# WHO & The Global Fund
# Joint Stakeholder Meeting on
# Quality Assurance of Essential Medicines

Held at

Château de Penthes, Geneva, Switzerland
30-31 August 2011

## Meeting Report

## Content

## ABBREVIATIONS

| | |
|---|---|
| ATM medicines | Antiretrovirals, anti-tuberculosis medicines and antimalarials |
| CHMP | Centrale Humanitaire Médico-Pharmaceutique |
| ECHO | The European Commission Directorate General for Humanitarian aid and Civil Protection (ECHO) |
| ERP | Expert Review Panel |
| GDF | Global Drug Facility |
| GMP | Good manufacturing practice |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICRC | International Committee of the Red Cross |
| IDA | International Dispensary Association |
| IHP | International Health Partnership |
| ITM | Institute of Tropical Medicine |
| MSF | Médecins sans Frontières |
| MSH | Management Sciences for Health |
| NMRA | National Medicines Regulatory Authority |
| Non-ATM medicines | Medicines other than antiretrovirals, anti-tuberculosis medicines and antimalarials |
| PFSCM | Partnership for Supply Chain Management |
| PIC/S | Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme |
| QA | Quality assurance |
| QC | Quality control |
| QUAMED | Quality of Medicine |
| SCMS | Supply Chain Management System |
| SRA | Stringent Regulatory Authority (i.e. an authority which is a member, observer or associate of ICH |
| UNFPA | United Nations Population Fund |
| UNICEF | United Nations Children's Fund |
| UNOPS | The United Nations Office for Project Services |
| USAID | The United States Agency for International Development |
| WHO | World Health Organization |
| WHO-MQAS | WHO Model Quality Assurance system for Procurement Agencies |
| WHO-PAR | WHO Public Assessment Reports (WHO Prequalification Programme) |
| WHO-PIR | WHO Public Inspection Reports (WHO Prequalification Programme) |

## EXECUTIVE SUMMARY AND RECOMMENDATIONS

While stringent donor-driven quality requirements exist for antiretrovirals, anti-tuberculosis medicines and antimalarials ("ATM medicines"), regulatory marketing authorization in the country of use is currently the only formal requirement for most other essential medicines. Donors, procurement agents and implementers are applying various additional measures to assure medicines quality, such as quality control testing and document reviews with various levels of insight and stringency.

However, most of these measures do not adequately verify whether quality is built into a pharmaceutical product and remains intact at every stage of its life cycle. In the absence of mechanisms to verify compliance of procured medicines with quality standards, the demand for essential medicines is essentially driven by price.

Harmonized, risk-based approaches are being introduced to achieve maximum impact of quality assurance (QA) measures as resources and independent technical expertise for pharmaceutical QA are becoming increasingly scarce worldwide. WHO is leading the work to categorize essential medicines into risk categories as a basis for QA measures in regulation and procurement. The WHO Model Quality Assurance System for Procurement Agencies (MQAS) defines commonly accepted standards which can serve as a basis for an independent qualification system, making quality assurance in procurement a competitive advantage.

Donors, procurement agents and implementers represented at the meeting recognized the importance of assuring the quality of life-saving essential medicines to stringent standards. They were committed to define and enforce harmonized quality requirements for essential medicines together with the countries that they serve. In working towards this aim, meeting participants agreed on the following recommendations.

### Recommendation 1: Risk-based categorization of essential medicines

WHO will continue its work, together with regulatory and industry representatives from relevant settings, to characterize risk factors for essential medicines and to develop a structured approach to allocate essential medicines to high, medium and low risk categories. Stakeholders will be consulted on how to use these categories to define and prioritize quality assurance measures.

### Recommendation 2: Tool to assess procurement agencies

a) Building on past work, an informal, voluntary working group consisting of representatives from QUAMED, PFSCM, UNICEF, MSF, IDA, Crown Agents, MSH, UNOPS, USAID, ICRC and CHMP, facilitated by the Global Fund, will propose a practical tool to assess procurement agencies, based on the WHO-MQAS. Workgroup members will explore possibilities to contribute to funding for this work.

b) Once a harmonized assessment tool has been developed, WHO will provide expert input to ensure its consistency with the WHO MQAS document[1] or subsequent revisions, and will formalize it as an instrument which can be used for qualification of procurement agencies by an independent body.

### Recommendation 3: Harmonization of quality assurance (QA) policies

Stakeholders represented at this meeting will work towards harmonizing their QA policies for essential medicines in order to maximize the efficiency of their quality assurance measures and to generate a common demand for quality-assured medicines meeting defined standards in order to impact the market.

### Recommendation 4: Information-sharing

WHO will host a website which is open to participating parties, to share information on manufacturing site inspections completed and planned by WHO and partners, including the date, site inspected, affiliation of the lead inspector and the contact details of the person responsible for clarification.)

[1] WHO. 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). WHO/PSM/PAR/2007.3. Geneva: World Health Organization, 2007 http://apps.who.int/medicinedocs/documents/s14866e/s14866e.pdf

## 1 BACKGROUND

Medicines quality in donor-funded programs is crucial for health program success. In the absence of effective regulatory medicines control in many countries[2], many donors have introduced stringent quality requirements for key health products, such as antiretroviral, anti-tuberculosis and antimalarial (ATM) medicines.

WHO has been supporting health program implementers in medicines quality assurance. The WHO prequalification program started in 2000, aiming to assure the quality, in principle, of key health products procured in UN programs. This internationally accepted assessment process has opened up access to quality-assured medicines, including both innovator and generic products, at competitive prices.

The Global Fund has had a quality assurance policy for health products purchased with its funds since its inception in 2002. Its policy requirements for ATM medicines were gradually strengthened, and similar requirements were introduced by a range of other donors, generating a demand for stringently quality-assured products. This is not currently the case for other life-saving essential medicines. In 2008, the Global Fund Board requested the Secretariat to consider additional quality requirements for the "non-ATM" medicines financed with grant funds.

Subsequent studies by the Global Fund[3], as well as partners' studies[4], pointed to the need to define harmonized quality requirements to ensure that essential medicines in resource-limited countries meet internationally acceptable quality standards. WHO and the Global Fund jointly hosted this meeting with partners to explore possibilities to generate a demand for key essential medicines meeting quality standards as defined in harmonized quality assurance policies.

## 2 MEETING AIM AND OBJECTIVES

### *Aim:*

To agree on a plan of action to improve and harmonize QA policies for essential medicines other than antiretrovirals, anti-tuberculosis products and antimalarials (non-ATM medicines).

### *Objectives:*

- To explore principles for categorization of products according to the quality risks involved in their manufacture and distribution.
- To discuss using a risk-based approach as a basis for defining QA policy scenarios
- To discuss a harmonized approach to QA for essential medicines among donors and other key stakeholders, supporting countries in strengthening their national QA systems.

[2] WHO. Assessment of Medicines Regulatory Systems in Sub-Saharan African Countries. An Overview of Findings from 26 Assessment Reports. Geneva: World Health Organization, 2010. http://apps.who.int/medicinedocs/documents/s17577en/s17577en.pdf

[3] JMC Caudron, C Pouget. Report on quality assurance of non-ATM medicines with a focus on opportunistic infections medicines. July 2010. Resource document GF/MDC3/03 submitted to the Global Fund's Market dynamics and Commodities Ad-hoc Committee at its Third Meeting (October 2010)

[4] European Commission for Humanitarian Aid (ECHO). Review of Quality Assurance (QA) Mechanisms for Medicines and Medical Supplies in Humanitarian Aid. Concept Paper 06/2006. http://ec.europa.eu/echo/files/policies/evaluation/drugs_quality_concept_paper.pdf

# 3 MEETING DISCUSSIONS

## SESSION 1: CURRENT SITUATION : POLICY AND PRACTICE

***Proposed outcome: "What have/what need" analysis of QA requirements for essential medicines***

### Current quality assurance mechanisms and challenges

The outcomes of a Global Fund study[5], of a WHO mapping study of procurement systems in countries[6], and the contributions by meeting participants converged into the observations summarized below.

### *Control by National Medicines Regulatory Authorities (NMRAs)*

| Current situation: | Challenges: |
|---|---|
| NMRAs are, and should remain, legally responsible to control medicines.<br>Registration in destination countries is supported by all donors, and systematically verified by some. Fast-tracking is encouraged. | In-country capacity for medicines regulation and QA in procurement is weak, and is affected by governance and contextual issues. Counterfeits and diversion of medicines are symptoms of weak control.<br>Country visits have indicated that there is limited awareness of the health risk associated with quality defects of some non-ATM medicines. |

► **Medicines registration in resource-limited countries is an administrative hurdle rather than a guarantee for quality. NMRAs are sidelined as quality assurance is delegated to donors and international procurement agencies, which weakens national regulatory capacity further.**

### *Donor requirements*

| Current situation: | Challenges: |
|---|---|
| While stringent requirements are in place for ATM medicines, registration in the country of use is the only formal requirement for other medicines.<br>Donors rely heavily on procurement agents – predominantly international ones - to adhere to best practices [5, 6]. | Donors' individual demand market shares of non-ATM products is too small to impact the supply side<br>There is a limited global offer of products meeting special requirements (e.g. language, labeling)<br>National tender requirements can be incompatible with donors' quality requirements<br>Donors are under pressure to support/deliver urgent aid. |

► **Reliance on international procurement agents results in complex procurement channels in countries; national procurement entities are often sidelined.**

### *Best procurement practice*

| Current situation: | Challenges: |
|---|---|
| Procurement agents are not necessarily competent in prequalifying pharmaceutical products.<br>Some have the capacity to verify that quality is "built into the product".<br>Many have limited approaches to QA, there is over-reliance on quality control testing. | There is competitive pressure on price and efficient service, disconnected from product quality.<br>QA and procurement decisions within the organization are not always separated, resulting in a conflict of interest.<br>Even if expertise exists, it can be difficult to obtain key documentation from manufacturers, limiting the usefulness of desk reviews. |

► **In the absence of quality policies with clearly defined and readily verifiable standards, QA is currently a competitive disadvantage for procurement agencies.**

[5] See Footnote 3

[6] Results from countries/WHO studies on mapping medicines procurement and supply management systems in 16 African countries (reports available at http://apps.who.int/medicinedocs/en/cl/CL9.2/clmd,50.html) indicated that 14 of 17 donors relied on international procurement agencies for medicines purchases.

## Perspectives

### *Donors*

Donors realize that national mechanisms in their recipient countries are not sufficient to assure the quality of essential medicines.

In the short term, they consider that they should strengthen and combine their efforts to generate a demand for medicines meeting stringent quality standards - such as the standards of the WHO Prequalification Programme and stringent regulatory authorities (SRAs) -, with risk-benefit mechanisms to ensure the availability of products on the market.

Given increasing resource limitations and small market shares of most essential medicines, donors recognize the need for harmonized quality policies and assessment tools for essential medicines.

### *Procurement agencies*

Procurement agencies act in a competitive economic environment and in "crisis mode" to protect their recipients from risks.

Pharmaceutical QA responsibilities are a specialized addition to the tasks of procurement agencies. Although technical guidance is available in specialized technical literature[7], it does not readily translate into tangible quality standards to which procurement agents can demonstrate competence. An objective qualification system would help procurement agencies to develop their QA capacity as a competitive asset.

### *Situation in recipient countries*

The need for capacity-building in countries has been recognized for many years. However, past efforts have been largely unsuccessful. Governance issues and loss of trained staff to less challenging environments have prevented sustained capacity gains.

Unlike antiretrovirals, other essential medicines are mostly provided on a cost recovery basis. Donor-driven quality assurance implemented without backing from countries will lead to double standards, with consequent administrative and ethical dilemmas.

A paradigm shift is needed to ensure that recipient countries and regions are ready to invest in medicines quality at the regulatory and procurement levels.

► **A common denominator for all actors is that they have to justify the costs that they invest in QA by demonstrating the efficiency of the process and the value of the outcomes.**

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## SESSION 2: RISK-BASED APPROACH TO QUALITY ASSURANCE OF ESSENTIAL MEDICINES

***Proposed outcome: Map the current market place of essential medicines and associated risk categories***

## Risk-based approach in regulation and quality assurance

Medicines regulation is becoming increasingly complex, while technical expertise and resources are scarce. As a result, a risk-based approach is now being incorporated into

[7] WHO. Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for National Medicines Regulatory Authorities (NMRAs) – 2nd edition (see Chapter 4.5 Risk Management). http://whqlibdoc.who.int/publications/2011/9789241501453_eng.pdf

regulatory processes at every level[7,8,9]. Risk-based categorizations are already widely used in regulation of diagnostic products and medical devices.

To make efficient use of limited resources, it is proposed to use a risk management approach to quality assurance of essential medicines by:

- classifying essential medicines into risk categories,
- defining standards used to control each category, and
- defining roles of partners in implementing these standards.

## Risk-based categorization of essential medicines

WHO has taken the lead in defining risk factors to classify essential medicines into a number of risk-based categories, aiming to target stringent measures towards those medicines which are at the highest risk of quality defects, with potentially serious implications for patients.

Literature on medicines quality defects and lists of recalls published on regulatory authorities websites were reviewed in an attempt to gain an overview of the quality defects occurring. There were difficulties with both of these approaches and the findings were not amenable to statistical analysis. Nevertheless participants at the meeting agreed the findings were consistent with their experience. A number of manufacture-related risks were identified (see Annex 2). An analysis of data on common failures found by the WHO Prequalification Programme and the Expert Review Panel could provide a further useful check.

Quality risks arise at various levels (see also Ref. 7), including the nature and quality of active ingredients, product design, manufacturing processes and control processes. The risks linked to the use of medicines with quality defects will also depend on the severity of the condition treated, the number of patients treated, and the duration of treatment.

It was noted that:

- Further work is needed in consultation with specialized regulatory experts and pharmaceutical industry representatives to define a risk-based classification framework for essential medicines
- The framework should capture underlying risks which will remain valid even if technologies evolve.

► **A risk-based classification framework for essential medicines will benefit both NMRAs and procurement agencies in maximizing the impact of available resources.**

Participants agreed on the following recommendation:

**Recommendation 1: Risk-based categorization of essential medicines**

**WHO will continue its work, in consultation with regulatory and industry representatives from relevant settings, to characterize risk factors for essential medicines and to develop a structured approach to allocate essential medicines to high, medium and low risk categories.**

[8] WHO. Application of hazard analysis and critical control point (HACCP) methodology to pharmaceuticals. Annex 7 to WHO TRS no 908, **2003** ; also in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Second updated edition. Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007. http://apps.who.int/prequal/info_general/documents/TRS908/WHO_TRS_908-Annex7.pdf
**A revised Quality Risk Management guideline advising regulatory authorities and manufacturers is in preparation.**

[9] ICH Harmonised Tripartite Guideline. Quality Risk Management, Q9. Current Step 4 version dated 9 November 2005. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

### Demand and supply of selected medicines purchased with Global Fund funding

The Global Fund presented the results of a study which compared purchases of key Global Fund-funded non-ATM medicines with information from 35 manufacturers about their supply of these medicines (see Annex 3). The key medicines included mainly anti-infectives, several of which are included on the list in the 10th invitation for expression of interest for WHO prequalification of HIV-related products.

It was found that the procurement agents included in the study sourced about two thirds of the key products (ranging from 5-100%) from sites which were compliant with stringent GMP (i.e. WHO-prequalified, SRA-authorized or successful line-specific PIC/S inspection), and that 98% of the remaining products could have been sourced from such sites. The cost increase if all products had been sourced from sites compliant with stringent GMP was estimated at 12% for the medicines included in the study, although the cost differential could be as high as 45% or more for certain dosage forms, such as injectable antibiotics.

It was noted that:

- A focus on anti-infectives procured in high volumes makes sense in prioritizing QA requirements. Ten anti-infectives account for 60% of the value of non-ATM medicines procured by the Global Fund's Voluntary Pooled Procurement (VPP) mechanism in 2010.
- Even without a formal requirement or assurance of the GMP status of their suppliers, some grant-recipient countries already pay comparatively high prices for non-ATM medicines[10]
- Stringent GMP was considered as a minimum quality requirement by some participants.
- The outcomes of this study suggest that sourcing from sites compliant with stringent GMP is feasible.

► **More research is needed into donors' demand market shares of essential medicines, and potential cost differentials if stringent quality criteria were to be applied.**

► **Where combined market shares have limited weight on the global markets, donors can work with manufacturers already offering WHO-prequalified products (e.g. antiretrovirals), and/or develop a market niche for stringently quality-assured products at fair prices which reward the investment in quality.**

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## SESSION 3: REVIEW OF POSSIBLE APPROACHES FOR STRENGTHENING QA OF ESSENTIAL MEDICINES

***Proposed outcome: Overview of QA approaches and challenges in implementation***

### Elements in quality assurance of essential medicines

Building on the outcomes of the Global Fund study5, an ongoing World Bank/MSH/USAID-SPS study aims to identify challenges and recommend approaches for harmonized quality requirements for essential medicines.

Preliminary outcomes of the study confirmed the needs to ensure country ownership, transparency and sharing scarce independent technical expertise. The importance of separating QA and procurement functions was also emphasized. The study report will be finalized for presentation to the next Interagency Pharmaceutical Coordination group (IPC) meeting in November 2011.

[10] See Footnote 3

A map of current quality requirements was used as a basis for discussion of a possible risk-based framework going forward (see below) presented but not endorsed/accepted by all participants. This framework would:

- Be based on a risk classification system for medicines to be proposed by WHO (see Recommendation 1).
- Define the criteria to be used to control each class, with more stringent criteria applied to the higher risk categories; and
- Define the role of each assessing body in ensuring compliance with these criteria

It was proposed to work towards a 5-year roadmap towards a harmonized approach.

**A risk-based approach to quality assurance of essential medicines** Proposed by MSH, not endorsed as there is a need for this table to be further developed. Adaptations made as per meeting discussions are shown in blue font.

| Assessing entity / *Approach* :<br><br>Risk level: | WHO Prequalification Program | Expert Review Panel (hosted by WHO): *Time-limited approval* | Stringent Regulatory Authority (SRA) approval | National Medicines Regulatory Authority (NMRA) approval *Capacity- building /cooperation* | Procurement Agency[11] *Qualified by an independent body (need common standards)* |
|---|---|---|---|---|---|
| High | HIV/AIDS, TB, Malaria ("ATM") medicines<br>Non-ATM medicines on WHO-EOI list (for opportunistic infections & other) | HIV/AIDS, TB, Malaria ("ATM") medicines<br>Could be extended to Non-ATM medicines | HIV/AIDS, TB, Malaria ("ATM") medicines and Non-ATM medicines<br><br>*Provides stringent control on registration*<br><br>*Post-market surveillance remains the responsibility of the NMRA in the country of use* | *Through WHO-Prequalification Programme / regional initiatives (e.g. Joint assessments)*<br>High-risk medicines (to be defined) | HIV/AIDS, TB, Malaria ("ATM") medicines and non-ATM medicines<br><br>*Can provide some assurance of quality in procurement, but not equivalent to stringent regulatory control* |
| Medium | ?<br>To be discussed | ?<br>To be discussed | | *Through regional initiatives (e.g. qualification for minimum regulatory functions):*<br>Non-ATM medicines<br>Medium-risk medicines (to be defined) | |
| Low | ?<br>To be discussed | ?<br>To be discussed | | Non-ATM medicines<br>Low-risk medicines (to be defined) | |

The elements represented in the above map, and their advantages and challenges, were discussed in further detail.

## The role of National Medicines Regulatory Authorities (NMRAs)

National Medicines Regulatory Authorities (NMRAs) have the legal mandate to safeguard the quality of the medicines circulating in their territories, controlling private sector activities in the interest of public health. Given this mandate, medicines regulation is subject to conflicts of interest and vulnerability to governance issues in countries.

[11] Defined in the WHO-MQAS (see Footnote 1) as: Any organization which is purchasing or otherwise acquiring any pharmaceutical product, vaccine or nutraceutical for human use. In the context of these guidelines it will normally be a not-for-profit organization, a non governmental organization (NGO) or a United Nations organization. A procurement agency in the context of this document is defined as any organization purchasing pharmaceutical products, vaccines, or other health sector goods or is otherwise involved in their prequalification (see above), purchasing, storage and distribution.

Worldwide levels of regulatory capacity vary greatly; 30% of countries – including many resource-limited ones - have no or very limited capacity ([12, 13]). Donor-funded medicines are often insufficiently controlled in the country of use: blanket exemptions from registration are granted to donated medicines in some countries in response to donors requests for fast-tracked authorization. To avoid further weakening of their functions, NMRAs should have a continued active role in medicines control.

In light of universal resource shortages in regulation, there is a trend towards sharing of functions on a global and regional basis. Such modular approaches are already used in other areas, e.g. PIC/S focuses on site inspection, and quality control laboratories are prequalified by WHO for specific functions.

It was noted that:

- Post-market surveillance, including pharmacovigilance, is an essential function that should be strengthened in resource-limited countries as a priority.
- Economic interests may prevent effective task sharing, as market authorization is potentially lucrative while post-market surveillance is not.
- First experiences with regional harmonization and task-sharing in the East African Community are encouraging.
- NMRAs in resource-limited countries could have a role in developing a risk-based classification of essential medicines.

► **NMRAs should remain involved in all medicines quality assurance initiatives affecting their territories. Collaboration and regional task-sharing initiatives appear to be the options of choice going forward. Performance of joint assessments with the WHO Prequalification Programme (for urgently needed, high-risk products) and accreditation of minimum regulatory functions (for medium-risk products) were proposed.**

## WHO prequalification

The WHO Prequalification Programme aims to assure the quality, safety and efficacy of medicines according to stringent standards. Its procedures provide for stringent assessment, variation control, periodic GMP inspections and follow-up of specific quality issues on request. All activities are coupled with extensive capacity-building for manufacturers and regulators in countries.

A recent quality testing study of antimalarials[14] showed that WHO-prequalified products had tenfold lower failure rates and less serious failures than other products. Many post-marketing quality issues are more likely to be followed up with the WHO Prequalification Programme's comprehensive procedures than with initial dossier assessment. Prequalification extends also to related services such as quality control laboratories.

Motivation of manufacturers is the most significant success factor for prequalification. 50% of prequalification time is spent on awaiting actions to be taken by manufacturers, with an increasing trend. Some manufacturers see prequalification as a step towards market authorization in industrialized countries.

It was noted that:

- As the WHO Prequalification Programme is now entirely donor-funded, the future scope of activities will be influenced by the international donor community.

[12] OMS, Comité Régional de l'Afrique. Cinquante-sixième session, Addis-Abéba, Ethiopie, 28 août – 1er septembre 2006. Autorités de réglementation pharmaceutique: situation actuelle et perspectives. Rapport du Directeur régional. www.afro.who.int/rc56/documents/french/afr_rc56_11_autorites_reglement_pharmaceutique.pdf

[13] See Footnote 2

[14] WHO. Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. WHO/EMP/QSM/2011.1 Geneva: World Health Organization, 2011. www.who.int/medicines/publications/WHO_QAMSA_report.pdf

► **The WHO prequalification process was supported as the gold standard by all organizations represented at the meeting. It is currently applied to key pharmaceutical products, and some non-ATM anti-infectives are already on the Expression of Interest List for HIV-related products. Prequalification of these products, and their use can be expected to have a high health impact in countries. However, manufacturers will only invest in achieving and maintaining WHO prequalification status if they see a prospect of a predictable demand over a sustained period of time.**

## Rapid risk assessment: The Expert Review Panel (ERP)

The ERP, established in 2009, is hosted by WHO and funded by the Global Fund. It assesses products based on a regulatory risk assessment review through a standardized, questionnaire-type product dossier with attachments, and information submitted to the WHO- Prequalification Programme as referenced by the applicant. The review outcome is an assignment of one of four risk categories to the product as a basis for decision by the Global Fund[15]. The advice is valid for one year.

The ERP will review products which are manufactured at a site complying with stringent GMP requirements and – if they are on the list for expression of interest for WHO prequalification – have been accepted for review by the WHO Prequalification Programme or an SRA. Products to which the latter condition does not apply can only be classified into one of the higher risk categories (i.e. 3 or 4), as there is no prospect of stringent regulatory follow-up.

Timeframes for actual review are 6-8 weeks. Assessments are done in groups with two calls for expression of interest per year, but ad-hoc reviews can be arranged in urgent cases. A total of 210 products have been assessed so far. The products with a current assignment to Categories 1 and 2 are listed on the product lists of ARVs, anti-tuberculosis products and antimalarials on the Global Fund's website. The Global Fund will consider communicating the actual specifications to procurement entities to assist in ongoing procurement monitoring.

It was noted that:

- Manufacturers submit increasingly good quality documentation and would welcome the extension of the process to other product categories.
- Interest in participating in a harmonized ERP procedure has been expressed by additional organizations
- The cost of ERP reviews is moderate, as it is a once-off, abbreviated assessment.
- The ERP group is composed of highly experienced regulatory professionals, and cannot easily be replicated by partners.

► **Rapid risk assessment by the ERP is an option for quality assurance of some non-ATM medicines where no WHO-prequalified products are available. On the other hand, ERP review is a time-limited process, which is not designed to impact the markets in the long term.**

[15] Categories 1 and 2: No objection to procurement; category 3: Objection to procurement; Global Fund will consult WHO disease programs for advice whether the clinical benefit in a specific context outweighs the risk; Category 4: Available data do not support an ERP advice. - Terms of reference and assessment criteria are available on the Global Fund's webpage on pharmaceutical quality assurance, http://www.theglobalfund.org/en/procurement/quality/pharmaceutical/#A_B

## Prequalification of procurement agents

Three organizations shared their experience of using the WHO Model Quality Assurance System for Procurement Agencies (MQAS)[16] as a basis to assess procurement agencies or wholesalers.

**QUAMED** is a program hosted by the Institute of Tropical Medicine (ITM) funded by the government of Belgium which works with not-for-profit partners to carry out research, provide technical assistance and advocate for medicines quality worldwide. QUAMED carries out assignments on behalf of its partners such as audits of manufacturers, assessments of pharmaceutical markets (countries) and audits of procurement agencies. The latter are based on the use of WHO-MQAS as the reference system. QUAMED has developed a rating system (based on 350 questions) to identify gaps in each of five main functions: Regulatory, QA systems and resources, qualification of sources, good distribution practices, and monitoring. Specialized expertise in pharmaceutical quality assurance is needed to use the tool appropriately.

A number of assessments have been carried out at the request of QUAMED's partners as a basis for strengthening their QA capacity, and the prequalification of finished products was consistently identified as the weakest function.

**The World Bank** has contracted Management Sciences for Health (MSH) to develop a tool and to assess procurement agencies based on the MQAS principles. MSH has applied its tool in 10 states of India, and is now using it to assess 4 procurement agencies in Bangladesh.

Based on this experience, the World Bank considers that it is feasible for a global convention of partners to use the MQAS to qualify procurement agencies. Agreement will be required on how to identify gaps and areas to strengthen before a procurement agency is eligible for assessment, how to define pass/fail criteria, and how to use and interpret the results.

**The Partnership for Supply Chain Management** (PFSCM) procures medicines for the Global Fund and Pepfar. PFSCM has developed a process for prequalification of wholesalers based on the WHO-MQAS. The assessment includes inspection of the applicant's quality system and audit of SOP using an inspection checklist based on the MQAS. Observations are classified into critical, major, and other; and a weighted rating system is applied to grade applicants into categories translating into approval, approval for certain functions only, request for improvement, or rejection. Risk-based considerations determine the extent of dossier review (done by PFSCM or the wholesaler) and the frequency of audits and sampling (done by the wholesaler).

The tool has been used in Africa; 2-yearly re-audits are about to start. Qualification of vendors was found to be the biggest problem by the partners using it. PFSCM is open to sharing its tool and to learning from others' experience.

It was noted that:

- Costly assessments of procurement agencies are currently duplicated by partners, based on different assessment tools used by assessors with potentially different capacity and competency.

It was agreed that:

- The WHO MQAS principles provide an appropriate common standard for qualification of procurement agents. An update will be scheduled by the WHO Expert Committee which owns the document.
- There is a need to produce a single harmonized tool to apply the WHO MQAS in practice.

[16] See Footnote 1

► **Partners are committed to work towards an independent qualification mechanism of procurement agents with transparent processes and outcomes. To avoid double standards in countries – which will result in administrative and ethical dilemmas – national procurement entities should be included in this harmonization process.**

Participants agreed on the following recommendation:

**Recommendation 2: Tool to assess procurement agencies**

**a) Building on past work, an informal, voluntary working group consisting of representatives from QUAMED, PFSCM, UNICEF, MSF, IDA, Crown Agents, MSH, UNOPS, USAID, ICRC and CHMP, facilitated by the Global Fund, will propose a practical tool to assess procurement agencies, based on the WHO-MQAS. Workgroup members will explore possibilities to contribute to funding for this work.**

**b) Once a harmonized assessment tool has been developed, WHO will provide expert input to ensure its consistency with the WHO MQAS document (ref) or subsequent revisions, and will formalize it as an instrument which can be used for qualification of procurement agencies by an independent body.**

## SESSION 4: HARMONIZED QA APPROACHES FOR ESSENTIAL MEDICINES

***Proposed outcome: Consensus on the way forward to a harmonized approach on strengthening QA requirements in procurement and distribution of essential medicines, with a clear plan of action***

### *Harmonization of QA policies*

The Global Fund shared its experience with harmonizing of quality requirements for anti-tuberculosis products:

The Global Fund introduced stringent quality requirements for all anti- tuberculosis products, including older, first-line anti-TB medicines, in July 2009.

Many grant-recipient countries use GDF for procurement of anti- tuberculosis products. GDF had similar policy requirements as the Global Fund, but some discrepancies remained. It took about one year of continued joint work to harmonize the criteria and to apply them in procurement.

Since 2010 the quality requirements are fully aligned, resulting in a common message being sent to countries and manufacturers, and increased transparency and efficiency of processes for assessment and quality testing. GDF continues to provide forecasts and to offer long term agreements, which has a stabilizing effect on the anti- tuberculosis product market. UNITAID is also participating in this process.

This harmonization process is a major step forward in QA of anti- tuberculosis medicines, which used to be a challenge for many years.

It was noted that:

- Small differences in quality policies can result in significant discrepancies in procurement outcomes and delays at country level
- Effective harmonization of quality policies reduces ambiguity and saves considerable time and costs.
- Once the proposed risk categorization of essential medicines is finalized, it will be possible to define the specific risks, determine which entities are best placed to control them and devise appropriate measures to mitigate the risks.

- **Partners are willing to establish and adhere to a joint, risk-based approach to essential medicines quality, and agreed on the following recommendation:**

**Recommendation 3: Harmonization of quality assurance policies**

**Stakeholders represented at this meeting will work together towards harmonizing their QA policies for essential medicines in order to maximize the efficiency and the market impact of their quality assurance measures.**

### *Transparency and information-sharing*

Transparency of processes and outcomes is the first condition if the findings of QA assessments are to be shared.

Currently, WHO Public Assessment Reports (PAR) and Public Inspection Reports (PIR) are available on the Internet[17], more layers of information can be added. Full reports are not currently shared, but these can be requested from manufacturers as and when required.

The difference between mutual recognition of decisions and sharing assessment reports for information was highlighted. In this context it was noted that:

- The final decisions taken based on assessments made by non-regulatory organizations are context-dependent and cannot be used directly as a basis for decision-making by others .
- For procurement agencies, disclosing assessment outcomes can be a competitive disadvantage.
- A system of accreditation of GMP auditors would be useful .

Participants agreed on the following recommendation:

**Recommendation 4: Information-sharing**

**WHO will host a website which is open to participating parties, to share information on manufacturing site inspections completed and planned by WHO and partners, including the date, site inspected, affiliation of the lead inspector and the contact details of the person responsible for clarification.**

## 4 CONCLUSIONS AND NEXT STEPS

The Global Fund and WHO thank all meeting participants for open, productive, discussions and their commitment to progress with harmonization of QA policies for essential medicines.

WHO is prepared to continue working with partners towards ensuring that quality medicines will be available to supply global health programmes.

To generate a demand for stringent quality assurance on the global market, it is essential that all partners commit to the proposed harmonized quality assurance framework, and that they involve the national regulatory and procurement structures in the countries that they serve.

Awareness must be raised that fair prices must be paid for products which meet internationally acceptable norms and standards. In addition, adequate resources are needed, to secure scarce independent expertise, and to establish and maintain a

[17] http://www.who.int/prequal

harmonized quality assurance network allowing the most efficient use of this expertise. These costs will be lower than those of maintaining parallel systems with duplications, ambiguous standards and a potential negative health impact in countries.

**Next steps:**

- The agreed report of this meeting will serve as a baseline for the implementation of the agreed recommendations.
- The agreed meeting report will be presented to the Global Fund's Market Dynamics and Commodities Ad-hoc Committee (MDC) on 6/7 October 2011 for discussion and onward reporting to the Global Fund Board.
- The World Bank-commissioned study funded by the International Health Partnership (IHP+) on harmonizing donor requirements and funding procurement activities in countries could further advance the work agreed at this meeting.

## ANNEX 1: LIST OF PARTICIPANTS

| NAME / ORGANISATION | CONTACT DETAILS |
|---|---|
| Mr Andreas Seiter<br><br>**The World Bank** | Senior Health Specialist,<br>Pharmaceuticals Health, Nutrition and Population<br>The World Bank<br>1818 H Str. NW, MS G7-701, Washington DC 20433, USA<br>Tel: +1-202-473-3629; Mobile: +1-202-390-4503<br>Email: aseiter@worldbank.org |
| Mr Peter Aardema<br><br>**DG - ECHO[18]** | European Commission, DG Humanitarian Aid and Civil Protection<br>Unit C2 External Audit Sector; Rue Arlon 88 - 1049 Brussels, Belgium<br>Tel: +32 2 296 59 61<br>Email: Peter.Aardema@ec.europa.eu |
| Ms Erin Seaver<br><br>**USAID** | Commodity Security and Logistics Division<br>Office of Population & Reproductive Health<br>USAID, Bureau for Global Health<br>United States of America<br>Email: eseaver@usaid.gov |
| Mr Francisco J. Blanco<br><br>**UNICEF Supply Division** | Chief, Medicines and Nutrition Centre<br>UNICEF Supply Division, Copenhagen, Denmark<br>Tel.: +45 35 27 30 70; Mob.: +45 24 69 46 85; Fax: +45 35 26 94 21<br>Email: fblanco@unicef.org |
| Mr Peter Svarre Jakobsen<br><br>**UNICEF Supply Division** | Quality Assurance Specialist<br>UNICEF Supply Division, Copenhagen, Denmark<br>Email: pjakobsen@unicef.org |
| Mr Morten Sorensen<br><br>**UNFPA** | Deputy Chief, PSB, Procurement Services Division<br>United Nations Population Fund (UNFPA)<br>Midtermolen 3, PO Box 2530, 2100 Copenhagen O - Denmark<br>Tel: +45 3546-7162<br>E-mail: sorensen@unfpa.org |
| Mrs Stephanie Arsac-Janvier<br><br>**ICRC** | Head Pharmacist<br>International Committee of the Red Cross (ICRC)<br>19 Avenue de la Paix, 1202 Geneva, Switzerland<br>Tel: + 41 22 730 34 68<br>Email: sarsacjanvier@icrc.org |
| Mrs Elodie Jambert<br><br>**MSF** | International Pharmacist Coordinator<br>Médecins sans Frontières (MSF) International Office<br>Campaign for Access to Essential Medicines<br>78, Rue de Lausanne, 1211 Geneva, Switzerland<br>Tel: +41 22 849 89 45<br>Email: Elodie.JAMBERT@geneva.msf.org |
| Mr José Moscoso<br><br>**UNOPS** | Senior Procurement Consultant<br>United Nations Office for Project Services (UNOPS)<br>Copenhagen, Denmark<br>Email: JoseM@unops.org |
| Murtada Sesay<br><br>**UNOPS** | Senior Procurement and Supply Chain officer<br>United Nations Office for Project Services (UNOPS)<br>UNOPS India Operations Centre<br>11 Golf Links<br>New Delhi -110 003<br>Email: MurtadaS@unops.org |
| Mr Edwin de Voogd<br><br>**IDA Foundation** | Managing Director<br>IDA Foundation<br>Slochterweg 35, 1027AA Amsterdam, The Netherlands<br>Tel: +31 20 4033051; Mobile: +31 6 20506998; Fax: +31 20 4031854<br>Email: edevoogd@idafoundation.org |
| Mr Steven Ijland<br><br>**IDA Foundation** | Manager, Product approval<br>IDA Foundation<br>Slochterweg 35, 1027AA Amsterdam, The Netherlands<br>Tel: +31 20 403 7180<br>Email: sijland@idafoundation.org |

[18] http://ec.europa.eu/echo/index_en.htm

| NAME / ORGANISATION | CONTACT DETAILS |
|---|---|
| Mr Thomas Layloff<br><br>**SCMS/PFSCM[19]** | Senior Quality Assurance Advisor, Supply Chain Management System<br>Partnership for Supply Chain Management (PFSCM)<br>1616 Fort Myer Drive, 12th Floor<br>Arlington, VA 22209 USA<br>Direct Tel: +1.571.227.8608; Mobile: +1.618.581.7213<br>Email: tlayloff@pfscm.org |
| Ms Chryste Best<br><br>**SCMS/PFSCM** | Product Quality Assurance Manager, Supply Chain Management System<br>Partnership for Supply Chain Management(PFSCM)<br>1616 Fort Myer Drive - 12th floor, Arlington, VA 22209-3100 USA<br>Office: +1.571.227.8609; Fax: +1.571.227.8601<br>Email: cbest@pfscm.org |
| Mr Jiru Bako<br><br>**Crown Agents** | Technical Manager – Health<br>Crown Agents Nigeria Ltd<br>Plot 512 Durban Street, Wuse II, Abuja, Nigeria<br>Tel: +234 9 670 1457-9<br>Email: Jiru.Bako@ng.crownagents.com |
| Mr David Lee<br><br>**MSH** | Management Sciences for Health (MSH)<br>Washington DC - USA<br>Email: dlee@msh.org |
| Dr Susan Walters<br><br>**Technical Advisor** | 12 Maria Place, Lyons, ACT 2606, Australia<br>Tel: + 61262816948<br>Email: susanw@netspeed.com.au |
| Mr Olivier Yameogo<br><br>**CHMP** | Quality Control Responsible<br>Centrale Humanitaire Médico-Pharmaceutique (CHMP)<br>63100 Clermont-Ferrand, France<br>Tel : + 33 4 73 98 24 66<br>Email: o.yameogo@chmp.org |
| Mr Christophe Luyckx<br><br>**Institute of Tropical Medicine[20]** | QUAMED Coordinator, Quality Medicines for All<br>Nationalestraat, B-2000 Antwerpen, Belgium<br>Tel: +32 3 247 65 95<br>Email: cluyckx@itg.be |
| Mr Jean Michel Caudron<br><br>**Technical Advisor** | Pharmacist consultant and QUAMED expert<br>Email: jean_michelcaudron@hotmail.com |
| Ms Corinne Pouget<br><br>**Technical Advisor** | Pharmacist Consultant and QUAMED expert<br>Email: pougetco@orange.fr; cpouget@quamed.org |
| Dr Anthony Gould<br><br>**Technical Advisor** | Emeritus Progamme Manager, WHO Prequalification Programme for Medicines, Australia<br>Email: tonygmp@gmail.com |
| Dr Sophie Logez<br><br>**The Global Fund** | Manager, Quality Assurance and Data Management, Pharmaceutical Management Unit<br>The Global Fund to Fight AIDS, Tuberculosis and Malaria<br>Chemin de Blandonnet 8 \| 1214 Vernier-Geneva, Switzerland<br>T: +41 58 791 1207 \| F: +41 58 791 1701 \| Mobile: +41 79 453 2133<br>Email: sophie.logez@theglobalfund.org |
| Dr Joelle Daviaud<br><br>**The Global Fund** | Senior Pharmaceutical QA Officer, Pharmaceutical Management Unit<br>The Global Fund to Fight AIDS, Tuberculosis and Malaria<br>Chemin de Blandonnet 8 \| 1214 Vernier-Geneva, Switzerland<br>T: +41 58 791 1758 \| F: +41 58 791 1701 \| M: +41 79 453 16 82<br>Email: joelle.daviaud@theglobalfund.org |
| s | Senior Technical Officer, Global Health Supply, Pharmaceutical Management Unit<br>The Global Fund to Fight AIDS, Tuberculosis and Malaria<br>Chemin de Blandonnet 8 \| 1214 Vernier-Geneva, Switzerland<br>T: +41 58 791 1887 \| Fax: +41 58 791 1701 \|M: +41 79 844 8152<br>Email: carmen.perezcasas@theglobalfund.org |

[19] www.scms.pfscm.org and www.pfscm.org
[20] http://www.itg.be/itg/ or www.quamed.org

| NAME / ORGANISATION | CONTACT DETAILS |
|---|---|
| Ms Monika Zweygarth<br><br>**The Global Fund** | Project Officer<br>Pharmaceutical Management Unit<br>The Global Fund to Fight AIDS, Tuberculosis and Malaria<br>Chemin de Blandonnet 8 \| 1214 Vernier-Geneva Switzerland<br>T: +41 58 791 1482 \| F: +41 58 791 1701<br>Email: monika.zweygarth@theglobalfund.org |
| Mr Martin Auton<br><br>**The Global Fund** | Senior Technical Officer, Procurement Support Services Team,<br>Pharmaceutical Management Unit<br>The Global Fund to Fight AIDS, Tuberculosis and Malaria<br>Chemin de Blandonnet 8 \| 1214 Vernier - Geneva Switzerland<br>T: +41 58 791 1577 \| F: +41 58 791 1701 \| M: +41 79 573 8071<br>Email: martin.auton@theglobalfund.org |
| Dr Magali Babaley<br><br>**WHO** | Technical Officer, World Health Organization, WHO/HSS/EMP/MAR<br>22, avenue Appia - 1211 Genève 27 - Switzerland<br>Tel. direct: +41 22 791 4031; Fax direct: + 41 22 791 4167<br>E-mail: babaleym@who.int |
| Dr Lembit Rägo<br><br>**WHO** | Coordinator, Quality Assurance & Safety: Medicines (QSM)<br>World Health Organization<br>22, avenue Appia - 1211 Genève 27 - Switzerland<br>Tel. direct: +41 22 791 2657; Fax direct: + 41 22 791 4730<br>E-mail: ragol@who.int |
| Dr Samvel Azatyan<br><br>**WHO** | Manager, Medicines Regulatory Support Programme<br>Quality Assurance & Safety: Medicines<br>World Health Organization<br>22, avenue Appia - 1211 Genève 27 - Switzerland<br>Tel. direct: +41 22 791 1506; Fax direct: + 41 22 791 4730<br>E-mail: azatyans@who.int |
| Dr Matthias Stahl<br><br>**WHO** | Head of Assessments, WHO Prequalification Programme for Medicines<br>World Health Organization<br>22, avenue Appia - 1211 Genève 27 - Switzerland<br>Tel. direct: +41 22 791 3717; Fax direct: + 41 22 791 4730<br>E-mail: stahlm@who.int |
| Dr Deusdedit Mubangizi<br><br>**WHO** | Technical Officer, WHO Prequalification Programme for Medicines<br>World Health Organization<br>22, avenue Appia - 1211 Genève 27 - Switzerland<br>Tel. direct: +41 22 791 1864; Fax direct: + 41 22 791 4730<br>E-mail: mubangizid@who.int |
| Ms Jacqueline K. Sawyer<br><br>**WHO** | Liaison Officer, WHO Prequalification Programme for Medicines<br>World Health Organization<br>22, avenue Appia - 1211 Genève 27 - Switzerland<br>Tel. direct: +41 22 791 3654; Fax direct: + 41 22 791 4730<br>E-mail: sawyerj@who.int |
| Mr Wondiyfraw Zeleke Worku<br><br>**WHO** | Technical Officer, WHO Prequalification Programme for Medicines<br>World Health Organization<br>22, avenue Appia - 1211 Genève 27 - Switzerland<br>Tel. direct: +41 22 791 2527; Fax direct: + 41 22 791 4730<br>E-mail: zelekew@who.int |

## ANNEX 2: MANUFACTURE-RELATED RISKS OF MEDICINES AND CONSEQUENCES FOR PATIENTS

| *No.* | *Risk* | *Possible consequence for patients if manufacture is deficient* | *Means of prevention &/or detection* | *EML examples* |
|---|---|---|---|---|
| 1 | Medicine is required to be sterile | Infection of patient | Validated manufacturing procedure.<br>Sterility test in QC[21]. | Bupivacaine injection.<br>Hydroxocobalamin injection. |
| 2 | Low efficacy is life threatening or presents a serious risk to health | Low efficacy if potency is low or if bioavailability is poor. | Validated manufacturing procedure.<br>Assay in QC. | Streptokinase powder for injection.<br>Enalapril tablets. |
| 3 | Steep dose-response curve and/or narrow therapeutic index | Toxicity if potency is high.<br>Low efficacy if potency is low or if bioavailability is low. | Pharmacological data prior to first registration. | Digoxin tablets.<br>Bisoprolol tablets. |
| 4 | Low dose solid or semisolid dosage forms | Poor content uniformity may lead to variable efficacy and toxicity. | Validated manufacturing procedure.<br>Assay of individual units in QC. | Digoxin tablets.<br>Betamethasone cream. |
| 5 | Toxic impurities<br>(Note that many of the reported cases are suspected but not proven) | Toxicity if the contents of impurities are high & they lead to a demonstrated adverse effect. | Validated method of synthesis.<br>Assay in QC of API.<br>Stability testing. | Hydralazine powder for injection.<br>Hydrocortisone injection. |
| 6 | Low or variable GI permeability (including narrow absorption window) (for oral dosage forms) | Higher risk of poor bioavailability. | Clinical data prior to first registration. | Ciclosporin capsules.<br>Methotrexate tablets. |
| 7 | Low water solubility (oral dosage forms) | Higher risk of poor bioavailability. | Chemical testing prior to first registration. | Carbamazepine tablets.<br>Dapsone tablets. |
| 8 | Systemic antimicrobial (excludes disinfectants and topical antimicrobials) | Development of resistance if:<br>potency is low or bioavailability is low<br>usage is profligate. | Validated manufacturing procedure & QC.<br>Rational use of antimicrobials. | Doxycycline tablets.<br>Ciprofloxacin tablets. |
| 9 | API is of biological origin. | Multiple risk factors with multiple consequences including:<br>- Multiple impurities<br>- High content of each impurity<br>- Microbial contamination<br>- Endotoxins -> adverse events<br>- Allergens -> adverse events<br>- Multicomponent actives (& consequently possibly variable potency) | Validation of methods of synthesis of the API, & of manufacture of FPP.<br>QC testing of APIs & FPPs. | Gentamicin injection.<br>Erythromycin tablets. |

[21] QC means the testing that is conducted either as in-process testing or for each batch prior to release.

## ANNEX 3: KEY FINDINGS FROM GLOBAL FUND STUDY ON QUALITY STATUS AND AVAILABILITY OF SELECTED ESSENTIAL MEDICINES

### Method:

1. Contacted 14 procurement agents : 9 responded

Obtained information about top 30 products (by value and volume), procured for Global Fund grants in 2010: strengths, dosage forms, packaging, total quantity and unit price, manufacturer's name, regulatory status of the manufacturing site

2. Shortlisted 39 key non-ATM medicines, including all anti-infectives procured by at least 2 procurement agents, and top 5 of other products by volume:

**Anti-infectives:**

1. Acyclovir 200mg, 400mg, 800mg tablet
2. Albendazole 200mg, 400mg chewable tab/ tablet and syrup 200mg/5ml
3. Amoxicillin 250mg, 500mg dispersible scored tablet/tab/cap , and powder for syrup 125mg/5ml, 250mg/ml, 100ml
4. Amoxycillin/Clavulanic Acid 250mg/62.5mg, 500mg/125mg) tablet and powder for syrup 100ml
5. Amphotericin B 50mg inj (deoxycholate)
6. Ampicillin 0.5, 1g Powder for inj
7. Azithromycin 250mg, 500mg tablet/ capsule
8. Benzathine penicillin inj, 2.4 MIU, 5 MIU
9. Bleomycin 15mg powder for injection
10. Cefixime 200mg, 400mg tablet
11. Cefotaxime 1g Inj
12. Ceftriaxone 0.5g, 1g Inj
13. Cephalexin 500mg caps
14. Ciprofloxacin 250mg 500mg tablet
15. Clarithromycin 250mg, 500mg tablet
16. Clindamycin 150mg, 300mg Capsule
17. Clotrimazole 100mg, 500mg Vaginal tab
18. Cloxacillin sodium 250mg, 500mg Caps
19. Doxycycline 100mg cap/tab
20. Erythromycin 250mg, 500mg Tab and powder for syrup 125mg/5ml, 100ml
21. Fluconazole 150mg 200mg capsule/tablet
22. Ganciclovir 250mg, 500mg injection, vial
23. Gentamicin 10mg/ml, 20mg/ml, 40mg/2ml inj
24. Griseofulvin 125mg, 500mg tablet.
25. Metronidazole 200mg, 400mg, 250mg, 500mg Tab and syrup 125mg/5ml
26. Miconazole 10mg muco adhesive tab
27. Nystatin 100000 IU/ml oral susp 30ml
28. Phenoxymethylpenicillin 250mg, 500mg tablet and powder for syrup 100ml.
29. Praziquantel 150mg, 600mg Tab
30. Pyrimethamine 25mg tablet
31. Sulfadiazine 500mg tablet
32. Sulfamethoxazole/trimethoprim 100/20mg, 400/80mg, 800/160mg scored tablet and syrup 240mg/5ml
33. Valganciclovir 450mg tab

**Other products:**

34. Water for injection, 10 ml, amp. Plastic
35. Ibuprofen 200mg, 400mg, 600mg tablet and syrup 100ml
36. Methadone 5mg/ml, 10mg/ml concentrate for oral sol. (hydrochloride)
37. Oral Rehydration salt 20.5g/ 1 lit
38. Paracetamol, 120mg/5ml oral sol, and tablet 100 mg, 500mg.
39. Zinc 20mg scored dispersible tablet/tablet

3. Contacted 250 manufacturers: 35 responded.
For short list of 39 non-ATM medicines, requested information on strength, dosage form, registration status, unit price (ex- works), minimum order quantity, and regulatory status of their manufacturing site.

### Key findings:

#### Percentage of key medicines sourced from site compliant with stringent GMP*, by 9 procurement agents

For the purposes of this study, stringent GMP was defined as: compliant with WHO GMP or International GMP requirements after line-specific production site assessment by WHO Prequalification Programme, an SRA or a PIC/S member.

| Procurement agent code | Number of key medicines procured | Number sourced from site compliant with stringent GMP* | Percentage |
|---|---|---|---|
| P1 | 27 | 12 | 44% |
| P2 | 25 | 15 | 60% |
| P3 | 30 | 25 | 83% |
| P4 | 20 | 17 | 85% |
| P5 | 11 | 5 | 45% |
| P6 | 18 | 10 | 56% |
| P7 | 8 | 8 | 100% |
| P8 | 26 | 25 | 96% |
| P9 | 20 | 1 | 5% |

## Supply of key medicines as indicated by 35 manufacturers

**Legend of column headings: VPP top 10:** rank amongh ten products making up 60% of VPP procurement of non-ATM medicines (June 2009-September 2010); **On PQ- EOI:** Included on the 10th WHO Expression of Interest list for HIV-related products; **WHO PQ'd:** WHO-prequalified; **SRA appr.:** Marketing authorization of a country with a stringent regulatory authority (SRA); **Stringent GMP:** produced at a site compliant with WHO GMP or International GMP requirements after line-specific production site assessment by WHO Prequalification Programme, an SRA or a PIC/S member**; Other GMP:** Produced at a site not compliant with "stringent GMP" as mentioned above.

| **Formulation:** | | | | **Number of finished pharmaceutical products:** | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **INN** | **Strength** | **VPP top 10** | **PQ-EOI** | **WHO PQ'd** | **SRA appr.** | **Stringent GMP** | **Sub-total** | **Other GMP** | **Total** |
| **Total finished products:** | | | | **9** | **262** | **259** | **530** | **444** | **974** |
| **Total formulations** | | | | **7** | **82** | **76** | **104** | **95** | **127** |
| 1. Ibuprofen | 200mg | | X | | 14 | 11 | **25** | 11 | 36 |
| 2. Ibuprofen | 400mg | | x | | 14 | 8 | **22** | 8 | 30 |
| 3. Paracetamol | 500mg | | | | 5 | 14 | **19** | 11 | 30 |
| 4. Ciprofloxacin | 500mg | | X | 2 | 10 | 5 | **17** | 17 | 34 |
| 5. Clarithromycin | 500mg | 9 | X | | 11 | 6 | **17** | 7 | 24 |
| 6. Co-trimoxazole | 800mg/160mg | | X | | 3 | 13 | **16** | 8 | 24 |
| 7. Co-trimoxazole | 400mg/80mg | 1 | **X** | | 2 | 13 | **15** | 13 | 28 |
| 8. Co-trimoxazole | 240mg/5ml | | | | 1 | 13 | **14** | 6 | 20 |
| 9. Clarithromycin | 250mg | | x | | 11 | 2 | **13** | 6 | 19 |
| 10. Ciprofloxacin | 250mg | | x | 2 | 8 | 3 | **13** | 8 | 21 |
| 11. Doxycycline | 100mg | | | | 8 | 5 | **13** | 16 | 29 |
| 12. Co-trimoxazole | 100mg/20mg | | | | | 12 | **12** | 6 | 18 |
| 13. Fluconazole | 150mg | | | 1 | 6 | 4 | **11** | 9 | 20 |
| 14. Amoxicillin | 500mg | | | | 8 | 2 | **10** | 12 | 22 |
| 15. Amoxicillin | 250mg | | | | 7 | 3 | **10** | 13 | 23 |
| 16. Paracetamol | 120mg/5ml | | | | 2 | 8 | **10** | 8 | 18 |
| 17. Aciclovir | 200mg | | x | 1 | 5 | 3 | **9** | 6 | 15 |
| 18. Fluconazole | 200mg tab/cap | | x | 1 | 4 | 4 | **9** | 7 | 16 |
| 19. Amoxicillin/clav. acid | 500mg/125mg | | | | 4 | 5 | **9** | 3 | 12 |
| 20. Aciclovir | 400mg | 7 | **X** | 1 | 5 | 2 | **8** | 6 | 14 |
| 21. Amoxicillin | 125mg/5ml | | | | 5 | 3 | **8** | 7 | 15 |
| 22. Ibuprofen | 100mg/5ml | | | | 4 | 4 | **8** | 2 | 10 |
| 23. Ceftriaxone | 1g | | x | | 6 | 1 | **7** | 3 | 10 |
| 24. Azithromycin | 250mg | | x | | 3 | 4 | **7** | 9 | 16 |
| 25. Ibuprofen | 600mg | | x | | 7 | | **7** | 3 | 10 |
| 26. Ceftriaxone | 0.5g | | | | 5 | 2 | **7** | 4 | 11 |
| 27. Aciclovir | 800mg | | | 1 | 4 | 1 | **6** | 3 | 9 |
| 28. Amoxicillin | 250mg/5 ml | | | | 4 | 2 | **6** | 7 | 13 |
| 29. Clotrimazole | 100mg | | | | 4 | 2 | **6** | 4 | 10 |
| 30. Griseofulvin | 500mg | | | | 4 | 2 | **6** | 2 | 8 |
| 31. Cefixime | 200mg | | | | 2 | 4 | **6** | 4 | 10 |
| 32. Erythromycin | 250mg | 6 | | | 2 | 4 | **6** | 11 | 17 |
| 33. Erythromycin | 125mg/5ml | | | | 1 | 5 | **6** | 6 | 12 |
| 34. Praziquantel | 600mg | | | | 1 | 5 | **6** | 4 | 10 |
| 35. Azithromycin | 500mg | 5 | x | | 2 | 3 | **5** | 9 | 14 |
| 36. Cefalexin | 500mg | 3 | | | 4 | 1 | **5** | 7 | 12 |
| 37. Cefotaxime | 1g | 4 | | | 4 | 1 | **5** | 3 | 8 |
| 38. Phenoxymethyl pen. | 250mg | | | | 3 | 2 | **5** | 7 | 12 |
| 39. Albendazole | 400mg | | | | 2 | 3 | **5** | 13 | 18 |
| 40. Cefixime | 400mg | | | | 2 | 3 | **5** | 4 | 9 |
| 41. Cloxacillin | 250mg | | | | 2 | 3 | **5** | 7 | 12 |
| 42. Paracetamol | 100mg | | | | 2 | 3 | **5** | 3 | 8 |
| 43. Metronidazole | 200mg | | | | | 5 | **5** | 10 | 15 |
| 44. Amoxicillin/clav. acid | 250mg/62.5mg | | x | | 3 | 1 | **4** | 3 | 7 |
| 45. Metronidazole | 250mg | | | | 3 | 1 | **4** | 9 | 13 |
| 46. Cloxacillin | 500mg | | | | 2 | 2 | **4** | 6 | 10 |
| 47. Griseofulvin | 125mg | | | | 2 | 2 | **4** | 4 | 8 |
| 48. Albendazole | 200mg | | | | 1 | 3 | **4** | 7 | 11 |
| 49. Amoxicillin/clav. acid | 125mg/31.25 mg p. 5ml | | | | 1 | 3 | **4** | | 4 |
| 50. Amoxicillin/clav. acid | 200/28.5 mg per 5 ml | | | | | 4 | **4** | | 4 |
| 51. Amoxicillin/clav. acid | 400/57 mg per 5 ml | | | | | 4 | **4** | 1 | 5 |
| 52. Paracetamol | 24mg/ml | | | | 4 | | **4** | | 4 |
| 53. Paracetamol | 48mg/ml | | | | 4 | | **4** | | 4 |
| 54. Metronidazole | 500mg | | | | 2 | 1 | **3** | 5 | 8 |
| 55. Erythromycin | 500mg | 2 | | | 1 | 2 | **3** | 7 | 10 |
| 56. Albendazole | 200mg/5 ml | | | | | 3 | **3** | 3 | 6 |
| 57. Metronidazole | 125mg/5ml | | | | | 3 | **3** | 5 | 8 |
| 58. Nystatin | 100000IU per ml | | | | | 3 | **3** | 4 | 7 |
| 59. Cefotaxime | 0.5g | | | | 3 | | **3** | | 3 |

| Formulation: | | | | Number of finished pharmaceutical products: | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **INN** | **Strength** | **VPP top 10** | **PQ-EOI** | **WHO PQ'd** | **SRA appr.** | **Stringent GMP** | **Sub-total** | **Other GMP** | **Total** |
| 60. Ibuprofen | 20mg/ml | | | | 3 | | **3** | | 3 |
| 61. Clindamycin | 150mg tab/cap | | x | | 1 | 1 | **2** | 4 | 6 |
| 62. Fluconazole | 50mg tab/cap | | x | | 1 | 1 | **2** | 4 | 6 |
| 63. Ganciclovir | 500mg vial | 8 | **X** | | 1 | 1 | **2** | | 2 |
| 64. Clotrimazole | 500mg | | | | 1 | 1 | **2** | 3 | 5 |
| 65. Ganciclovir | 250mg | | | | 1 | 1 | **2** | | 2 |
| 66. Paracetamol | 100mg per 5 ml | | | | 1 | 1 | **2** | | 2 |
| 67. Amoxicillin/clav. acid | 1000mg | | | | | 2 | **2** | | 2 |
| 68. Co-trimoxazole | 480mg/5ml | | | | | 2 | **2** | | 2 |
| 69. Metronidazole | 400mg | | | | | 2 | **2** | 4 | 6 |
| 70. Oral rehydration salt | 20.5g/1lit | | | | | 2 | **2** | 3 | 5 |
| 71. Phenoxymethyl pen. | 125mg/5ml | | | | | 2 | **2** | 5 | 7 |
| 72. Phenoxymethyl pen. | 250mg/5 ml | | | | | 2 | **2** | | 2 |
| 73. Zinc | 20mg | | | | | 2 | **2** | 3 | 5 |
| 74. Ampicillin | 0.5g | | | | 2 | | **2** | 2 | 4 |
| 75. Ampicillin | 1g | | | | 2 | | **2** | 1 | 3 |
| 76. Cefotaxime | 2g | | | | 2 | | **2** | | 2 |
| **77. Amphotericin B** | **50mg per 5 ml** | | x | | | 1 | **1** | 1 | 2 |
| **78. Clindamycin** | **300mg** | | x | | 1 | | **1** | 4 | 5 |
| 79. Albendazole | 800mg | | | | | 1 | **1** | | 1 |
| 80. Amoxicillin | 125mg | | | | | 1 | **1** | | 1 |
| 81. Amoxicillin/clav. acid | 375 mg | | | | | 1 | **1** | | 1 |
| 82. Amoxicillin/clav. acid | 625 mg | | | | | 1 | **1** | | 1 |
| 83. Bleomycin | 15 IU | | | | | 1 | **1** | | 1 |
| 84. Clotrimazole | 2%w/w | | | | | 1 | **1** | 1 | 2 |
| 85. Oral rehydration salt | 4.9g/200ml | | | | | 1 | **1** | | 1 |
| 86. Amoxicillin/clav. acid | 250mg/125mg | | | | 1 | | **1** | | 1 |
| 87. Amoxicillin/clav. acid | 875mg/125mg | | | | 1 | | **1** | 1 | 2 |
| 88. Azithromycin | 200mg/5 ml | | | | 1 | | **1** | 3 | 4 |
| 89. Ceftriaxone | 2g | | | | 1 | | **1** | | 1 |
| 90. Ciprofloxacin | 100mg, 10ml | | | | 1 | | **1** | | 1 |
| 91. Ciprofloxacin | 100mg, 50ml | | | | 1 | | **1** | | 1 |
| 92. Ciprofloxacin | 200mg, 100ml | | | | 1 | | **1** | | 1 |
| 93. Clarithromycin | 125mg | | | | 1 | | **1** | | 1 |
| 94. Erythromycin | 250mg/5 ml | 10 | | | 1 | | **1** | 1 | 2 |
| 95. Fluconazole | 100mg | | | | 1 | | **1** | | 1 |
| 96. Fluconazole | 100ml | | | | 1 | | **1** | | 1 |
| 97. Gentamicin | 40mg/2ml | | | | 1 | | **1** | 2 | 3 |
| 98. Gentamicin | 80mg/2ml | | | | 1 | | **1** | 1 | 2 |
| 99. Methadone | 5mg | | | | 1 | | **1** | | 1 |
| 100. Miconazole | 10mg | | | | 1 | | **1** | | 1 |
| 101. Paracetamol | 125mg | | | | 1 | | **1** | | 1 |
| 102. Phenoxymethyl pen. | 500mg | | | | 1 | | **1** | 3 | 4 |
| 103. Phenoxymethyl pen | 750mg | | | | 1 | | **1** | | 1 |
| **104. Valganciclovir** | **450mg** | | | | 1 | | **1** | | 1 |
| 105. Pyrimethamine | 25mg | | x | | | | **0** | 2 | 2 |
| 106. Albendazole | 100mg per 5 ml | | | | | | **0** | 1 | 1 |
| 107. Amoxicillin | 400mg per ml | | | | | | **0** | 1 | 1 |
| 108. Amoxicillin | 750mg | | | | | | **0** | 1 | 1 |
| 109. Azithromycin | 100mg per 5 ml | | | | | | **0** | 1 | 1 |
| **110. Benzathine pen.** | **2.4MIU** | | | | | | **0** | 2 | 2 |
| 111. Cefalexin | 125mg | | | | | | **0** | 1 | 1 |
| 112. Cefalexin | 125mg/5ml | | | | | | **0** | 1 | 1 |
| 113. Cefalexin | 250mg | | | | | | **0** | 3 | 3 |
| 114. Cefalexin | 250mg/5 ml | | | | | | **0** | 2 | 2 |
| 115. Clotrimazole | 0.2g | | | | | | **0** | 1 | 1 |
| 116. Gentamicin | 10mg/ml | | | | | | **0** | 2 | 2 |
| 117. Gentamicin | 20mg/ml | | | | | | **0** | 2 | 2 |
| 118. Griseofulvin | 250mg | | | | | | **0** | 1 | 1 |
| 119. Metronidazole | 200mg/5 ml | | | | | | **0** | 1 | 1 |
| 120. Metronidazole | 800mg | | | | | | **0** | 1 | 1 |
| 121. Paracetamol | 125mg/5ml | | | | | | **0** | 1 | 1 |
| 122. Paracetamol | 150mg | | | | | | **0** | 1 | 1 |
| 123. Paracetamol | 250mg | | | | | | **0** | 1 | 1 |
| 124. Paracetamol | 300mg | | | | | | **0** | 1 | 1 |
| 125. Sulfadiazine | 500mg | | | | | | **0** | 2 | 2 |
| 126. Zinc | 10mg/5 ml | | | | | | **0** | 1 | 1 |
| 127. Zinc | 20mg/5ml | | | | | | **0** | 1 | 1 |