

2.A.3.1 For categories b and c, the name and address of the manufacturer producing the dosage form is:[9] .....

2.A.4 Is a summary basis for approval appended?[10] ☐ Yes ☐ No

2.A.5 Is the attached, officially approved product information complete and consonant with the licence?[11] ☐ Yes ☐ No ☐ Not provided

2.A.6 Applicant for certificate, if different from licence holder (name and address):[12]

.....

2.B.1 Applicant for certificate (name and address): .....

2.B.2 Status of applicant: (Key in appropriate category as defined in footnote 8) .....

2.B.2.1 For categories b and c, the name and address of the manufacturer producing the dosage form is:[9] .....

2.B.3 Why is marketing authorization lacking?
☐ Not required ☐ Not requested ☐ Under consideration ☐ Refused

2.B.4 Remarks:[13] .....

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? ☐ Yes ☐ No ☐ Not applicable[14] .....

*If not or not applicable, proceed to question 4.*

3.1 Periodicity of routine inspections (years): .....

3.2 Has the manufacture of this type of dosage form been inspected? ☐ Yes ☐ No

3.3 Do the facilities and operations conform to GMP as recommended by the World Health Organization?[15] ☐ Yes ☐ No ☐ Not applicable[14]

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product:[16] ☐ Yes ☐ No

If no, explain: .....

Address of certifying authority: .....

Telephone: .....

Fax: .....

Name of authorized person: .....

Signature: .....

Stamp and date: .....



## *Explanatory notes*

[1] This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only, as manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

[2] Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

[3] The formula (complete composition) of the dosage form should be given on the certificate or be appended.

[4] Details of quantitative composition are preferred, but their provision is subject to the agreement of the product-licence holder.

[5] When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.

[6] Sections 2A and 2B are mutually exclusive.

[7] Indicate, when applicable, if the licence is provisional or the product has not yet been approved.

[8] Specify whether the person responsible for placing the product on the market:

a. manufactures the dosage form;

b. packages and/or labels a dosage form manufactured by an independent company; or

c. is involved in none of the above.

[9] This information can be provided only with the consent of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the product licence. If the production site is changed, the licence has to be updated or it is no longer valid.

[10] This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

[11] This refers to product information approved by the competent national regulatory authority, such as summary product characteristics

[12] In this circumstance, permission for issuing the certificate is required from the product-licence holder. This permission has to be provided to the authority by the applicant.

[13] Please indicate the reason that the applicant has provided for not requesting registration.

a. The product has been developed exclusively for the treatment of conditions – particularly tropical diseases – that are not endemic in the country of export.

b. The product has been reformulated with a view to improving its stability under tropical conditions.

c. The product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import.

d. The product has been reformulated to meet a different maximum dosage limit for an active ingredient.

e. Any other reason, please specify.

[14] 'Not applicable' means that manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.

[15] The requirements for good practice in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series No. 823, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

[16] This section is to be completed when the product-licence holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in manufacture of the product. In these circumstances, the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

# ANNEX 2.
# Stringent regulatory authorities

Regulatory authorities participating in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (**http://www.ich.org**, web page, last accessed on 27 January 2009):

A2

## Members:

- European Union Member States (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Netherlands, United Kingdom)
- Japan
- United States of America

**Observers** (updated from time to time):

- European Free Trade Association represented by Swissmedic, Health Canada, WHO

**Associates** through mutual recognition agreements (updated from time to time):

- Australia, Iceland, Liechtenstein, Norway

**Special regulatory schemes** for medicines used exclusively outside the ICH region:

- Under European Union Article 58, EMEA's Committee for Medicinal Products for Human Use gives opinions, in cooperation with WHO, on medicinal products for human use (**http://www.emea.europa.eu/htms/human/non_eu_epar/background.htm**) (*41*).
- The Canada S.C. 2004, c. 23 (Bill C-9) procedure (*42*) and the United States Food and Drug Administration tentative approval (*43*) relate only to the provision of antiretroviral and HIV-related medicines.

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Members of the Pharmaceutical Inspection Cooperation Scheme (http://www.picscheme.org) are not considered to be SRAs, although GMP certificates issued by them are recognized to reflect stringent standards.

The Pharmaceutical Inspection Cooperation Scheme is a Swiss association of inspectorates, which provides a forum for GMP training. Its GMP guidelines are based on those of the WHO Global Malaria Programme but have evolved separately from the WHO guidelines for a number of years. The Pharmaceutical Inspection Cooperation Scheme has no provisions for marketing authorization or legislatory functions in terms of regulation. Its membership is rapidly expanding. Scheme members (as of July 2009) were: Argentina* (since January 2008), Australia, Austria, Belgium, Canada, Czech Republic, Cyprus (since July 2008), Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel* (since January 2009) Italy, Latvia, Liechtenstein, Lithuania, Malaysia*, Malta (since January 2008), Netherlands, Norway, Poland, Portugal, Romania, Singapore*, Slovakia, South Africa*, Spain, Sweden, Switzerland, United Kingdom.

* countries that are not members, observers or associates of ICH

## ANNEX 3.

# Questionnaire on finished pharmaceutical products[1]

### Table of contents



[1] This questionnaire, with annexes as mentioned, was adapted from the technical questionnaire shown in Appendix 6 of WHO's *Model quality assurance system for procurement agencies* (*1*) and is used by the Expert Review Panel to collect technical information on products.

Response to invitation of expression of interest No. ..... for ..... (product type)

Dated: .....

## SECTION 1. PREAMBLE

### 1. Contact details of bidder

Name of company submitting expression of interest: .....

Physical address: .....

Postal address: .....

City: ..... Country: .....

Telephone: ..... Fax: .....

E-mail: ..... Web site: .....

Link with the product:

☐ Marketing license holder ☐ Distributor/wholesaler ☐ Manufacturer

☐ Other (*please specify*): .....



### 2. Contact details of responsible persons

| Subject | Name of contact person | Telephone and cell phone | E-mail |
|---|---|---|---|
| Technical specifications and product quality | | Tel:<br>Cell: | |
| Regulatory and patent | | Tel:<br>Cell: | |
| Commercial or business | | Tel:<br>Cell: | |
| General enquiries | | Tel:<br>Cell: | |

### 3. Note for the applicant

The information in this questionnaire will be forwarded by the GFATM to its Expert Review Panel, hosted by WHO, to facilitate the Panel's review of the applicant's submission and advice the GFATM on procurement.

The information in this questionnaire may be shared confidentially among WHO, ICRC, Médecins Sans Frontières and UNICEF for procurement purposes. If you have any objection, please indicate in the section provided at the end of this questionnaire.

Please fill out one form separately for each pharmaceutical product.

If you have previously filled out an interagency pharmaceutical product questionnaire and provided the necessary information in relation to this product, please indicate below (all that apply).

☐ ICRC Most recent submission date: .....

☐ Médecins Sans Frontières Most recent submission date: .....

☐ UNICEF Most recent submission date: .....

☐ WHO Most recent submission date: .....

☐ Other (*specify*): ..... Most recent submission date: .....

## SECTION 2. FINISHED PHARMACEUTICAL PRODUCT

### 4. Identification

☐ **Single pharmaceutical entity**

Approved nonproprietary name of product (*Pharmaceutical form, including route(s) of administration, active ingredient, amount in dosage form or amount per unit): .....

Inactive ingredients (excipients) of medical or pharmaceutical relevance, amount in dosage form or per dosage unit (e.g. 'contains alcohol 10%'): .....

Brand or trade name (if any): .....

☐ **Fixed-dose combination**

| Content | Active pharmaceutical ingredient | Amount in dosage form or amount per unit | *Pharmaceutical form, including route(s) of administration |
|---|---|---|---|
| Active ingredient 1 | | | |
| Active ingredient 2 | | | |
| Active ingredient 3 | | | |

Inactive ingredients (excipients) of medical or pharmaceutical relevance, amount in dosage form or per dosage unit (e.g. 'contains alcohol 10%'): .....

Brand or trade name (if any): .....

☐ **Co-pack**

| Content | Active pharmaceutical ingredient | Amount in dosage form or amount per unit | *Pharmaceutical form, including route(s) of administration |
|---|---|---|---|
| Item 1 | | | |
| | | | |
| Item 2 | | | |
| | | | |

Inactive ingredients (excipients) of medical or pharmaceutical relevance, amount in dosage form or per dosage unit (e.g. 'contains alcohol 10%'): .....

Brand/or trade name (if any): .....

*__Pharmaceutical forms__ (*use all that apply from the selection below*)

**Tablets**

☐ Scored

☐ Solid

☐ Dispersible

☐ Chewable

☐ Buffered (*specify buffers*)

☐ Film coated

☐ Enteric coated

☐ Sublingual

☐ Bilayered

☐ Delayed release

☐ Controlled release

**Capsules**

☐ Enteric coated

☐ Delayed release

☐ Controlled release

☐ Sublingual

☐ Other (*specify*): .....

**Oral liquids**

☐ Solution

☐ Suspension

☐ Powder for liquid

☐ Powder for suspension

**Oral powders**

**Injections**

☐ Solution for Injection

☐ Powder for Injection

☐ Oily Injection



## 5. Packaging

Number of dosage units per unit pack: .....

Numbers of unit packs per secondary pack (multiples of unit packs): .....

Language(s) of label, packaging and pack insert

☐ English ☐ French ☐ Other (*specify*): .....

Attach package insert.

Description and composition of primary packaging materials: .....

Description and composition of secondary packaging materials: .....

## 6. Monograph specifications (tick and answer, as applicable)

| Pharmacopoeia | Volume | Edition | Year published |
|---|---|---|---|
| ☐ British | | | |
| ☐ United States | | | |
| ☐ International | | | |
| ☐ Other (*specify*): | | | |

☐ In house Year documented: ..... Explain: .....

Indicate any specifications additional to those in the pharmacopoeia (e.g. dissolution, syringeability): .....

Attach a copy of the internal finished product specifications.

Attach a copy of the certificate of analysis for the last three batches released.

Manufacturing method for each standard batch size is validated.

☐ Yes ☐ No Explain: .....

Attach a copy of the internal finished product specifications.

List the validated batch size quantities:

## 7. Stability of finished product

Stability testing data available

☐ Yes ☐ No Explain: .....

Attach copies of study results, including graphical or pictorial interpretations where applicable.

If yes, indicate type and conditions of testing: .....

Satisfactory accelerated testing at (*state months*): .....

Type and material of packaging: .....

Conditions (temperature/relative humidity/duration): .....

Number of batches: .....

Batch sizes: .....

Date of beginning of study: .....

Date of end of study: .....

Satisfactory real-time (long-term) testing at (state months): .....

Type and material of container: .....

Conditions (temperature/relative humidity/duration): .....

Number of batches: .....

Batch sizes: .....

Date of beginning of study: .....

Date of end of study (if applicable): .....

Attach copies of testing protocols.

Stability testing has been done on a product of the same formula, manufactured on the same site and packed in the same packaging material as the product that will be supplied.

☐ Yes ☐ No

If no, describe differences: .....

Stability testing done on (*tick all that applies*)

☐ Pilot batch (not less than 10% of full production batch)

☐ Production batch

Stability studies for this product are ongoing.

☐ Yes ☐ No

Attach status report of any ongoing stability studies

## 8. Shelf-life and storage conditions

Guaranteed shelf-life (based on stability studies): .....

Maximum possible shelf-life: .....

Shelf-life as it appears on the packaging: .....

Shelf-life after primary package is opened or product is reconstituted: .....

Product suitable for use in:

☐ Zone I

☐ Zone II

☐ Zone III

☐ Zone IVa

☐ Zone IVb

☐ Other (*specify*): .....

Specific storage conditions for this product as they appear on the packaging and based on stability studies:

Temperature: .....

Light: .....

Humidity: .....

Other (*specify*): .....

## 9. Safety and efficacy or therapeutic equivalence

### 9.1 For innovator products

Please attach a summary of the pharmacology, toxicology and efficacy of the product.

### 9.2 For generic products

**9.2.1 ☐ Demonstrated**

a) by in vivo bioequivalence studies

Study period (dd/mm/yyyy): from ..... to .....

### Reference product

Generic name: .....

Dosage form: .....

Strength: .....

Brand or trade name: .....

Manufacturer: .....

Manufacture site: .....

Batch number: .....

Expiry date: .....

### Study protocol

Contract research organization name: .....

Country of study: .....

Number of volunteers: .....

Study design (*describe in detail*): .....

Attach schematic representation of study design.

Attach study protocol summary.

Bio batch size: .....

Bio batch number: .....

Bio batch API(s) source(s): .....

Study conclusion: .....

Attach graphical/pictorial representation of summary study results.

b) ☐ by another method (*please describe briefly*): .....

Study conclusion: .....

Attach graphical or pictorial representation of summary study results.

c) ☐ by comparative in vitro dissolution tests according to conditions described in WHO biopharmaceutics classification system document (WHO Technical Report Series No. 937) or later)

☐ Yes ☐ No (*explain*): .....

Biopharmaceutics classification system class: .....

### Reference product

Generic name: .....

Brand or trade name: .....

Manufacturer: .....

Manufacture site: .....

Batch number: .....

Expiry date: .....

Name and contact details of laboratory performing tests: .....

*N.B. Reference product must have undergone successful in vivo bioequivalence studies.*

### Study results

F2 (similarity factor) value: ..... (standard, 50–100%)

F1 (difference factor) value: .....

Study conclusion: .....

Attach graphical or pictorial representation of summary study results

**9.2.2 ☐ Not demonstrated**

**9.2.3 ☐ Not relevant, please explain why:** .....



Attach full reports of all studies done to prove therapeutic equivalence with clear study conclusions.

The product used in the therapeutic equivalence study is essentially the same as that which will be supplied (same materials from the same suppliers, same formula and same manufacturing method).

☐ Yes ☐ No (*explain what the differences are*): .....

Please provide (as an attachment) a flow diagram describing the manufacture and control of this product with relevant parameters.

## 10. Regulatory status

Certificate of pharmaceutical product No.: ..... Valid until: .....

Certificate of pharmaceutical product issued by (*name of agency*): .....

Country: .....

Attach certificate of pharmaceutical product according to the WHO Certification Scheme (WHO Technical Report Series No. 863) (earlier version is not acceptable) or equivalent document.

☐ Certificate of pharmaceutical product not available (*state reason and attach equivalent document if any*):

Not yet WHO prequalified: date of dossier submission (*attach evidence*)

Not applied for WHO prequalification: Explain .....

## 11. Licensing status

Tick and fill in all fields that apply:

☐ Product registered and currently marketed in the country of manufacture

License No.: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

☐ Product registered for marketing in the country of manufacture but not currently marketed

License No.: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

☐ Product registered for export only

License No.: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

☐ Product not registered in country of manufacture (*please clarify*): .....

Provide copies of all licenses that apply

This product is registered or licensed and currently marketed in the following countries:

| Country | License No. | Valid until | Issuing agency |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

Attach additional pages if necessary

## 12. Samples for technical evaluation

Product sample provided conforms in all forms to product offered as it will be supplied on purchase.

☐ Yes ☐ No (*explain*): .....

Attach a certificate of analysis relevant to the sample.

*N.B. If you are not able to provide a certificate of analysis, please explain*: .....

Shelf-life on sample: .....

Storage conditions on sample: .....

Pack insert available: ☐ Yes ☐ No: .....

Attach copy of label

Attach pack insert

## SECTION 3. MANUFACTURER

### 13. Identification

Repeat this section for each manufacturing site relevant to this product.

Name of manufacturer: .....

Physical address of manufacturing site(s), including unit/block number: .....

Postal address: .....

City: ..... Country: .....

Telephone: ..... Fax: .....

E-mail: ..... Web site: .....

Activities of manufacturer (*fill in all that apply*)

| Activity | License No. | Valid until | Issuing agency | Country |
|---|---|---|---|---|
| Manufactures APIs (drug substance) | | | | |
| Manufactures finished product (drug product) | | | | |
| Primary packaging | | | | |
| Secondary packaging | | | | |
| Contract manufacture | | | | |
| Other (specify) | | | | |

A3

### 14. Good manufacturing practice (GMP)

WHO GMP certificate no: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

GMP inspections carried out by (*tick all that apply*):

☐ WHO prequalification programme Date: ..... Outcome: .....

☐ National regulatory authority Date: ..... Outcome: .....

☐ UNICEF Supply Division Date: ..... Outcome: .....

☐ Médecins Sans Frontières International Date: ..... Outcome: .....

☐ ICRC Date: ..... Outcome: .....

☐ United States Food and Drug Administration Date: ..... Outcome: .....

☐ Other (*specify*) Date: ..... Outcome: .....

## SECTION 4. ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

If more than one API or manufacturer is used, please replicate this question.

### 15. Active pharmaceutical ingredients (API)

Name of API (INN if available): .....

Certificate of suitability for the European Pharmacopoeia No.: .....

API expiry date: .....

API retest date: .....

The open part of the drug master file is registered in (country): .....

Name of original manufacturer: .....

Physical address of manufacturing site(s), including unit/block number: .....

Postal address: .....

City: ..... Country: .....

Telephone: ..... Fax: .....

E-mail: ..... Web site: .....

Activities of original API manufacturer (*tick all that apply for each site separately*)

☐ Manufacture of Intermediates only

License No.: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

☐ Manufacture of APIs (drug substance)

License No.: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

☐ Repacking and/or reprocessing APIs

License No.: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

☐ Agent or broker for APIs

License No.: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

☐ Manufacturer of finished product (drug product)

License No.: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

☐ Other (*specify*)

License No.: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

☐ GMP certificate for API (No.)

License No.: ..... Valid until: .....

Issued by: Agency: ..... Country: .....

Attach copy of GMP certificate for manufacturer of API or intermediates.

Specifications and standard test methods exist for this API.

☐ Yes ☐ No

API specifications (tick as appropriate):

☐ *British Pharmacopoeia* Edition: ..... Volume: .....

☐ *United States Pharmacopeia* Edition: ..... Volume: .....

☐ *European Pharmacopoeia* Edition: ..... Volume: .....

☐ *International Pharmacopoeia* Edition: ..... Volume: .....

☐ Other (*specify*): .....

☐ No pharmacopoeial monograph exists*

* Attach a copy of the internal specifications and analytical methods for the API(s).

Attach a copy of the in-house finished product specifications.

Attach a copy of analytical methods for products with in-house specifications or specifications other than those listed above

Attach a copy of the model certificate of analysis for batch release of API.

Attach certificates of analysis of the last three production batches of API from the API manufacturer.

Attach certificate of analysis of API from the finished product manufacturer.

## SECTION 5. COMMITMENT AND AUTHORIZATION

### 16. Commitment

I (full name) ....., certify that: .....

☐ The product offered is identical in all aspects of manufacturing and quality to that tentatively approved by the United States Food and Drug Administration, reference ....., including formulation, method and site of manufacture, sources of active and excipient starting materials, quality control of the product and starting material, packaging, shelf-life and product information.

*or*

☐ The product offered is identical in all aspects to that registered and marketed in (name of country) .....

Explain any exceptions .....

Signature: ..... Date: .....

## 17. Authorization

I, the undersigned, confirm that the company has no objection to the information contained herein being shared with the agencies listed on page 1, except .....

I, the undersigned, certify that the information provided above is accurate, correct, complete, up to date and true at the time of submission.

Full name: .....

Full title or position in company: .....

Company name: .....

Signature: ..... Date: .....

Telephone number: .....

E-mail: .....

Company seal or stamp: Stamp here:

## APPENDIX: CHECKLIST OF ATTACHMENTS REQUIRED

Please ensure that all documents necessary to enable objective evaluation of your product are attached. This checklist may not be exhaustive.

☐ A. Formulation of the product (complete qualitative and quantitative composition, including active ingredient(s) and excipients)

☐ B. Flow diagram of the manufacturing and control processes with relevant parameters

☐ C. GMP certificate(s) of finished pharmaceutical product manufacturing site(s)

☐ D. Certificate of pharmaceutical product according to the WHO certification scheme

☐ E. Copy of the relevant WHO prequalification approval letter signed by your company

☐ F. WHO acceptance letter for product dossier review mentioning the WHO reference number assigned by WHO for this specific product

☐ G. Copy of internal finished product specifications

☐ H. Copies of the certificates of analysis for the three last batches released

☐ I. Validated analytical methods if specifications for finished product are in-house specifications, different from those in the British, United States and International pharmacopoeias

☐ J. Protocol and report for accelerated and real-time stability testing

☐ K. Description and composition of primary packaging materials

☐ L. Description and composition of secondary packaging materials

☐ M. Product registration licences in country of manufacture

☐ N. Sample of the finished product(s) offered together with the certificate of analysis relevant to the sample

☐ O. Label artwork or copy of actual label

☐ P. Package insert or leaflet

☐ Q. Copy of the report of the proof of therapeutic equivalence (e.g. bioequivalence study, comparative dissolution profile, dissolution tests, including graphical presentations)

☐ R. GMP certificate(s) of API manufacturing site

☐ S. Copy of internal API specifications

☐ T. Validated analytical methods in case of in-house API specifications

☐ U. Copy of the certificate(s) of analysis of the API from the API manufacturer as well as from the finished product manufacturer

☐ V. Copy of the certificate of suitability to the European Pharmacopoeia and its annexes.

## ANNEX 4.

# Elements of product quality, safety and efficacy

Based on the structure of the *Common technical document* in the ICH region (*71*)

✓ Regulatory assessment should be sufficient to ensure quality
■ Technical experts should evaluate these aspects;
○ Experts in procurement and pharmaceutical quality assessment should evaluate these aspects

| Element | | Innovator assessed by SRA | Generic assessed by SRA | New formulation not assessed by SRA | Generic, not assessed by SRA |
|---|---|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | | | |
| Reference | | ✓ | ✓ | ✓ | ✓ |
| Application status; fast track, special assessment request | | ■ | ■ | ■ | ■ |
| Dispute resolution | | ✓ | ✓ | ○ | ○ |
| Annual report | | ✓ | ✓ | ○ | ○ |
| Labelling | | ■ | ■ | ■ | ■ |
| Promotional material | | ■ | ■ | ■ | ■ |
| Risk management plan | | ✓ | ✓ | ○ | ○ |
| **QUALITY** | | | | | |
| API | General information | ■ | ■ | ■ | ■ |
| | Manufacture | ■ | ■ | ■ | ■ |
| | Characterization (structure, isomerism) | ✓ | ✓ | ○ | ○ |
| | Control of API (specifications, analytical methods, validation) | ■ | ■ | ■ | ■ |
| | Reference standards | ■ | ■ | ■ | ■ |
| | Container or closure system | ✓ | ✓ | ○ | ○ |
| | Stability | ✓ | ✓ | ○ | ○ |
| FPP | Description (form, composition) | ■ | ■ | ■ | ■ |
| | Pharmaceutical development | ✓ | ✓ | ○ | ○ |
| | Manufacture at approved site (GMP) | ✓ | ✓ | ○ | ○ |
| | Control of excipients | ■ | ■ | ■ | ■ |
| | Control of FPP (specifications, analytical methods, validation) | ■ | ■ | ■ | ■ |
| | Reference standards | ■ | ■ | ■ | ■ |
| | Labelling | ■ | ■ | ■ | ■ |
| | Packaging | ■ | ■ | ■ | ■ |
| | Container or closure system | ■ | ■ | ■ | ■ |
| | Stability in hot, humid climate zone | ✓ | ✓ | ○ | ○ |

| Element | | Innovator assessed by SRA | Generic assessed by SRA | New formulation not assessed by SRA | Generic, not assessed by SRA |
|---|---|---|---|---|---|
| **NONCLINICAL STUDY REPORTS** | | **Own trials** | **Literature (innovator)** | **Literature and own trials** | **Literature (innovator)** |
| Pharmacology | Pharmacodynamics | ✓ | ✓ | ○ | ○ |
| | Safety pharmacology | | | | |
| | Pharmacodynamics of drug interactions | | | | |
| Pharmacokinetics | Analytical methods and validation for studies | ✓ | ✓ | ○ | ○ |
| | Absorption, distribution, metabolism, excretion | | | | |
| | Pharmacokinetics of drug interactions | | | | |
| Toxicology | Single-dose toxicity | ✓ | ✓ | ○ | ○ |
| | Repeat-dose toxicity | | | | |
| | Genotoxicity | | | | |
| | Carcinogenicity | | | | |
| | Reproductive and developmental toxicity | | | | |
| | Local tolerance | | | | |
| **CLINICAL STUDY REPORTS** | | **Own trials** | **Literature (innovator)** | **Literature and own trials** | **Literature (innovator)** |
| Bioavailability (BA) study reports | Comparative BA and bioequivalence (BE) | BA | BE | BA/BE | BE |
| | In vitro–in vivo correlation | ✓ | ✓ | ○ | ○ |
| | Bioanalytical and analytical methods | | | | |
| Pharmacokinetics studies | Plasma protein binding | ✓ | ✓ | ○ | ○ |
| | Hepatic metabolism and drug interactions | | | | |
| | In healthy subjects and initial tolerability | | | | |
| | In patients and initial tolerability | | | | |
| | Intrinsic and extrinsic factors | | | | |
| | Population studies | | | | |
| Human pharmacodynamics studies | In healthy persons and in relation to pharmacokinetics | ✓ | ✓ | ○ | ○ |
| | In patients and in relation to pharmacokinetics | | | | |
| Efficacy and safety studies | Controlled clinical studies | ✓ | ✓ | ○ | ○ |
| | Uncontrolled clinical studies | | | | |
| | Reports of analysis | | | | |
| Reports of postmarketing surveillance | | ■ | ■ | ■ | ■ |

## ANNEX 5.

# Confirmed long-term stability testing conditions for countries

| Country | Temperature (°C) | Relative humidity (%) | Source |
|---|---|---|---|
| Afghanistan | 30 | 65 | 1 |
| Albania | 25 | 60 | 3 |
| Algeria | 25 | 60 | 3 |
| Andorra | 25 | 60 | 3 |
| Angola | 30 | 65 | 3 |
| Antigua and Barbuda | 30 | 75 | 3 |
| Argentina | 25 | 60 | 2 |
| Armenia | 25 | 60 | 3 |
| Australia | 25 or 30 | 60 or 65 | 2 |
| Austria | 25 or 30 | 60 or 65 | 1 |
| Azerbaijan | 30 | 65 | 2 |
| Bahamas | 30 | 65 | 3 |
| Bahrain | 30 | 65 | 1 |
| Bangladesh | 30 | 65 | 3 |
| Barbados | 30 | 75 | 2 |
| Belarus | 25 | 60 | 3 |
| Belgium | 25 or 30 | 60 or 65 | 1 |
| Belize | 30 | 65 | 3 |
| Benin | 30 | 65 | 3 |
| Bhutan | 30 | 65 | 2 |
| Bolivia (Plurinational State of) | 30 | 70 or 75 | 3 |
| Bosnia and Herzegovina | 25 | 60 | 3 |
| Botswana | 25 | 60 | 3 |
| Brazil | 30 | 75 | 1 |
| Brunei Darussalam | 30 | 75 | 1 |
| Bulgaria | 25 or 30 | 60 or 65 | 1 |
| Burkina Faso | 30 | 60 | 2 |
| Burundi | 30 | 65 | 3 |
| Cambodia | 30 | 75 | 1 |
| Cameroon | 30 | 75 | 2 |
| Canada | 30 | 65 | 1 |
| Cape Verde | 30 | 65 | 3 |
| Central African Republic | 30 | 75 | 2 |
| Chad | 30 | 65 | 3 |
| Chile | 30 | 65 | 2 |
| China | 30 | 65 | 3 |
| Colombia | 30 | 75 | 3 |

| Country | Temperature (°C) | Relative humidity (%) | Source |
|---|---|---|---|
| Comoros | 30 | 65 | 3 |
| Congo | 30 | 65 | 3 |
| Cook Islands | 30 | 65 | 3 |
| Costa Rica | 30 | 65 | 2 |
| Côte d'Ivoire | 30 | 65 | 3 |
| Croatia | 25 | 60 | 3 |
| Cuba | 30 | 75 | 2 |
| Cyprus | 25 or 30 | 60 or 65 | 1 |
| Czech Republic | 25 or 30 | 60 or 65 | 1 |
| Democratic People's Republic of Korea | 25 | 60 | 3 |
| Democratic Republic of the Congo | 30 | 65 | 3 |
| Denmark | 25 or 30 | 60 or 65 | 1 |
| Djibouti | 30 | 65 | 1 |
| Dominica | 30 | 65 | 3 |
| Dominican Republic | 30 | 65 | 3 |
| Ecuador | 30 | 65 | 3 |
| Egypt | 30 | 65 | 1 |
| El Salvador | 30 | 65 | 3 |
| Equatorial Guinea | 30 | 65 | 3 |
| Eritrea | 30 | 65 | 3 |
| Estonia | 25 or 30 | 60 or 65 | 1 |
| Ethiopia | 30 | 65 | 3 |
| Fiji | 30 | 65 | 3 |
| Finland | 25 or 30 | 60 or 65 | 1 |
| France | 25 or 30 | 60 or 65 | 1 |
| Gabon | 30 | 65 | 3 |
| Gambia | 30 | 65 | 1 |
| Georgia | 25 | 60 | 3 |
| Germany | 25 or 30 | 60 or 65 | 1 |
| Ghana | 30 | 75 | 2 |
| Greece | 25 or 30 | 60 or 65 | 1 |
| Grenada | 30 | 65 | 3 |
| Guatemala | 30 | 65 | 3 |
| Guinea | 30 | 65 | 3 |
| Guinea-Bissau | 30 | 65 | 3 |
| Guyana | 30 | 70 or 75 | 3 |
| Haiti | 30 | 65 | 3 |
| Honduras | 30 | 65 | 3 |
| Hungary | 25 or 30 | 60 or 65 | 1 |
| Iceland | 25 | 60 | 3 |
| India | 30 | 70 | 1 |
| Indonesia | 30 | 75 | 1 |
| Iran (Islamic Republic of) | 30 | 65 | 1 |
| Iraq | 30 | 35 | 1 |
| Ireland | 25 or 30 | 60 or 65 | 1 |

| Country | Temperature (°C) | Relative humidity (%) | Source |
|---|---|---|---|
| Israel | 30 | 70 or 75 | 2 |
| Italy | 25 or 30 | 60 or 65 | 1 |
| Jamaica | 30 | 65 | 3 |
| Japan | 25 or 30 | 60 or 65 | 1 |
| Jordan | 30 | 65 | 1 |
| Kazakhstan | 25 | 60 | 3 |
| Kenya | 30 | 65 | 3 |
| Kiribati | 30 | 65 | 3 |
| Kuwait | 30 | 65 | 1 |
| Kyrgyzstan | 25 | 60 | 3 |
| Lao People's Democratic Republic | 30 | 75 | 1 |
| Latvia | 25 or 30 | 60 or 65 | 1 |
| Lebanon | 25 | 60 | 1 |
| Lesotho | 30 | 75 | 2 |
| Liberia | 30 | 65 | 3 |
| Libyan Arab Jamahiriya | 25 | 60 | 1 |
| Lithuania | 25 or 30 | 60 or 65 | 1 |
| Luxembourg | 25 or 30 | 60 or 65 | 1 |
| Madagascar | 30 | 65 | 1 |
| Malawi | 25 | 60 | 2 |
| Malaysia | 30 | 75 | 1 |
| Maldives | 30 | 65 | 3 |
| Mali | 30 | 65 | 3 |
| Malta | 25 or 30 | 60 or 65 | 1 |
| Marshall Islands | 30 | 65 | 3 |
| Mauritania | 30 | 65 | 3 |
| Mauritius | 30 | 65 | 3 |
| Mexico | 25 | 60 | 3 |
| Micronesia (Federated States of) | 30 | 65 | 3 |
| Monaco | 25 or 30 | 60 or 65 | 1 |
| Mongolia | 25 | 60 | 3 |
| Montenegro | 25 | 60 | 3 |
| Morocco | 25 | 60 | 1 |
| Mozambique | 30 | 75 | 2 |
| Myanmar | 30 | 75 | 1 |
| Namibia | 30 | 65 | 1 |
| Nauru | 30 | 65 | 3 |
| Nepal | 30 | 75 | 2 |
| Netherlands | 25 or 30 | 60 or 65 | 1 |
| New Zealand | 25 or 30 | 60 or 65 | 2 |
| Nicaragua | 30 | 65 | 3 |
| Niger | 30 | 65 | 3 |
| Nigeria | 30 | 75 | 2 |
| Niue | 30 | 65 | 3 |
| Norway | 25 | 60 | 3 |

| Country | Temperature (°C) | Relative humidity (%) | Source |
|---|---|---|---|
| Oman | 30 | 65 | 1 |
| Pakistan | 30 | 65 | 1 |
| Palau | 30 | 65 | 3 |
| Panama | 30 | 75 | 3 |
| Papua New Guinea | 30 | 65 | 3 |
| Paraguay | 30 | 65 | 3 |
| Peru | 30 | 75 | 1 |
| Philippines | 30 | 75 | 1 |
| Poland | 25 or 30 | 60 or 65 | 1 |
| Portugal | 25 or 30 | 60 or 65 | 1 |
| Qatar | 30 | 65 | 1 |
| Republic of Korea | 25 or 30 | 60 or 65 | 2 |
| Republic of Moldova | 25 | 60 | 3 |
| Romania | 25 or 30 | 60 or 65 | 1 |
| Russian Federation | 25 | 60 | 3 |
| Rwanda | 30 | 65 | 3 |
| Saint Kitts and Nevis | 30 | 65 | 3 |
| Saint Lucia | 30 | 75 | 2 |
| Saint Vincent and the Grenadines | 30 | 75 | 3 |
| Samoa | 30 | 65 | 3 |
| San Marino | 25 | 60 | 3 |
| Sao Tome and Principe | 30 | 75 | 2 |
| Saudi Arabia | 30 | 65 | 1 |
| Senegal | 30 | 65 | 3 |
| Serbia | 25 | 60 | 3 |
| Seychelles | 30 | 65 | 3 |
| Sierra Leone | 30 | 75 | 2 |
| Singapore | 30 | 75 | 1 |
| Slovakia | 25 or 30 | 60 or 65 | 1 |
| Slovenia | 25 or 30 | 60 or 65 | 1 |
| Solomon Islands | 30 | 65 | 3 |
| Somalia | 30 | 65 | 1 |
| South Africa | 30 | 65 | 1 |
| Spain | 25 or 30 | 60 or 65 | 1 |
| Sri Lanka | 30 | 65 | 3 |
| Sudan | 30 | 65 | 1 |
| Suriname | 30 | 70 or 75 | 3 |
| Swaziland | 25 | 60 | 3 |
| Sweden | 25 or 30 | 60 or 65 | 1 |
| Switzerland | 25 or 30 | 60 or 65 | 1 |
| Syrian Arab Republic | 25 | 60 | 1 |
| Tajikistan | 25 | 60 | 3 |
| Thailand | 30 | 75 | 1 |
| The former Yugoslav Republic of Macedonia | 25 or 30 | 60 or 65 | 1 |
| Timor-Leste | 30 | 65 | 3 |

| Country | Temperature (°C) | Relative humidity (%) | Source |
|---|---|---|---|
| Togo | 30 | 75 | 2 |
| Tonga | 30 | 65 | 3 |
| Trinidad and Tobago | 30 | 65 | 3 |
| Tunisia | 25 | 60 | 1 |
| Turkey | 25 | 60 | 3 |
| Turkmenistan | 25 | 60 | 3 |
| Tuvalu | 30 | 65 | 3 |
| Uganda | 30 | 65 | 1 |
| Ukraine | 25 | 60 | 3 |
| United Arab Emirates | 30 | 65 | 1 |
| United Kingdom | 25 or 30 | 60 or 65 | 1 |
| United Republic of Tanzania | 30 | 75 | 2 |
| United States of America | 25 or 30 | 60 or 65 | 1 |
| Uruguay | 25 | 60 | 3 |
| Uzbekistan | 25 | 60 | 3 |
| Vanuatu | 30 | 65 | 3 |
| Venezuela (Bolivarian Republic of) | 30 | 70 or 75 | 3 |
| Viet Nam | 30 | 75 | 1 |
| Yemen | 30 | 65 | 1 |
| Zambia | 25 or 30 | 60 or 65 | 1 |
| Zimbabwe | 30 | 75 | 2 |

From reference *4*

1. Information obtained from regional harmonization groups (e.g. Association of South-East Asian Nations, ICH and GCC) and from official communications from national medicines regulatory authorities to WHO.
2. Information collated during the 13th International Conference of Drug Regulatory Authorities, 16–18 September 2008, in Bern, Switzerland, from representatives of national medicines regulatory authorities.
3. Information provided by the International Federation of Pharmaceutical Manufacturers and Associations on the basis of the following references:

   Ahrens CD. 2001. *Essentials of meteorology*, 3rd ed. Belmont, California, Thomson Books/Cole, p. 433.

   Kottek M et al. 2006. World map of Köppen-Geiger climate classification updated. Meteorologische Zeitschrift, 15:259–263.

   Zahn M. et al. 2006. A risk-based approach to establish stability testing conditions for tropical countries. *Journal of Pharmaceutical Sciences*, 95:946–965. Erratum: *Journal of Pharmaceutical Sciences*, 2007, 96:2177.

   Zahn M. 2008. Global stability practices. In: Kim HB ed. *Handbook of stability testing in pharmaceutical development*. New York, Springer.

## ANNEX 6.

# WHO model certificate of good manufacturing practice (GMP)

This certificate is available on WHO's web site (*60*).

[Letterhead of regulatory authority]

This one-page certificate conforms to the format recommended by WHO (general instructions and explanatory notes attached).[1]

Certificate No: .....

On the basis of the inspection carried out on ..... [date] ....., we certify that the site indicated on this certificate complies with good manufacturing practice for the dosage forms, categories and activities listed in Table 1.

1. Name and address of site:

.....

2. Manufacturer's licence number:

.....

3. Table 1:

| Dosage form(s) | Category(ies) | Activity(ies) |
|---|---|---|
| | | |

The manufacturer is responsible for the quality of the individual batches of the pharmaceutical products manufactured through this process.

This certificate remains valid until ..... [date] ..... It becomes invalid if the activities and/or categories certified herewith are changed or if the site is no longer considered to be in compliance with GMP.

Address of certifying authority:

.....

Name and function of responsible person:

.....

E-mail: ..... Telephone No.: ..... Fax No.: .....

Signature: ..... Stamp and date: .....

[1] This model certificate for GMP is not part of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

### *Explanatory notes*

This certificate, which is in the format recommended by WHO, certifies the status of the site listed in point 1 of the certificate.

The certification number should be traceable within the regulatory authority issuing the certificate.

When the regulatory authority issues a licence for the site, this number should be specified. Record 'not applicable' if there is no legal framework for the issuance of a licence.

In Table 1, list the dosage forms, starting materials, categories and activities. Examples are given below.

| **Example 1** | | |
|---|---|---|
| Pharmaceutical product(s),[1] dosage form(s) | Category(ies) | Activity(ies) |
| Tablets | Cytotoxic | Packaging |
| | Hormone | Production, packaging, quality control |
| | Penicillin | Repackaging and labelling |
| Injectables | Cefalosporin | Aseptic preparation, packaging, labelling |
| **Example 2** | | |
| Pharmaceutical product(s),[2] starting material(s)[3] | Category(ies) | Activity(ies) |
| Paracetamol | Analgesic | Synthesis, purification, packing, labelling |

Use, when available, International Nonproprietary Names (INNs) or national nonproprietary names.

The certificate remains valid until the specified date. The certificate becomes invalid if the activities and/or categories certified are changed or if the site is no longer considered to be in compliance with GMP.

The requirements for good practice in the manufacture and quality control of drugs referred to in the certificate are those included in *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Good manufacturing practices and inspection*, Volume 2, 1999. Geneva, World Health Organization, and subsequent updates.

[1] Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage for or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

[2] This model certificate for GMP is not part of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

[3] Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

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