



TOGETHER TO HEAL



UNITAID

REQUEST FOR PROPOSAL  
BID REFERENCE 2010.005

IMPLEMENTATION OF MID-TERM REVIEWS OF  
UNITAID-SUPPORTED PROJECTS

**MID-TERM REVIEW OF THE UNITAID-  
FUNDED WHO PREQUALIFICATION  
PROGRAMME**

**EVALUATION REPORT**

*February-April 2011*

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## List of Abbreviations

ACT	Artemisinin-based ( <i>medicines</i> ) Combination Therapy
AEDES	Agence Européenne pour le Développement et la Santé ( <i>European Agency for Development and Health</i> )
API	Active Pharmaceutical Ingredient
ARV	Antiretrovirals
ATM	Antiretrovirals, Anti-Tuberculosis medicines, Antimalarials
CPH	Copenhagen ( <i>evaluation sessions</i> )
CRO	Contract Research Organisation
CTD	Common Technical Document
DIA	Drug Information Association
EAC	East African Community
EMA	European Medicines Agency
EDQM	European Directorate for the Quality of Medicines and Health Care
EML	Essential Medicines List
EMP	Department of Essential Medicines and Pharmaceutical Policies
EOI	Expression of Interest
ERP	Expert Review Panel
FDC	Fixed-Dose Combination
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practices
GDF	Global Drug Facility
GFTAM	Global Fund to fight AIDS, Tuberculosis and Malaria
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GSM	Global Management System
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Conference on Harmonisation of Technical Requirements of Registration of Pharmaceuticals for Human use
KPI	Key Performance Indicator
MSF	Médecins Sans Frontières ( <i>Doctors Without Borders</i> )
MTR	Mid-Term Review
NGO	Non-Governmental Organisation
NMRA	National Medicines Regulatory Authority
PA	Procurement Agent
PEPFAR	President's Emergency Plan for AIDS Relief
Ph.Int.	International Pharmacopoeia
PQP	Prequalification Programme
RFP	Request for Proposals
QA	Quality Assurance
QC	Quality Control
QCL	Quality Control Laboratory
QSM	Quality and Safety of Medicines Team
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authority
TB	Tuberculosis

UN	United Nations
UNAIDS	Joint United Nations Programme for HIV/AIDS
UNFPA	United Nations Population Fund
UNICEF	United Nations Children’s Emergency Fund
UNICEF-SD	UNICEF Supply Division
USA	United States of America
USFDA	Food and Drug Administration (of the USA)
USP	United States Pharmacopeia
WHO	World Health Organisation
WHOPAR	WHO Public Assessment Report
WHOPIR	WHO Public Inspection Report
WHO-PQP	WHO Prequalification of Medicines Programme

# Executive Summary

The objective of this mid-term review was to assess the progress made towards the UNITAID-funded WHO Prequalification Project's agreed objectives and make recommendations on how project management can be improved to help the project achieve its objectives more effectively and efficiently.

The assessment included several meetings with WHO-PQP and UNITAID teams, and also representatives of other WHO departments, stakeholders (organisations and industry) and experts involved in the WHO-PQP, review of a large set of documentation (provided by WHO-PQ and UNITAID or found on websites).

The project is relevant and contributes to the UNITAID's overall goal: WHO-PQP is now a well-known and widely recognised system. It represents a unique global system, independent from any government, ensuring, through a rational procedure close to those applied by stringent regulatory authorities, that priority medicines meet international and unified standards of quality, safety and efficacy. The published list of prequalified products is a reference tool, guiding procurement decisions by UN (and also non-UN) organisations.

WHO-PQP also builds for the long term by undertaking:

- capacity building with national regulators and quality control laboratories (QCLs), to promote regulatory expertise in countries, and
- technical assistance to manufacturers, selected to develop sources of targeted needed products supplied with UNITAID fund.

Through the confidence built in countries, which helps in accelerating regulatory approval of prequalified products and harmonising national registration procedures, WHO-PQP contributes to facilitating access to quality products, representing value for money.

Effectiveness: altogether the results of the assessment show that WHO-PQP, as managed today, is consistent with and allows the achievement of the objectives and expected outcomes as described in the Project Plan 2009-2012; e.g. in 2010 for the two first objectives:

- on the 36 products prequalified (targeted at 35), 15 were UNITAID priority medicines.
- 53 dossiers received passed the screening, of which 29 for UNITAID priority products (10 HIV/AIDS products, 11 TB products and 8 antimalarials) for a target set at 17.
- 6 QC laboratories were prequalified (target at 3).
- and the 2 first API were prequalified in 2011.

The situation today is good regarding the likelihood the objectives are met until the end of the project, provided the efforts and improvements made by WHO-PQP in the organisation and management of the project are maintained and even developed (including for the financial reporting to UNITAID).

Efficiency: the collaboration with concerned stakeholders, in particular national authorities of the beneficiary countries is developed through the involvement of national regulators/inspectors in the process, and the capacity building for regulators and manufacturers. This objective is of main importance for increasing capacity in production quality of priority products, facilitating the development of national regulatory process and quality control for medicines in recipient countries, but is a long-term objective, the impact of which is difficult to evaluate during the four-year course of the project, through objective and measurable indicators. However results can already show its efficiency (improvement in the quality of the received dossiers, increase in number of QCL prequalified and the successful joint evaluations and inspections). This activity, in such scale and provided with such expertise, is unique, has a growing interest and can certainly valuably participate in improving the Quality in

procured medicines: the expected benefits certainly balance the resources invested so far and estimated in the Project Plan.

The estimated funding of the Project Plan 2009-2012 appeared adequate for the objectives and expected outcomes. However a reallocation of funds for 2011-2012 per objectives/activities based on the experience in the project and a better budget management, is necessary and was submitted to UNITAID for approval.

The likelihood of the WHO-PQP achieving the objectives initially set in the UNITAID-WHO agreement also obviously depends on external factors, difficult to influence on, such as the manufacturers incentive, and on the human and financial resources available.

Nevertheless some proposals for further improvements (e.g. to develop an expedite procedure similar to existing ones (ERP, PEPFAR initiative)) and perspectives (extension of the WHO-PQP scope, advocacy to stakeholders) can be considered to answer the challenges.

The relevance to maintain the quite ambitious objectives of the agreement could be questioned in particular as regard the current crisis at WHO and the general economical situation. However all these objectives are well based to effectively and efficiently ensure that medicines that are procured for the ATM treatment programmes with UNITAID funds, meet unified quality standards and to contribute to increase the number of ATM priority medicines prequalified. WHO-PQP with its various and supplementary activities, including long-term objectives like capacity building in regulation and production, is a unique system that plays a role in the protection of public health, in close cooperation with national regulatory authorities and partner organisations. It is certainly worth the resources invested so far. It is beneficial to all stakeholders involved in the procurement of medicines to populations in need and its existence is essential. As such sustainable financial resources are needed and other donors should contribute to the UNITAID major funding.



# 1 INTRODUCTION

## 1.1 CONTRACT REFERENCES

**UNITAID Ref.:** RFP Bid Reference 2010.005 – Implementation of Mid-Term Reviews of UNITAID-Supported Projects.

**AEDES internal Ref.:** Project N° 2109 – AEDES contract N° 234.

**Timeline of the consultancy:** from February to April 2011; Report to be delivered by 30<sup>th</sup> of April; Debriefing meeting at UNITAID on 10<sup>th</sup> of May.

**Expert consultant:** Corinne Pouget, pharmacist

**AEDES Backstopping:** Daniel Vandenberg, pharmacist

## 1.2 OBJECTIVES OF THE CONSULTANCY

The frame of the consultancy is described in the Terms of Reference of the mission issued by UNITAID (see annex 1).

The overall objective was to assess the progress made towards the UNITAID-funded WHO Prequalification Programme's agreed objectives and to make recommendations on how project management can be improved to help the project achieve its objectives more effectively and efficiently. For that purpose AEDES was expected to provide:

- Assessment of the likelihood of WHO Prequalification Programme (WHO-PQP) achieving the objectives that were set initially by UNITAID and WHO and the progress of the project at mid-term review; such assessment would include identification of the WHO-PQP's strengths, weaknesses, opportunities and threats, in order to contribute to improving the chances that the project's end outcomes are achieved.
- The evaluation was also intended to focus on the relevance of the programme funding, its effectiveness, its efficacy and its impact on the overall UNITAID goal (summarised as "increasing the availability of high quality ATM medicines at affordable price"). The WHO-PQP role in this goal clearly sits in assuring the high quality level of ATM medicines and contributes to increase the number of ATM priority medicines prequalified.
- Recommendations and advice on how to improve the effectiveness and efficiency of project management, including WHO-PQP reporting on project activities and finance and UNITAID internal project management related to the WHO-PQP.

## 2 PROGRAMME AND METHOD

The assessment consisted in:

- A review of a large set of documentation provided by WHO-PQ and UNITAID or found on websites, regarding all the various activities directly or indirectly linked to WHO-PQP and including the legal agreements between UNITAID and its implemented partners for the WHO-PQP; the annual/interim progress reports on activities and follow-up done by UNITAID portfolio managers; the financial reports; and all other relevant documents for the review (see *list in annex 3*).
- Meetings with people within WHO-PQP team, UNITAID team, other WHO services/departments in relation with to WHO-PQP (HIV/TB/Malaria treatment departments, norms & standards, IT, finances...), representatives of the two companies having done the manufacturers surveys (as per the WHO-PQP demand), stakeholder organisations (GF, UNICEF-SD, GDF, MSF), manufacturers, and some external experts (assessors and inspectors) that are (or have been) involved in the PQP (see *list in annex 2*).
- Participation to the annual WHO PQP stakeholders meeting in Geneva (05<sup>th</sup> of April 2011).
- Participation to a PQP evaluation session in Copenhagen (CPH session).

The exchange of information was facilitated by the use of a WEB-based tool with restricted access providing a rapid and uniform access to the concerned group, and respecting confidentiality (UNITAID Basecamp dedicated to the WHO-PQP MTR).

## 3 ASSESSMENT OF THE WHO-PQP AT MID-TERM (SWOT ANALYSIS)

### 3.1 BACKGROUND AND GENERAL OVERVIEW OF THE WHO-PQP

In the last decade, the international community has recognised that sustained supplies of affordable medicines of assured quality are vital to treatment goals relating to HIV/AIDS, tuberculosis (TB) and malaria. However, many of the medicines that have become available for treating these diseases, such as combination products of antiretrovirals (ARVs), artemisinin-based malaria combinations (ACT) and children's formulations, were not generally used in industrialised countries, either because the diseases did not exist there (i.e. paediatric HIV, TB, malaria) or because generic manufacturers did not make products for the low volumes and low value markets in high income countries; and experience in regulating these medicines were minimal. This represented a major challenge to those parts of the UN system with responsibility for procuring these medicines for treatment programmes.

The WHO Prequalification of Medicines Programme (WHO-PQP) was initiated in 2001, as a collaborative programme supported by UNAIDS, UNICEF, UNFPA and the World Bank, in response to this challenge. The main objective of the programme was to standardise the quality of medicines so that UN Agencies could produce from generic sources. UNITAID with its mission to contribute to the scale up of access to treatment for HIV/AIDS, malaria and TB by leveraging price reductions of high quality medicines, is now by far the main funding organisation for the WHO-PQP. The current UNITAID-funded US\$ 40 million project was established for 2009-2012 to facilitate activities to the prequalification of UNITAID funded priority medicines, including a strengthened programme of capacity building to speed up the prequalification of UNITAID priority medicines and their regulatory uptake in target countries, and the field sampling and quality testing of products supplied through UNITAID to users.

#### BASIC PRINCIPLE OF THE PQP

WHO-PQP gathered together the expertise required for evaluating and verifying, through assessments and inspections, the quality, safety and efficacy of medicines for treating HIV/AIDS, TB, malaria and, since 2006, medicines for reproductive health, influenza and acute diarrhoea in children. Participation in the programme is voluntary, open to innovator and multi-source/generic manufacturers, and free of charge for applicants. It is a continuous process that assures the quality of products already prequalified through: assessment of changes made in products and to be reported by the manufacturers; sampling and testing of prequalified products; routine and ad-hoc inspections at production sites and contract research organisations (CROs).

The assessment of the WHO-PQP is done through a SWOT analysis following the objectives fixed in the UNITAID-funded project plan<sup>1</sup>.

<sup>1</sup> Project Plan for 2009-2012 WHO-PQP- Annex 1 to UNITAID Project Support for Quality Assurance of Medicines, 2009-2012- WHO Prequalification of Medicines programme ; 22 December 2008.

## 3.2 WHO-PQP STRENGTHS

WHO-PQP strengths mainly lie in a pragmatic approach for organisation and procedures.

They are coherent with objectives fixed in the UNITAID-funded project plan<sup>2</sup>.

### WHO-PQP IS BASED ON A RATIONAL, ROBUST AND SAFE PROCEDURE

It includes:

- Comprehensive and stringent assessment of pharmaceutical product data and information on quality, safety and efficacy submitted by the manufacturer (including details about the purity of all ingredients used in manufacture, data about finished products, such as information about stability, and the results of in vivo bioequivalence tests);
- Inspection of pharmaceutical manufacturing sites both for finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (systematically for API prequalification, on a risk-based approach for FPP prequalification) to assess compliance with GMP; inspection of contract research organisations (CROs) according to GCP and GLP as appropriate; inspection of quality control laboratories;
- Maintenance of the list of prequalified medicinal products through evaluation of the changes (variations) and re-qualification, regular inspections of the manufacturing sites, quality control laboratories and CROs.
- Recognition (where possible) of dossier assessments and inspections by Stringent Regulatory Authorities in order to avoid duplication.

The process flow of the procedure for prequalification of pharmaceutical products or APIs (see annex 4) is coherent and includes defined decision-making steps that allow WHO to refuse or terminate an evaluation of a specific product if the manufacturer is not able to provide the required information and/or is unable to implement any corrective actions, or when the information supplied is inadequate to complete the procedure, and of course at receipt (screening) if the application is not eligible (product not listed in invitations for Expression of Interest (EOI)). The manufacturer/applicant is given the right to answer.

The procedure applies clear and strict requirements internationally recognised (WHO or ICH), complemented by quality assurance tools (guidelines, forms, templates, etc.) that are adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (whose secretariat is hosted in the Quality Assurance and Safety Medicines (QSM) team) and which give guidance to manufacturers/applicants and contribute to uniformity in evaluation amongst experts.

A systematic independent review (for assessment and inspection) ensures coherence and integrity in evaluations and represents a strong point of the procedure. It also enables knowledge sharing between experts and participates to capacity building and to recognition of the procedure by the country authorities where the products will be used.

It is not an on-off exercise but includes continuous monitoring (assessment of variations in dossiers, re-qualification, regular re-inspections and independent testing on random sampling) and complaints handling (according to a specific SOP, results of investigation of reported complaint are transmitted to

<sup>2</sup> Project Plan for 2009-2012 WHO-PQP- Annex 1 to UNITAID Project Support for Quality Assurance of Medicines, 2009-2012- WHO Prequalification of Medicines programme; 22 December 2008.

the concerned manufacturer and NMRA, and, as necessary from a Public Health perspective, to other authorities of WHO Member States and interested UN agencies). This is of main important for the maintenance of prequalification status. Indeed if it is found that a product or a manufacturing site no longer complies with the WHO recommended standards, it may be suspended or removed from the list of prequalified products.

The WHO rules on confidentiality and conflict of interest apply to any experts (assessors and inspectors) involved in the procedure.

The procedure is similar to those applied in most of stringent regulatory authorities (SRAs) in terms of process flow, information required and stringency; it could even be considered more appropriate to receiving countries since evaluations are conducted by mixed teams of experts from developed and developing countries and some data (such as stability studies or package leaflet) are evaluated according to the countries specificity/needs.

### THE WHO-PQP IS WELL DOCUMENTED

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Even if a formal quality assurance system (as described in a Quality Manual and its related documents) is not yet in place (except for the inspection unit), quality documents/SOPs exist for the main steps and process flows.

The appropriate norms and standards (guidelines, monographs) exist and are applied; they are regularly revised or new ones are elaborated in cooperation with the secretariat of the WHO Expert Committee on Specifications for Pharmaceutical Preparations; recently new guidelines reflecting the current requirements (preparation of dossier and description of the requirements for the quality part of dossiers, Site Master Files, GMP, etc.), and the revision of the 'procedure for prequalification of pharmaceutical products' have been adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

### THE WHO-PQP IS TRANSPARENT

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A lot of information is publicly available on the website under WHO-PQP page (done and maintained by the WHO-PQP itself): information and guidelines to applicants (in particular the procedure and guides on submission of documentation for each of the concerned category of products) and the lists of prequalified products (FPP and API) and Quality Control Laboratories (QCL), the status of products evaluation, the Notice of concern (in case of product/site default), that are systematically and rapidly updated after any decision (approval, refusal, suspension), the WHO Public Assessment and Inspection Reports (WHOPAR, WHOPIR) that are documents not commonly published by other Regulatory Authorities.

Possibility of direct contacts is offered to manufacturers and other stakeholders, through general and individual meetings, e-mail consultations (dedicated e-mail address: [prequal@who.int](mailto:prequal@who.int)).

### THE WHO-PQP ENSURES GOOD QUALITY OF UNITAID PRIORITY MEDICINES

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There is no backlog and all dossiers are treated according to the timelines, defined in internal documents and as indicators for annual activity reviews.

The target numbers for prequalified medicines, including UNITAID priority products, are achieved (36 prequalified products in 2010, of which 30 generics and 15 UNITAID priority products; in total at end 2010: 252 manufactured in 20 countries).

The prequalification of API was initiated end 2010; 9 submissions were received so far and the first two have just been prequalified (12 and 19 April 2011). The WHO-PQP for API is of major interest considering the potential problems caused by non-assured quality API in the current global market context. It will also shorten the time taken to reach prequalification for FPPs that are manufactured using WHO-prequalified APIs.

A new collaborative procedure for facilitating registration procedures in East African Countries (EAC) was piloted in 2010: the joint assessment by WHO and EAC assessors of 2 (HIV) products from an Indian manufacturer concluded to be both prequalified and registered in 3 EAC Countries (Kenya, Tanzania, Uganda). This successful joint assessment and approval gives appreciable advantages: an immediate access for the products to countries market; contribution to integration of such assessment into national regulatory decision-making and therefore to harmonisation of regulatory requirements at regional level.

In the same aim (to prevent duplication and contribute to the recognition and harmonisation of requirements), a new collaborative procedure for joint inspections was initiated at the beginning of 2010 between PQP and the East African Community countries (EAC) on the basis of sharing of inspection plans, joint inspections and sharing of inspection reports. A secure web site was created and is being used by participating countries. The first of such inspections was scheduled and planned but had to be postponed due to unrest at the manufacturing site.

## PREQUALIFICATION OF QC LABORATORIES

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This activity, at the beginning limited to African QCLs, was extended to other regions and expanded since 2007: target number was doubled last year (6 QCL prequalified), with now 1 or more prequalified QCL in each of the 6 WHO's regions.

This activity represents a major interest for most of the stakeholders including NMRA, by identifying QCLs compliant with GLP and applicable aspects of GMP, more accessible for local organisations or local studies and at a lower cost compared to QCL in strictly regulated countries.

## CAPACITY BUILDING OF REGULATORS AND MANUFACTURERS AND TECHNICAL ASSISTANCE

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PQP organised (co-organised) in many countries technical training courses, workshops, on general or specific issues, and also provides technical assistance for both the public and private sectors: manufacturers, regulatory and QCL staff, etc. The manufacturers requesting technical assistance are selected on defined and relevant criteria (commitment to participate in the WHO-PQP, found to be capable and willing to improve, product poorly represented in the PQP list and prioritised for Public Health purpose), that are published on the website. This activity is growing in compliance with Objective 3 of the Project Plan 2009-2012: 21 training and workshops in 2010 with an average number of attendees of 34 for NMRA and 42 for manufacturers (16 in 2009, with respectively 17 and 23 participants); 11 technical assistance missions to national QCLs in 9 countries; 22 technical assistance missions for selected manufacturers (8 in 2009, with a baseline of 10 in the Project Plan) focussing on GMP, GCP, GLP compliance, and regulatory support. The big increase of the latter is linked to a pilot project conducted in China for FDC anti-TB medicines manufacturers, funded by the Gates Foundation.

PQP also answers to individual manufacturers' request relating to their application, either by correspondence (e-mail/phone) or through one-to-one meetings organised at Geneva, in conjunction with Copenhagen assessment sessions or at the occasion of event such as the Stakeholders meetings.

Participation of NMRA staff as experts in Copenhagen evaluation sessions, in inspections (where local inspectors are also invited as observers), and in 'Rotational posts' for hands-on experience in everyday PQP work at WHO headquarters (for 3 months), also widely contribute to building capacity of regulators.

This activity has shown an important development for the past 2 years, all targets being almost doubled last year.

## IMPROVE AWARENESS OF THE PREQUALIFICATION OF MEDICINES THROUGH COMMUNICATION AND ADVOCACY

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WHO-PQP promotes its programme and its advantages through participation in several seminars, workshops in collaboration with external organisations (e.g. EMA, EDQM, DIA) or other WHO services/departments, the organisation of the annual stakeholders meeting and by publishing information on the WHO-PQP website and in WHO publications. In addition WHO PQP is promoted at many other international forum including the biennial International Conference of Drug Regulatory Authorities (ICDRA), meetings organized by stakeholders and numerous PQP introduction seminars in various WHO regions, etc. WHO PQP has also published articles in Lancet, in the WHO Drug Information and other journals.

PQP has played a major part in the development the quality assurance policies of GFTAM and other major players. This has led to considerable increase in the awareness of WHO PQP.

If the need of this activity is obvious in particular to encourage manufacturers participation, awareness of the danger inherent in sacrificing quality for the sake of lower medicines prices is also to be promoted.

## STAFF RESOURCES

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The WHO-PQP staff is competent, skilled, and shows motivation and team interest (i.e. common work on specifications for future electronic Data Management System) despite the important workload. The team seems sufficient in number for the current workload, provided all posts are fulfilled (see the *Organisational Chart in annex 5*).

The WHO-PQP works with a pool of external assessors and inspectors with adequate expertise in the various fields covered by the WHO-PQP scope, with a core group of 'seniors' involved for long in the programme.

The sufficient number of highly qualified staff and the availability of national experts are key factors for managing the programme efficiently and achieving its objectives, but these resources are fragile (see § 3.5-Threats).

## STAKEHOLDERS' SATISFACTION IS QUITE GOOD

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The WHO-PQP is well known and recognised by all categories of stakeholders as a reliable and efficient tool (for prequalification of both medicines and QCLs).

According to a survey of manufacturers satisfaction performed last year on WHO-PQP's initiative for developing greater 'client' focus, and on feed-back from some participants at the 2011 Stakeholders meeting, WHO-PQP is considered as a well-designed and well-executed programme; manufacturers are satisfied by WHO-PQP services, and appreciate the efforts made recently by WHO-PQP on providing support and technical assistance. However they still express some concerns regarding communication and problem or disagreement resolution during the process of assessment, process timelines, and, above all, the absence of guarantee to sell products when prequalified. Therefore the decreasing interest from manufacturers seems more due to commercial issues than problems with the WHO-PQ programme itself.

## 3.3 WHO-PQP WEAKNESSES

### PROCESS TIMEFRAME IS TOO LONG

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The time required to prequalify products is relatively long when compared to other systems used for qualifying medicines for procurement e.g. the US FDA Tentative Approval process (see discussion under chapter 5). This creates staff burden and limits manufacturers' incentive, which is prejudicial in particular when the market requires high reactivity. However, much of the total time for prequalification is "manufacturer time".

Parts of the process flow are under the manufacturers' responsibility and depends on the quality of the information provided (some submission being by far incomplete in particular regarding the efficacy and safety part), on the time taken by applicant to answer, and also on the level of GMP compliance of the manufacturing sites. The possibility for WHO-PQP to impact on it is limited. However the internal process flow could still be improved.

### ABSENCE OF AN APPROPRIATE AND TAILORED ELECTRONIC DATA MANAGEMENT SYSTEM

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The existing database is disused and replaced by too many supports, manually handled by several persons. That makes the management of data and process flow complex with redundant steps, and unsafe with risk of mistakes and missing information. That puts a big burden on the team and slows down the process.

### COMMUNICATION IS NEVER FOUND SUFFICIENT BY USERS

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Both NMRA for their regulatory decision making and procurement agents (PA) for checking conformity of the selected products, need more details on the prequalified products than the information available from the website (e.g. approved API and FPP specifications, API sources, storage conditions, packaging, changes approved after variations...).

Some stakeholders (PA, NGO, ...) criticize the lack of easy and obvious ways for contacting WHO-PQP and their inability to be involved in the process or provide feed-back. Even if not shared by all stakeholders, this criticism should be considered since it may challenge the confidence in the programme and limit valuable comments, reporting on problems.

### DECREASING NUMBER OF APPLICATIONS

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The decrease in the number of applications received the past 2 years (92 of which 36 priority products in 2008; 51 of which 25 priority products in 2010) should be carefully investigated. It can be due to various factors such as a relative saturation of the market for some products, a lack of producers for others, a disinterest or lack of knowledge from manufacturers about the WHO-PQP benefits and category of products urgently needed.

According to the results of two recent surveys on manufacturers, this situation seems more due to economical reasons than to WHO-PQP services dissatisfaction. Indeed some manufacturers do not perceive business benefit in WHO-PQP; they criticize the absence of guarantee to sell the products once they are prequalified because of tender processes and practices. In addition some procurement



agents/organisations still put price before quality despite the UNITAID policy. The UNITAID policy is not always fully respected and not copied by other donors (e.g. World Bank), weakening its impact.

Last but not least, the manufacturers consider the WHO-PQP procedure too long (compared to others like the USFDA tentative approval system linked to the PEPFAR initiative), jeopardizing their market access. There is a time gap between the call for medicines, i.e. the publication of the invitation for EOI, and the moment where medicines, once prequalified, can be purchased, that can be detrimental to manufacturers either because other approved medicines will take the market or the interest in the product will be lower (change in WHO treatment guidelines).

## UNITAID LIST OF PRIORITY PRODUCTS NOT PROMOTED ENOUGH

The rationale for elaborating such a list is obvious: identifying urgently needed medicines requiring to be treated in priority. However its existence is not transparent for stakeholders (in particular manufacturers), jeopardizing its purpose and application and putting WHO-PQP in an awkward position. Manufacturers may complain having their applications delayed on profit of others for priority products, if they are not aware of a possible prioritization by WHO-PQP; at the contrary they would be motivated to apply for priority products.

Some of the priority products listed are not in the EOI list (eg tenofovir tablets 75mg; artemesinin suppository 100, 200, 300, 400, 500; isoniazid + rifampicin, tablet 60 mg+60 mg; amoxicillin + clavulanate 500mg+125mg) and therefore are not eligible to WHO-PQP according to the current procedure. That may be prejudicial if these products urgently needed or for specific need. Some flexibility in the elaboration of the list and the PQP procedure should be considered.

Some of the stakeholders met expressed the wish to more involved in the elaboration of the list, providing feed-back on the needs from the users and countries.

Such a list is crucial for the achievement of the main project objective and should be promoted to enable urgently needed medicines requiring to be treated in priority by both the manufacturers (incentive to rapid submission) and WHO-PQP (fast and priority evaluation).

## 3.4 OPPORTUNITIES

To answer the stakeholders' expectations and meet the UNITAID main objective, the WHO-PQP should be more attractive and 'unavoidable'. It does not only depend on WHO-PQP but also on behaviour of other stakeholders, in particular the interest of manufacturers, the quality of the dossiers submitted, the respect of procurement policy. However WHO-PQP can work on the following:

- To reinforce and improve WHO-PQP process management, in particular reducing process timeframe;
- To improve recognition of WHO-PQP by national regulatory authority in order to limit duplication of work and speed-up the national registration procedures;
- To develop communication and information sharing strategies;
- To reinforce others key activities: capacity building/technical assistance and QCL prequalification;

- To develop manufacturers incentives.

Based on stakeholders feed-back, WHO-PQP started last year with an improvement action plan (some actions have already been put in place, such as developing communication with manufacturers and information on the possibility and tools offered for contact and assistance), that should be continued and complemented.

## **TO REINFORCE AND IMPROVE WHO-PQP PROCESS MANAGEMENT ENABLING A REDUCTION OF THE PROCESS TIMEFRAME**

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### **SETTING UP A TAILORED ELECTRONIC DATA MANAGEMENT SYSTEM**

The development of an electronic data management system, delayed last year, is currently under development with a target go-live date of December 2011. Such system will help in the administrative tasks, in the production and management of documents related to PQ procedure and in the follow-up of applications and products; it would also facilitate the maintenance of the website and enable direct consultation from outside (in first for experts, it might also be extended to other organisations) through a secure and restricted access.

### **DEVELOPING A MORE CONTINUOUS AND STRUCTURED PROCESS**

Improvement of the structure and management of the process flow have already started and helped improving the total time for prequalification, i.e. by implanting internal deadlines for the main steps (median number of days for assessment steps and finalisation of reports), clock-stop times (when response/action from the applicant is awaited) and deadlines for manufacturers to answer. The follow-up will be facilitated when the electronic data management system is in place.

That could be further improved by developing 'internal' assessment, i.e. assessment by WHO-PQP team between Copenhagen evaluation sessions (e.g. for additional information or even for doing 'pre-evaluation' to be then confirmed by external assessors). That would allow a more continuous process, shortening the timelines and reducing frequency and cost of CPH sessions. However these sessions should be maintained since they greatly participate in the regulators capacity building (widening the assessors experience and knowledge), recognition of WHO-PQP and international standards, harmonisation of assessments, sharing information, developing informal network amongst assessors, etc.

## **TO IMPROVE RECOGNITION OF WHO-PQP ASSESSMENT AND HARMONISATION OF NATIONAL REGULATIONS**

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WHO-PQP has planned to repeat the pilot joint evaluation done with EAC and is hoping to use the same model for assessing selected, technically complex, high priority products. Several partners and stakeholders see joint assessment as an effective mean of speeding up access to much needed products. That would both meet the UNITAID objective and the manufacturers' expectations to enter more rapidly countries market, and probably positively balance the additional costs carried by such joint assessment.

One joint inspection with EAC inspectors has also already taken place in India and another is planned for June 2011 in Kenya and another two later in 2011.

Additional support may be needed by participating national authorities in establishing appropriate revised regulation to enable recognition of WHO-PQP in their national registration procedures and then mutual recognition between other states/countries.

PQP is working together with QSM regulatory support programme, which is the lead in African Medicines Registration Harmonization Initiative. The project starting in EAC countries IIIQ 2011 will offer further opportunities for harmonization of regulatory requirements and mutual recognition as these are the key elements of the project. Recently PQP adopted the ICH CTD dossier format and it is foreseen that EAC countries switch to harmonized CTD format soon as well.

## TO DEVELOP COMMUNICATION AND INFORMATION

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### COMMUNICATION WITH PARTNERS

WHO-PQP made efforts for offering direct contacts for manufacturers:

- with one-to-one consultations that are proposed after the stakeholders meeting, during the CPH sessions and all along the year at Geneva on manufacturers formal request (registration form and procedure on web site).
- Manufacturers can also contact WHO-PQ through a specific e-mail address.
- Contact details (including telephone numbers) for all key PQP staff are published on the PQP website.

This is time and resources (human and money) consuming but it is highly beneficial to all: it was mentioned as premium advantage during the manufacturers survey, and improvement noticed in the quality of dossiers submitted by manufacturers that are familiar with the system (or having received support) can certainly be linked to it.

Concerning other partners, the annual stakeholders meetings are a privileged way for developing contacts and collecting feed-back from the WHO-PQP users. However other possibilities (through regular meetings, preferred communication channel) could be envisaged to facilitate communication, in particular with procurement organisations (e.g. UNICEF-SD, MSF) for better and rapid reporting in case of problem, specific request, comments, etc.

### COMPLEMENTING INFORMATION ON PREQUALIFIED PRODUCTS (WHO-PQ LIST AND WHOPAR/WHOPAR)

The new approach recently implemented for API (April 2011) seems to be an appropriate answer to the stakeholders requesting more information:

- the list of prequalified APIs published on the web page includes more relevant information (APIMF version number, API specifications number, re-test period, storage conditions);
- confirmation of WHO API prequalification sent by WHO-PQP to the API manufacturer, contains copies of the accepted API specifications, assay and related substances test methods, and can be provided at the discretion of the API manufacturer to other parties (such as FPP manufacturers). The validity of the document can be checked in two ways: first the authorisation box included in the document, which should be filled out by the API manufacturer in the name of the manufacturer or agent seeking to use the document; second, by comparing the date on the document with the one published on the list of prequalified APIs.

Such approach should be extended as soon as possible to FPPs.

Information coming from pharmacovigilance programmes and possible impacts on prequalified products should be made publicly available as soon as possible after notification; existing cooperation

with other relevant WHO services (e.g. QSM safety programme) should enable rapid analysis and decision of actions after signals are received.

## TO REINFORCE OTHER KEY ACTIVITIES

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### CAPACITY BUILDING/TECHNICAL ASSISTANCE ACTIVITY

This support provided by WHO-PQP is unique and unanimously welcomed and recognised as an efficient tool to develop quality assurance amongst national governments, regulatory authorities (including QCLs), manufacturers, and even NGOs.

WHO-PQP has planned to develop in 2011 technical assistance for regions and countries (such as sub-Saharan Africa, China and Bangladesh) where a growing number of manufacturers are interested in submitting product dossiers to WHO-PQP. Other countries with manufacturing potential (e.g. Turkey) could also be included.

Technical assistance focused on manufacturers of globally needed APIs, as WHO-PQP planned to do in China, should be developed rapidly considering the crucial benefit (for both FPP manufacturers and evaluators) to have the most of such APIs prequalified.

Even if time and resources consuming, this activity is greatly valuable for all, since it develops a mutual understanding concerning quality, safety and efficacy and therefore promote global harmonisation of regulatory activities and standards, and improvement of the quality of dossiers submitted. The conditions for provision of technical assistance should be carefully respected in order to avoid useless burden.

### QCLS PREQUALIFICATION

The big development of this activity is to be continued in order to have more QCLs prequalified in more countries. This will contribute to organizing well structured sustainable QC testing of UNITAID funded products in the relevant regions and countries. However the technical assistance and monitoring that will consecutively be required should be considered since it is resource demanding.

## TO DEVELOP MANUFACTURERS INCENTIVE

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Following the survey of manufacturers' satisfaction regarding WHO-PQP services, WHO-PQP initiated a study to help it describe and quantify the potential benefits to manufacturers of having a product or products prequalified by the WHO. WHO-PQP will use the results to develop a "business case for participation in WHO medicines prequalification" for presentation to manufacturers. That would certainly be beneficial also to WHO-PQP for identifying other actions to be undertaken. However some possible proposals can already be considered (see below under § 7).

The newly launched UNITAID initiative '**Medicines Patent Pool**' may encourage manufacturers in particular for new FDC in HIV-AIDS treatments for adults and children. However that may also generate further needs in highly qualified experts (internal/external) for assessing dossiers and providing any technical support requested.

A market mapping for the therapeutic areas where WHO-PQP is engaged, would also help in identifying manufacturers and countries to approach for promoting the WHO-PQP advantages and activities. WHO-PQP has already started working in this direction, gathering information on

manufacturers in India (from trade directories) and Africa (from NMRA information) to feed a database. A post (still vacant) of Supplier Relations will be dedicated to such proactive communication.

### **TO STAY 'CLIENT' FOCUSED**

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Considering the benefit of the surveys for identifying weak points and users expectations, it may be worth to monitor the manufacturers satisfaction through repeated surveys and to conduct satisfaction surveys on other stakeholders categories: NGOs, including UN agencies/organisations, procurement organisations, national regulatory authorities.

Closer collaboration with UNITAID, in particular its Market Dynamics team, would be profitable to identify opportunities for market developments.

In better answering the stakeholders expectations, WHO-PQP would be more attractive, more used and therefore more efficient regarding its impact on the market dynamics, by contributing to increase the global market volume of assured quality ATM and reduce the prices.

## **3.5 THREATS**

The management of WHO-PQP activities and their developments for a better achievement of UNITAID objectives may be jeopardized by the following:

### **STAFF RESOURCES ARE FRAGILE**

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There is too much burden on the WHO-PQP staff that is just enough for the current activities. In addition the staff capacities are challenged by the turn-over in WHO-PQP team, the reorganisation with reduction in staff under way at WHO Headquarters and the recruitment that is hindered by WHO's rules and current contract conditions (maximum 12 months at a time, with no guarantee for renewal).

Availability of national assessors and external experts/trainers remains a problem, in particular in the current situation where several NMRAs are facing financial and human resources constraints and are therefore reluctant to let their experts participating in WHO-PQP activities (in particular for inspection). Maintaining the core group of senior external experts is also crucial for procedure efficiency.

### **FINANCIAL RESOURCES ARE SHORT**

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In the current situation, WHO regular funds are drastically reduced, even stopped. WHO-PQP is now requested to contribute to e.g. Director's office salaries and costs of the Department of Essential Medicines and Pharmaceutical Policies (EMP), the cost of the WHO Expert Committee meetings and activities (including its secretariat) associated with development of pharmaceutical norms and standards (however, many of the guidelines produced through the Expert Committee process give added value and legitimacy to the operations of PQP).

WHO-PQP therefore now depends on external funds. In 2010, UNITAID covered 55% of expenditure. Currently, UNITAID funds around 80% of PQP. But this percentage is expected to decline (once additional funds from the Gates Foundation are received). Too great a dependence on a single donor is evidently unwise since delayed or blocked disbursement could jeopardize WHO-PQP operations.

## 4 EVALUATION OF THE PROJECT AND ITS PROGRESS REGARDING THE OBJECTIVES ACHIEVEMENT AT MID-TERM

From the SWOT analysis the classical evaluation criteria can be addressed, discussing (i) relevance, (ii) effectiveness, (iii) efficacy and (iv) impact of the project at mid-term.

### 4.1 RELEVANCE OF THE PROJECT

#### FOREWORD

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From a theoretical point of view, the key aspect of “relevance” consists in assessing if the project is contributing to UNITAID overall objectives. Evaluating the project relevance mainly consists in assessing the activities and outputs of the projects, comparing it to the activities and expected results as described in the project plan.

From the mission’s ToR, the questions under “Relevance” are:

- Are the activities and expected outputs of the project consistent with the objectives described in the Project Plan 2009-2012?
- Does the project contribute to UNITAID’s overall goal?

#### DISCUSSION

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WHO-PQP is now a well-known and widely recognised tool. It represents a unique global system, independent from any government, ensuring that priority medicines meet international and unified standards of quality, safety and efficacy, through evaluations and inspections.

It also builds for the long term by undertaking capacity building with national regulators, QCLs and manufacturers.

Through the list of prequalified products guiding procurement decisions by UN and non-UN organisations, and the confidence built in countries, which helps in accelerating and harmonising national registration procedures, WHO-PQP contributes to facilitating access to quality products, representing value for money.

From this, we can clearly state that this project, from UNITAID objectives point of view, is fully relevant.

We can add to this statement that UNITAID is probably one of the most-relevant donors to support WHO-PQP.

## 4.2 EFFECTIVENESS

### FOREWORD

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From a theoretical point of view, it mainly consists in assessing if the project's objectives and expected results were achieved and if the project's timeframe was respected. A particular aspect of the evaluation, regarding the effectiveness, is to identify and carefully analyse the factors that influenced the project's results achievements in a positive (enhancing factors) and/or negative way (problems).

From the mission's ToR, the questions under "Effectiveness" are:

- To what extent are the project's objectives and expected results achieved/likely to be achieved?
- What are the main factors influencing their achievement/non-achievement?

### DISCUSSION

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The principal objectives of the WHO-PQP as listed in the agreement between UNITAID and WHO on the Project Plan for 2009-2012, have globally been met so far:

- Facilitate availability of good-quality UNITAID priority medicines;
- Increase number of prequalified products in UNITAID priority areas;
- Capacity building in production and regulation;
- Development and updating of global norms and quality standards;
- Testing of medicines quality;
- Communications and advocacy activities.

For some of the activities, WHO-PQP has now exceeded the annual targets chosen as indicators for 2010-2012:

- Capacity building and technical assistance to regulators, QCLs and manufacturers;
- Number of QCLs prequalified;
- Maintenance and usage of the PQP website;
- Process time for assessment and inspection (time taken to organise an inspection, to finalise the report, for screening applications received, for their assessment, for completing assessment of variations).

Some recent key accomplishments complement this global achievement:

- Initiated prequalification of APIs: with the 2 first recently approved and the second invitation for EOI published;
- Completed an in-depth analysis of the survey results of antimalarials circulating in 6 African countries; showing the effectiveness of WHO-PQP, the quality of prequalified products far exceeding that of others for this category of products affected by a high ratio of failure rate (less than 4% for prequalified products, compared to 60 %, failed to comply with specifications (Ph.Int. or USP))<sup>3</sup>;

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<sup>3</sup> Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. WHO-January 2011.

- Started a more 'client focus' approach.

However some are not yet or not regularly met and should be carefully monitored:

- The total number of new submissions received, that have been decreasing for the past two years;
- The number of inspections performed, not sufficient compared to the target number because of an incomplete team until the third quarter 2010;
- Post-prequalification sampling and testing, that was not performed last year by absence of any finalised programme received from UNITAID;
- New electronic data management system implementation delayed.

## 4.3 EFFICIENCY

### FOREWORD

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From a theoretical point of view, there are two key issues in terms of efficiency: (i) the efficiency of the PQ process itself (linking the means/investments and the results) and (ii) the coordination process with the relevant national authorities in the project's beneficiary countries and their capacity building for all QA policies and product qualification from quality point of view at country level.

From the mission's ToR, the unique question under "Efficiency" is:

- Is WHO-PQP working closely with the relevant national authorities in the project's beneficiary countries?

### DISCUSSION

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For the past 2 years WHO-PQP has putting emphasis on support and collaboration with regulators, national control laboratories and national government: capacity building through trainings and hands-on practice, but also workshops and conferences to develop awareness on WHO-PQP.

This was complemented last year by a successfully completed joint assessment with EAC and a just initiated inspection programme with EAC.

These joint evaluations and inspections are of most importance to improve recognition of WHO-PQP assessment and harmonisation of national regulations, and therefore to improve local access to essential medicines, and in a longer term perspective to develop authorities' capacity to control their local markets.



## 4.4 IMPACT

### FOREWORD

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From a theoretical point of view, the impact of the project is probably the most important aspect of the evaluation as it should indicate how the project's achievements (activities, strategies that were implemented, etc.) do influence the environment and, in a larger view, do participate to the achievement of global UNITAID objectives.

From the mission's ToR, the questions under "Impact" are:

- What are the possible ways to reduce the time to prequalify product?
- What are mechanisms in place to encourage manufacturers application and are they enough for motivation?
- Is the UNITAID priority medicines list too specific or not specific enough to promote the production of new, better formulated medicines?

### DISCUSSION

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#### REDUCING TOTAL PROCESS TIMEFRAMES

For the time under WHO-PQP control, by developing a more continuous evaluation process with more internal assessment (more WHO-PQP assessors would be required). In addition, when implemented the new IT system will facilitate more continuous assessment, by better communication of information to external assessors and management/monitoring of processes. Part related to manufacturers can nevertheless be positively impacted by technical assistance.

#### DEVELOPING MANUFACTURERS INCENTIVES

WHO-PQP is widely recognised, but should become more attractive: proposing a faster procedure for some specific and well identified products i.e. the priority products would satisfy the manufacturers but also the procurements organisations/agents and contribute to one of the UNITAID main objectives (to speed-up the access to qualified priority medicines).

Such fast processes are already used for qualifying medicines for procurement (e.g. the US FDA Tentative Approval or the ERP review) and have demonstrated their effectiveness (see *discussion under chapter 5*).

Besides proposing a faster procedure that would certainly encourage manufacturers to apply to WHO-PQP, the economical aspects should be considered; as mentioned above, the study focusing on the potential benefits to manufacturers, will help in developing a "business case for participation in WHO medicines prequalification" for presentation to manufacturers.

## UNITAID LIST OF PRIORITY PRODUCTS

As specified in objectives 1 and 2 of the Project Plan, focus on UNITAID priority medicines is intended to increase the number of suppliers by creating a market (pull-mechanism). Delays should to be avoided in the prequalification of these medicines and the dissemination of the information when prequalified.

Therefore priority medicines should be paid a particular attention:

- More flexibility in the elaboration process of the list would enable rapid revisions, to closely and promptly follow the evolutions of the market and the changes in treatments; it would make it possible the introduction of products urgently needed or for specific needs even if not in the published EOI lists;
- Developing consultation with stakeholders involved to benefit from a better and rapid feedback from the field; if needed a consultation process could be formalised later;
- Various priority levels may be necessary with prioritisation in assessment, provided this approach is justified and transparent to users;
- The highest priority products could benefit from an expedited procedure.

## 5 PUTTING THE WHO/PQP IN PERSPECTIVE WITH SIMILAR/ALTERNATE SYSTEMS EXISTING IN THE SAME CONTEXT

### 5.1 DISCUSSION

Besides WHO-PQ, other systems exist for qualifying ATM medicines before they can be procured by UN agencies for their treatment programmes: the US FDA Tentative Approval or the ERP review. It is interesting to put into perspective the WHO-PQP and the two others systems, considering their efficiency and impact. This discussion would enable to support possible recommendations for developing a specific faster procedure within WHO-PQP, as identified above in answer to stakeholders expectations (promoting rapid access to quality medicines and encouraging manufacturers to submit applications) and deserves a separate paragraph.

#### USFDA TENTATIVE APPROVAL USED THROUGH PEPFAR INITIATIVE

USFDA's TENTATIVE APPROVAL means that although a product meets all of the safety, efficacy and manufacturing quality standards required for marketing in the U.S., existing patents and/or proprietary issues currently prevent marketing of the product in the United States. Upon expiry of the patent protection or other exclusive rights in the USA, tentatively approved products will be authorised for marketing in the USA. Tentative approval, however, does qualify the product for consideration for purchase under the PEPFAR (President's Emergency Plan for AIDS Relief) programme.

These products have been added to the list of products prequalified by WHO (with reference "USFDA?"), on the basis of assessments and inspections conducted by the USFDA. Provision is made for the exchange of relevant information between the US FDA and WHO (under the terms of a corresponding confidentiality agreement), as explained in the WHO PQP list.

That signs the WHO-PQP endorsement of stringency of the US FDA assessment, recognising the Tentatively Approval as equivalent as the WHO prequalification.

WHO-PQP does not conduct any further assessment, only a prior administrative checking with the manufacturer concerning data to be included in the PQ list, and its permission for such inclusion. The manufacturer is given the possibility to stop its WHO-PQP application for the same dossier when tentatively approved. That already occurred with an Indian manufacturer who withdrew all its applications.

Tentative approval procedure run through an expedited review process; due to the significant public health impact of these products (single entity, FDC and co-packaged version of the previously approved ARV therapies), US FDA prioritises their review and commits to complete them as fast as possible (6 months, even 2 to 6 weeks for high-quality applications), in any cases, much faster than the WHO-PQP.

#### **Instead of being complementary, both procedures may be competing!**

WHO-PQP considers that there are no significant differences between the US FDA requirements for approval of generics compared to the WHO prequalification with respect to the most crucial items, the quality, safety and efficacy of the products. Products that receive a tentative approval indeed undergo the same US FDA review as products that are approved and marketed in the US. However tentative

approval is a step prior the final approval for entering the US market; the final approval may not be a pure administrative step but the moment to complete the assessment of additional data such as:

- further stability data (e.g. data supporting use in climatic zones III and IV);
- on significant changes made to the products or manufacturing processes since tentative approval (e.g. addition of new manufacturing facilities, important new safety information, addition/change of the API source).

Some products remain tentatively approved for long, waiting for the final approval (e.g. some are tentatively approved since 2005) and can be procured through the PEPFAR program. It can be questioned whether, during that period, the update regarding any significant change made by the manufacturer or their manufacturing site monitoring is adequately assessed and by whom.

In addition, US FDA states that if different packaging is selected after tentative approval, it is anticipated that procurement organisations, applicants, and regulatory authorities will cooperate to share information on equivalence of protection.<sup>4</sup>

Therefore, if the US FDA expedited review process is obviously safe and robust, the use of products tentatively approved, i.e. at a stage prior the final approval for US market, may represent a risk of incomplete assessment if no further system for reporting and assessing significant changes, and complementing information during their use through PEPFAR programme is in place.

Nevertheless, PEPFAR initiative supported by the US FDA expedited review for antiretroviral therapies is obviously a good way for promoting rapid access to quality medicines and encouraging manufacturers to submit applications.

## EXPERT REVIEW PANEL (ERP)

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For medicines meeting eligibility criteria (such as submission of a dossier for prequalification) WHO-PQP hosted and makes expertise available in support to an Expert Review Panel process developed in conjunction with the GFTAM and now adopted by others such as GDF, UNFPA and UNITAID.

In the absence of a needed prequalified product, an expert review of relevant dossiers that are currently undergoing assessment by WHO-PQP or a stringent regulatory authority is conducted. The aim of the review is to ascertain whether any of the products under assessment can be considered for procurement ahead of their possible prequalification by WHO.

This is a risk-based process that gives added value (flexibility/faster access to international funds) to what WHO-PQP does from the procurement and manufacturers point of view without compromising the quality in long-term perspective.

In 2010 a total of 207 products (32 for HIV of which 9 for UNITAID, 142 for TB, 24 for malaria, and 9 for neglected tropical diseases) have been reviewed. The costs of reviewing ERP dossiers for GFATM and GDF are covered by the former and time assigned to ERP reviews is managed carefully by WHO-PQP team so as not to detract from regular assessment activities.

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<sup>4</sup> “Guidance for industry: fixed dose combinations, co-packaged drug products, and single-entity versions of previously approved antiretrovirals for the treatment of HIV”-US Dpt of Health and Human Services-FDA-CDER- Procedural October 2006

## 5.2 PROPOSAL

WHO-PQP could develop an approach similar to ones of these two: an expedited review of products identified as high priority by UNITAID, through a safe and risk-based process, therefore with strict and defined conditions (temporary approval, no renewal, with possibility to stop/refuse the application in case of non compliance) and subject to satisfactory completion of a WHO-prequalification and maintenance of prequalified status.

It would enable to increase the number of products eligible for procurement, in particular for products which are identified by as urgently or highly needed and when no or few prequalified products or SRA authorized product are available on the market; satisfying one of the UNITAID main objectives.

WHO-PQP team has already shown reactivity and ability in operating with such fast process, through the management of the Expert Review Panel (ERP) and would certainly be able to rapidly set up such a system. However it will require a careful process monitoring and is subject to adequate human resources (at least the maintenance of the internal staff and the external expert pool) and adequate funding (and may require a reallocation of estimated funds), the two identified threats for the management and development of the WHO-PQP system.

## 6 RECOMMENDATIONS AND ADVICES ON HOW TO IMPROVE THE EFFECTIVENESS AND EFFICIENCY OF THE PROJECT MANAGEMENT

### 6.1 WHO-PQP REPORTING ON PROJECT ACTIVITIES AND FINANCE

WHO-PQP has to provide UNITAID secretariat with interim and annual progress reviews to report on the progress made on the implementation of the project and the financial status, according to the schedule of Disbursements and Reporting included in the Project Plan for 2009-2012. The disbursements of UNITAID funds are subject to submission in due time and UNITAID approval of the annual reports submitted. In addition regular intermediate updates and products dashboards, listing the status of the assessment of the UNITAID priority products, are provided to UNITAID Secretariat. The production of these reports should be facilitated by the implementation of the new financial reporting system and the future Electronic Data Management System (in particular for the products dashboard).

#### REPORTING ON PROJECT ACTIVITIES

WHO-PQP provides UNITAID secretariat with an interim and an annual review to report on the progress made on the implementation of the project objective according to the agreed objectives and performance key indicators (KPI). The objectives and KPIs, originally defined in annex of the UNITAID Project Plan for 2009-2012, have been reviewed by WHO-PQP based on the experience in the project (as foreseen in the agreement). They have been submitted to UNITAID secretariat and approved and have been used for 2010 review, and when relevant and possible, also used retrospectively to compare 2008 and 2009 performance. If this revision enables a more accurate monitoring of the activities and assessment of the progress made (by detailing some activities, gathering others under key activities, including assumption for achievement), further revision could be done to include qualitative KPIs, more appropriate to some of the activities: e.g. the number of prequalified products is not an appropriate quality performance indicator and could be complemented by e.g. the length taken for process steps related to WHO-PQP (as already done for screening and variations) and the number of complaints received from users). That could be done when incorporating the new matrix adapted to the UNITAID logical framework approach.

WHO-PQP has elaborated a proposed logical framework matrix, on UNITAID's request, that is a totally new presentation of the agreed goal and objectives of the WHO-PQP, through objectives, outputs and activities, including for each of them, indicators of achievement, means of verification, important risks and assumptions; that would help in a more accurate review of the activities and facilitating the planning and management of the project. This proposed matrix has already been discussed with UNITAID Secretariat and should, as soon as possible, end to an approved version, in order not to delay its implementation for the 2011 activity review.

#### REPORTING ON FINANCE

WHO-PQP is expected to provide in annual and interim reports a detailed statement of all income and expenditures for each of the activities, including justification of any variance. However the 2009 interim and annual reports and the 2010 interim report on finance did not satisfy UNITAID Secretariat for the level of information given, in particular for justifying the numerous variances, detailing the levels of funding necessary to achieve the objectives, explaining underspending (for using other donor's funds) or

overspending (for lack of WHO funding), etc. Since disbursements are subject to approval of the progress reports as stated in the Grant Agreement, none of the estimated disbursements were paid (for October 2009, June 2010, October 2010), after the initial payment (\$8,000,000) at signature of the Project Plan. Despite meetings in July 2010 and January 2011 between UNITAID and WHO-PQP, the problem remains and the last WHO-PQP disbursement request was not accepted: only 2010 deficit (US\$6,000,000) was covered (in March 2011) and further instalment is still pending subject to submission and approval of an adequately revised 2011 budget.

The issue seems more due to a problem of inadequate initial allocations of provisions (described in the Project Plan), insufficiently detailed financial reporting (from UNITAID's perspective) by WHO-PQP due to lack of clarity regarding UNITAID expectations (from PQPs perspective), than to a problem of not justified expenditure. However WHO-PQP should have systematically officially reported every budget heading variance over 10% for UNITAID prior approval, according to the signed agreement. Difficulties encountered earlier with WHO global management system (GMS), lack of time and specific expertise to be dedicated to financial issues in WHO team, lack of UNITAID staff continuity seemed to exacerbate the problem. The WHO structure, extremely centralised, does not facilitate the development of a project-based approach for financial review at departments/services level. All together these conditions, in respect to financial matters, have not facilitated communication and mutual understanding of UNITAID expectations and WHO-PQP constraints.

The situation needs to be resolved as soon as possible.

In 2010 WHO-PQ requested an external support (Pricewaterhouse Coopers) to help in improving the budget management and review. The proposed template, workable with the WHO GMS, seems answering the WHO-PQP expectations and should enable a more efficient and accurate management of the WHO-PQP financial resources:

- Helping to give the detailed supporting information to be put in the financial annual review to UNITAID;
- Helping WHO-PQP managers in deciding on priorities, elaborating strategies for the activities, planning and funding.

Discussions initiated recently (April) on presentation of this template, revised reporting indicators and format, proposed logframe, should continue and end to an agreement as soon as possible on the logframe and on the consecutive revision of the financial reporting, concerning its format and the level of details in the information to be provided.

The WHO-PQP estimation for the funding required for 2011 (US\$ 14.95 million) is in line with the amount estimated in the project agreement for 2011 and 2012 (US\$15 million). The proposed allocation of funds for 2011 per objectives/activities includes the unspent funds from 2009 and 2010, and takes into account the other available funds (Gates, GFATM) and, mainly, the experience in the project and a better budget management. This proposal (submitted with the financial report) includes big changes and therefore needs to be discussed to come to a formal approval by UNITAID, according to the agreement.

## 6.2 UNITAID INTERNAL MANAGEMENT RELATED TO WHO-PQP

According to the Project plan for 2009-2012, UNITAID is responsible for:

- Timely provision to WHO to enable continuation of prequalification process within a budget not exceeding US\$ 40,000,000;
- Ongoing review of the financial and activity progress of the project;
- Collaboration with partners and other international procurement agencies to stimulate continued interest of manufacturers to participate in the prequalification process.

The first one is subject to evidence of need, technical soundness of the programme and submission of technical and financial progress reports satisfactory to UNITAID. As seen above, if satisfied by the technical part of the reports submitted by WHO-PQP, UNITAID is not by the financial ones, and therefore did not approve disbursement requests. The current situation is critic, financially for WHO-PQP who does not have other funding to cover its activities expenditures, but also for UNITAID regarding the management of this funded project and the need to have the main objective met thanks to the WHO-PQP activities: to facilitate and maintain the prequalification of UNITAID-funded medicines.

Despite these reports are obviously necessary to a good management of the project for both parties, they are time consuming and it is crucial that they meet the UNITAID expectations. Discussion between both parties should continue to come soon to an agreement on the financial reporting pending issues (above mentioned).

The UNITAID management of WHO-PQP is of course not limited to the review and approval of interim and annual reports, and requires an ongoing review of the project progress. That would be facilitated by enlarging of the 'contact teams'. From UNITAID side the project managers should be assisted by a contact person, who could dedicate sufficient time to the regular project follow-up and would preferably have a scientific background. From WHO-PQP side, the PQP manager and the liaison officer should be accompanied by a person with strong financial skills, who may be contracted to overcomes problems of recruitment within WHO.

Collaboration with partners and other international procurement agencies to stimulate continued interest of manufacturers is one of the UNITAID responsibilities to be promoted. Its role and influence, as major donor, is crucial regarding the manufacturer incentive, but also regarding its partners and other organisations adherence to UNITAID quality procurement policy.



## 6.3 IMPROVEMENT OF THE EFFECTIVENESS AND EFFICIENCY OF THE PROJECT AND CHALLENGES

Altogether the results show that the situation today is good regarding the likelihood the objectives are met, provided the efforts and improvements made by WHO-PQP in the organisation and management of the project (as discussed above) are maintained, and further improvements are considered (i.e. developing an expedite process for identified high priority products).

That also obviously depends on external factors, difficult to influence on, such as the manufacturers incentive, and last but not least the human and financial resources available.

The relevance to maintain the quite ambitious objectives of the 2009-2012 agreement could be questioned in particular as regard the current crisis at WHO and the general economical situation. However these objectives are well based to effectively and efficiently ensure that medicines that are procured for the ATM treatment programmes with UNITAID funds, meet unified quality standards and are increased in number for priority medicines.

Furthermore these objectives include activities of capacity building for regulators and manufacturers, that are of main importance for increasing capacity in production quality of priority products, facilitating the development of national regulatory process and promoting capacity building for quality control of medicines in recipient countries. It should bear in mind that it is a long-term objective, the impact of which is difficult to evaluate during the four-year course of the project, through objective and measurable indicators. However results can already show its effectiveness and efficiency: from the manufacturers side, the improvement in the quality of the received dossiers (e.g. noticed from the increase in number of dossiers passing the screening step and the decrease in rejected dossiers); from the regulators side, the increase in number of QCL prequalified and the successful joint evaluations and inspections. This activity, in such scale and provided with such expertise, is worth the resources invested since it is unique and can certainly valuably participate in improving the Quality in procured medicines.

However improvements in the project and, even, the continuation of the current level of activity are subject to:

- A reinforcement of the staff capacity and maintenance of the external expert involvement:
  - o Could some autonomy be given for temporary posts financed with non-WHO funding? i.e. specific recruitment procedures with more flexible rules. Could the use of external contracts be developed?
  - o How to secure the input for external experts? Is a commitment for experts' participation from member states possible?
- Sufficient and sustainable financial resources:
  - o To find other funding (new or renewal); also for sake of independence and limiting any risk of influence by having a unique donor;
  - o To ask for fees from applicants, in particular for technical assistance but also for evaluation/inspection and/or for maintenance of prequalification for a product? Application fees exist for prequalification of vaccines and diagnostics and the possibility of cost recovery is described in the Procedure for prequalification of pharmaceutical products. However the appropriate moment to implement it in order not to be a break to manufacturers' incentive should be considered.

## 7 TO GO FURTHER: PROPOSALS FOR FUTURE DEVELOPMENTS

### 7.1 EXTENDING THE WHO-PQP SCOPE

The expression of interest (EOI) is the starting point of the WHO-PQ procedure: only products listed in the invitations for EOI are eligible and they are currently limited to products included in the WHO treatment guidelines for HIV/AIDS, malaria and tuberculosis. It is too restricted according to stakeholders, who expect to have it extended to other (non ATM) essential medicines. Such extension would develop manufacturer incentive and would meet the WHO-PQP role (making quality priority medicines available for the benefit of those in need).

Some medicines for opportunistic infections are already included in the EOI list for Medicines to treat HIV/AIDS (such as antiviral, antibacterial, antifungal agents, palliative care drugs). However it may be difficult to define a list and discussion with partners in Public Health sector should be considered.

It may be worth to go step by step starting with anti-infectives of WHO Model List of Essential Medicines. Not only because they are most likely included in countries' EML and national treatment guidelines, showing their major interest at country level, but mainly because it would meet the recent WHO warning on loss of Essential Medicines. The WHO has just published (April 2011)<sup>5</sup> a policy package that sets out the measures governments and their national partners need to combat drug resistance. The policy steps recommended by WHO include developing and implementing a financed national plan; strengthening surveillance and laboratory capacity; ensuring uninterrupted access to essential medicines of assured quality; and regulating and promote rational use of medicines.

WHO-PQP has an obvious role to play in this call to "Combat Drug Resistance".

### 7.2 ADVOCACY TO STAKEHOLDERS

In order to harmonise the QA procurement policies to the valuable one: 'assured quality before price'.

UNITAID, as promoter of this policy and major donor, has a role to play in advocating to, first, other donors and also others stakeholders. Reinforcing such policy and its implementation at all stages would also promote manufacturers incentive and participate in fair price competition.

Discussion with donors and buyers may also consider manufacturers request for better forecasting from buyers and possible guarantee on sales for prequalified products (e.g. through long-term contract).

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<sup>5</sup> [http://www.who.int/mediacentre/news/releases/2011/whd\\_20110406/en/index.html](http://www.who.int/mediacentre/news/releases/2011/whd_20110406/en/index.html); World Health Day 2011-Urgent action necessary to safeguard drug treatments-News release

### 7.3 POST-MARKETING SURVEILLANCE – BATCH MONITORING

The sampling and testing programmes (to be developed, with UNITAID and also other partners) could be complemented by a surveillance of the circulating products:

- At the manufacturers level, by a batch monitoring, checking the coherence of the batches produced with those supplied; such control could be delegated to national/local inspectors; a system to collect the information on the batches procured would be needed;
- At the distribution channel and end-users level, by collecting any quality incident detected on products, in addition to the pharmacovigilance programmes when in place.

## Table of Annexes

- Annex 1 Terms of reference (SPHQ11-APW-11)
- Annex 2 List of Persons Met
- Annex 3 List of Documents Consulted
- Annex 4 Process Flow of the Procedure for Prequalification of Pharmaceutical Products or APIs
- Annex 5 Organization Chart of WHO PQP of Medicines Team (as at 31 December 2010)

# **Annex 1 – Terms of Reference of the Mission**

## **IMPLEMENTATION OF MID TERM REVIEWS OF UNITAID-SUPPORTED PROJECTS**

### **1. PURPOSE OF THESE TERMS OF REFERENCE**

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These Terms of Reference (TOR) serves as an overall framework for the services to be provided by the European Agency for Development and Health (AEDES), which has been selected to conduct the mid term review of the UNITAID funded WHO Prequalification project on the basis of their proposal submission in response to UNITAID's Request for Proposal (RFP) Bid Reference 2010.005.

### **2. OVERVIEW KEY CONCERNS TO BE ADDRESSED**

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The objective of the consultancy is to assess the progress made towards the UNITAID funded WHO Prequalification project's agreed objectives and make recommendations on how project management can be improved to help the project achieve its objectives more effectively and efficiently.

AEDES is expected to provide an assessment of the likelihood of the WHO Prequalification project achieving the objectives that were initially set by UNITAID and WHO and of the progress of the project at mid-term review.

In addition, AEDES should provide recommendations on how to improve the effectiveness and efficiency of project management, including partner reporting on project activities and finance.

AEDES is expected to work closely with the UNITAID Secretariat to undertake reviews of the projects using official documents, evaluation checklists, questionnaires and other associated tools that may be used to evaluate UNITAID-funded projects. UNITAID requires that AEDES consider the following information:

- the legal agreements between UNITAID and its implementing partners for the WHO Prequalification project;
- the progress reports and the follow-up performed by UNITAID Portfolio Manager(s) with regards to semi-annual and annual reports from implementing partners; and
- the financial reports from implementing partners in order to assess the relationship between the financial information provided in each progress report and the information provided on activities, results and for the associated M&E indicators.

Assessment of the above-mentioned documentation will facilitate the identification of the WHO Prequalification project's strengths, weaknesses, opportunities and threats and contribute to improving the chances that the project's end outcomes are achieved.

AEDES will propose a project rating in line with the criteria developed by the UNITAID Secretariat according to UNITAID's strategic objectives.

UNITAID will provide AEDES with project plans, legal agreements, project reports, including financial reports, from Implementing Partners as well as any other information deemed necessary to perform a thorough review of the project. The scope of the project reviews shall not extend beyond the scope of the relevant programmatic review provisions contained in the applicable agreements that UNITAID has with its implementing partners.

In its proposal submission, AEDES has presented a proposed Approach and Workplan. AEDES, in consultation with UNITAID, will submit to UNITAID a more detailed Approach and Workplan, to be refined jointly with UNITAID in accordance with Logical Framework approach. The Approach/Workplan will address the specific questions listed below:

**Relevance:**

1. Are the activities and expected outputs of the project consistent with the objectives and expected outcomes as described in the project plan?
2. Is it possible to show how the project has contributed to UNITAID's overall goal of using innovative, global market-based approaches to improve public health by increasing access to quality products to treat, diagnose and prevent HIV/AIDS, tuberculosis and malaria?

**Effectiveness:**

1. To what extent were the objectives of the project achieved
2. To what extent are they likely to be achieved?
3. What are the main factors influencing the achievement or non-achievement of the objectives?

**Efficiency:**

1. Are the project partners working closely with the relevant national authorities in the project's beneficiary countries (where applicable to the project)?
2. Is the project's procurement model well defined and designed to identify and solve procurement-related problems as they arise?

**Impact:**

1. What are the possible ways to reduce the time lag between dossier submission by companies and the final decision by WHO to prequalify the drugs or diagnostics of such companies?
2. What mechanisms are in place to encourage manufacturer submission of dossiers for prequalification?
3. Are the current mechanisms in place to encourage manufacturer submission of dossiers enough to motivate manufacturers to make submissions to the WHO Prequalification Programme?
4. Is the UNITAID priority medicines list too specific or not specific enough to promote the production of new, better formulated medicines?

### 3. TASKS AND RESPONSIBILITIES

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In addition to the refinement of the mid term review approach and work plan, the tasks and responsibilities for the review will include meeting with UNITAID Secretariat members and other stakeholders to:

1. review the project documentation, including project specific monitoring indicators and financial reports;
2. Work with implementing partners to incorporate the logical framework approach into the project plan to improve monitoring indicators and facilitate reporting to UNITAID;
3. review the current reporting templates for both project activity and project financial reporting and suggest improvements to routine project reports and modify, if necessary, the frequency and timing of reporting;
4. provide an assessment of the project management of each project under review, including strengths, weaknesses, opportunities and threats;
5. provide a rating of each project management using criteria developed by the UNITAID Secretariat, based on the UNITAID Strategy 2010-2012 and adjusted to the specific goals and objectives of each project; and
6. advise and assist in the development of an action plan to incorporate the lessons learnt from internal project management of specific projects and partners over the course of UNITAID's operational activities.

### 4. REPORTING REQUIREMENTS

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AEDES is expected to submit:

1. Written recommendations and advice to the UNITAID Secretariat on the progress of WHO Prequalification project under mid-term review, including on the extent to which goals and objectives have been met by the project and/or the likelihood of achieving these by the end of the project;
2. Written recommendations and advice to the UNITAID Secretariat on how to improve the effectiveness and efficiency of partner reporting on project activities and finance including suggestions for revising the information related to M&E, procurement processes and finance currently requested from implementing partners;
3. Written recommendations and advice to the UNITAID Secretariat on how to improve the effectiveness and efficiency of UNITAID internal project management related to the WHO Prequalification project; and
4. A final written assessment of the WHO Prequalification project under mid term review including a rating based on criteria developed by the UNITAID Secretariat.

## 5. DURATION AND TIMELINES

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This consultancy is for a period of 6 months. The work should start on 05 December 2010 or as soon as possible thereafter and will end on 31 May 2011.

See below the specific deliverables and timelines:

Deliverable	Due date
Written recommendations and advice to the UNITAID Secretariat on how to improve the effectiveness and efficiency of partner reporting on project activities and finance including suggestions for revising the information related to M&E, procurement processes and finance;	28 February 2011
Written recommendations and advice to the UNITAID Secretariat on how to improve the effectiveness and efficiency of UNITAID internal project management related to the WHO Prequalification project;	28 February 2011
Written recommendations and advice to the UNITAID Secretariat on the progress of WHO Prequalification project under mid-term review, including on the extent to which goals and objectives have been met by the project;	21 March 2011
A final written assessment of the WHO Prequalification project under mid term review including the project-specific LogFrame and a rating based on criteria developed by the UNITAID Secretariat.	31 May 2011

## 6. GUIDANCE AND COORDINATION

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The consultancy shall be conducted under the overall guidance of the Director of Market Dynamics and Operations. During the consultancy period, the selected consultants shall be working in close cooperation with UNITAID staff, partners and other stakeholders, and may be required to report upon request to members of the UNITAID Executive Board.

## 7. PAYMENT SCHEDULE

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Payment shall be made on completion of the work and on submission of invoice.

## 8. GENERAL AND CONTRACTUAL CONDITIONS

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Any and all of the Contractor's (general and/or special) conditions of contract are hereby explicitly excluded from the Contract, i.e., regardless of whether such conditions are included in the Contractor's offer, or printed or referred to on the Contractor's letterhead, invoices and/or other material, documentation or communications



The reviews to be conducted under this consultancy shall not amount to audits or operational/administrative reviews of WHO departments or of WHO hosted partnerships that have benefitted from UNITAID funding.

The scope of the project reviews shall not extend beyond the scope of the relevant programmatic review provisions contained in the applicable agreements that UNITAID has for this project.

This contract will be governed by the general and contractual conditions of the Agreement for the Performance of Work (APW) to be signed between WHO/UNITAID and AEDES, and section seven (7), General and Contractual Conditions as presented in the Request for Proposal (RFP) Bid reference 2010.005.

## Annex 2 – List of Persons Met/Contacted During the Evaluation Study

### WHO (GENEVA)

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Hans Hogerzeil, Director, Department of Essential Medicines and Pharmaceutical Policies

Lembit Rägo, Coordinator, Quality Assurance and Safety Medicines

Sabine Kopp, Manager, Quality Assurance Programme, Quality Assurance and Safety: Medicines

Marco Antônio de Ávila Vitória, Medical Officer, Department of HIV/AIDS

Andrea Bosman, Coordinator, a.i. Diagnosis, Treatment and Vaccines, Global Malaria Programme

Paloma Marroquín Lerga, Technical Officer, The Global Drug Facility, Stop TB Partnership Secretariat

Joerg Hetzke, Knowledge & Information management, Health Systems and Services

Eric Georget, Finance (FNM),

### PREQUALIFICATION OF MEDICINES TEAM

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Anthony R. Gould, Programme Manager

Jacqueline Sawyer, Liaison Officer

Matthias Stahl, Medical Officer, Head of Assessments

Adriaan J. van Zyl, Technical Officer, Head of Inspections

Jitka Sabartova, Technical Officer, Quality Control Laboratories

Milan Smid, Technical Officer, Training and Technical Assistance

Antony Fake, API assessor

Hua Yin, Quality assessor (variations)

Laura Oakes, Prequalification Secretariat

Angela Lopes, secretary (website)

Natasa Moravecic, Technical specialist (in Copenhagen)

## UNITAID (GENEVA)

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Philippe Duneton, Deputy Executive Director

Raquel Child, Director, Market Dynamics & Ops

Kate Strong, Programme Monitoring Officer

Brenda Warning, Coordinator, Market Dynamics

Lorenzo L. Witherspoon, Supply Advisor

Ambachew Yohannes, Technical Officer, Malaria; PQP

Imelda de Leon, Portfolio Manager, Malaria

Jane Galvao, Technical Officer, HIV/AIDS

Greg Martin, Technical Officer, HIV/AIDS

Lisa Regis, portfolio manager, TB

Gauri Khanna, Officer, Monitoring and Evaluation

Kvetka Dzackova, Finance Officer

## STAKEHOLDERS

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Atieno Ojoo, Technical Specialist Pharmaceuticals, UNICEF-Supply Division, Copenhagen

Sophie Logez, Senior Global Health Supply Policy Officer, QA and Data Management Team, GFATM, Geneva

Joëlle Daviaud, Senior Technical Officer, Quality Assurance for Pharmaceuticals, GFATM, Geneva

Elodie Jambert, pharmacist, MSF/Campaign for Access to Essential Medicines, Geneva

Zeba Ahmad Shuja, Director Technical, Shazoo Zaka (Pvt) Ltd, Pakistan (*manufacturer*)

## EXTERNAL ASSESSOR/INSPECTORS

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Lynda Paleshnuik, senior Quality assessor, Canada

Theo Dekker, senior Quality assessor, South Africa

John Gordon, senior BE assessor, Canada

Senoi Mogatle, Quality assessor, Botswana

Gabriel K Kaddu, Quality assessor, Uganda

Olivier Gross, Senior Public Health Inspector, French Ministry of Health (*former WHO-PQP team member*)

## OTHERS

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Mark A. Kays, Interclarity Research & Consulting, Inc., USA

Lou Riceberg, Principal, Biobridge Strategies, USA

Harald Rinde, Principal, Biobridge Strategies, Switzerland

## Annex 3 – List of Documents and Web Sites Consulted During the Evaluation Study

### UNITAID

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#### Website

<http://www.unitaid.eu>

#### Documents provided by UNITAID or found from the Website

- Resolution-EB1/10, Oct 2006
- MOU-2006
- Resolution-EB2/10, Nov 2006
- Letter of Agreement- March 2007 (Grant number UP 6208)
- Project proposal 2008-2012 (Part I : Administrative Information ; Part II : Project Proposal)
- Resolution-EB7/6, April 2008
- Project Agreement 2009-2012
- Project plan for 2009-2012 (Annex 1 ; exhibits)
- Using the Logical Framework Approach at UNITAID
- Main terms of the Agreement between UNITAID and Partner(s)- Template
- Organigram 2010
- 2010 List of UNITAID Priority Medicines for PQ
- WHO-PQP Interim Financial Statement Dec 2009
- Finance assessment: PQP disbursement request 27/01/2011
- WHO PQP project Financial report 2009-2010, september 2010 (letter from PQP to UNITAID)
- WHO-PQP letter 27 Jan 2011
- UNITAID letter 18 Feb 2011
- Interim reporting on progress of approved projects, opérations
- The Medicines Patent Pool initiative-UNITAID factsheet-July 2010
- The Medicines Patent Pool initiative-Frequently asked questions-July 2010
- The Medicines Patent Pool initiative-Stimulating innovation, improving access-Jan 2011
- The Medicines Patent Pool launches Patent information resource to aid people working to increase access to HIV medicines-4 April 2011

### Websites

<http://apps.who.int/prequal>

<http://www.who.int/world-health-day/2011>

[www.who.int/medicines](http://www.who.int/medicines)

### Documents provided by WHO-PQP or found from the Websites

- 2008 Annual report to UNITAID (May 2009)
  - 2009 Interim Report to UNITAID (at 30 June 2009)
  - 2009 Annual report to UNITAID (May 2010)
  - 2010 Interim Report to UNITAID (at 30 June 2010)
  - 2010 Annual report to UNITAID (15 March 2011)
  - Financial report to UNITAID 2009-2012
  - Update n°13 : UNITAID project support for quality assurance of medicines, 2009-2012 – WHO Prequalification Of Medicines Programme (PQP)- 16 March to 30 September 2010
  - Overview workplan, actuals and funds (period 2010 & 2011)
  - PQP indicators 2010-2011 25Mar10 REV.xls
  - WHO-PQP facts and figures for 2010
  - WHO Prequalification of Medicines Programme: survey of service quality provided to manufacturers- WHO Drug Information Vol. 24, No. 4, 2010
  - Meeting with manufacturers – Copenhagen 26-27 July 2010- WHO-PQP in a new decade- Pharmaceutical manufacturer Survey-report of research findings- WHO-PQP team and Interclarity consulting presentation
- 
- WHO's role in measures to ensure the availability of good-quality, safe, efficacious and affordable medicinal products- Working group of member states on substandards/spurious/falsely-labelled/falsified/counterfeit medicinal products-provisional agenda item 4 (A/SSFFC/WG/2; 7 Feb 2011)
  - WHO's role in the prevention and control of medical products of compromised quality, safety and efficacy such as substandards/spurious/falsely-labelled/falsified/counterfeit medicinal products-provisional agenda item 5 (A/SSFFC/WG/3 Rev.1; 17 Feb 2011)
  - Drug manufacturing in Africa- Lembit Rago, Jitka Sabartova, Jacqueline Sawyer- [www.thelancet.com](http://www.thelancet.com) Vol 376; Sept 18, 2010.
  - Registering new drugs for Low-income Countries: the African Challenge- M. Moran, N. Strub-Wourgarft, J. Guzman, P. Boulet, L. Wu, B. Pecoul- PLOS Medicine, [www.plosmedicine.org](http://www.plosmedicine.org), Vol8, issue 2; Feb 2011
- 
- Mutual confidentiality arrangement and commitment between USFDA (HHS) and WHO-QSM: medicines; signed August 2005
  - Cooperation arrangement between WHO-QSM: medicines and biologicals and PIC/S; signed May 2009

- Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa- Jan 2011- WHO/EMP/QSM/2011.1 (QAMSA report)
- Survey of the Quality of antimalarial medicines-Recommendations on the content of a Survey protocol
- WHO quality monitoring project for drugs supplied Under UNITAID funding- version3, June 2009
- Deficiencies in generic product dossiers as submitted to the WHO Prequalification of Medicines Programme (draft)
- Invitation to manufacturers to submit an Expression of Interest: 10<sup>th</sup> invitation for TB (Aug 2010+ amendment Feb 2011; 10<sup>th</sup> for HIV (Nov 2010); 8<sup>th</sup> for malarials (Aug 2009); 1<sup>st</sup> and 2<sup>nd</sup> for APIs;
- Guidelines for registration of fixed-dose combination medicinal products WHO Technical Report Series, No. 929, 2005
- Guidelines on the requalification of prequalified dossiers-WHO Technical Report Series, No. 957, 2010
- Guidelines for the preparation of a contract research organization master file-WHO Technical Report Series, No. 957, 2010
- Guidance for assessors in Copenhagen rev (CP58-Nov 2010)
- Procedure For Prequalification Of Pharmaceutical Products-WHO Technical Report Series, No. 953, 2009
- Procedure For Prequalification Of Pharmaceutical Products. Proposal For Modification- Working document QAS/10.392, September 2010
- Procedure For Prequalification Of Pharmaceutical Products. Amended after comments- Feb 2011-
- Procedure for assessing the acceptability, in principle, of APIs for use in pharmaceutical products-WHO Technical Report Series, No. 953, 2009
- Declaration of interests for WHO experts/ temporary advisers (2010)
- Confidentiality agreement for evaluators of product dossiers and for inspectors (2010)
- Pre-assessment template: HA999 (Jan2011)
- Screening Checklist – Generic Product SRA Approved (Nov 2010)
- Screening Checklist – Generic Product (Jan 2009)
- Screening Checklist – Innovator (May 2009)
- SOP for WHOPAR compilation for generic products-version 2.0 (Jan 2011)
- SOP for ERP : *Ad hoc comparative\* quality\*\* risk assessment reviews of finished pharmaceutical products (FPPs) - advise on potential acceptability, in principle, of certain FPPs for one-time procurement in the absence of products meeting all the required standards (Oct 2010)*
- SOP for review of notifications (April 2010)
- SOP for Processing of expression of interest for prequalification of a QCL (SOP 701.1)
- SOP for Handling of complaints (SOP 411.2- Jan 2010)
- SOP for communication between assessors and inspectors (SOP 412.1-Nov 2009)
- SOP for Inspection frequency and scheduling (SOP 401.1- Sept 2008)
- SOP for Preparing for an Inspection (SOP 402.2-March 2010)
- SOP for Conducting an Inspection (SOP 403.1-Sept 2008)
- SOP for Preparing an Inspection Report (SOP 404.3-Sept 2010)
- SOP for Closing out an inspection (SOP 405.3-May 2009)
- SOP for Tracking of Inspections (SOP 406.1-Dec 2008)
- SOP for Notice of concern (SOP 404.7-Sept 2008)
- SOP for Preparing a World Health Organization Public Inspection Report (WHOPIR)(SOP 408.3-July 2009)
- SOP for training of inspectors (SOP 409.1-Oct 2010)
- SOP for Inspection letters templates (SOP 410.3-Jan 2010)

- Letter template for :
  - Efficacy/safety Assessment- acceptability (2010)
  - Efficacy/safety Assessment-request for additional information- (rev jan 2011)
  - Quality assessment-request for additional information- (rev jan 2011)
  - Variation assessment-request for additional information (2010)
  - Variation assessment-acceptability (2010)
  - API master file assessment-request for additional information (2010)
  - API master file assessment-acceptance (2010)
  - 
  - API master file assessment of amendment-acceptance (2010)
  - API master file assessment of amendment-request for additional information (2010)
  - New API master file –acceptance (2010)
  - API prequalification approval (2010)
  - Publication in prequalified products list + Main characteristics of the prequalified medicinal product-Generic Template
  - Publication in prequalified products list + Main characteristics of the prequalified medicinal product-Innovator Template
  - Notice of suspension
  - Site Master File or Laboratory Information File-reception
  - WHOPIR publication
  - Notice of concern
  - Agreement with the terms of Technical Assistance organized by the World Health Organization (WHO) Prequalification of Medicines Programme
  - Proposal for technical assistance
  - Request/proposal for technical assistance for manufacturer/CRO/QCL
  
- Prequalification of Medicines Information management solution- Request for Proposal (RFP) –Bid Reference # 5090
- Requirements specification document- Request for Proposal Bid Reference # 5090 R1

## OTHER WHO DEPARTMENTS

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### Websites

<http://www.who.int/world-health-day/2011>

<http://www.who.int/medicines>

### Documents found from the other WHO Departments

- Prequalification of Diagnostics (update) –Diagnostics and Laboratory Technology- WHO-Issue 6 Q1 2011
- Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes- WHO/IVB/07.08
- Frequently asked questions on the prequalification of medicines for reproductive health- Concept Foundation
  
- WHO Expert Committee on Specifications for Pharmaceutical preparations: outcome of 44 meetings-2011



- Director-General statement- WHO World Health Day 201- Combat drug resistance- No action today, no cure tomorrow- <http://www.who.int/world-health-day/2011/en/>
- Urgent action necessary to safeguard drug treatments- WHO press release

## OTHER SOURCES

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### Websites

[www.pepfar.gov/](http://www.pepfar.gov/)

[www.fda.gov/InternationalPrograms](http://www.fda.gov/InternationalPrograms)

[www.fda.gov](http://www.fda.gov)

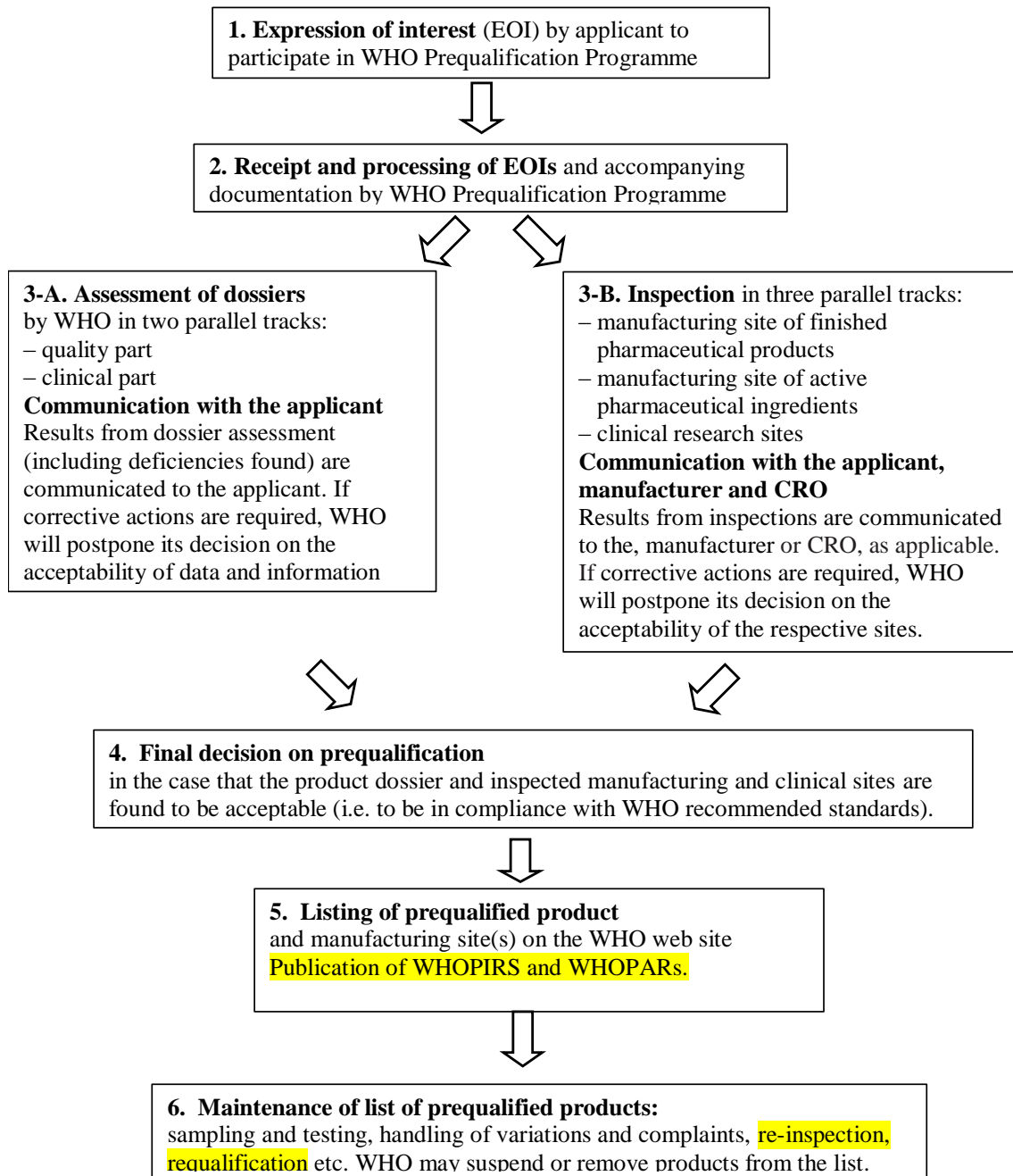
[DRUGINFO@fda.hhs.gov](mailto:DRUGINFO@fda.hhs.gov) (CDER DRUG INFO)

### Documents

- WHO warn loss of Essential Medicines; Pharmaceutical Technology.com- April 08 2011
- 5th Invitation to manufacturers of antiretroviral medicines to submit an Expression of Interest (Eoi) for product evaluation by Expert Review Panel (ERP) (DEC 2010)  
([www.theglobalfund.org/en/procurement/pharmaceutical](http://www.theglobalfund.org/en/procurement/pharmaceutical))
- The US President's Emergency Plan for AIDS Relief (PEPFAR)- What is PEPFAR-FactSheet 475- The AIDS InfoNet ([aidsinfonet.org](http://aidsinfonet.org))
- PEPFAR- International programs- webpage of USFDA
- PEPFAR- approved and tentatively approved ARV in association with the President's Emergency Plan
- Guidance for Industry- fixed dose combinations, co-packaged drug products, and single-entity versions of previously approved antiretrovirals for the treatment of HIV- USFDA CDER-Procedural – Oct 2006

# Annex 4 – Process Flow of the Procedure for Prequalification of Pharmaceutical Products or APIs

Flowchart of WHO prequalification of pharmaceutical products



# Annex 5 – Organisational Chart of WHO PQP of Medicines Team (as at 31 December 2010)

WHO Prequalification of Medicines Team: as at 31 December 2010

