



East African Community

A Situation Analysis on the Postmarket Surveillance Systems and
Activities for pharmaceutical products in the East African Community
Partner States

Final Report

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List of Abbreviations

AAS	Atomic Absorption Spectroscopy
ACT	Artemisinin combination therapy
ADDO	Accredited Drug Dispensing Outlets
AOP	Annual Operations Plans
API	Active pharmaceutical ingredient
ARV	Anti-retrovirals
BP	British Pharmacopoeia
C of A	Certificate of Analysis
CAMEBU	La Centrale d'achat des médicaments Essentiels du Burundi
CDC	Centre for Disease Control
DLDB	Duka la Dawa Baridi (Drug Stores)
DMCP	Director of Medicines and Complementary Medicines
DPML	Department of Pharmacy, Medicines and Laboratories, Burundi
DQCL	Drug Quality Control Laboratory
EAC	East African Community
EDQM	European Directorate for the Quality of Medicines
FTIR	Fourier Transform Infra-red Spectrophotometer
GC	Gas Chromatography
GMP	Good Manufacturing Practice
GPHF	Global Pharma Health Fund
HIV/AIDS	Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome
HPLC	High Pressure Liquid Chromatography
IRCA	The International Register of Certificated Auditors
ISO	International Standards Organization
JMS	Joint Medical Stores, Uganda
KEMSA	Kenya Medicines Supply Agency
M&E	Monitoring and evaluation
MEDS	Mission for Essential Drugs and Supplies, Kenya
MHRA	Medicines and Healthcare Products Regulatory Agency, UK
MIPV	Medicines Information and Pharmacovigilance Unit
MMIE	Manager for Medicines and Cosmetics Inspection and Enforcement
MOH	Ministry of Health
MoHSW	Ministry of Health and Social Welfare, Tanzania
MPPD	Medical Procurement and Production Division, Rwanda
MRH	Medicines Registration Harmonization (Project)
MSD	Medical Stores Department, Tanzania
NASCOP	National Aids and STI Control Program, Kenya
NDA	National Drug Authority, Uganda
NDQCL	National Drug Quality Control Laboratory, Uganda
NGO	Non-Government Organization
NHS	National Health Services (UK)
NMRA	National Medicines Regulatory Authority
NMS	National Medical Stores, Uganda
NQCL	National (Drug) Quality Control Laboratory, Kenya
NMRA	National Medicines Regulatory Authority
NTDs	Neglected Tropical Diseases

OMCL	Official Medicines Control Laboratory, European Union
PMI	President's Malaria Initiative, USA
PMS	Postmarket Surveillance / Post-market surveillance
PMSCO	PMS Coordinator
POE	Port of entry
PPB	Pharmacy and Poisons Board, Kenya
PPM	Planned Preventive Maintenance
PSK	Pharmaceutical Society of Kenya
PTB	Physikalisch-Technische Bundesanstalt (German Metrology Institute)
QA	Quality assurance
QAMSA	Quality of Anti- Malarials in Sub-Saharan Africa
QC	Quality control
QMS	Quality Management Systems
RASCI	Responsible, Accountable, Support, Consulted, Informed
RBC	Rwanda Biomedical Centre
SADC	South African Development Community
SSFFC	Suspicious, Sub-standard, Falsified, Falsely labelled, Counterfeit
TFDA	Tanzania Food and Drugs Authority
TLC	Thin layer chromatography
UK	United Kingdom
UoW	Uniformity of weight
US FDA	United States Food and Drug Administration
USA	United States of America
UV-VIS	Ultraviolet-Visible spectrophotometer
WHO	World Health Organization
ZFDB	Zanzibar Food and Drugs Board

Glossary of Terms

Counterfeit medicine¹: A counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredient, without active ingredients, with insufficient ingredients, or with fake packaging.

Defective medicines²: a medicine that may prove to be harmful under normal conditions of use; that is found to be lacking in therapeutic efficacy; whose benefit-risk balance may not be favourable under the authorised conditions of use, due to faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or any other serious quality problem; whose qualitative or quantitative composition is not as declared; whose controls (on the medicine itself or its ingredients) or whose controls at an intermediate stage of the manufacturing process have not been carried out; for which some other requirement or obligation relating to the granting of the manufacturing authorisation has not been fulfilled.

Falsely labelled medicine: European terminology to include a deliberate intention to deceive.

Falsified medicine: European terminology to include intention to deceive.

Healthcare professional: A trained professional person, usually a doctor, dentist, pharmacist, or nurse, responsible for the provision of care to patients and/or the supply of medicines to patients and the general public .

ISO 9001:2008³: a standard which sets out the criteria for a quality management system and is a standard that can be certified to (although this is not a requirement). It can be used by any organization, large or small, regardless of its field of activity

ISO/IEC 17025⁴: a standard which specifies the general requirements for the competence to carry out tests and/or calibrations, including sampling. It covers testing and calibration performed using standard methods, non-standard methods, and laboratory-developed methods.

Pharmacovigilance (PV): the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Postmarket/Post-Marketing Surveillance (PMS)⁵: an integrated set of activities for the monitoring, assessment (evaluation), and risk management of marketed health products. It is also a continuation of the regulated health product review process initiated in the pre-approval areas of the product development process. The goals of post-market surveillance include identifying, as early as possible, potential safety and effectiveness issues; refining and adding to information on suspected or known reactions and interactions between drugs; and communicating new safety information to health professionals and the public in order to improve therapeutic practice. A positive benefit/risk balance is maintained by the continuous function of information gathering, monitoring and processing, signal detection and assessment, and risk management and intervention. Specific steps involved with these processes are described below. PMS can be demand led

¹ WHO Definition

² http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000576.jsp&mid=

³ http://www.iso.org/iso/home/standards/management-standards/iso_9000.htm

⁴ http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=39883

⁵ Health Canada. http://www.hc-sc.gc.ca/dhp-mpps/pubs/medeff/_fs-if/2008-pmsc-csamm-max/index-eng.php

or **passive** when it is in response to an outside request, or non-demand led or **active** when it is based on a systematic sampling procedure⁶.

Raman spectra/spectroscopy⁷: is a spectroscopic technique used to observe vibrational, rotational, and other low-frequency modes in a system. Raman spectroscopy is commonly used in chemistry to provide a unique fingerprint by which molecules, hence drug formulations, can be identified.

Screening: a process of identifying products of suspect quality for further testing. The process uses fast indicator tests or thin layer chromatography, provided as a kit by GPHF Minilab[®]. Products failing this test are usually subjected to full compendial analysis to confirm the results.

Spurious medicines: Terminology used in South Asia for products falsely labelled or intended to deceive.

SSFFC⁸: An acronym used by the WHO and based on misrepresentations that may, intentionally or unintentionally, results in a patient receiving a product that is not of the nature and quality expected:

Standard Operating Procedures (SOP)⁹: established or prescribed methods to be followed routinely for the performance of designated operations or in designated situations

Substandard medicine: Medicines that are outside specification; excluding genuine manufacturing errors, but may include intentional, reckless or negligent errors.

Suspected/suspicious (defective) medicine¹⁰: a medicine about which a report has been received suggesting that it is not of the correct quality, as defined by its marketing authorisation.

TruScan^{®11}: The Truscan is a hand-held device used for on -the -spot detection of counterfeit medicines.

Vertical programs¹²: programmes that focus on one particular disease or group of diseases. Just as smallpox was ended through a global programme of action, the idea is that HIV, tuberculosis (TB), malaria and other devastating diseases can be addressed in a similar way.

⁶ Charvill, A., Lee, G. And Heddell, G. The MHRA medicines testing scheme: working to protect the public. *The Pharmaceutical Journal* 275 1 – 4 (2005)

⁷ http://en.wikipedia.org/wiki/Raman_spectroscopy

⁸ Substandard, Spurious, Falsely-labelled, Falsified, Counterfeit (SFFC) Medical Products. Global Surveillance and Monitoring Project. World Health Organization. <http://media.medfarm.uu.se/play/attachmentfile/video/3529/Handouts.pdf>

⁹ <http://www.merriam-webster.com/dictionary/standard%20operating%20procedure>

¹⁰ As above

¹¹ <http://www.nafdac.gov.ng/component/content/article/187-nafdac-innovations/240-cutting-edge-technologies>

¹² <http://www.healthpovertyaction.org/policy-and-resources/health-systems/health-funding/vertical-and-horizontal-funding/>

Executive summary

The East African Community (EAC) in collaboration with Partner States and development partners has put in place several programs to support the development and growth of the pharmaceutical sector. Postmarket surveillance (PMS) is recognised as a key regulatory control of the quality of medicines and so the EAC have commissioned an up-to-date situation analysis report regarding the legal regulations, actual practice, efficiency and existing capacities of market surveillance for pharmaceutical products within the East African Community partner states. The primary aim of the study was to provide up-to-date information on 1) the current status of postmarket surveillance of the quality of medicines 2) the capacities (systems, equipment and manpower) in the relevant institutions responsible for PMS, 3) the national policy, legislative authority, and regulatory oversight for market surveillance and 4) make recommendations for the improvement of PMS, in the East African Community Partner States.

Methodology

In order to achieve the objectives of the study the assessment team examined the key areas of regulatory activities and controls that were relevant to the overall process of assuring the quality of medicines on the market. A review of the current legislation and statutory provisions for the regulation of medicines was performed. Data was collected on the numbers and types of inspections performed, the type and range of products tested, the numbers of samples and how and where they were taken, methods of analysis and specifications used, actions and outcomes from the surveillance programs, and enforcement of regulatory action. Interviews were conducted with senior staff with line management responsibility for inspections, PMS, laboratory services, and enforcement action. Where data were available capacity analyses were performed.

Observations

- The level of activity and availability of data varied significantly between the different Partner States and this is reflected in the sections that cover the situations in the individual Countries and in the discussion which highlights the areas that are common and the differences between the EAC Partner States
- It was observed that all the Partner States have a legal framework for the regulation of medicines. There are however substantial differences between Partner States in the application of these provisions. In some the responsibility is split between different government departments which can create communication problems. There is no legal provision in any of the Partner States for manufacturers, importers, or distributors to inform the regulatory authority of suspicious or defective products they become aware of.
- Although there is no legal obligation to report suspicious or defective medicines, all Partner States have procedures in place for the receipt, investigation, and regulatory control of reported quality defects. There is however significant variations between these procedures in the various Partner States.
- Of the countries visited, only Kenya, Tanzania, and Uganda were performing active PMS that was not in response to an outside demand for the work but was initiated by the Authority as an active sampling and analysis program to assess product quality.
- There are effective and operational laboratory services in only three Partner States, Kenya, Uganda, and Tanzania. Burundi has a laboratory but it is underequipped for the work it needs to do. Zanzibar has a laboratory which is also underequipped and would appear to be non-operational. Rwanda has no laboratory; one is being developed but it will not be within the Pharmacy Division. Only two of the operational laboratories, Kenya and Tanzania, are established under the regulatory framework, and only two, Tanzania and Uganda, are within the same management structure as the PMS team.
- Burundi, Rwanda and Tanzania (Zanzibar) are not undertaking active PMS. Resources and facilities are not available to enable this. As a consequence, risks of suspicious or defective products may be greater in these Countries

- PMS programs are not shared or co-ordinated within the EAC. This leads to potential duplication of testing and lack of optimisation of resources
- Results from PMS programs are not publicised and information and data on findings is not shared throughout the EAC
- Resources are limited and so it is only possible to cover a small percentage of essential medicines in any one year. Priorities have to be set according to appropriate risk assessments.
- **Laboratory analyses are costly but necessary. Improved screening will enable laboratory resources to be targeted at suspicious samples. Improved screening methods that allow optimisation of laboratory resources need to be developed.**
- Maintenance and servicing of equipment is a major problem that impacts upon laboratory capacity and throughput. In many of the laboratories key items of equipment were non-operational awaiting servicing.

Logistics and cost of PMS was evaluated and the following observations made: -

- PMS is a collaborative and not a stand-alone activity. It uses staff and resources from several departments and external organizations. This needs to be coordinated. Therefore, the role of the PMS unit is mainly as the co-ordinator of this work.
- Due to the collaborative nature of the activity it is not possible to account for all costs and requirements in the PMS budget. For example, in Tanzania (Mainland) the cost of planning, analysis and M&E is not included in the PMS budget but carried in regular departmental budgets.
- Screening of samples is the most demanding PMS activity with regard to manpower requirement followed by laboratory analysis, monitoring and evaluation, training, sampling, planning and procurement; in that order. In Tanzania (Mainland) screening of samples uses 45.3% of planned person-hours; laboratory analysis 28.3%; monitoring and evaluation 7.6%; training 7.2%; sampling 6.1%; planning 4.7%; and procurement 0.8%.
- Implementing PMS as a campaign implies that a large proportion of financial costs will be used to pay allowances to campaign staff. This is the case in Tanzania where 63.5% of the financial budget is used to pay various allowances, 12.1% used to procure laboratory consumables; 10.7% on sampling costs; 9.2% on travelling and 4.5% on dissemination of findings.

Recommendations

At EAC Secretariat level

1. To strengthen the coordination of PMS activities in the region it is recommended that:-
 - a. A Regional PMS coordination program should be established to co-ordinate activity in the Partner States and facilitate collaboration in the Region. Key elements of this program will be:-
 - i. An annual meeting of PMS program managers is held to share information and experiences from the previous year's program. This should include sample plans, results, outputs, and outcomes.
 - ii. PMS programs are circulated to all EAC NMRA's in confidence when finalised. This need only include the information on products to be sampled.
 - iii. PMS reports are circulated to other EAC Partner States
 - b. Purchasing specifications for laboratory equipment such as chromatograms and spectrophotometers should be similar throughout the region and include a requirement for service engineers to be based locally at least within the EAC.
 - c. Local internal training on equipment maintenance should be coordinated with a view to developing in-house competencies for routine maintenance and annual validation.
 - d. Support exchange or twinning programmes between the NMRA's that have more established PMS systems with the weaker ones.
2. To strengthen the implementation of PMS activities within the region it is recommended that:-:

- a. A project should be initiated to determine the potential of **TLC/FID as a screening method** for market surveillance. This work could be shared throughout the EAC and the findings circulated to all partner states.
- b. A research project should be initiated to assess the potential of the Raman spectroscopy to screen for suspicious and non-compliant medicines, since Raman spectroscopy will detect counterfeit medicines provided standard spectra are available.
- c. Initiate training and capacity building programmes.
3. To enable uniform implementation of PMS procedures it is recommended that a regional counterfeit detection program be instituted and coordinated at EAC level. The program should include:
 - a. training of inspectors in the detection of SSFFC products,
 - b. **provision of technical facilities e.g. Minilab service centre**, product sample reference library and Raman spectra library,
 - c. establishment of a central planning and monitoring unit within the EAC secretariat for this purpose and to further strengthen recommendation (1) above.
 - d. co-ordination of collaborative projects with International enforcement agencies and anti-counterfeit organisations (e.g. Interpol, WHO) in survey projects to detect illegal and counterfeit medicines.

At Partner State level

1. Burundi, Rwanda and Tanzania (Zanzibar) should initiate PMS programs based on the practices outlined above. This should be a risk based approach that **initially targets programme medicines such as anti-malarials, anti-retrovirals, anti-tuberculosis medicines, and antibiotics but has the scope for extension. The laboratories in these three Partner States should concentrate their financial resources and technical competencies on product screening. This currently uses the Minilab but could in the future use Raman spectroscopy.**
2. All EAC Partner States should introduce legislation that requires all parties involved in the manufacture, importation, supply, distribution and laboratory testing of medicines in the EAC to report any incidence of suspicious products or quality defects in medicines that have been marketed in the EAC to the relevant Regulatory Authority.
3. All EAC Partner States should ensure that reporting tools are available to all healthcare workers and to the general public for the reporting of suspicious or defective products to the Regulatory Authorities in the EAC. These should be available as hard copy and electronically.
4. **All EAC Partner States should be equipped with Minilab systems for the routine monitoring of PMS samples. Regular user training programmes should be undertaken to ensure all staff who operate the systems are competent to do so.**
5. Procedures and funding should be in place to ensure the analysis and follow up of all suspect samples.

At NMRA level

1. All NMRAs should have formal written procedures for the investigation of defect reports. These should define the roles and responsibilities of the key staff involved in the process, the person or persons responsible for managing the investigation, key milestones, the approval process for follow up actions, the monitoring of outcomes, and the communication process with stakeholders.
2. Random sampling should be an integral part of the PMS program. Sample numbers should be based on an assessment of risk, based on historical test results, supplier assessments, and product history.
3. If a defect report is confirmed, whether from passive (defect reports) or active (PMS), the outcome should be published on the Authority website and other EAC Regulatory Authorities should be informed.
4. Reports of non-compliant products that have been confirmed should be circulated immediately to all NMRAs in confidence.

5. Inspectors at the ports of entry should receive training in the identification and detection of SSFC products

1. Background

1.1 Preamble

The East African Community (EAC) is a regional inter-governmental organization of the five Partner States, namely; the Republic of Kenya, the Republic of Uganda, Republic of Burundi, Republic of Rwanda and the United Republic of Tanzania, with its Headquarters located in Arusha, Tanzania. The five Partner States have continued to strengthen regional cooperation and integration in social, political, economic and culture areas of common interest including the harmonization of policies, regulations, strategies, standards and systems in the Health Sector under Chapter 21 (Article 118) of the EAC Treaty for establishment of the East African Community.

The pharmaceutical industry in the East African Region is currently undergoing significant changes towards evolving to a globally competitive sector that adopts international best practices. The East African Community Secretariat and the Partner States recognize the strategic importance of the pharmaceutical sector in promoting access to affordable quality essential medicines, including those for the treatment of diseases such as HIV/AIDS, malaria, tuberculosis and various neglected tropical diseases (NTDs) among others. The Secretariat in collaboration with Partner States and development partners has put in place several programs to support the development and growth of the pharmaceutical sector.

The National Medicines Regulatory Authorities (NMRA), or equivalent in the Partner States assure the safety, efficacy and quality of medicines. Their functions include the assessment of manufacturers in accordance with the national GMP standards prior to the approval of new medicines; the control of imported medicines; and to survey the domestic market (post market surveillance). The optimal situation is that substandard or counterfeit medicines do not enter the EAC market and are identified either during the production or importation process. But for the identification of counterfeit and substandard medicines which are on the market, it is necessary to have a functioning decentralized market surveillance system that is able to protect EAC citizens from falsified drugs.

The EAC/PTB project on the establishment of a regional quality infrastructure for the pharmaceutical sector in the EAC seeks to support the strengthening of market surveillance of pharmaceutical products in the Partner States. In this regard the EAC seeks to provide an up to date situation analysis report regarding the legal regulations, actual practice, efficiency and existing capacities of market surveillance for pharmaceutical products within the East African Community partner states. Based on the situation analysis report, recommendations will be given to further strengthen market surveillance and to ensure the good quality of pharmaceutical products.

1.2 Aims and Objectives of the Mission

The primary aim of the study is to provide up-to-date information on 1) the current status of postmarket surveillance (PMS) of the quality of medicines 2) the capacities (systems, equipment and manpower) in the relevant institutions responsible for PMS, 3) the national policy, legislative authority, and regulatory oversight on market surveillance and 4) recommendations for the improvement of PMS, in the East African Community Partner States.

It should be noted that the scope of the study did not include pharmacovigilance and only covered post market surveillance of the quality of medicines.

The assessment will have the following objectives:-

- To undertake an inventory of the relevant national policies and laws that govern quality assurance of pharmaceutical products on the market in all the six partner states.
- To document the institutional framework and arrangements for market surveillance in all the six partner states.
- To assess the capacity of the (NMRAs) including human resource (skills and skill mix), equipment and other infrastructure requirements to undertake quality assurance of pharmaceutical products. These should include but not be limited to the assessment of their capacity to undertake the following:-
 - (i) local manufacture of essential medicines
 - (ii) assessment, approval, and registration of medicines
 - (iii) market entry control (import inspection)
 - (iv) collection of suspicious samples in easy to reach and hard to reach areas
 - (v) analysis of suspicious drugs
 - (vi) investigation of quality defects in medicines and product recall mechanisms including the communication strategy
 - (vii) active sampling and analysis of medicines
- To assess the enforcement capacity among the relevant regulatory institutions in all the six partner states.
- To identify best practice and give recommendations on how to further strengthen market control mechanisms for the quality of medicines.

2. Methods Used in the Study

2.1 Documentation Review of Medicines Legislation and Control Processes

A review was undertaken before the mission of current Medicines Legislation in the 5 Partner States insofar as it relates to the objectives of the study regarding the quality of medicinal products. This included:-

- regulatory controls for the quality of manufactured and imported medicines;
- requirements for sampling and analysis of medicines;
- reporting of quality defects and product recall provisions
- enforcement provisions

The consultants collected as much information as possible from currently available sources and this was expanded upon and clarified during the visits. In parallel with this, internal policies, standard operating procedures (SOPs), and internal reports were requested and evaluated. These data were confirmed and validated during the visits.

2.2 Data collection

A review was undertaken of current market surveillance activities. Data was collected for the following:-

- target products, product type and product range;
- sampling processes, sampling sources and sampling methods;
- sample numbers
- analytical procedures, standards and specifications, reference standards;
- outcomes of surveillance studies, examples and case studies;
- enforcement of findings, examples and case studies.

A questionnaire was developed to obtain detailed information on the conduct of PMS activities in each country. The questionnaire sought information on legal frameworks, current PMS volumes, standards and procedures, and accreditation in each of the EAC member states. This information was validated during interviews performed during the visits.

2.3 Interviews

The questionnaire was sent to NMRAs well in advance of the mission. This provided adequate time to the MRAs to collect the required information. During the mission the consultants reviewed the information provided and asked questions to fill any gaps observed. During the visits we interview the following people:-

- senior staff in the NMRA who can explain the authority and interrelationship between the different functions who are responsible for ensuring the quality of medicines;
- managers and staff responsible for the sampling and analysis program;
- managers and staff of laboratory services;
- managers and staff of enforcement section.

2.4 Capacity analysis

In order to analyse the capacities of NMRAs in undertaking PMS the consultants collected data on all PMS activities undertaken by MRAs for the last three years or more where available. The following information was collected in order to accomplish this task:

- How many inspections were made per category – import consignments, locally manufactured products, distributors, surveillance samples. .
- How many samples were collected per category as listed above.
- How many samples were analysed in the laboratory per formulation category: tablets, injections, creams and ointment
- How many tests were performed per technique: Visual, physical (disintegration, friability...), chemical assays, spectroscopy, chromatography etc.
- How many people were involved by category
- Inspectors (sample collectors)
- Laboratory analysts
- Support staff (drivers, police etc)

Using this information the consultants determined the PMS cost structure, the PMS manpower outlay and the PMS laboratory workload. Since only Tanzania (Mainland) provided the full set of data as requested the capacity analysis only provided a reference benchmark.

For indicative purposes exchange rates of the three countries with active PMS activities as on 2nd January 2015 were as follows:

1 USD = KES 90.7031¹³

1 USD = TSh 1,713.31¹⁴

1 USD = UGX 2,779.02¹⁵

However, all monetary references in this report are based on local currencies.

On the basis of the information and data collected the stage reached by each country was rated along 7 levels:-

Stage	Characteristics
Legislation	evidenced by presence of pharmaceutical regulatory legislation
Planning	evidenced by presence of PMS plan, protocols or guidelines
Capacity	evidenced by presence of a dedicated PMS Unit and a functioning laboratory
Implementation	evidenced by implemented active PMS
Extended scope	evidenced by a variable range of products surveyed
Visibility	evidenced by active PMS reports published on time
Useful outcomes	evidenced by regulatory action resulting from active PMS activity

It should be noted that, in the time available to the consultants, it was only possible to undertake an information gathering exercise. It was not possible, in many cases, to validate the extent to which the procedures and regulations were being applied. With regards to controls for local manufacturing, import controls, and procurement procedures this was considered to be outside the scope of the study. For PMS

¹³ <https://www.centralbank.go.ke/index.php/rate-and-statistics/exchange-rates-2>

¹⁴ <https://www.bot-tz.org/FinancialMarkets/IFEMsummaries/IFEMsummaries.asp>

¹⁵ http://www.bou.or.ug/bou/rates_statistics/statistics.html

studies published sampling plans, reports, and outcomes have been used where available and details are included in the individual Country reports.

3. Overview of PMS Activities in Partner States

3.1 National Policies and Laws Regarding Postmarket Surveillance of Pharmaceutical Products

3.1.1 Legal and Regulatory Framework

All the Partner States have a legal framework for the regulation of medicines. These generally include provisions for:-

- The inspection and licensing of local manufacturers
- The inspection and approval of wholesale distributors
- The authorization of importers
- The approval and registration of locally manufactured and imported products
- Rights of entry to premises for inspectors to perform their duties
- Powers to seize and confiscate suspect products

In Burundi however, pharmaceutical regulatory activities are divided between three legislations administered by three separate bodies: the Department of Pharmacy, Medicines and Laboratories of the Ministry of Health (DPML), which deals with product registration and import control; the department of Inspection of Pharmacy, Medicines and Laboratories under the General Inspectorate of Public Health; and the Fight against AIDS, which licences and inspects manufacturers, wholesalers and pharmacies; and the Pharmacy Council, which registers pharmacists.

In Tanzania (Mainland), Kenya, and Zanzibar, there are legal provisions for the sampling and testing of medicines to assess compliance with regulatory requirements. For these three Authorities, the regulations also establish a national laboratory for the testing of medicines.

Except in Rwanda, there is no legal provision in the other partner states for manufacturers, importers, or distributors to inform the regulatory authority of suspicious or defective products they become aware of. In many cases this information is provided to the Authority but not always and so valuable data regarding an indicator of product quality is not recorded. However, steps have already been taken to address this situation in Tanzania (Mainland) and Tanzania (Zanzibar) where regulations requiring this are in advanced stages.

3.1.2 Regulation of manufacturers

All Partner States have legal provisions for the inspection and licensing of manufacturers and manufacturing is undertaken in all 5 countries to varying extents but the ZFDB does not have any manufacturing facilities under its jurisdiction. All products manufactured locally must be approved and registered by the Regulatory Authority before they can be placed on the market. The internal procedures for monitoring the quality of manufactured products vary from country to country and are dictated by local needs. In Kenya, Uganda and Tanzani (Mainland) a locally manufactured products are included in the PMS sampling programs.

3.1.3 Regulation of Imported Medicines

For all partner states of the EAC, the majority of medicines that are used are imported. It follows therefore that the regulatory control of imported medicines is a significant factor for the quality assurance of medicines that are on the market in the EAC. In all cases there are procedures and systems in place to regulate imported medicines. The site of manufacture must be authorized or licensed either by the Regulatory Authority in the Country in which they are sited or, in some cases, by the Authority in the EAC

Country. Importers and distributors must be registered and the imported products must be registered with the Authority. At the ports of entry there are various procedures in place to monitor and approve individual consignments of imported medicines. To varying degrees these involve visual inspection of products, sampling and screening of batches, importation certificates, and product release onto the market. In all cases there are procedures for follow up of suspect samples.

3.1.4 Investigation of suspicious or defective medicines

Although there is currently no legal obligation to report suspicious or defective medicines, all partner states have procedures in place for the receipt, investigation, and regulatory control of reported quality defects. There is however significant variations between these procedures in the various partner states. In Kenya, Uganda and Tanzania, forms are made available to healthcare workers and can be downloaded from the Authority website for reporting quality defects. In Uganda there is a committee constituted under their Quality Management Systems (QMS) to investigate and follow up defect reports.

3.1.5 Other legislations relevant to PMS

Other legislation that was relevant to the PMS procedure was also evaluated as part of the study. This included the destruction of unfit medicines and the ability of Authorities to initiate their own litigation proceedings. Generally all countries have adequate environmental laws and the respective NMRAs strive to comply as best as they can. Rwanda has an environmental desk at the Ministry of Health Headquarters which monitors compliance to the laws in the health sector.

With regard to initiation of litigation there are marked differences in approach within the region. In most countries (Burundi, Rwanda, Tanzania (Zanzibar) and Uganda) cases requiring litigation are handed over to police for prosecution. In Kenya the PPB contracts private lawyers who provide such services. In Tanzania (Mainland) the TFDA has a full-time team of lawyers for the same purpose although the final prosecution must be led by the lawyers from the Directorate of Public Prosecution.

3.2 Institutional Framework for Supporting Market Surveillance

Of the Countries visited, only Kenya, Tanzania (Mainland), and Uganda were performing active PMS that was not in response to an outside demand for the work but was initiated by the Authority as an active sampling and analysis program to assess product quality. However, in Uganda no formal procedure for postmarket surveillance was evident: there is no annual plan or strategy but there is an informal meeting whereby staff from the inspectorate, medical information, and the laboratory, meet to agree the sampling protocol and requirements for the next 3-6 months.

3.2.1 Organization

In Kenya postmarket surveillance is an activity within the Directorate of Medicines Information and Pharmacovigilance. Collaboration between the various departments of PPB involved in PMS is the responsibility of the respective directors, who meet regularly to plan and review progress. Individual Directorates can contribute to the plan and the AOP is approved by the Management Committee which includes all directors. The Directorate of IS&E contributes during the preparation of AOP plan by making its inspection reports available and providing inspectors to do the sampling.

In Tanzania (Mainland) all PMS activities are coordinated by the PMS Coordinator (PMSCO) who reports to the Manager for Medicines and Cosmetics Inspection and Enforcement (MMIE) who in turn reports to the Director Of Medicines and Complementary Products (DMCP). PMS is a collaborative activity led and

overseen by a task force comprising of the Manager for Medicines and Cosmetics Inspection and Enforcement, the PMS Coordinator, the Manager for Medicines and Cosmetics Analysis, the appointed Registration Officer, the Eastern Zone Manager, the Manager for Medical Devices Assessment and Enforcement, and the appointed drug inspector. The Manager for Medicines and Cosmetics Inspection and Enforcement chairs the task force. The PMS Task Force is responsible for conducting routine monitoring of the programme include data evaluation and risk assessment which will then form the basis for conducting further PMS. The task force is also responsible for programme review, publication of results and advice to DMCP on matters related to PMS activities. It meets at least 3 times during a phase whereby most meetings are held on ad-hoc basis. More meetings can be held if necessary depending on the situation.

In Uganda the Drug Inspectorate Services Department is responsible for ensuring that all medicines manufactured locally and imported into the country are of good quality and are properly handled. The department is responsible for drug inspection at all major ports of entry to minimise entry of sub-standard and counterfeit drugs into the Country, inspection and licensing of all pharmaceutical handling facilities and postmarket surveillance¹⁶.

Generally PMS programmes in the three countries involves other stakeholders such as the Pharmaceutical Societies, Medical Associations, Nursing Councils, EAC and SADC Secretariats responsible for medicines regulation, WHO, and MOH pharmaceutical departments, Aids Control Programs, Malaria Control Programs and TB and Leprosy Programs. Cooperation with these organizations/agencies helps in sharing information, improve control at border entries, and reduce surveillance costs. Furthermore, working in close collaboration with healthcare providers and consumers promotes reporting of product defects including counterfeit products.

3.2.2 PMS strategies/guidelines

The Pharmacy and Poisons Board in Kenya has a detailed PMS strategy¹⁷. It describes roles and responsibilities, how a PMS plan should be made and executed, sample testing and regulatory action. In Tanzania (Mainland) guidelines on postmarket surveillance of Medicines and Medical Devices¹⁸ have been developed on the basis of which 3-year PMS programs are prepared. In addition to the PMS guidelines the authority's Inspectors' Handbook (2002)¹⁹ includes detailed SOPs for:-

- Inspections at POE
- The physical examination of pharmaceutical products
- The anti-malaria surveillance program
- Inspections of dispensing outlets
- The surveillance program for suspicious samples
- Chain of custody, packing and shipping procedures

The manual also provides instructions to inspectors on the use of the GPHF Minilab kits. However, it became apparent during the interview that screening with Minilab kits is done by laboratory staff at the headquarters.

¹⁶ http://www.nda.or.ug/page.php?k=dept_head

¹⁷ Strategy for Post-Market Surveillance (PMS) Of Medicines in Kenya, Ministry of Medical Services, Pharmacy and Poisons Board. June 2010

¹⁸ National Guidelines for Monitoring Medicines Safety. Second edition. Tanzania Food and Drugs Authority. November 2010

¹⁹ Inspectors Handbook. The Pharmacy Board, Ministry of Health, United Republic of Tanzania. November 2002

3.2.3 PMS programs

The PMS programs in Tanzania (Mainland) often have 9 phases, 3 implemented in each operational year (the 2014 – 2017 Program has only 6 phases). The first PMS program was implemented from 2007 to 2009, the second from 2011 to 2013 and the third, 2014 to 2017, is under implementation. Each program articulates among other things, the way PMS should be effectively conducted and managed by TFDA in the three financial years based on lessons learnt from the previous programme.

3.2.4 Annual plans

In Kenya the Directorate of Medicines Information and Pharmacovigilance develops and implements the Annual Operations Plan (AOP) for PMS and there is a lead manager in MIPV who is responsible for its implementation. The plan is informed by previous PMS reports, complaints reports, the public health programs and inspection reports. The plan is drafted within MIPV and the final draft circulated to other Directorates with an interest. The final plan is approved by the PPB management Board who also allocate the budget.

3.3 Capacity of the National Regulatory Authorities in Each Partner State to Undertake Postmarket Surveillance of Pharmaceutical Products

3.3.1 Human resources

All NMRAs have officers assigned to PMS with varying degrees of workload. In the Burundi, Rwanda and Tanzania (Zanzibar) where no active PMS is undertaken staff from the inspectorate wing are responsible for any demanded action. In Kenya, Tanzania (Mainland) and Uganda where active PMS is undertaken there are PMS sections established within their organization structures with full-time staff dedicated to PMS activities. The number of staff varies from country to country but they appear to be adequate for the purpose. All three countries rely on staff from the inspectorate and sometimes staff from local government or other health departments during the intensive sample collection stages. For this reason PMS plans and protocols in these countries always make provisions for training of sample collectors.

As will be discussed later, the heaviest activity in terms of manpower requirement during a PMS exercise is sample testing (screening and confirmatory tests). In most cases the NMRAs rely on their laboratory or specially trained inspectors to perform the task. In view of the large number of samples collected and requiring screening or full analysis, special allowances are paid to workers involved in the exercise. For this reason the cost of conducting a PMS exercise is very high.

3.3.2 Cost

PPB's protocols do not give much detail on organization and cost of the activities; they dwell mainly on number of samples, distribution of sampling sites and sampling techniques. The 2014 protocol for PMS of reproductive health medicines provides a rough indication of PMS cost centers in Kenya Shillings as follows:

Purchase of samples	250,000 (40%)
Stationery	100,000 (16%)
Thermohygrometers	20,000 (3%)
Training and pre-testing	250,000 (40%)
Total	620,000 (100%)

However, since all but one of the surveys were conducted in collaboration with partner/donor organization it is not known how these costs were apportioned.

Since PMS in Tanzania (Mainland) is a collaborative activity it is not possible to assess its capacity separately. We can only conclude that what has been accommodated in the past is indicative of the capacity and capability of TFDA in conducting active PMS. The 2014 – 2017 plan shows that staff from various departments will provide a total of 3,177 person-days of which 45.3% will be used on screening of samples; 28.3% on laboratory analysis; 7.6% on monitoring and evaluation; 7.2% on training; 6.1% on sampling; 4.7% on planning and 0.8% on procurement. Furthermore, Table 8 of Appendix 4 shows that a total of Tanzania Shillings 397, 850,000.00 is planned to be used during the period of which 63.5% will be used to pay various allowances, 12.1% will be used to procure laboratory consumables, 10.7% on sampling costs, 9.2% on travelling, and 4.5% on dissemination of findings. The absence of budgetary allocations for planning, analysis and M&E reflects the collaborative nature of the activity whereby costs have been absorbed under the respective departmental budgets.

The collaborative approach to PMS uses inspectorate staff and sometimes additional staff from local government authorities. This way each of the participants need provide only a few hours to the total hours required for the activity. In Phases I and II of the 2011 – 2013 program the authority used 57 sample collectors in this fashion so that regular inspection activities did not suffer. This explains why a large proportion of the budget is allocated to payment of allowances.

The workload of PMS on laboratory analysis is very significant despite the extensive use of screening. Samples taken for confirmatory testing include all samples that fail screening test, all samples with doubtful screening test results and 10% of samples which comply with screening test results. This number is unpredictable but based on experience it could be large. In phase I of the 2011 – 2013 programme a total of 130 were taken for confirmatory testing out of 281 samples i.e. 46.3%. We shall assume this worst-case scenario and take 46.3% of 400 i.e. 185 samples as requiring confirmatory testing each year during the 2014 – 2017 PMS program. In 2013/2014 the laboratory analysed a total of 1462 samples. If this is taken as the laboratory's capacity it means that PMS samples will take up 185 of 1462 i.e. 13% of the laboratory's analytical capacity.

In Uganda the NDA relies on its inspectors to collect samples during PMS activities. It is estimated that 450 samples would be collected by 7 inspectors in a 10 day countrywide operation (see Appendix 5 section 5.4). This averages at 6.4 samples per person-day. The exercise would also cost NDA Uganda Shillings 140,000 per person-day.

The above calculations do not reflect the reality of an active surveillance program where reference standards and other laboratory consumables have to be procured, training conducted, screening undertaken and a very comprehensive report written.

Another survey of anti-malarials whose protocol was prepared in February 2013 targeted 350 samples across Uganda²⁰. The main motivation for the study was to update and expand the knowledge and information about the quality of ACT anti-malarial medicines in Uganda following results of QAMSA study which reported that approximately 26% of the anti-malarial medicine samples from Uganda were found to be of poor quality. The exercise was to use 186 person-days (51 person days for drivers are excluded) and cost US\$ 47,201.64.

Using Tanzania (Mainland) as a benchmark, logistics and cost of PMS was evaluated and the following observations made: -

²⁰ A protocol for quality monitoring of ACT anti-malarial medicines circulating on the Ugandan market using GPHF Minilabs, National Drug Authority-AMFm Project. February, 2013

- PMS is a collaborative and not a stand-alone activity. It uses staff and resources from several departments and external organizations. This needs to be coordinated. Therefore, the role of the PMS unit is mainly as the co-ordinator of this work.
- Due to the collaborative nature of the activity it is not possible to account for all costs and requirements in the PMS budget. For example, in Tanzania (Mainland) the cost of planning, analysis and M&E is not included in the PMS budget but carried in regular departmental budgets.
- Screening of samples is the most demanding PMS activity with regard to manpower requirement followed by laboratory analysis, monitoring and evaluation, training, sampling, planning and procurement; in that order. In Tanzania (Mainland) screening of samples uses 45.3% of planned person-hours; laboratory analysis 28.3%; monitoring and evaluation 7.6%; training 7.2%; sampling 6.1%; planning 4.7%; and procurement 0.8%.
- Implementing PMS as a campaign implies that a large proportion of financial costs will be used to pay allowances to campaign staff. This is the case in Tanzania (Mainland) where 63.5% of the financial budget is used to pay various allowances, 12.1% used to procure laboratory consumables; 10.7% on sampling costs; 9.2% on travelling and 4.5% on dissemination of findings.

3.3.3 Laboratory services

The consultants visited laboratories in the EAC that were responsible for the analysis of samples of medicines. These included 5 national government laboratories, one laboratory in a national medical store, and one laboratory in a private organisation working on behalf of Christian churches in Kenya.

There are effective and operational laboratory services in only three partner states, Kenya, Uganda, and Tanzania (Mainland). Burundi has a laboratory but it is underequipped for the work it needs to do. Tanzania (Zanzibar) has a laboratory which is also underequipped and would appear to be non-operational. Rwanda has no laboratory; one is being developed but it will not be within the Pharmacy Division. Only two of the operational laboratories, Kenya and Tanzania (Mainland), are established under the Regulatory framework, and only two, Tanzania (Mainland) and Uganda, are within the same management structure as the PMS team.

The three major laboratories are all accredited under the WHO pre-approval scheme for medicines testing laboratories. NQCL in Kenya is seeking **ISO/IEC 17025** accreditation and at the time of the visit this assessment was imminent. It was not the role of the consultants to assess the quality management system (QMS) in the laboratories, nor was it their role to assess compliance with the QMS. It was important however to confirm that procedures for receiving samples, sample analysis, evaluation of results, and reporting of results were in place that ensured effective management of the PMS samples received into the laboratory. Furthermore, a robust out-of-specification procedure for handling suspect results is essential when dealing with the pharmaceutical industry after failure reports. WHO pre-approval confirms that these are in place.

The resources, equipment and staff, accreditation status, and annual workload for the laboratories that were visited are summarised in Table 1. A comparison of the data in this table highlights some of the issues and challenges that the EAC face in implementing effective PMS programs. The NQCL in Kenya is the more established and best equipped laboratory however it is required to generate its income through its analytical work. Consequently analytical costs can be high and are not subsidised. With a limited budget, PPB and KEMSA are restricted in the number of samples they can send for analysis to the NQCL. KEMSA are developing their own laboratory to address this problem but this is not an option for PPB. In both Uganda and Tanzania the laboratory is a division of the NMRA. As a consequence the only samples they analyse are submitted from the NMRA but may be from different departments. Their only source of income is the NMRA funding and they have no opportunity to generate income. This eliminates conflicts of interests but restricts potential alternative sources of income

Table 1. Summary of equipment, staff resources, accreditation, and annual workload for the laboratories visited

	Laboratory equipment							Accreditation		Staff	Annual samples	
	HPLC	UV-VIS	FTIR	AAS	GC	Dissolution testing	Minilab	ISO 17025	WHO Pre-qual.		Screening	Full analysis
Tanzania TFDA	6	1	1	1 ¹		2	1	No	Yes			
Zanzibar ZFDB	1							No	No		Nil	nil
Kenya NQCL	12	1	1	1	1	13	11	No ²	Yes	45		
Kenya MEDS	6	2	1		1	2	1	No	Yes	8		~1000
Kenya KEMSA	2	1				1	1	No	No	5	~250	
Uganda NDA	5	2	1		2	4	7	No	Yes	22	~800	~600
Rwanda ³												
Burundi	1	1				1	1	No	No			

Note 1. Available for use in adjacent food laboratory

Note 2. At the time of the visit the laboratory was preparing for an ISO 17025 inspection

Note 3. A laboratory is being equipped and commissioned but, at the time of the visit was not operational

In the various laboratories a number of instruments were non-operational awaiting servicing. This was a general problem for all laboratories including Burundi and Tanzania (Zanzibar). Whilst some calibration and servicing can be performed locally, PPM programs that meet the requirement of accreditation programs are expensive especially when engineers from outside Africa are needed. The result is that equipment is taken out of service and the laboratory capacity is reduced. As an example, two of 6 HPLC in the Tanzania (Mainland) laboratory were non-operational awaiting maintenance. The one HPLC in the Tanzania (Zanzibar) laboratory was non-operational awaiting service. For many laboratories the availability of HPLC equipment is the step that limits throughput and so it is essential that this equipment is maintained and fully operational.

Laboratory outputs depend very much on inputs. These are sample numbers, laboratory resources (staff and equipment), and, most importantly, NMRA priorities. Laboratory resources limit the number of analyses they can perform. Efficiency and productivity in any laboratory should be maximised and comparisons with equivalent organisations is a good benchmark. However, output should not be increased at the expense of quality. Since many of the samples tested by the PMS programs will be tablets or capsules, the rate-limiting step for laboratory analysis of the majority of medicines is the availability of either HPLC equipment or dissolution testing apparatus. Consequently the availability and maintenance of these is a key capacity indicator.

The EAC collaboration in medicines regulation provides an opportunity for the partner states to share experiences on a number of levels. This is particularly so for laboratory services. The following are examples:-

- Staff development through secondment to more established facilities
- Collaboration on research projects
- Development of QMS
- The establishment of local expertise for equipment PPM
- Sharing experience and expertise in the screening of test samples

3.3.4 Screening of samples

The Minilab screening system is the method of choice within the EAC for the initial screening of PMS samples. It is a system of qualitative testing to confirm the identity of the active ingredient in medicines. It has been developed using the WHO essential medicines list as its basis and so covers products that are included in the essential medicines lists of the EAC Countries. Currently it can only be used for 75 active compounds and so many products cannot be screened. It uses a combination of colorimetric tests and thin layer chromatography (TLC) to identify the active ingredients in the samples to be tested. TLC is a rapid and

effective identification method for active ingredients in medicines. It is easy to use and does not require sophisticated laboratory facilities. However, no figures are available for the quantitative detection limits of the tests but products that are marginally outside their specification limits of +/-10% of the active will not be detected. Only gross failures will be found.

The Uganda laboratory has invested in three TruScan instruments for the screening of medicines. There are many advantages with this technique for the identification of illegal and counterfeit medicines but compared with the Minilab it requires a protracted method development phase including the establishment of a library of reference spectra of authentic compliant samples of each product including different brands of the same generic medicine before it can be used effectively. The Minilab is based upon the identification of the active ingredient of the test sample. It is effective in identifying samples which do not contain the labelled active ingredient and can be used semi-quantitatively to identify out-of-specification products that need further investigation. The TruScan produces a Raman spectrum for a specific, individual formulation and compares that spectrum with those previously recorded and stored in its data library. This is the same procedure as that used for the identification of raw materials using infra-red spectrophotometry but, in the case of Raman spectrophotometry, the formulation is compared. The TruScan requires a reference sample in its library for comparison in order to authenticate a test sample. If there is no library sample, authentication is not possible. Like infra-red spectrophotometry it can be used to identify and authenticate raw materials and APIs but it can also be used to authenticate tablets and capsules provided there is a suitable library spectrum for comparison. It has been used by both the US FDA Forensic Chemistry Centre and by the UK MHRA laboratory for the screening of illegal and counterfeit medicines. For this work a list of high risk products is identified, a reference spectrum library of these products is created and test samples are compared against these library spectra. Samples not complying with the comparison criteria are investigated further. There are limitations in using the TruScan for product quality surveillance in areas such as the EAC. In Countries such as the UK and the USA the primary target for counterfeiters is the high cost, lifestyle medicines such as Zantac, Lipitor, PDE-5 inhibitors, and anti-obesity drugs. Using TruScan as a screen for these products is less problematic because a single formulation is used as the library comparator. This is not true for the EAC where counterfeiting of medicines is not solely targeted at high cost, lifestyle medicines and many products on their essential medicines list could be counterfeit targets. However, for products with multiple sources of generics, unless each of these generic formulations has been scanned and recorded in the TruScan library, authentication will not be possible. Currently the TruScan are not being used to their full potential but the recommendations give proposals how this might be achieved.

3.4 PMS Performance in Partner States

3.4.1 Passive PMS activities

All NMRAs in the Partner States undertake passive PMS. The process is usually initiated on receiving a complaint through the reporting system established in the Country or by other means, analysing the credibility of the complaint, sending a team to investigate and collect samples (sometimes involving mini surveys) and taking regulatory action on the basis of the results of the investigation and laboratory results. There are records of such regulatory activity in all 5 partner states.

The passive surveillance system seems to work out well in all countries. However, the consultants noted during interviews with officials of public sector medicines supply organizations that these organizations sometimes carry out their own investigations after receiving complaints relating to products they have supplied. Sometimes the medicine supply organization acts independently and does not communicate with the respective NMRA. This weakens the NMRA by denying it information over an area of its jurisdiction and the opportunity to take regulatory action where necessary.

All partner states participate in Interpol-coordinated operations targeting organized trafficking of counterfeit medical products e.g. operations “Mamba” and “Giboia”. Such operations have had successful outcomes in uncovering counterfeit products circulating in the region, led to significant prosecutions and generated greater public awareness of the dangers posed by counterfeit medical products.

3.4.2 Active PMS activities

(a) Stages reached by each country

The capacity for PMS varies greatly within the region. Burundi, Rwanda and Tanzania (Zanzibar) have no demonstrable capacity, no guidelines, no protocols and no plans. While Uganda has the capacity to plan and execute PMS activities it has not been able to establish regular surveillance. Evidence presented indicates a certain degree of donor dependence, which inhibits the use of NDA’s available capacity and requires them to focus on a few categories of medicines of donors’ choice. On the other hand, Kenya does undertake regular surveillance of but its range is restricted to donor funded therapeutic categories. While Tanzania (Mainland) has in place a regular and working PMS structure with fairly regular outputs, the communication of PMS outcomes to stakeholders and general public needs to be strengthened.

The following chart displays the stage reached by each country in implementing PMS activities basing on the scheme explained in the methodology section:-

Fig. 1: Stages reached by each Partner State in Implementing Active PMS

	Legislation stage	Planning stage	Capacity stage	Implementation stage	Extended scope stage	Visibility stage	Useful outcomes
Burundi	Completed						
Rwanda	Completed						
Tanzania (Z)	Completed						
Uganda	Completed	Completed	Completed	Completed			
Kenya	Completed	Completed	Completed	Completed	Completed	Completed	Completed
Tanzania(M)	Completed	Completed	Completed	Completed	Completed	Completed	Completed

(b) PMS procedures

Detailed process maps for Kenya, Tanzania (Mainland) and Uganda were developed and are presented in the appendices of the individual Country reports. For the different PMS activities, whilst sampling programs, surveillance priorities, screening procedures, analytical protocols, reporting of results, and publication of findings, will vary between Countries, there are a number of steps in the PMS protocol that are common to all. These can be summarized as follows:-

- Step 1: Preparing PMS program
- Step 2: Preparing sampling plan
- Step 3: Training of sample collectors
- Step 4: Sampling
- Step 5: Dispatching samples (to the laboratory)
- Step 6: Analytical screening of samples
- Step 7: Identifying samples for full analysis
- Step 8: Evaluating results
- Step 9: Drafting and approval of report
- Step 10: Publication of report

When each of these steps is examined it is possible to evaluate how each Country approaches PMS and propose how the activity can be optimised.

In general, the process for screening samples and identifying samples for full analysis is the same for all Countries performing routine PMS. Following screening, all suspicious samples plus 10% of screened samples shown to be satisfactory are submitted to the laboratory for full analysis. In Kenya, Tanzania (Mainland) and Uganda surveillance programs for anti-malarials delivered a sustained period of compliant results. It was therefore decided to discontinue the full analysis of random samples and focus on suspicious samples. However, compliant results are also important to PMS programs since they are an indicator that the regulatory controls are being effective and confirm the effectiveness of the product screening. Reducing the random sampling from 10% to 5% or less would free up resources that could be used elsewhere in the PMS program, to increase screening testing for example, but some level of random sampling is recommended.

(c) Detection of Counterfeit Medicines

One of the objectives of any PMS program is to detect counterfeit medicines that have penetrated the distribution chain. This presents a number of difficult logistical and analytical challenges for the following reasons:-

- The packaging of the counterfeit is often identical to authentic product
- The counterfeit product may comply with the genuine product specification with regard to identity and content of active ingredient.
- There are a number of examples of chemical analogues of approved APIs being used to avoid detection during screening;
- There is still a low incidence rate for counterfeit medicines, sample numbers for PMS are small and so the probability of detection of counterfeits from PMS studies is low.
- The distribution of counterfeit medicines is irregular and opportunistic, therefore planned programs of sampling and analysis are difficult to manage.
- Costs of sampling and analysis are high for PMS programs. Increasing sample numbers and the subsequent additional analysis costs would require a substantial annual revenue investment.

The Minilab screening system is now widely used within the EAC for the initial screening of PMS samples. It is a system of qualitative testing to identify medicines that are included in the essential medicines lists of the EAC Countries. Its limitation is that currently it can only be used for 75 active compounds and so many products cannot be screened. Additionally it uses a combination of colorimetric tests and thin layer chromatography (TLC) to identify the active ingredients in the samples to be tested. This limits its effectiveness to detect sub-standard and counterfeit products because, in many cases, quantitative analysis is necessary to confirm lack of compliance.

Despite its limitations the Minilab system provides an efficient and cost effective method for screening PMS samples. The risks presented by counterfeit medicines including examples of counterfeit products that have been found on the UK market are summarised in Table 2. It also indicates those areas where the Minilab would be effective in detecting the type of counterfeit product. Where it is least effective is in those situations where quantitative analysis is needed. The Minilab does not need a laboratory environment to be used but just a dedicated room in an office or storage area. Kenya, Uganda, and Tanzania have much experience in using this technique and have shown its value. Where the costs and logistics of establishing laboratory services are problematic it provides a first line defence to detect poor quality and counterfeit medicines. Those Partner States with limited or no laboratory resources should develop this technique as a first line monitoring procedure together with a strategy and financial resource for follow up analysis of suspect samples.

Table 2. Risks from counterfeit medicines

COUNTERFEIT DEFECT	EXAMPLES	DETECTION BY MINILAB SCREENING
No active ingredient	Tamiflu capsules	Yes
	Plavix tablets	Yes
	Sildenafil tablets	yes
Wrong active ingredient	sildenafil/tadalafil/vardenafil	Yes
	Lovastatin in place of atorvastatin	yes
Unapproved active ingredient	Lovastatin in place of atorvastatin	Yes
Content of active outside specification	Viagra, 150mg sildenafil (100 mg)	No
	Zyprexa, 5.6-6.5 mg olanzapine (10 mg)	No
	Plavix, 50-60 mg clopidogrel (75 mg)	No
Sub-standard manufacturing facilities	Lack of GMP	
	Unapproved facilities	
	Contaminated products	Yes/no
Product quality	Friable, powdery tablets	Yes/no
	Wide variation in uniformity of weight	No
	Wide variation in uniformity of content	No
	Different impurity profile	No
	Unknown impurities	No

It is possible also to use TLC in combination with flame ionisation detection (fid) as a quantitative technique. This would be able to use the known tlc methods but provide a semi-quantitative result that would possibly identify out-of-specification products during screening. This technique would justify further investigation.

Whilst the analysis and identification of counterfeit medicines can be complicated and inconclusive there are some relatively simple techniques that can be applied as a first stage screening process.

- **Appearance:**
However careful the manufacturer has been, there will always be differences between the illegal and genuine product. These may be labelling differences, colour or appearance of the product, or markings or embossing of the product.
- **Uniformity of weight:**
Counterfeit manufacturers take very little care about the quality of the products they manufacture. Their concerns are the appearance of the product and their profits. Tablets and capsules that have been manufactured under conditions of GMP will typically have a uniformity of weight (UoW) of +/- 1% whereas the figure for counterfeit products is typically +/- 10% or more. This test can be a quick and simple indicator.
- **Uniformity of content:**
The same arguments for UoW apply to uniformity of content. The testing of this is however more complex and the results are not so easy to interpret.
- **Reconciliation of batch number and expiry date:**
Counterfeiters will routinely use a genuine batch number for their products but want to give their products the maximum market coverage and so use an expiry date that maximises the shelf life of their products but does not correspond to the expiry date associated with the original batch number. This can be a simple check to confirm the provenance of a product.

(d) Scope of PMS activities in each Partner state

The consultants have noted that several PMS studies were conducted in Kenya between 2007 and 2013 under the auspices of the WHO and other international organizations. Since these do not reflect internal

capacity they have not been considered in this evaluation. Principal among these studies are the 2007 and 2011 QAMSA studies²¹ and the 2013 UNCoLSC²² report.

It appears that despite the long history of PMS activities in Kenya, the PPB has initiated and funded on its own only one study, the 2010 Cough and Cold Medicines Survey²³. All other surveys have support and input from other organizations, which might imply that they were initiated by these external organizations. Furthermore, this has limited the scope of PMS conducted by PPB to therapeutic areas of interest to vertical program and international development/humanitarian organizations.

Tanzania has implemented fully two PMS programs between 2008 and 2013 and is now implementing a 3rd program which started in 2014 and is due to be completed in 2017. The second program conducted between 2011 and 2014 had 9 phases; each phase with defined categories of medicines, a comprehensive sampling plan and a budget. Four groups/categories of medicines were surveyed, which were: antimalarials, ARVs, antibiotics and painkillers. The third PMS program is divided into 6 phases during which 18 types of medicines in 8 categories will be surveyed. These are: veterinary products (6 products), antibiotics (4 products), antihelminthic (1 product), antihypertensives (2 products), endocrine preparation (1 product), ophthalmic preparation (1 product), pain killer (1 product) and uterotonics (2 products).

Evidence provided by NDA limits PMS activities in Uganda to antimalarials and antibiotics.

(e) Visibility of PMS activities in each member state

PPB and TFDA use their websites to publish PMS reports. They also circulate their reports to pre-identified stake-holders. However, the consultants did not find evidence of high profile launches specifically targeting the public at large.

In Uganda final reports of post-marketing surveillance are usually published for distribution to the Ministry of Health and other stakeholders.

(f) PMS outcomes in Partner States

From PPB reports that were reviewed, it is evident that some non-conforming products were found during the surveys. The following are specific observations made in the reports relating to quality of medicines in circulation in Kenya:

In the 2010 Anti-malaria survey²⁴:

Some of the regulatory actions that were taken based on the findings of this survey included quarantine of products yet to be marketed, notifications to companies on the failure of compendial testing and closure of the manufacturing plant.

²¹ Report on the meeting on the survey of the quality of antimalarials in Sub-Saharan Africa (QAMSA), Silver Springs Hotel, Nairobi Kenya. World Health Organization. 6 – 8 July 2010

²² Survey of the quality of medicines identified by the United Nations Commission on Life-Saving Commodities for Women and Children. WHO Prequalification Team, Regulation of Medicines and other Health Technologies, Essential Medicines and Health Products. 2015.

²³ Report on a Post-Market Surveillance of Paediatric Cough and Cold Preparations t Pharmaceutical Retail Outlets in Nairobi City. Ministry of Medical Services, Pharmacy and Poisons Board. October 2010

²⁴ Monitoring the Quality of Antimalarial Medicines Circulating in Kenya. Ministry of Public Health and Sanitation & Ministry of Medical Services, Division of Malaria Control & Pharmacy and Poisons Board. November 2011

In the 2010 Cough and cold medicines survey:

46% i.e. 95 out of 205 of cough and cold products were found to be not registered with the PPB. It was recommended that importers or manufacturers of the same be *put on notice*, the products be recalled, withdrawn and destroyed and the respective importers *be made to answer on how the products were made available into the market*.

In the 2011 Anti-malaria survey²⁵:

Six samples failed compendial testing of which 4 were of AL, the first line treatment for uncomplicated malaria

In the 2012 Anti-malaria survey²⁶:

All the ACTs including those locally manufactured meet the specified quality standards

In the 2012 Anti TB survey²⁷:

The failure rate in laboratory analysis for anti-TB medicines in Kenya is 8.3% and mainly related to paediatric formulations

In the 2012 ARV survey²⁸:

- The 92 products surveyed comprised of 14 APIs of which 7 were not in the national ART guidelines.
- One third of the products sampled from the market were not registered by the PPB
- Most of the samples analyzed were of good quality with only one failing and this was because the analysis was done after the product had expire

In the 2014 Reproductive health medicines survey²⁹:

The consultants were provided with the protocol for the study and could therefore not determine regulatory action that resulted from the study.

There is evidence that regulatory action is taken and made public, for example through the PPB Lifesaver Newsletter³⁰. A classical example is the Newsletter of September 2011 where two manufacturers were closed down and several anti-malarials were recalled, mopped up and destroyed³¹.

In Tanzania (Mainland) final reports of post-marketing surveillance are usually published for distribution to the Ministry of Health and other stakeholders. During the study we were shown the report for phases I and II of the 2011 - 2013 PMS program which covered for antimalarials, antibiotics and ARVs³². The report was also

²⁵ Monitoring the Quality of Antimalarial Medicines Circulating in Kenya. Ministry of Public Health and Sanitation & Ministry of Medical Services, Division of Malaria Control & Pharmacy and Poisons Board. April 2012

²⁶ Monitoring the Quality of Antimalarial Medicines Circulating in Kenya. Ministry of Public Health and Sanitation & Ministry of Medical Services, Division of Malaria Control & Pharmacy and Poisons Board. May 2013

²⁷ Report on Post-Market Surveillance of First Line Anti-Tuberculosis Medicines in Kenya. Ministry of Public Health and Sanitation. October 2012

²⁸ Post Market Survey of Antiretroviral Medicines in Kenya. Ministry of Public Health and Sanitation and Ministry of Medical Services. October 2012

²⁹ Proposal for the Post-Market Surveillance of Products Used in Reproductive Health in Kenya. Pharmacy and Poisons Board and Division Of Reproductive Health, Ministry of Health February, 2014

³⁰ The Lifesaver, A publication of the Pharmacy and Poisons Board. The Kenya National Medicine Information and Pharmacovigilance Newsletter, 5th Edition. November 2014

³¹ The Lifesaver, A publication of the Pharmacy and Poisons Board. The Kenya National Medicine Information and Pharmacovigilance Newsletter, 1st Edition. September 2011

³² Quality Survey Of Selected Antimalarials, Antibiotics And Antiretrovirals Circulating In Tanzania. Medicine Post Marketing Surveillance Programme 2011-2013 Phase I & II. Tanzania Food and Drugs Authority. February 2014

published on the authority's website³³. The report of the 2007 – 2009 surveillance program was not available.

According to the TFDA report, results obtained in the 2011 – 2013 program indicated the presence of substantial problems in the quality of Cloxacillin formulations in several regions. However, in the cases of Quinine, Artemether + Lumefantrine and Antiretrovirals, the quality was proven to be reasonably good. The region which demonstrated high failure rate in both Cloxacillin formulations was Mtwara and the least were for Mbeya and Dodoma regions. In terms of distribution levels, highest failure rate was observed for samples collected in pharmacies, DLDMs and DLDBs. These observations led to the following regulatory actions:

- Distribution outlets which were associated with highest failure rates of cloxacillin formulations were to be inspected to verify compliance with good distribution practice.
- Registration of affected cloxacillin formulations withdrawn from the market.

In Uganda we were shown the report for the PMS for antimalarials conducted in 2012. During the activity 436 samples were collected of which 104 samples were sent to the laboratory for level II testing. Out of the 92 samples there were ultimately tested, 5 samples failed which include 4 samples of quinine bisulphate tablets and one sample of quinine sulphate tablets. The report concluded that “the quality of anti-malarial medicines in all regions of Uganda was found to be good but with 1.2% failure”. It recommended that sampling for the second round be adjusted for sample prices to cater for samples in the ACT categories where few samples were collected namely Artesunate/Amodiaquine, Dihydroartemisinin/Piperaquine sulphate and Artemisinin/Naphthoquine in order to assess their quality on a large scale.

There was no information provided on the regulatory action or follow up of the failed samples.

3.5 Challenges Facing Partner States in Implementing PMS

1. Three partner states are not undertaking active PMS. Resources and facilities are not available to enable this. As a consequence, risks of suspicious or defective products may be greater in these Countries and could find their way to other countries through cross border trade or porous borders.
2. PMS programs are not shared or co-ordinated within the EAC. This leads to potential duplication of testing and lack of optimisation of resources
3. Results from PMS programs are not publicised and information and data on findings is not shared throughout the EAC
4. Resources are limited and so it is only possible to cover a small percentage of essential medicines in any one year. Priorities have to be set according to appropriate risk assessments.
5. Laboratory analyses are costly but necessary. Improved screening will enable laboratory resources to be targeted at suspicious samples. Improved screening methods that allow optimisation of laboratory resources need to be developed

Basing on the chart of stages it was possible to determine the general challenges facing each country in implementing PMS and the type of support they would need.

1. Burundi, Rwanda and Tanzania (Zanzibar) need support to establish entire PMS systems and capacities;
2. Uganda needs support to operationalize its PMS unit;

³³ www.tfda.or.tz

3. Kenya needs support to extend the scope of its PMS activities beyond those of interest to donors; and
4. Tanzania (Mainland) needs support to enhance the role of PMS in providing vital market information by expanding its coverage and increasing its visibility so as to gain more public confidence in TFDA's regulatory efficiency.

As reported in the country sections, each country faces specific challenges in implementing PMS. Most of these challenges are common and can be addressed simultaneously by technical collaboration and harmonization of procedures. Common specific challenges are:-

1. To amend pharmaceutical legislation so as to legally oblige manufacturers, importers and distributors to report quality defects in medicines that they become aware of. In this regards other countries can learn from Rwanda whose act carries such legal requirement.
2. To reduce loss or damage of reference samples by improving storage facilities.
3. To adequately map the PMS process in order to capture all critical process parameters and avoid sub-optimal process management.
4. To strengthen controls by putting in place performance indicators for as many process steps as possible.
5. To put in place effective planning, analysis and reporting systems that will build public satisfaction in PMS outcomes.
6. To reducing negative perceptions by predicting possible negative reactions from some sections of the public and to prepare for them e.g. resistance from sampling sites.

Other challenges specific to each country as listed in the individual sections can be addressed by improving management systems within the NMRA.

3.6 Lessons learnt

Basing on the procedures of the three NMRAs that undertake Active PMS activities the consultants are recommending:

1. That each country should put in place a committee or task force to coordinate PMS activities. The committee should be chaired by the head of the PMS section and include representatives from all other departments participating in PMS activities.
2. PMS activities should be based on 3 to 5 year programs divided into phases. Based on these phases detailed action plans should be written outlining number of samples to be collected for each product, cost, human resources requirements and other administrative arrangements e.g. transportation and storage of samples.
3. The following 10-step standard procedure should be adopted across the region:

Step 1: Preparing PMS program

- Input from inspectors, product registration, laboratory, pharmacovigilance
- Informed by previous reports, inspection reports, defect reports, supplier performance
- Approved by designated senior manager
- Circulated to all relevant staff

Step 2: Preparing Sampling Plan

- Include all products that are to be sampled
- Define timeframe for sampling phase
- Identify sample sites
- Define and approve budget

- Inform laboratory for planning purposes

Step 3: Training of Sample Collectors

- Written training procedures
- Cover all sample collectors
- Include how sample forms should be completed
- Confirm that training is understood

Step 4: Sampling

- Samples to be taken close to the point of use of the products
- Samples taken from importers, wholesalers, hospitals, clinics, and pharmacies.
- Healthcare staff at sampling site informed of sampling program and the reasons for it
- Sample record form completed at the time of sampling. Form includes details of product name, product strength, pack size, batch number, expiry date, site of sampling, and storage conditions

Step 5: Dispatching of Samples

- Sample form included with all samples
- Reconciliation procedure for samples received against dispatch records
- Approved delivery company

Step 6: Analytical Screening of Samples

- Screening performed at the point of sampling for optimum response times
- Annual training programs for staff in the interpretation of results
- Staff trained to understand semi-quantitative analysis
- Suspicious samples prioritised for further analysis

Step 7: Samples for full analysis

- Analysis is performed to approved pharmacopoeial specifications
- Protocols are defined and are relevant to the potential non-compliance of the products
- Out-of-specification procedures are followed when non-compliant samples are identified
- Non-compliant results are reported immediately to the NMRA

Step 8: Evaluation of results

- The committee/ body that is responsible for the PMS program and sampling plan should receive the results from the laboratory and advise on regulatory actions
- Additional PMS actions should be identified and followed up. This could involve inspections, further targeted sampling and analysis, or further laboratory analysis

Step 9: Report preparation

- Process should involve all departments involved in the planning, sampling, screening, analysis, and evaluation within the PMS program
- The report should be approved by the Head of the NMRA

Step 10: Publication of the report

- Report should be made available through the website
- EAC member states should receive the report

4. Conclusion and Recommendations

4.1 Conclusion

There is not a consistent approach to PMS within the EAC. Only Kenya, Tanzania (Mainland), and Uganda are undertaking active PMS that is non-demand led and is initiated by the NMRA. The approach in each of these three countries also varies. Tanzania (Mainland) plans a 3-year program which is conducted in phases whereas Kenya and Uganda plan their programs in annual cycles. The process maps in Appendices 2, 4 and 5 highlight the different procedures which vary in respect of surveillance priorities, sampling programs, screening procedures, analytical protocols, reporting of results, and publication of findings. Active PMS needs to be initiated in Burundi, Rwanda, and Tanzania (Zanzibar). This presents significant challenges on resources which are not currently available and will need to be identified. These include sample costs, sampling officers, laboratory resources, analytical costs, program management, and dissemination of results. The report contains recommendations of a standard PMS procedure based on lessons learnt during the study to be adopted for the optimisation of PMS programs. These can also form the basis of new PMS activities in those NMRAs who currently do not undertake active PMS.

Passive PMS in response to reports of suspicious or defective medicines is performed in all countries. To varying degrees there are procedures in place to investigate and take action when defective medicines are reported to the NMRA. Kenya, Tanzania (Mainland), and Uganda actively promote reporting by making reporting forms available to manufacturers, suppliers, healthcare workers. In those countries with no operational medicines control laboratory, investigation and analysis can be a challenge and could potentially lead to an inadequate follow up. Formal investigation procedures and adequate testing resources are critical to this process. Recommendations are made in the report to improve the reporting, investigation and follow-up of suspicious or defective medicines. This activity is one of the key areas of PMS that can identify illegal or counterfeit medicines and so it is important that it is managed efficiently and effectively. National Medical Stores have their own internal procedures for the investigation of complaints relating to defective and suspicious products. In many cases these are independent of the NMRA procedure and therefore do not inform the PMS planning process.

Between EAC partner states, there are a number of missed opportunities for collaboration on PMS and sharing of information and data. Such collaboration would improve greatly the efficiency of PMS in the region and optimise use of resources. Sharing details of PMS sampling plans, analytical results, defective medicines reports, PMS reports, and outcome measures could reduce duplication of testing, better inform purchasing programmes, and improve the PMS planning cycle. Additional coverage of the surveillance of the East African market would be possible, gaps in this coverage could be identified, and a better picture of supplier performance would be created because more data would be available to make this assessment. The report includes specific recommendations in the areas of communication and co-operation that would be expected to improve the efficiency and effectiveness of PMS in the EAC. The establishment of formal networks for PMS and the laboratories would facilitate this.

Only four countries, Burundi, Kenya, Tanzania (Mainland), and Uganda have functional, operational laboratories. The laboratory in Burundi is a part of the National Institute for Public Health and is separate from the department responsible for product registration and import control. Suspicious products are analysed in the laboratory. The laboratories in Kenya, Tanzania (Mainland) and Uganda are established under medicines legislation as is the laboratory in Tanzania (Zanzibar). The laboratories in Tanzania and Uganda are within the authority of the NMRA and operate within the same management structure as the PMS team. As such they only receive samples from the regulatory authority. The NQCL in Kenya is established independently of the Kenya PPB and has its own line management accountabilities. The NQCL is required to generate its income through its analytical work. The PPB and its PMS program must therefore compete for its laboratory service within the priorities of the laboratory. There was no suggestion that this

was a problem but, going forward, it could impact upon plans to expand the PMS program. The fact that KEMSA, the NMS in Kenya, is developing its own laboratory facilities is an indicator that costs of analysis at NQCL are high. The laboratories in Kenya, Tanzania (Mainland), and Uganda are all accredited under the WHO pre-approval scheme for medicines testing laboratories. This indicates that the laboratory QMS has been audited and approved. This will include the procedures for handling of samples, sample analysis, and reporting of results. The NQCL in Kenya is also seeking ISO 17025 accreditation. This will enable it to expand its contract testing business. PPM and servicing of critical equipment is a major problem leading to equipment downtime and reduced analytical capacity. This is a problem that needs to be addressed across the EAC. It is not just a problem for medicines testing laboratories but will also affect food testing and other government laboratories. A centralised approach is needed to create a solution to this problem. The report contains recommendations on how this might be approached. A significant phase of the PMS analysis is the screening of samples. A cost effective way of increasing PMS sample numbers is to screen more samples and to make better use of the screening test to detect suspicious samples that require further analysis. In the longer term alternative technology to the Minilab such as the TruScan may be the better option but the Minilab is the best option at this time, particularly for those member states who have yet to introduce active PMS. It is important therefore that the Minilab test is used to its maximum capabilities for the detection of suspicious samples and that analysts are trained in detecting unusual spot patterns or differences in the chromatograms that might indicate a suspicious sample.

The PMS program should be able to identify counterfeit medicines. In the first instance it will need to be detected by the screening test. Since counterfeit medicines are very often grossly defective with no active ingredient, the wrong active ingredient, or the content of active well below strength, the minilab screen should detect them. As a suspicious sample they will then be submitted to the laboratory for further analysis. This analysis needs to focus on whether the sample is a defective authentic product or a counterfeit product. Once the defect has been confirmed additional tests should be applied to determine if the product is counterfeit. Examples of these tests are included in the recommendations.

In summary, PMS is established in some EAC partner states, these programmes need to be extended to cover all the EAC. The focus of the programmes should be the detection of defective and counterfeit products but confirmation of product compliance is an important outcome of PMS. Collaboration between EAC partner states for PMS will improve efficiency, optimise the use of resources, increase market surveillance coverage within the EAC, and improve outcomes.

4.2 Recommendations

At EAC Secretariat level

1. To strengthen the coordination of PMS activities in the region it is recommended that:-
 - a. A Regional PMS coordination program should be established to co-ordinate activity in the Partner States and facilitate collaboration in the Region. Key elements of this program will be:-
 - i. An annual meeting of PMS program managers is held to share information and experiences from the previous year's program. This should include sample plans, results, outputs, and outcomes.
 - ii. PMS programs are circulated to all EAC NMRA's in confidence when finalised. This need only include the information on products to be sampled.
 - iii. PMS reports are circulated to other EAC Partner States
 - b. Purchasing specifications for laboratory equipment such as chromatograms and spectrophotometers should be similar throughout the region and include a requirement for service engineers to be based locally at least within the EAC.
 - c. Local internal training on equipment maintenance should be coordinated with a view to developing in-house competencies for routine maintenance and annual validation.

2. To strengthen the implementation of PMS activities within the region it is recommended that:-:
 - a. A project should be initiated to determine the potential of TLC/FID as a screening method for market surveillance. This work could be shared throughout the EAC and the findings circulated to all partner states.
 - b. Raman spectroscopy will detect counterfeit medicines provided standard spectra are available for comparison. These spectra are transferrable between instruments and so a collaborative project would enhance the capabilities of the laboratories. A research project should be initiated to assess the potential of the TruScan to screen for suspicious and non-compliant medicines. The proposed programme for this study is as follows:-
 - i. Locate the TruScan in the National Medical Store. Since the instruments are owned by the Uganda NMRA, this would be the NMS in Uganda.
 - ii. For a two year period, require all tenderers for medicines supply contracts to provide a tender evaluation sample when submitting their tender
 - iii. When the contract is awarded, use the tender sample to create a reference spectra library for the TruScan
 - iv. Screen each subsequent delivery of that product by comparison with the library spectra
 - v. Submit all suspicious samples for full laboratory analysis
 - vi. Begin with a single class of medicines, eg anti-malarials, then extend this to other programme medicines and then to the essential medicines list. Since library data can be shared, it is possible to transfer reference spectra between instruments and share the workload.
3. To enable uniform implementation of PMS procedures it is recommended that a regional counterfeit detection program be instituted and coordinated at EAC level. The program should include:
 - a. training of inspectors in the detection of SSFFC products,
 - b. provision of technical facilities e.g. Minilab service centre, product sample reference library and Raman spectra library,
 - c. establishment of a central planning and monitoring unit within the EAC secretariat for this purpose and to further strengthen recommendation (1) above.
 - d. co-ordination of collaborative projects with International enforcement agencies and anti-counterfeit organisations (eg Interpol,WHO) in survey projects to detect illegal and counterfeit medicines.

At Partner State level

1. Burundi, Rwanda and Tanzania (Zanzibar) should initiate PMS programs based on the practices outlined above. This should be a risk based approach that initially targets programme medicines such as anti-malarials, anti-retrovirals, anti-tuberculosis medicines, and antibiotics but has the scope for extension. The laboratories in these three Partner States (assuming the Rwanda laboratory is commissioned) should concentrate their financial resources and technical competencies on product screening. This currently uses the Minilab but could in the future use Raman spectroscopy.
2. All EAC Partner States should introduce legislation that requires all parties involved in the manufacture, importation, supply, distribution and laboratory testing of medicines in the EAC to report any incidence of suspicious products or quality defects in medicines that have been marketed in the EAC to the relevant Regulatory Authority.
3. All EAC Partner States should ensure that reporting tools are available to all healthcare workers and to the general public for the reporting of suspicious or defective products to the Regulatory Authorities in the EAC. These should be available as hard copy and electronically.
4. All EAC Partner States should be equipped with Minilab systems for the routine monitoring of PMS samples. Regular user training programmes should be undertaken to ensure all staff who operate the systems are competent to do so.

5. Procedures and funding should be in place to ensure the analysis and follow up of all suspect samples.

At NMRA level

1. All NMRAs should have formal written procedures for the investigation of defect reports. These should define the roles and responsibilities of the key staff involved in the process, the person or persons responsible for managing the investigation, key milestones, the approval process for follow up actions, the monitoring of outcomes, and the communication process with stakeholders.
2. Random sampling should be an integral part of the PMS program. Sample numbers should be based on an assessment of risk, based on historical test results, supplier assessments, and product history.
3. If a defect report is confirmed, whether from passive (defect reports) or active (PMS), the outcome should be published on the Authority website and other EAC Regulatory Authorities should be informed.
4. Reports of non-compliant products that have been confirmed should be circulated immediately to all NMRAs in confidence.

The following procedure for detection of counterfeit products, to be adopted by all NMRAs, is recommended:

1. When a product is approved and added to the register of approved products, electronic copies of the packaging should be provided to the NMRA. These should be provided to the inspectors at the ports of entry as comparators when checking import consignments.
2. Inspectors at the ports of entry should receive training in the identification of SSFFC products.
3. Tests for uniformity of weight and uniformity of content should be performed routinely on all suspicious samples.
4. For suspicious samples, batch numbers and expiry dates should be confirmed with the original manufacturer. It may be wise to include this as part of the tender requirements.
5. All importers and suppliers of counterfeit medicines should be blacklisted in the EAC.

Appendix 1: Burundi situational report

The Department of Pharmacy, Medicines and Laboratories of the Ministry of Health (DPML) is the body that regulates medical products in Burundi.

1.1 Legal and regulatory framework

Framework for Pharmaceutical regulation

Burundi is reviewing its pharmaceutical legislation to establish a food and drugs authority with the intention that it will introduce a legal framework for the regulation of medicines. At the moment pharmaceutical regulatory activities are divided between three legislations administered by three separate bodies which are: the Department of Pharmacy, Medicines and Laboratories of the Ministry of Health (DPML), which deals with product registration and import control; the department of Inspection of Pharmacy, Medicines and Laboratories under the General Inspectorate of Public Health and the Fight against AIDS, which licences and inspects manufacturers, wholesalers and pharmacies; and the Pharmacy Council, which registers pharmacists. Furthermore the Drug Quality Control Laboratory operates under the Institute for Public Health.

Regulation of products manufactured inside the country

There is only one local manufacturer in Burundi, Siphar. The licensing of manufacturing sites is under the General Inspectorate for Public Health. Since drug registration has not yet begun, the DPML has registered locally manufactured products and included them in the List of Notified Medicines. No further monitoring is done unless a complaint is lodged.

Regulation of imported products

The DPML controls the importation of medicines. Importers apply for a permit from the department to import medicines. The application is checked against the list of notified medicines and approved for importation. When the consignment arrives, inspectors from the department check the goods for physical defects and against the permit. If any suspicion arises the product is quarantined and a sample is sent for analysis to the Drug Quality Control Laboratory of the National Institute for Public Health. If the product fails, it is destroyed by the importer under supervision of the DPML and representatives from Ministry of Trade, Security (Police) and the Revenue Authority. A copy of the destruction report is kept by DPML.

Regulation of defective medicines

There is no regulatory requirement or formal procedure for the reporting of defective medicines and manufacturers have no legal obligation to report quality defects in medicines that they become aware of. Suspicious products that are identified at the port of entry by inspectors during physical inspection will be quarantined and investigated. Passive surveillance is conducted in response to complaints. Last year 6 samples of suspected products were sent to the laboratory for analysis and their Certificates of Analysis are available. One of them failed. Procedures for regulatory action are still under way.

Product recall and destruction of defective products is the responsibility of the importer under the supervision of DPML.

La Centrale d'achat des médicaments Essentiels du Burundi (CAMEBU) has a procedure for regularly checking the quality of products in its warehouse that is under its Quality Assurance department. If a suspect product is found, samples will be sent to the laboratory at the National Public Health Institute for analysis and, if confirmed, defective products are recalled and destroyed under the supervision of the DPML, the Revenue Authority, the police and the Ministry of Trade.

Legal and regulatory framework for Post-marketing Surveillance

The Department of Pharmacy, Medicines and Laboratories of the Ministry of Health is the department that currently undertakes postmarket surveillance but it lacks the legal authority to enter pharmacies and take

samples. For this reason inspectors from the DPML obtain temporary letters of authority from the Director General of Clinical Services. The DPML is empowered to perform the following functions:

- The licensing and authorisation of medicines
- The control of the importation of medicines

No active PMS is undertaken at the moment though an unplanned attempt was made in 2014. Passive PMS is undertaken on receiving a complaint of a defective product. The DPML send out its inspectors to investigate the complaint and collect samples, which are sent to the Drug Quality Control Laboratory. Regulatory actions are taken if the defect is confirmed, these include product recall and destruction, which are the responsibility of the importer (see 1.3).

Specific roles performed by the two bodies in implementing activities related to PMS are as follows:

Inspection of manufacturers - General Inspectorate for Public Health and DPML for GMP
Inspection of importers – DPML
Inspection of distributors – General Inspectorate of Public Health and DPML
Market surveillance for quality of medicines – DPML
Defective medicines and product recall – DPML
Enforcement activities and prosecution - DPML

What the table illustrates is that, under the present arrangements, effective postmarket surveillance requires collaboration between the two different Ministerial departments and the Drug Quality Control Laboratory.

Supplementary laws

(a) Destruction of defective medicines

There is currently no legal provisions for the destruction of medicines

(b) Prosecution of offenders

There is no legislation for this at the moment. It is a part of the review of legislation for the control of medicines

1.2 Planning and approach

Not applicable since there is no active PMS

1.3 Technical capacity for active PMS

Organization structure

Not applicable since there is no active PMS.

Internal collaboration

Not applicable since there is no active PMS.

External collaboration

Not applicable since there is no active PMS.

PMS procedure

There are no procedures for active post-marketing surveillance at the moment.

Field support

Not applicable since there is no active PMS.

Laboratory support

The Drug Quality Control Laboratory is located at the National Institute for Public Health. The Head of the Laboratory reports to the Manager (pharmacist) in Charge of Quality Management who in turns reports to the Director of Drug Quality Control. It has sections for physical analyses, wet chemistry and instrument rooms. The laboratory is neither ISO certified nor WHO pre-qualified although the process of obtaining such accreditation is under way.

Samples are received in the receiving room and registered. They are sent to Manager who gives them unique code numbers. After that they are sent to the laboratory, registered again and given internal laboratory number before storage in a designated sample store. When analysis is due the samples are assigned to an analyst. The SOP for sample handling is not written yet. Tasks are assigned as a weekly programme of work.

Analysis is done according to written protocols. Results are calculated by the analyst and checked by another person before approval by the head of the laboratory. A certificate of analysis is issued and part of the sample is retained for future reference.

Analyses are done against international pharmacopoeias such as the British Pharmacopoeia, United State Pharmacopoeia, International Pharmacopoeia, Indian Pharmacopoeia and the Japanese Pharmacopoeia. The law does not specify which Pharmacopoeias are to be used.

The laboratory has an OOS procedure.

Equipment available in the laboratory is shown in Table 1.

Preventive maintenance is done by analysts while corrective maintenance is done by internal technicians. If the service cannot be done by these personnel, an external technician is called (e.g. for HPLC). Preventive maintenance procedures are available. Calibration of balances is done by the Bureau of Standards while other equipment is calibrated internally. Obtaining reference standards is a big problem due to their expense and unavailability, hence there is a chronic shortage of reference standards. Facilities for storing reference samples are available.

Administrative support

Not applicable since there is no active PMS.

1.4 Implementation

This section does not apply since there is no active PMS.

1.5 PMS scope and cost

This section does not apply since there is no active PMS.

1.6 Visibility of PMS activities

This section does not apply since there is no active PMS.

1.7 PMS outcomes

Not applicable since there is no active PMS.

1.8 Quality assurance by importing organizations

La Centrale d'achat des médicaments Essentiels du Burundi (CAMEBU)

Supplies are procured mainly by tender, mostly by international competitive bidding. These tenders are normally called once a year. In cases where stocks run out, local tenders are called to fill the gap from locally available products. Restricted tenders are only occasionally used. There is no supplier register. Suppliers are qualified for 1 year and re-assessment is done every year based on specifications (quality) of required products. The tender award is based on price (lowest).

CAMEBU's stock list is guided by the National List of Essential Medicines and is not restricted to medicines on DPML's notification list. It supplies medicines primarily to government health facilities although some items may be supplied to private facilities in response to a written request and depending on the stock position.

Once a contract is signed a supply program is prepared and agreed upon between CAMEBU and the supplier. Implementation of the program is monitored by the supply department. Penalties are imposed in case of non-compliance to the program which include financial penalties and blacklisting. No company has been blacklisted in the last two years.

When goods arrive the Quality Assurance department checks the product physically and takes samples. Suspected samples are sent to Drug Quality Control Laboratory or international laboratories in Malagasy, France or Belgium. 150 samples were sent for analysis last year.

There is a program of monitoring storage conditions in the warehouse using thermometers and humidity meters. Regular inspection of products in its warehouses is undertaken by Quality Assurance in collaboration with Supply Services. One defective product was found in the warehouse last year and recalled (Methergin inj. 0.2mg/). CAMEBU is responsible for product recall and destruction under the supervision of the DPML, Revenue Authority etc. CAMEBU has no active surveillance of products circulating in health facilities. Recalls are based on complaints received from customers.

Appendix 2: Kenya situational report

The Pharmacy and Poisons Board (PPB) is the National Medicine Regulatory Authority established in 1957 by an Act of parliament, the Pharmacy and Poisons Act, Cap 244 of the Laws of Kenya.

2.1 Legal and Regulatory Framework

Framework for pharmaceutical regulation

The Regulatory framework for the control of medicines in Kenya is the Pharmacy and Poisons Act Chapter 244 (Revised Edition 2009) and its related rules. It contains the following regulatory Authorities:-

- The licensing of manufacturers, wholesale dealers, and retail premises
- The regulation of premises for the storage and distribution of drugs
- The approval and registration of products manufactured in Kenya
- The registration of importers of medicines into Kenya
- The approval and registration of products imported into Kenya.
- The establishment of the National Drug Quality Control Laboratory (NQCL)
- The analysis of drugs locally manufactured and imported into Kenya. The NQCL issues a certificate of analysis for all analyses undertaken
- Inspectors rights of access and powers of seizure

Regulation of products manufactured inside country

All locally manufactured products are registered before being marketed in the country. To obtain a marketing authorization a manufacturer must submit to the Board a full dossier of product information and the premises must be inspected and licensed as compliant to GMP. All registered products are published in the product register.

Regulation of imported products

All products manufactured outside the country must be registered before being marketed in the country. To obtain a marketing authorization a manufacturer must submit to the Board a full dossier of product information and the premises must be inspected and licensed as compliant to GMP by the Regulatory Authority in the country in which they are based. PPB also undertake overseas GMP inspections. There are about 150 conducted each year. All registered products are published in the product register.

Anyone wishing to import medicines must hold an import permit issued by the PPB. Manufacturers and wholesale dealers from outside Kenya must operate through a local distributor or representative who holds a wholesale dealer's licence. An import permit is required for each consignment.

At the ports of entry Inspectors from the PPB perform checks of all imported medicines. They do a visual inspection of the product and confirm the import permit, product registration, and importer licence. Presently PPB do not routinely sample products at the ports of entry. The Board has acquired minilabs that have been placed at the points of entry and are intended to be used in screening of imported products. Suspicious samples that have been identified through a risk assessment procedure will be investigated but otherwise the importers and distributors are responsible for the quality of their products.

Regulation of Defective Medicines

There is a good process in place for reporting quality defects to the PPB. A defect reporting form, "the pink form" is available to healthcare workers and is also on the PPB website. There is also an online reporting system (www.pv.pharmacyboardkenya.org) that one can use either a computer or telephone to report any suspicious product to the board. Incoming reports are assigned to a member of the Medicines Information and Pharmacovigilance (MIPV) unit. The investigation can involve staff from the program agencies, product

registration staff, the inspectorate, and the laboratory. The data are reviewed and a recommendation is sent to the Quality, Safety, and Efficacy Committee who initiate regulatory action.

Postmarket surveillance

There is no legal obligation for manufacturers, importers, or distributors to report information about known quality defects to the PPB. According to the PPB its core mandate is to ensure the provision of quality, safe and efficacious pharmaceutical products and services. However, the Act does not contain specific provisions to regulate the quality, safety and efficacy of medicines except by extrapolation. For example, section 45 of the act requires an order from a magistrate to a police officer in order to enter and search premises, vehicle or container suspected to contain evidence that an offence has been or is being or is about to be committed. Furthermore, section 35(A)(5) of the Act empowers the Director of the National Drug Quality Control Laboratory or any member of the Laboratory staff authorized by him to enter and sample any medicinal substance under production in any manufacturing premises and certify that the method of manufacture approved by the Board is being followed.

Supplementary laws

(a) Destruction of unfit medicines

PPB has issued guidelines on disposal of pharmaceutical waste.

(b) Prosecution of offenders

PP does not have a resident lawyer but there is a lawyer on contract who handles legal issues. Plans are underway to recruit a lawyer. Furthermore, the Board uses public prosecutors but inspectors are trained in prosecution procedures.

2.2 Planning and approach

Postmarket surveillance is an activity within the Directorate of Medicines Information and Pharmacovigilance. The Directorate develops and implements the Annual Operations Plan (AOP) for PMS and there is a lead manager in MIPV who is responsible for its implementation. The plan is informed by previous PMS reports, complaints reports, the public health programs and inspection reports. The plan is drafted within MIPV and the final draft circulated to other Directorates with an interest. The final plan is approved by the PPB management Board who also allocate the budget.

PPB has a detailed PMS strategy. It describes roles and responsibilities, how a PMS plan should be made and executed, sample testing and regulatory action.

2.3 Technical capacity for active PMS

Organizational structure

In the PPB, PMS is a section under the department of Pharmacovigilance and Post-Market Surveillance, which is part of the Directorate of Medicines Information and Pharmacovigilance. No information was provided on its staffing.

Internal collaboration

Although PMS is a collaboration of various departments within the PPB, there is no specific committee that oversees such collaboration. Individual Directorates can contribute to the plan and the AOP is approved by the Management Committee which includes all directors. The Directorate of IS&E contributes during the preparation of AOP plan by making its inspection reports available and providing inspectors to do the sampling.

Secondary procedures contributing to the success of the PMS process are summarised in Table 5. They include procedures for laboratory analysis, investigative inspection, preparing training materials for sample and data collectors and procedures for training inspectors and healthcare workers.

External collaboration

Collaboration with other stakeholders

PPB's PMS programme involves other stakeholders such as NQCL, public health programs, development partners, procurement agencies, patients and the general public, pharmacy practitioners and other healthcare workers, pharmaceutical industry, programs in the Ministries of Health, private and public procurement and distribution Agencies, testing facilities, Regulatory bodies, and professional organizations such as PSK, KPA, Medical Board, Nursing Council, NGOs, WHO. Cooperation with these stakeholders helps in sharing information and reducing surveillance costs. Furthermore, working in close collaboration with healthcare providers and consumers promotes reporting of product defects including counterfeit products.

PMS Procedure

(a) Active PMS

Each time before carrying out a PMS activity, a protocol is developed. A step-by-step process map for PMS is not available but the following steps became evident during the interview with PMS staff:-

- Step 1: Making the Annual Operations Plan (AOP) of the Directorate
- Step 2: Developing proposals for the specific PMS plan
- Step 3: Developing a sampling plan
- Step 4: Training sample and data collectors
- Step 5: Collecting the samples
- Step 6: Dispatching the samples to PPB Headquarters.
- Step 7: Handling and storing the samples at PPB Headquarters.
- Step 8: Secondary sampling
- Step 9: Compiling the preliminary report
- Step 10: Compiling the final report
- Step 11: Disseminating the final report

A process map was developed during the interview (Figure 2) linking these steps to inputs and output as well as secondary procedures associated with the inputs and outputs. Detailed descriptions of the steps, evaluation of responsibility assignment along the RASCI model and secondary processes related to the PMS processes are appended (see Tables 4 and 5).

Sampling officers comprising of staff from regional offices and local healthcare workers undergo a training program to familiarise them with the sampling plan. Samples are taken from distributors, hospitals, pharmacies, and other retail outlets over a 2-3 week period. Samples are then sent to the PPB. At the PPB samples are "stratified". This is a process that reviews the samples received to ensure that all manufacturers and importers of that product are covered by the sample subset and that the laboratory does not receive too many samples from a single batch. The samples are then sent to the laboratory for analysis. The samples are accompanied by a sample request form which has a checklist of tests and defines the parameters to be tested. After analysis, reports are submitted to PPB. The PPB are notified immediately of failures which are followed up through the defect system. Otherwise reports are submitted weekly. When testing has been completed a report is prepared by MIPV staff. When finalised, the report is approved and signed by the Registrar and published.

The PMS program report when completed is reviewed by the MIPV Directorate. The report includes a section on lessons learned which contributes to the subsequent AOPs.

(b) PMS for anti-malarials

There is an on-going program, since 2010, of surveillance for anti-malarials using the minilab kits funded by the GFATM, USAID and PMI through USPOM. 11 minilabs are kept in PPB's regional offices (not necessarily based on government's administrative structure). Annually, in each of these regions, a team comprising of an inspector, a laboratory technician, and a local pharmacist carry out a program of sampling and screening.

100 samples are taken from a representative sample of outlets. All suspicious samples plus 10% of all satisfactory samples are sent to NQCL for analysis. The survey is designed and conducted by PPB staff and reports published on the organization's website.

(c) Survey of the quality of medicines identified by the United Nations Commission on Life-Saving Commodities for Women and Children, 2013

This survey, conducted in 2013/2014, aimed at identifying products which were of good quality or the quality of which could be improved in short period of time. The study, designed and supervised by the WHO, was conducted in 10 countries across the world including Kenya, Uganda and Tanzania. It was not a programmed active PMS survey aimed at regulatory enforcement.

Passive PMS

(a) Defective reports

The PPB also undertakes other programs in response to recognised needs. Mini surveys can be conducted following complaints reports. Surveys may be undertaken following an approach from a partner agency such as WHO or from procurement agencies. In 2014-15 a special program of testing for anti-malarials and antibiotics is planned.

There is a good process in place for reporting quality defects to the PPB. A defect reporting form, "the pink form" is available to healthcare workers and is also on the PPB website. There is also an online reporting system (www.pv.pharmacyboardkenya.org) that allows someone use either a computer or telephone to report any suspicious product to the Board. Incoming reports are assigned to a member of the Medicines Information and Pharmacovigilance (MIPV) unit. The investigation can involve staff from the program agencies, product registration staff, the inspectorate, and the laboratory. The data are reviewed and a recommendation is sent to the Quality, Safety, and Efficacy Committee who initiate regulatory action.

Regulatory action resulting from defective products reports are published on the website as e-shots and reported in the pharmacovigilance newsletter.

(b) International operations

PPB also participates in Interpol coordinated operations to disrupt the activities of transnationally organized criminals involved in the trafficking of counterfeit medical products in Eastern Africa. It also aims to raise awareness, generate resources, and improve educational efforts and capacity building on the issue.

Operation Mamba II took place in August 2009. The participating countries were Kenya, Tanzania and Uganda. The results of this operation were 1) more than 270 premises raided; 2) 83 police cases opened; 3) prosecution of several individuals suspected of being involved in the illicit trafficking of medical products with at least 4 convictions; and 4) thousands of tablets seized. Operation Mamba III took place in July and August 2010. The participating countries were on this occasion Burundi, Kenya, Rwanda, Tanzania (Mainland and Zanzibar) and Uganda. The outcomes of Mamba III were 1) more than 375 premises targeted; 2) nearly 200,000 tablets and capsules seized; 3) at least 120 police cases opened; 4) 78 cases were sent to court; and 5) at least 34 convictions pronounced. The operation led to the adoption of the Declaration of Zanzibar by participating agencies and other organizations supporting the activities. This significant step will lead to enhanced partnerships, increased sharing of information, more intelligence-led operations, and greater public awareness on the dangers posed by counterfeit medical products.

Field support

Both PPB inspectors and regional local healthcare workers participate in the sampling program. For PPB these are GDP inspectors. This inspectorate is also responsible for import checks at the ports of entry

Laboratory support

The National Quality Control Laboratory (NQCL) is established under the Pharmacy and Poisons Act. It is independent of the PPB and has a clearly defined mandate in the Act as the designated testing laboratory for

medicines. The visit to the laboratory was brief and did not allow an in-depth assessment but it is clear that the laboratory has an independent program and different priorities from those of the PPB.

Samples are received into the laboratory and logged into the laboratory management programme where they are allocated an internal code number. They are moved to the sample store which is environmentally controlled and has cold storage facilities. The test request form is approved and signed by the laboratory manager who issues a laboratory analysis form together with the sample issue form.

An inventory of the laboratory resources, equipment and staff is given in Table 1 together with its accreditation status and the annual workload. The laboratory is well equipped and well organised.

Samples are analysed according to designated standard methods and procedures according to the QMS. The NQCL is WHO prequalified, certified since 2008. It has an established and comprehensive quality management system (QMS). It was audited on behalf of the EAC-PTB project in March 2013 in preparation for an ISO 17025 accreditation inspection which was imminent at the time of our visit.

The 2013 EAC-PTB report notes that PMS is in place but limited to anti-malarials and anti-retrovirals.

Administrative support

The administration gives support to PMS activities through

1. Approving the PMS activity
2. PPB releases officers to participate in the PMS activities
3. Providing resources for the sample collection from the health facilities
4. PPB paying for the analysis of the samples collected from the field
5. PPB supports Partners who come in to support the PMS activities
5. PPB trains officers on monitoring of SSFFCs
6. The Registrar has also appointed officers to MIPV to be specifically in charge of PMS

2.4 Implementation

During the course of the years, the following active PMS activities have been undertaken by PPB:-

Table 3: Active PMS activities undertaken by the PPB between 2010 and 2015

Year	Category	Planned by	Funded by
2010	Anti malarials (minilab 1)	PPB/NQCL/DOMC/USP	GFATM/USAID/PMI/PPB
2010	Cough and Cold Medicines	PPB	PPB
2011	Anti malarials (minilab 2)	PPB/NQCL/DOMC/USP	GFATM/USAID/PMI/PPB
2012	Anti malarials (minilab 3)	PPB/NQCL/DOMC/USP	GFATM/USAID/PMI/PPB
2012	ARVs	PPB/NASCOP/NQCL	CDC/PPB
2012	Anti TB medicines	PPB/NQCL/NLTP	PPB/NLTP
2013	Anti malarials (minilab 4)	PPB/NQCL/DOMC/USP	GFATM/USAID/PMI/PPB
2014	Anti malarials (minilab 5)	PPB/NQCL/DOMC/USP	GFATM/USAID/PMI/PPB
2014	Reproductive health medicines	PPB/RHP	PPB
2015	Anti TB medicines	PPB/NQCL/NLTP/KEMSA	PPB/NLTP
2015	ARVs	PPB/NQCL/NASCOP/KEMSA/KP	PPB/NASCOP
2015	Antibiotics	PPB/NQCL/NASCOP/NLTP	PPB

Unfortunately, reports for PMS activities conducted from late 2013 to 2015 have not been published yet. Their outcomes are therefore not verifiable.

2.5 PMS Scope and cost

Scope

The consultants have noted that several PMS studies were conducted in Kenya between 2007 and 2013 under the auspices of the WHO and other international organizations. Since the funding for these was externally provided, they may not be a measure of the internal capacity to perform PMS Principal among these studies are the 2007 and 2011 QAMSA studies and the 2013 UNOCL Commodities report.

It appears that despite the long history of PMS activities in Kenya, the PPB has initiated and funded on its own only one study, the 2010 Cough and Cold Medicines Survey. All other surveys have support and input from other organizations. In general, PPB looks to work with sponsors and programme agencies to share the costs of the PMS programs and this has limited the scope of PMS conducted by PPB to therapeutic areas of interest to vertical programs and international development/humanitarian organizations.

Cost of PMS

PPB's protocols do not give much detail on organization and cost of the activities; they dwell mainly on number of samples, distribution of sampling sites and sampling techniques. The 2014 protocol for PMS of reproductive health medicines provides a rough indication of PMS cost centres in Kenya Shillings as follows:

Purchase of samples	250,000 (40%)
Stationery	100,000 (16%)
Thermohygrometers	20,000 (4%)
Training and pre-testing	250,000 (40%)
Total	620,000 (100%)

However, this breakdown is probably more reflective of contributions expected from partner/donor organization rather than a full evaluation of the total cost of conducting the survey.

2.6 Visibility of PMS activities

PPB uses its website to publish PMS reports. It also circulates the reports to pre-identified stake-holders. However, the consultants did not find evidence of high profile launches specifically targeting the public at large.

2.7 PMS Outcomes

From the reports that were reviewed, it is evident that some non-conforming products were found during the surveys. The following are specific observations made in the reports relating to quality of medicines in circulation:

- In the 2010 Anti-malaria survey: Some of the regulatory actions that were taken based on the findings of this survey included quarantine of products yet to be marketed, notifications to companies on the failure of compendial testing and closure of the manufacturing plant.
- In the 2010 Cough and cold medicines survey: 46% i.e. 95 out of 205 of cough and cold products were found to be not registered with the PPB. It was recommended that importers or manufacturers of the same be put on notice, the products be recalled, withdrawn and destroyed and the respective importers be made to answer on how the products were made available into the market.
- In the 2011 Anti-malaria survey: Six samples failed compendial testing of which 4 were of AL, the first line treatment for uncomplicated malaria.
- In the 2012 Anti-malaria survey: All the ACTs including those locally manufactured meet the specified quality standards.
- In the 2012 Anti TB survey: The failure rate in laboratory analysis for anti-TB medicines in Kenya is 8.3% and mainly related to paediatric formulations.

- In the 2012 ARV survey: (1) the 92 products surveyed comprised of 14 APIs of which 7 were not in the national ART guidelines (2) one third of the products sampled from the market were not registered by the PPB and (3) most of the samples analyzed were of good quality with only one failing and this was because the analysis was done after the product had expired.
- In the 2014 Reproductive health medicines survey: The consultants were provided with the protocol for the study and could therefore not determine regulatory action that resulted from the study.

There is evidence that regulatory action is taken and made public e.g. through the PPB Lifesaver Newsletter. A classical example is the Newsletter of September 2011 where two manufacturers were closed down and several anti-malarials were recalled, mopped up and destroyed.

2.8 Quality assurance by importing organizations

Kenya Medical Supply Authority (KEMSA)

(a) General activities

KEMSA is a government agency and is accredited to ISO 9001:2008.

(b) Quality assurance at KEMSA

The tender process is an open international tender. Tenders are managed by a committee comprising of the medicines program manager, a KEMSA pharmacist, a QA person, and a person from the procurement department. Local manufacturers must have a GMP certificate issued by the PPB. Manufacturers from outside Kenya must have a GMP certificate issued by their own country Authority. Supplier audits are conducted locally but not outside Kenya. These audits are conducted for new suppliers and will include GMP assessments and capacity checks. Preference is given to local manufacturers during the tender process, 15% is added to the bid of an importer prior to adjudication. QA will check the tender documentation to confirm that the required specifications are met, documentation is correct, stability data is satisfactory and the certificate of analysis is correct. A pre-delivery sample is requested which is checked against the submitted tender information and can be analysed. When all requirements have been met the contract is awarded on price.

Consignments are inspected when received. Shelf life must be >75%. The product is sampled ($n+1$) and samples tested using the minilab or sent to NQCL for analysis – anti-malarials and anti-retrovirals. If the evaluation is satisfactory the product is released into the stock management system.

KEMSA has 7 depots in Kenya which act as holding warehouses. These depots operate within the KEMSA stock management system. All orders are processed centrally but can be supplied from one of the regional depots if it is more convenient geographically.

The computerised stock management program does not allow stock with less than 6 months shelf life to be picked. A manual supply procedure operates for these products which are supplied to hospitals and clinics with high turnovers that allow rapid use of the product within its expiry date

KEMSA has 14 field officers. These can handle local quality issues and can also assess and advise upon storage of medicines by customers. When a quality complaint is received, samples are obtained from the field officer who will also check other storage sites in the locality for further evidence. If a wider problem is identified, stocks are quarantined and samples sent to NQCL for analysis. The QA section in KEMSA is responsible for the investigation. If necessary a recall is initiated. PPB is informed of the complaint but the timing of this can vary. KEMSA are not obliged to inform PPB

(c) KEMSA Laboratory

KEMSA is developing its own laboratory which will be completed by December 2015. Details of the current resources for the laboratory are included in Table 1. It is currently able to perform minilab screening of

products as well as a limited number of full specification analyses. It is not WHO pre-qualified and will need to be so if it is to operate effectively as a medicines testing laboratory.

Mission for Essential Drugs and Supply (MEDS)

(a) General

MEDS is a private organisation working on behalf of Christian churches in Kenya. It is a not for profit body that supplies to hospitals and clinics run by the churches or that operate on a not for profit basis.

Its product range is based on its formulary which is reviewed and amended annually. The formulary is reviewed and revised by a formulary committee whose membership include healthcare professionals, academia, MEDS staff and, occasionally, PPB staff. The committee meets annually to review the product list. It considers requests from clients for additions or omissions from the formulary. It uses both the Kenyan and the WHO list of essential medicines. It also looks at usage data.

There is a list of approved suppliers. Pre-qualification is essential for inclusion on the list. The supplier must be GMP certified by PPB before they can apply. QA are responsible for the pre-qualification assessment. They have a program of supplier audits for local manufacturers and distributors and check compliance with WHO guidelines for GMP and GDP. If approved they are added to the list of pre-qualified suppliers.

Tenders are closed and restricted to the list of pre-qualified suppliers. Tenders are evaluated by an evaluation committee. If the supplier is tendering a product for the first time, a tender sample is requested which is analysed in the laboratory. The committee makes its decision based on QC results, quality history, supplier performance, and cost. A recommendation is made to the tender board who approve the decision. A supply contract is issued to the successful tenderer. Contract performance is monitored jointly by the purchasing manager and by QC.

Deliveries to the store come to a receiving team who perform a visual inspection, check paperwork, and confirm compliance with the contract. QA will check on technical aspects using a checklist which is tailored to the needs of different formulations. Samples for analysis will only be taken if the product is considered suspicious.

Stock control is managed by a program called CYSPRO. It manages the inventory to batch level. Orders, product receipt, storage, and supply are managed electronically. MEDS has its own van which delivers within a radius of 60km of the store otherwise delivery is outsourced. Meds have a field team that conduct supplier and customer training. They do not routinely check on client storage facilities but will provide advice as needed when visiting clients.

Complaints are received and recorded by customer service. Quality complaints are sent to the laboratory for analysis. The investigation is the responsibility of the technical evaluation committee. They will make a recommendation to the head of operations who decides on the follow up action. If a recall is initiated PPB are informed.

(b) MEDS Laboratory

Meds has a well equipped laboratory for physico-chemical analysis. Details of the resources in the laboratory are provided in Table 1. In addition to the equipment list given there is also a polarimeter. At the time of the visit the gc was not operational. The laboratory is pre-approved by WHO. The laboratory retains samples of products analysed in a retained sample store and also has a separate store for discarded samples.

(c) MEDS PMS Activities

The laboratory has a monthly plan of random sampling from the warehouse. Sampling is randomised and covers all stock lines on an annual basis. High risk products (e.g. high volume usage, historical quality defects, products from the local market with a history of deficiencies) are sampled more frequently. All suspicious

samples are reported to the technical evaluation committee for follow up action. A monthly report is produced of all results. Approximately 1000 samples are tested annually. It was not established how many were screened using the minilab and how many were subjected to full analysis.

Fig. 2: PMS Process Map in Kenya

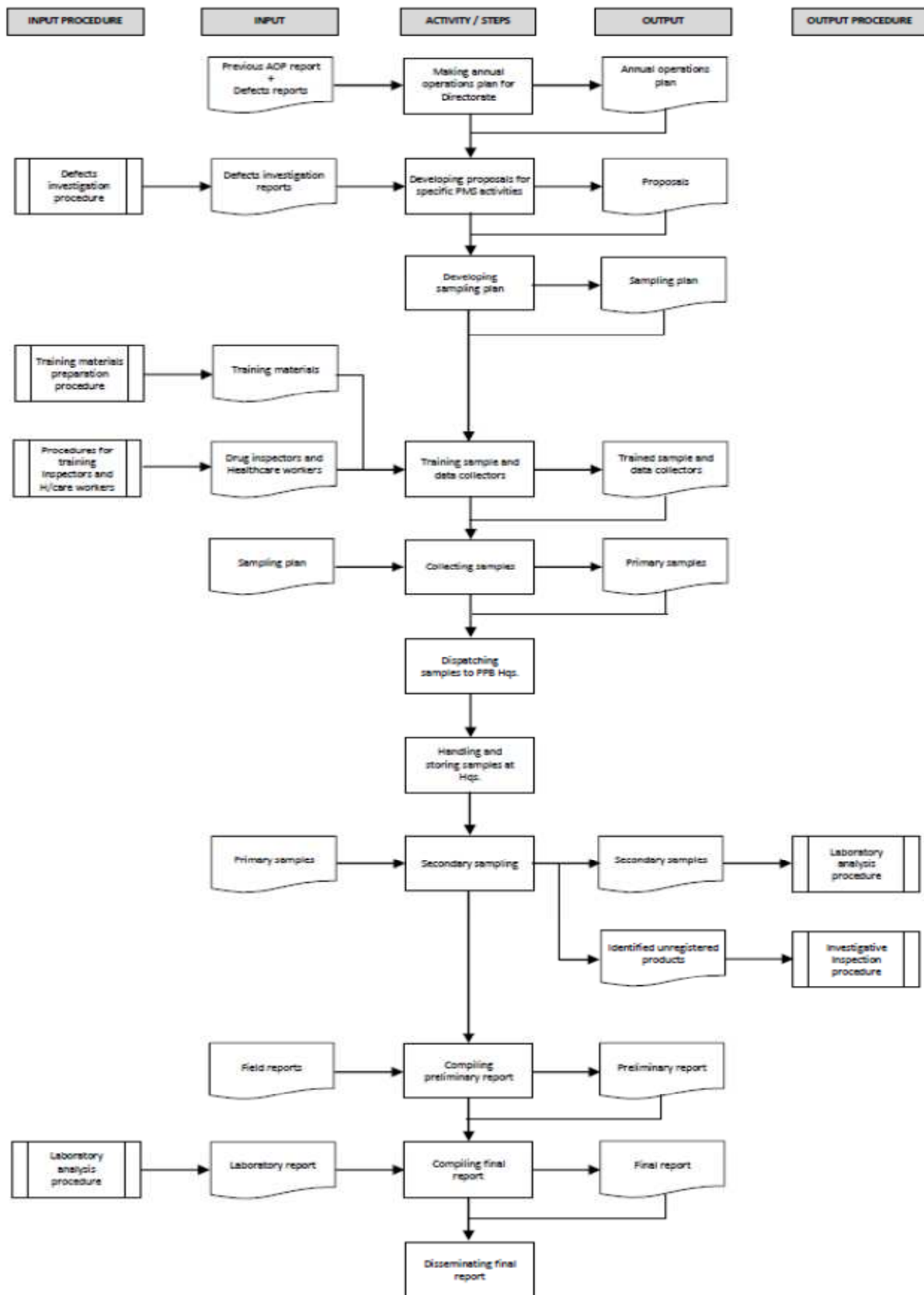


Table 4. Table of PMS responsibilities and outcomes in Kenya

What is the step/activity?	Making Annual Operations Plan for the Directorate	Developing proposals for specific PMS activities	Developing sampling plan	Training sample and data collectors
How is the activity done?	Meeting of directorate	1. Identify specific activity in the AOP 2. (follow guidelines)	Developed individually by the Director based on his expertise in the subject (Ideally a template should be provided)	Workshop with presentation on the sampling process and demonstration of sampling tool
With what?	Reports from other departments, plans of public health program, Registrars performance contract	Approved AOP	Proposal for the activity	Sampling plan and training materials
Who is responsible for performing the activity?	Director	Director	PMS Coordinator	PMS Coordinator
Who is ultimately accountable to the management for the activity?	Director	Director	Director	Director
Who (if any) provides direct support to the person discharging the activity?	MIPV staff	Other MIPV staff	MIPV staff	MIPV staff, Program staff
Who (if any) should be consulted for the performance of the activity?	Other Directors, the Registrar, Program Officers responsible for PMS	Director of Inspectorate Laboratory Program Officer	Director	
Who (if any) should be informed of any aspect of the activity?	NQCL	Program Managers Registrar		Registrar
What are the performance indicators for the activity?	By January each year	To be ready one month before sample collection	Sampling plan in place 1 month before sampling	No. of sample and data collectors trained
What internal controls are used?	Approval by Management Team	Approval by Registrar		Attendance
What challenges are expected/encountered and how do you manage them?	Budget constraints Planning expertise	Expertise in proposal writing (Lack of guidelines)	Lack of planning tools	Training of mixed cadres Controlling participants not under direct control of PPB is difficult since they may have other commitments

What is the step/activity?	Collecting samples	Dispatching samples to PPB Hqs	Handling and storing samples at HQs	Secondary sampling
How is the activity done?	Use the sampling plan, visit pre-selected sites, use sample forms	By courier or own (PPB/Program) transport	Receive the samples, verification, storage, for products requiring special conditions this is taken into account	1. Identify the products 2. Stratify similar products according to manufacturer (brand name)
With what?	Sampling plan and sample forms	Same as above	Store room Cold boxes for storage of labile samples	Random tables
Who is responsible for performing the activity?	Sample collectors	Sample collectors	PMS Coordinator	PMS Coordinator
Who is ultimately accountable to the management for the activity?	Director	Directors	Director	Director
Who (if any) provides direct support to the person discharging the activity?	Support staff e.g. drivers		PMS Coordinator	Other MIVP staff and inspectors at the Board
Who (if any) should be consulted for the performance of the activity?		PMS Coordinator		Laboratory
Who (if any) should be informed of any aspect of the activity?	Facility managers	PMS Coordinator		Registrar
What are the performance indicators for the activity?	No. of samples correctly collected, sites covered and adherence to sampling plan	Dispatch within one working day	Records of storage conditions No samples lost or damaged	Rationalization of sample sizes
What internal controls are used?		Informing the PMS Coordinator immediately after samples have been dispatched	Records of storage conditions	Listing of samples and linking them to their manufacturers (brands)
What challenges are expected/encountered and how do you manage them?	1. Price variations in case samples are bought 2. Suspicion from some members of the public 3. Poorly accessible places may not be reached	No control over courier	Storage space, especially since many samples are received at one time	Secondary sampling must be done immediately the samples are received.

What is the step/activity?	Compiling preliminary report	Compiling final report	Disseminating the final report	
How is the activity done?	Meeting of all team leaders under the leadership of PMS coordinator to share their field reports and review the exercise. The Director also attends.	The lab results are analyzed for compliance to specifications and trends. Observations are merged with the preliminary reports to produce a final report.	Website Stakeholders forum Published report circulated to specified individual	
With what?	Field reports	Preliminary report and Lab results	Printed report	
Who is responsible for performing the activity?	PMS Coordinator	PMS Coordinator	Registrar	
Who is ultimately accountable to the management for the activity?	Director	Director	Registrar	
Who (if any) provides direct support to the person discharging the activity?	MIPV staff	MIPV team Other PPB staff with relevant expertise Board may recruit a consultant Program Officers	Director and other MIPV staff IT staff Procurement (for printing the report)	
Who (if any) should be consulted for the performance of the activity?	Registrar	Registrar		
Who (if any) should be informed of any aspect of the activity?	Registrar Program managers		Ministry of health Development partners	
What are the performance indicators for the activity?	The meeting to be held within a month of sample collection	Report produced within 6 months of the sampling	Report disseminated within 6 months of the sampling	
What internal controls are used?	Attendance		Approval for dissemination by the Registrar	
What challenges are expected/encountered and how do you manage them?		Expertise in report writing Slow analysis at the lab Shortage of staff at the Board	1. The procurement process for printing is slow 2. Printing can take a long time 3. Negative feedback after publishing report	

Table 5. Secondary procedures contributing to PMS activities in Kenya

Name of procedure	Laboratory analysis procedure	Investigative inspection procedure	Preparation of training materials (for training of sample and data collectors)	Training of Inspectors and Healthcare Workers
Aim of the procedure	To analyse samples collected during the surveillance	To confirm the presence and extent of a defect	To produce training package	To enable inspectors and healthcare workers who will be entrusted with the task of sample collection
Inputs used	Reagents, Equipment, Staff	Inspectors Samples Import permit	Proposal Sampling plan Reference material	Training program Training materials Sampling plan Facilitators Trainees
Activities of the procedure	Receiving samples, storage, issue of samples, analysis, reporting	<ol style="list-style-type: none"> 1. Information received e.g. through pink form 2. Director of Medicines assigns case to an officer to assess the information 3. Review of assessment by Director of Medicine 4. If need for further action discuss with Director of inspection 5. If significant Director of inspection assigns inspectors and briefed 6. Inspection 7. Samples and report with recommendation 8. Report reviewed by Director of Inspectorate then discussed to Director of Medicines 9. Director of Medicines tables report at Quality Safety and Efficacy Committee with recommendations 10. Committee discusses and recommends action to the Board of Directors of action to be taken 11. Board of Directors decides 12. Registrar takes action on behalf of Board of Directors 	Review all material available, discuss amongst facilitators, prepare the presentations and manual	Planning the date of the training, identify trainers, identify trainees, identify the venue, send invites, train.
Outputs	Certificate of analysis	<ol style="list-style-type: none"> 1. Preliminary assessment 2. Investigative report 3. Decisions of QSE Committee 4. Decisions of the Board of Directors 5. Regulatory action 	Minutes of meetings, Training materials (manuals and presentations)	- Trained sampling and data collectors - Database of trained sampling and data collectors
Outcomes	Approved analysis report	Regulatory action	Competent sampling and data collectors	Competent sampling and data collectors

Appendix 3: Rwanda situational report

In Rwanda the regulation of medicines is the responsibility of the Pharmaceutical Services in the Directorate general of Clinical and public health services of the Ministry of Health.

3.1 Legal and regulatory framework

Regulatory Framework for Post-Market Quality Surveillance

The authority for the post-market quality surveillance (PMS) in Rwanda is the Pharmaceutical Services Department in the Ministry of Health. The Ministry of Health enforces the law No. 47/2012 of 14/01/2013 relating to the Regulation and Inspection of Food and Pharmaceutical Products to regulate Food, Medicines, Cosmetics, and Herbal medicines. This Law provides the following regulatory functions:-

- The licensing of manufacturers, and retail premises
- The regulation of premises for the storage and distribution of drugs
- The approval and registration of products manufactured in Rwanda.
- The licensing of importers of medicines into Rwanda
- The approval and registration of products imported into Rwanda.
- The maintenance and publication of a register of approved medicines
- The sampling and analysis of medicines.
- The quarantine of unfit products
- Inspectors rights of access and powers of seizure

Article 3 of the Act requires the registration of importers and distributors of pharmaceuticals. The Act also provides a definition of a pharmacopoeia but does not mention any specific ones. The Act does not establish a government laboratory for the testing of medicines. But it does, under section 44, require all persons (and by implication manufacturers, importers or distributors) to inform the MPP division of unfit or defective medicines.

Regulation of products manufactured inside country

There is only one manufacturer in the country, the Medical Production Unit of the Medical Procurement and Production Division (MPPD) of the Rwanda Biomedical Centre (RBC)³⁴, which produces infusions. Since it is a public institution there is no special manufacturing licence granted.

Regulation of imported products

The MOH (Pharmaceutical Services) maintains a register of approved medicines that can be imported into Rwanda. Registration is by notification; full registration has not started yet. Before a consignment can be imported the importer must provide a pro-forma invoice, which is checked against the registration details. When approved, an import visa is issued which is sent to the supplier as the shipment permit. Importers must be licensed. When the consignment arrives, documents are brought to the Ministry, checked against the import visa and an import permit issued. The importer can then proceed to customs to clear the goods. Rwanda Standards Board does the verification at the port of entry, which is based on a visual inspection. If a consignment is non-compliant MOH inspectors go to POE to do further checks. There are no permanent inspectors at POE. Rejected consignments can be re-exported or destroyed. There is a single public importer, the Warehouse and Distribution Unit of the Medical Procurement and Production Division (MPPD) of the Rwanda Biomedical Centre (RBC), and 62 licensed private importers.

³⁴ <http://www.rbc.gov.rw/spip.php?rubrique6>

Regulation of Defective Medicines

Counterfeit and unfit pharmaceutical products are defined in the Act and restrictions to their sale are defined. Complaints and defect reports are received into the Pharmaceutical Services of the ministry of health.

If a defective product is reported, it is quarantined and a sample sent for analysis in South Africa, Niger or Singapore. These are WHO prequalified laboratories. If part of the batch is in circulation, a notice is issued for all recipients of the product to stop using it and send details of the quantities used. If the defect is confirmed the product is recalled. Recalled products are received at the National Store or Importer's store and destroyed by the store in collaboration with the supplier.

Legal and regulatory framework for Post-marketing surveillance

Postmarket surveillance is not specifically mentioned in the law. Passive PMS is undertaken on receiving a complaint of a defective product. No active PMS is undertaken.

Supplementary laws

(a) Destruction of defective medicines

No information was provided regarding the control of destruction of defective medicines.

(b) Prosecution of offenders

No information was provided regarding the prosecution of offenders.

3.2 Planning and approach

There is no active postmarket surveillance of medicines in Rwanda. There is no sampling plan and samples for analysis are not collected.

3.3 Technical capacity for PMS

Organization structure

Not applicable since there is no active PMS.

Internal collaboration

Not applicable since there is no active PMS.

External collaboration

Not applicable since there is no active PMS.

PMS procedure

Not applicable since there is no active PMS.

Laboratory support

There is no government laboratory for the testing of medicines. The National Procurement and Production Division (NPPD) has QA specialists who inspect every delivery. Suspicious samples are sent for analysis. Warehouse staff also monitor the storage of products and samples can be identified from this. Annually, 100 to 200 samples are sent for analysis. This is the only testing performed.

Administrative support

Not applicable since there is no active PMS.

3.4 Implementation

This section does not apply since there is no active PMS.

3.5 PMS scope and cost

This section does not apply since there is no active PMS.

3.6 Visibility of PMS activities

This section does not apply since there is no active PMS.

3.7 PMS outcomes

This section does not apply since there is no active PMS.

3.8 Quality assurance by importing organizations

The Warehouse and Distribution Unit of the National Procurement and Production Division (NPPD)³⁵

The Warehouse and Distribution Unit is part of the Medical Production and Procurement Division of the Rwanda Biomedical Centre (RBC). Its operations are controlled by the Public Procurement Act. The unit uses both open competitive tenders and restricted tenders. The majority of contracts are awarded under restricted tenders. For anti-malarials, anti-retrovirals, and anti-tuberculosis medicines the tender is restricted to the WHO list of pre-qualified suppliers. Restricted tenders are also used for a number of products on the essential medicines list. Other than the WHO list, the list of approved suppliers for restricted tenders are selected from suppliers who submit for an open technical tender. For the open competitive tender expressions of interest in the form of bids are received. Suppliers are evaluated using a documentation check and, from this, a list of pre-qualified suppliers are identified which is used for the restricted tenders. Most procurement is done by International competitive bidding or restricted tenders.

The QA department is responsible for checking the products supplied. Random sampling of about 5 – 10% of the delivery is done, which equates up to 100 - 200 samples tested each year. An in-house laboratory check is available based on the Minilab. However, most of the testing is based on visual and physical checks.

Goods are also inspected while in the store. The quality unit (QA and QC combined) is responsible for the checks. If a defective product is found, distribution is stopped and an investigation performed. If the defect is confirmed the supplier is contacted. Most defective products are ultimately destroyed. The Unit is not obliged to report to the MOH if defective products are found.

Suspicious products are quarantined and investigated. Samples are analysed, and suppliers and customers are informed (see above). If necessary the product is recalled and the Ministry informed.

³⁵ <http://www.rbc.gov.rw/spip.php?rubrique6>

Appendix 4: United Republic of Tanzania situational report

(a) Tanzania (Mainland)

The Tanzania Food and Drugs Authority (TFDA) is the National Medicine Regulatory Authority established in 2003 by the Tanzania Food, Drugs and Cosmetics Act Chapter 219 of the laws of Tanzania.

4.1 Legal and regulatory framework

Regulatory Framework for Post-Market Quality Surveillance

The Regulatory Authority responsible for the post-market quality surveillance (PMS) of medicines in Tanzania is the Tanzania Food and Drugs Authority (TFDA). As far as medicines are concerned, this Act further provides the following regulatory framework:-

- The licensing of manufacturers and importers of medicines
- The inspection of premises for the storage and distribution of medicines
- marketing authorizations for medicines
- Import and export control
- Control of promotion activities
- The establishment of the Tanzanian Food and Drugs Authority (TFDA) Laboratory
- The analysis of samples of medicinal products.
- The quarantine, recall, and destruction of adulterated or defective products
- Powers of inspectors

Regulation of medicines manufactured inside the country

Under this Act manufacturing sites must be licensed. They are inspected and approved prior to the issue of a licence. Products manufactured in Tanzania must be approved and registered before they can be sold. Details are recorded and published in an official register. A Registration Number is assigned and a certificate of registration issued that is valid for 5 years.

Among the medicines for treating diseases of public health importance (i.e verical programme medicines) only anti-malarials are manufactured inside the country. **Each batch of anti-malarials that is manufactured domestically is sampled and tested by TFDA before it is released into the market.**

Regulation of imported products

Under the TFDC Act, importers must be registered to import medicines. . Before the product is registered the manufacturing site will be inspected. Importers must apply for approval to import individual drugs. A pro-forma invoice is submitted to the TFDA which contains details of the port of entry, the manufacturer, manufacturer address, supplier, and price; after approval an import permit is issued. All imports are inspected at the port of entry. Details are checked against the pro-forma invoice and the previously issued import permit.

During the inspection of imported medicines at ports of entry samples of anti-retrovirals, anti-malarials, anti-tuberculosis drugs, and antibiotics , are collected by the inspector for quality checks.

Regulation of defective medicines

The Authority has put in place system for reporting of defective medicines through complaint handling procedure and forms for reporting poor quality products (Blue forms). Through this system, manufacturers, distributors, health practitioners, and the general public are encouraged to report quality defects in medicines that they become aware of.

The TFDC Act also gives powers for inspectors to quarantine, confiscate, take samples and investigate any suspicious products that are identified during physical inspection at the port of entry or any distribution point during routine inspection.

Legal and regulatory framework for Post-marketing surveillance

PMS is one of the legal activities of TFDA of monitoring the quality, safety and efficacy of registered medicinal products or medical devices on the market. However, there is no legal obligation for manufacturers, importers, or distributors to report information about known quality defects to the TFDA and postmarket surveillance is not specifically mentioned in the Tanzania Food, Drugs and Cosmetics Act (2003).

Activities conducted to monitor the quality, safety and performance of registered products that are on the market are risk-based since it is not possible to test everything that's on the market (see section 4.3 below). Products that present higher risks merit higher priority for surveillance

Supplementary laws

(a) Destruction of unfit medicines

Section 85 of the TFDC Act requires, and empowers, the Director General of the authority to destroy by incineration or other approved method any consignment forfeited by the court after communicating with the Inspector General of Police, the Commissioner of Customs and the Attorney General. However, under section 106(1) of the Management of Environment Act 2004 it is an offence for any person to pollute or permit any other person to pollute the environment in violation of any standards. For this reason the TFDA, in collaboration with the WHO, the National Environment Management Council (NEMC) and the Ministry of Finance and Economic Affairs, have prepared Guidelines for Safe Disposal of Unfit Medicines (2009).

(b) Prosecution of offenders

The authority has employed its own lawyers to advise the management on legal matters and to prepare cases against offenders for prosecution by the National Prosecution Services as required under the National Prosecutions Service Act No. 27 of 2008. Lack of prosecution powers implies that the authority does not have legal jurisdiction over its operations and could subject it to political interference.

4.2 Planning and approach

Guidelines on Postmarket Surveillance of Medicines and Medical Devices have been developed on the basis of which 3 year PMS programs are prepared. The programs often have 9 phases, 3 implemented in each operational year (the 2014 – 2017 Program has only 6 phases). The first PMS program was implemented from 2007 to 2009, the second from 2011 to 2013 and the third, 2014 to 2017, is under implementation. Each program articulates among other things, the way PMS should be effectively conducted and managed by TFDA in the three financial years based on lessons learnt from the previous programme.

In addition to the PMS guidelines the authority's Inspectors' Handbook (2002) includes detailed SOPs for:-

- Inspections at POE
- The physical examination of pharmaceutical products
- The antimalaria Surveillance Program
- Inspections of dispensing outlets
- The surveillance program for suspicious samples
- Chain of custody, packing and shipping procedures

The manual also provides instructions to inspectors on the use of the GPHF Minilab kits. However, it became apparent during the interview that screening with minilab kits is done by laboratory staff at the headquarters.

4.3 Technical capacity for PMS

Organization structure

All PMS activities are coordinated by the PMS Coordinator (PMSCO) who reports to the Manager for Medicines and Cosmetics Inspection and Enforcement (MMIE) who in turn reports to the Director Of Medicines and Complementary Products (DMCP). The Directorate of the Medicines and Complementary Products is one of TFDA's directorates whose chief executive officer is the Director General.

Internal collaboration

PMS is a collaborative activity led and overseen by a task force comprising of the Manager for Medicines and Cosmetics Inspection and Enforcement, the PMS Coordinator, the Manager for Medicines and Cosmetics Analysis, the appointed Registration Officer, the Eastern Zone Manager, the Manager for Medical Devices Assessment and Enforcement, and the appointed drug inspector. The Manager for Medicines and Cosmetics Inspection and Enforcement chairs the task force. The PMS Task Force is responsible for conducting routine monitoring of the programme include data evaluation and risk assessment which will then form the basis for conducting further PMS. The task force is also responsible for programme review, publication of results and advice to DMCP on matters related to PMS activities. It meets at least 3 times during a phase whereby most meetings are held on ad-hoc basis. More meetings can be held if necessary depending on the situation.

Secondary procedures contributing to the success of the PMS process are summarised in Table 10. They include procedures for laboratory analysis, investigative inspection, preparing training materials for sample and data collectors and procedures for training inspectors and healthcare workers.

External collaboration

TFDA's PMS programme involves other stakeholders such as the Pharmaceutical Society of Tanzania, the Medical Association of Tanzania, EAC and SADC Secretariats responsible for medicines regulation, WHO, and MoHSW departments such as the Pharmaceutical Services Section, National Aids Control Program, National Malaria Control Program and National TB and Leprosy Program. Cooperation with these organizations/agencies helps in sharing information, improve control at border entries, and reduce surveillance costs. Furthermore, working in close collaboration with healthcare providers and consumers promotes reporting of product defects including counterfeit products.

PMS procedure

(a) Active PMS

A step-by-step process map for PMS is not available but the following steps became evident during the interview with PMS staff:-

- Step 1: Preparing PMS program
- Step 2: Preparing sampling plan
- Step 3: Training of sample collectors
- Step 4: Sampling
- Step 5: Dispatching samples (to the laboratory)
- Step 6: Screening
- Step 7: Identifying samples for full analysis
- Step 8: Evaluating results

A process map was developed during the interview (Figure 3) linking these steps to inputs and output as well as secondary procedures associated with the inputs and outputs. Detailed descriptions of the steps and evaluation of responsibility assignment along the RASCI model are appended (Tables 9 and 10).

(b) Program initiated PMS

No information was provided on these activities.

(c) Survey of the quality of medicines identified by the United Nations Commission on Life-Saving Commodities for Women and Children, 2013

This survey, conducted in 2013/2014, aimed at identifying products which were of good quality or the quality of which could be improved in short period of time. The study, designed and supervised by the WHO, was conducted in 10 countries across the world including Kenya, Uganda and Tanzania. It was not a programmed active PMS survey aimed at regulatory enforcement.

Passive PMS

(a) Defective medicines reports

The Authority has put in place system for reporting of defective medicines through complaint handling procedures and forms for reporting poor quality products (Blue forms). Through this system, manufacturers, distributors, health practitioners, and the general public are encouraged to report quality defects in medicines that they become aware of. The authority investigates all complaints received and takes regulatory action where appropriate. **TFDA records indicate that 33 counterfeit products and 61 substandard products were encountered in the market between 2004 and 2014³⁶. These products were mainly a result of passive PMS.**

(b) International operations

TFDA also participates in Interpol coordinated operations to disrupt the activities of transnational organized criminals involved in the trafficking of counterfeit medical products in Eastern and Southern Africa. It also aims to raise awareness, increase resources, and enhance educational efforts and capacity building on the issue. Operation Mamba I took place between 29 September and 5 October 2008. Participating countries were Tanzania and Uganda. The results were 1) 226 pharmacies, wholesalers, hospitals and market stalls inspected; 2) 82 police cases opened; and 3) more than 100 different products seized. Operation Mamba II took place in August 2009. Participating countries were Kenya, Tanzania and Uganda. The results from this operation were 1) more than 270 premises raided; 2) 83 police cases opened; 3) the prosecution of several individuals suspected of being involved in the illicit trafficking of medical products and 4) at least 4 convictions with thousands of tablets seized. Operation Mamba III took place in July and August 2010. Participating countries were Burundi, Kenya, Rwanda, Tanzania (+ Zanzibar) and Uganda. The results from Mamba III were even better than I and II.; 1) more than 375 premises were targeted; 2) nearly 200,000 pills were seized; 3) at least 120 police cases were opened; 4) 78 cases were sent to court and 34 convictions pronounced. The operation led to the adoption of the Declaration of Zanzibar by participating agencies and other organizations supporting the activities. This significant step will lead to enhanced partnerships, increased sharing of information, more intelligence-led operations, and greater public awareness on the dangers posed by counterfeit medical products.

TFDA also participated in Operation Giboia 2013, a multi-country operation against pharmaceutical crime in Southern Africa (Angola, Malawi, Swaziland, Tanzania and Zambia). During the operation almost 100 tonnes of illicit medicines worth approximately USD 3.5 million were seized, including illicit and counterfeit versions of antibiotics, birth control medicines, and anti-malarial and analgesic medicines; 181 suspects were arrested or placed under investigation; 9 outlets unauthorized to sale medicines were closed across the five participating countries; and 2 illegal clinics employing unqualified staff were closed in Malawi.

Field support

Sample collection during a PMS surveillance campaign is complex and technical.

Collection of samples is based on a sampling plan. Samples are collected from MSD, public and private hospitals, health centres, dispensaries, retail pharmacies, DLDB and DLDM- Accredited Drug Dispensing Outlets (ADDOS). Sampling may focus on certain type of health facilities or locations (regions) based on selected criteria such as:-

³⁶ Data provided by Ms. G. Shimwela, January 2015

- Regions bordering other countries
- Regions that are not frequently inspected
- Areas reported to have medicines quality problems
- Regions not involved in the previous PMS programmes
- Disease prevalence

Sampling forms are used during sample collection. Sample collectors fill a sampling form for each sample collected. Samples together with corresponding sampling forms are sent to TFDA Headquarters for further testing.

Each sample is coded according to a prescribed coding format. Coding is done to identify samples collected from different regions. This helps in differentiating samples and avoiding mix up. After collection, samples are stored according to the manufacturer's recommended storage conditions as proscribed on the drug product labels. Inspectors collect samples that have an "identifiable" name of the drug product and its active ingredients (APIs) and the manufacturer's address on the label. Samples are collected in their original containers and/or packages. Measures are taken to ensure that samples are transported in good condition from collection sites to TFDA HQ.

All physical samples and labels are reviewed for conformity to appearance and labelling requirements. Each sample is visually examined against information provided in the respective dossier and the sample submitted during registration process.

Oral solids are checked for spots, moulds, abrasions, colour, odour, shape and other physical descriptions. Oral liquids are examined for container leakage, particles, homogeneity, tampering, fill volume, odour, colour and other physical descriptions.

Labels and package inserts are examined for information, size and type of container, format, shape, print, stickiness, legibility and indelibility.

All observations for each sample are entered into the product information review form.

During Phases I and II program a total of 57 trained drug inspectors were used. Inspectors were drawn from TFDA and local government authorities. Zonal offices are responsible for sampling and dispatching of samples to the laboratory for analysis.

Laboratory support

All samples are sent to TFDA laboratory for screening and confirmatory testing. Samples are received into the laboratory and logged into the laboratory management programme where they are allocated an internal code number. They are moved to the sample store which is environmentally controlled and has cold storage facilities. The test request form is approved and signed by the laboratory manager who issues a laboratory analysis form together with the sample issue form.

All samples received into the laboratory are screened using the minilab. This is essentially a TLC identification check with an element of semi-quantitative analysis. Following screening, all suspicious samples and approximately 10% of all samples submitted are subjected for full compendial analysis. The remaining units of screened samples are retained for at least one year and stored according to manufacturer's recommended storage conditions. This applies to the samples from importers taken by inspectors and the samples from the PMS programme. All suspicious samples that are reported to the TFDA or to the Medical Stores Department are subjected to full analysis. An algorithm is available to guide analysts on systematic testing involving the following methods:-

- Screening
- Physical/ visual inspections
- Simple disintegration test
- Thin Layer Chromatography (TLC)
- Laboratory testing (full or partial monograph)

Samples are analyzed according to designated standard methods and procedures. Depending on the dosage form the test parameters may include description, identification, related substances/impurities (where applicable), dissolution, disintegration, dosage uniformity, re-suspendability, pH, appearance after reconstitution, fill mass/volume, sterility, endotoxins and particulate matter. Special analytical methods might be developed to reduce time of analysis. The method has to be validated against the standard method.

About 1% of sample testing is subcontracted to laboratories in South Africa, NQCL (Kenya), MEDS (Kenya) and the Government Chemical Lab Agency (forensic samples only).

A report is prepared of the results of the sample screening testing, the report is approved and signed by the laboratory manager and issued. The same process applies to samples submitted for full analysis. The reports of the PMS testing go to the programme management team who decide what regulatory action is needed.

An inventory of the laboratory resources, equipment and staff, is given in Table 1 together with its accreditation status and the annual workload. The laboratory has 6 hplc's but at the time of the visit two were not operational and one was dedicated to the programme for the monitoring of the quality of trypanocides in East and Central Africa for which the TFDA laboratory is the reference laboratory. According to the equipment log, samples for this program were last tested in October 2014.

The laboratory is WHO pre-qualified but not ISO accredited. The most recent pre-qualification inspection took place in January 2014. The report concluded that the laboratory was operating at an acceptable level of compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories within its scope of physico-chemical analysis of finished pharmaceutical products. During the inspection, the SOPs for: incoming samples, assuring the quality of test results, test methods, method validation, uncertainty of measurement, method transfer for pharmaceutical analysis, handling out of specification results, and assuring the quality of test results were reviewed. These are particularly relevant to the PMS programme.

Administrative support

The Directorate of Business Development (DBD) is responsible for timely release of financial and material resources as well as provision and management of information technology (IT) services while the Directorate of Medicines and Complementary products is responsible for planning, coordinating and supervising programme activities include scrutinizing risk assessment reports, preparation of surveillance schedules, conducting surveillance and taking appropriate regulatory action after receiving analytical results from the Directorate of Laboratory Services (DLS). The Directorate is also responsible to oversee all PMS activities in the zones and the establishment of the PMS Task Force.

4.4 Implementation

At TFDA, PMS activities are carried out as programs and in phases. The first post-marketing surveillance by TFDA was conducted between 2007 and 2009, the second between 2011 and 2013 and the third is in progress (2014 – 2017). Data on the first program was not provided. The following is a summary of products surveyed during the 2nd and 3rd programs according to the report for the 2nd program and the plan for the 3rd program as provided by TFDA.

Table 6: Active PMS undertaken and to be undertaken by the TFDA between 2011 and 2017

Year	Program	Phase	Category	Planned by	Funded by
2011/12	2	I	Antibiotics	TFDA	TFDA
2011/12	2	I	Antimalarials	TFDA	TFDA
2011/12	2	II	Antimalarials	TFDA	TFDA
2011/12	2	II	ARVs	TFDA	TFDA
2011/12	2	III	Antimalarials	TFDA	TFDA
2012/13	2	IV	Antibiotics	TFDA	TFDA
2012/13	2	V	ARVs	TFDA	TFDA
2012/13	2	VI	Antimalarials	TFDA	TFDA
2013/14	2	VII	ARVs	TFDA	TFDA
2013/14	2	VIII	Pain killer	TFDA	TFDA
2013/14	2	IX	Antibiotics	TFDA	TFDA
2014/15	3	I	Veterinary (Trypanocide)	TFDA	TFDA
2014/15	3	I	Antibiotics	TFDA	TFDA
2014/15	3	II	Veterinary (Anthelmintic)	TFDA	TFDA
2014/15	3	II	Uterotonic	TFDA	TFDA
2015/16	3	III	Veterinary (Trypanocide)	TFDA	TFDA
2015/16	3	III	Antiprotozoa	TFDA	TFDA
2015/16	3	III	Antidiabetic	TFDA	TFDA
2015/16	3	IV	Uterotonic	TFDA	TFDA
2015/16	3	IV	Antibiotic	TFDA	TFDA
2015/16	3	IV	Antihypertensive	TFDA	TFDA
2016/17	3	V	Veterinary (Antibiotic)	TFDA	TFDA
2016/17	3	V	Pain killer	TFDA	TFDA
2016/17	3	V	Anthelmintic	TFDA	TFDA
2016/17	3	VI	Ophthalmic	TFDA	TFDA
2016/17	3	VI	Antihypertensive	TFDA	TFDA

4.5 PMS scope and cost

Scope

The second PMS program had 9 phases; each phase with defined categories of medicines, a comprehensive sampling plan and a budget. Four groups/categories of medicines were surveyed, which were: antimalarials, ARVs, antibiotics and painkillers. The third PMS program covering the period 2014 - 2017 is now in progress. The program is divided into 6 phases during which 18 types of medicines in 8 categories will be surveyed. These are: veterinary products (6 products), antibiotics (4 products), anthelmintic (1 product), antihypertensives (2 products), endocrine preparation (1 product), ophthalmic preparation (1 product), pain killer (1 product) and uterotonic (2 products).

Cost of PMS

Since PMS is a collaborative activity it is not possible to assess its capacity separately. We can only conclude that what has been accommodated in the past is indicative of the capacity and capability of TFDA in conducting active PMS. The PMS Program 2014 – 2017 provides sufficient information to analyse the capacity of TFDA on this activity as follows:-

Table 7: Person-days planned for active PMS by the TFDA in the 2014 – 2017 program

Person days planned for each phase of 2014 – 2017 PMS Program						Total	%
I	II	III	IV	V	VI		
25	25	25	25	25	25	150	4.7%
5	4	4	3	4	4	24	0.8%
40	36	48	32	40	32	228	7.2%
35	30	45	25	35	25	195	6.1%
300	240	240	180	240	240	1440	45.3%
150	150	150	150	150	150	900	28.3%
50	40	40	30	40	40	240	7.6%
Total person days						3177	100%

The plan shows that staff from various departments will provide a total of 3,177 person days of which 45.3% will be used on screening of samples; 28.3% on laboratory analysis; 7.6% on monitoring and evaluation; 7.2% on training; 6.1% on sampling; 4.7% on planning and 0.8% on procurement. Furthermore, Table 8 shows that a total of Tanzania Shillings 397, 850,000.00 is planned to be used during the period of which 63.5% will be used to pay various allowances, 12.1% will be used to procure laboratory consumables, 10.7% on sampling costs, 9.2% on travelling, and 4.5% on dissemination of findings. The absence of budgetary allocations for planning, analysis and M&E reflects the collaborative nature of the activity whereby costs have been absorbed under the respective departmental budgets.

Table 8: Breakdown of cost in TFDA's 2014 – 2017 PMS programme

Item	Budget	Expense category	Total for expense category	%
Conference charges	18,750,000.00	Allowances	252,450,000.00	63.5%
Facilitation	3,600,000.00			
Per diem	97,200,000.00			
Special allowance	132,900,000.00			
Prepare and disseminate Phase I and II reports	-	Dissemination	18,000,000.00	4.5%
Publication	18,000,000.00			
M&E	-	M&E	-	0.0%
Prepare sampling plan	-	Planning	-	0.0%
Procurement	48,000,000.00	Procurement	48,000,000.00	12.1%
Sample analysis	-	Analysis	-	0.0%
Sample screening	-			
Sample dispatch	1,700,000.00	Sampling costs	42,650,000.00	10.7%
Sample purchase	39,000,000.00			
Sampling	-			
Sampling tools	1,950,000.00			
Training sample collectors	-	Training		
Fuel	21,600,000.00	Travelling	36,750,000.00	9.2%
Transport to QA centers	1,800,000.00			
Travelling	13,350,000.00			
Total budget	397,850,000.00		397,850,000.00	100.0%

The collaborative approach to PMS uses inspectorate staff and sometimes additional staff borrowed from local government authorities. This way each of the participants need provide only a few hours to the total hours required for the activity. In Phases I and II of the 2011 – 2013 program the authority used 57 sample collectors in this fashion so that regular inspection activities did not suffer. This explains why a large proportion of the budget is allocated to payment of allowances.

The workload of PMS on laboratory analysis is very significant despite the extensive use of screening. Samples taken for confirmatory testing include all samples that fail screening test, all samples with doubtful screening test results and 10% of samples which comply with screening test results. This number is unpredictable but based on experience it could be large. In phase I of the 2011 – 2013 program a total of 130 samples were taken for confirmatory testing out of 281 samples i.e. 46.3%. We shall assume this worst-case scenario and take 46.3% of 400 i.e. 185 samples as requiring confirmatory testing each year during the 2014 – 2017 PMS program. In 2013/2014 the laboratory analysed a total of 1462 samples. If this is taken as the laboratory's capacity it means that PMS samples will take up 185 of 1462 i.e. 13% of the laboratory's analytical capacity.

4.6 Visibility of PMS activities

TFDA uses its website to publish PMS reports. It also circulates the reports to pre-identified stake-holders. However, the consultants did not find evidence of high profile launches specifically targeting the public at large.

4.7 PMS outcomes

Final reports of post-marketing surveillance are usually published for distribution to the Ministry of Health and other stakeholders. During the study we were shown the report for phases I and II of PMS for antimalarials, antibiotics and ARVs that was conducted between 2011 and 2013. The report was also published on the authority's website. The report of the 2007 – 2009 surveillance program was not obtained.

According to the report, results obtained in the 2011 – 2013 program indicated the presence of substantial problems in the quality of Cloxacillin formulations in several regions. However, in the cases of Quinine, Artemether + Lumefantrine and Antiretrovirals, the quality was proven to be reasonably good. The region which demonstrated high failure rate in both Cloxacillin formulations was Mtwara and the least were for Mbeya and Dodoma regions. In terms of distribution levels, highest failure rate was observed for samples collected in pharmacies, DLDMs and DLDBs. These observations led to the following regulatory actions:

- Distribution outlets which were associated with highest failure rates of cloxacillin formulations were to be inspected to verify compliance with good distribution practice.
- Registration of affected cloxacillin formulations withdrawn in the country.

4.8 Quality assurance by importing organizations

Medical Stores Department

The Medical Stores Department (MSD) is a public sector medicines supply organization. It is ISO 9001 accredited. It does not have an approved list of suppliers but relies upon the TFDA lists of registered manufacturers and registered importers. There is a master list which is an historical list of suppliers for previous tenders but the tender process is an open process. To be eligible for the tender the product to be imported must be registered with the TFDA. This, by implication, means that the manufacturing site will have been inspected. Tenders for imported products require that the manufacturer be registered in the country of origin.

There is no restriction or exclusivity on the MSD product range although non-registered products must obtain special clearance from the TFDA. MSD holds a wholesale dealers licence and is a sampling site for

PMS. It also has its own sampling programme and submits samples for analysis which it funds from its budget.

Complaints from customers are investigated by an internal investigation team. If the complaint is validated, distribution of the product is suspended and a report sent to TFDA.

MSD are informed of product registrations that are suspended by TFDA. If the product has been supplied to the store, it is quarantined and a sample is taken and sent to the laboratory for testing. If the laboratory testing is satisfactory the product is released from quarantine and distributed.

Fig. 3: PMS Process Map in Tanzania (Mainland)

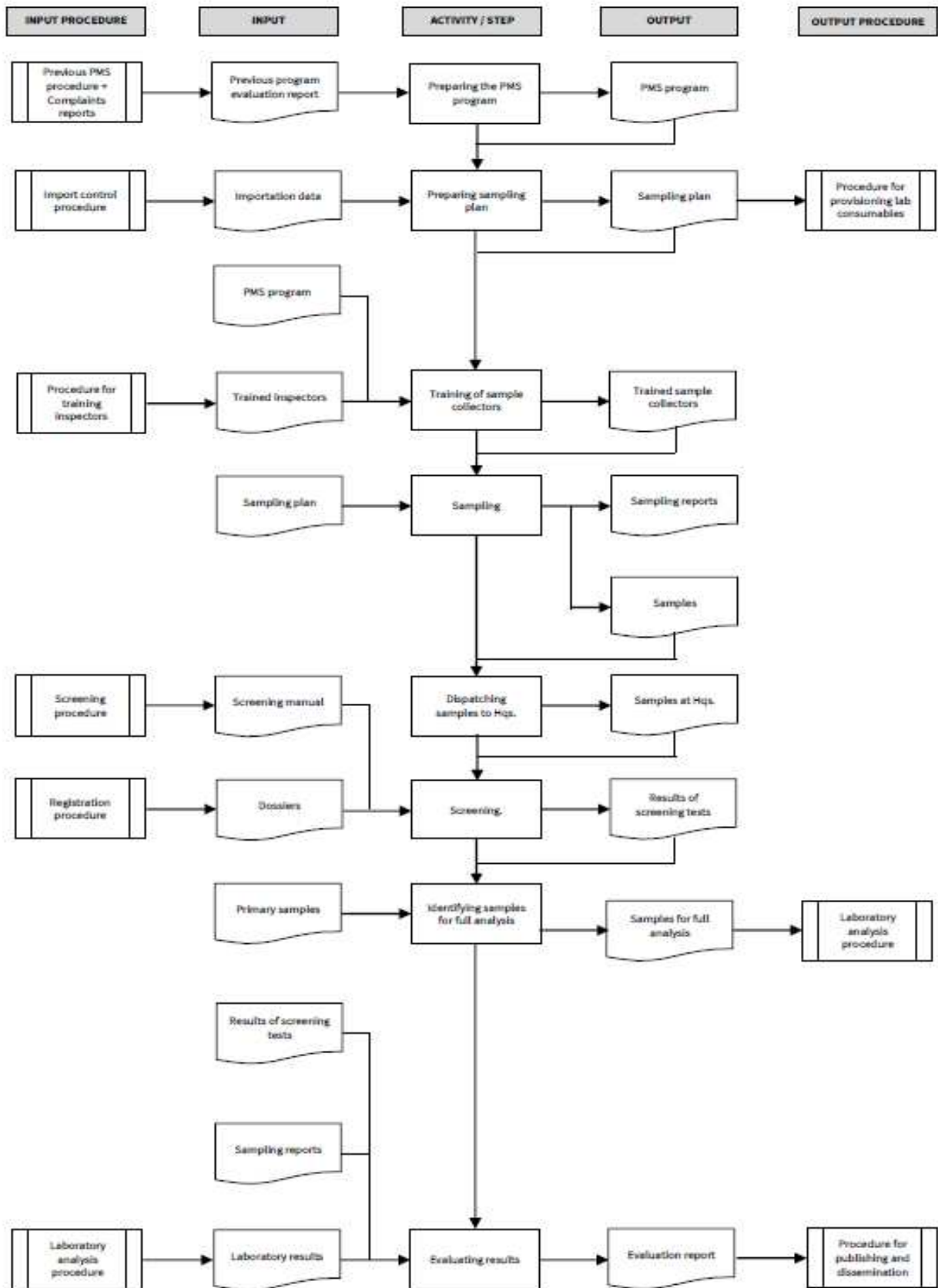


Table 9: Table of PMS responsibilities and outcomes in Tanzania

What is the step/activity?	Preparing PMS program	Preparing sampling plan	Training of sample collectors	Sampling
How is the activity done?	Meetings of task force	Compare the information in the program and importation data to see if the products have been imported. Details of batch numbers imported collected	Training of inspectors from areas samples will be collected. Training on sampling plan, sampling methodology, how samples can be sent to TFDA lab	According to sampling plan
With what?	Previous PMS program Evaluation reports Various inspection reports Complaints reports Literature on PMS and quality		PMS program Sampling plan	
Who is responsible for performing the activity?	Task force comprising of Manager for Inspection and Enforcement of Medicines and Cosmetics, PMS Coordinator, Manager Medicines and Cosmetics Analysis, Appointed Registration Officer, Eastern Zone Manager, Manager for Medical Devices Assessment and Enforcement, Appointed Drug inspector Chair: Manager for Inspection and Enforcement of Medicines and Cosmetics	PMS coordinator	Manager Inspection and enforcement	Sample collectors
Who is ultimately accountable to the management for the activity?	Director of Medicines and Complementary Products	Manager for Inspection and Enforcement	Director of Medicines and Complementary Products	Zonal managers
Who (if any) provides direct support to the person discharging the activity?	Drug inspectors PV Officers	Importation Officers	The PMS Task Force	PMS coordinator
Who (if any) should be consulted for the performance of the activity?	Academic institutions Importers (especially MSD and PSU) Vertical programs	Importation Officers Hospital Pharmacists MSD Vertical programs Manager Analysis	Zonal Managers District Executive Directors	MSD Vertical Program
Who (if any) should be informed of any aspect of the activity?	Zonal managers Director of Laboratory Services Director of Medicines and Complementary Products Director of Business Development ZOLGAC (Zonal and Local Government Coordinator) Quality Management System Manager	Manager Analysis Manager Inspection and Enforcement Zonal managers	District Medical Officer	DMOs RMOs
What are the performance indicators for the activity?				No. of samples collected Timeframe
What challenges are expected/encountered and how do you manage them?		Differences between sampling plan and products actually imported	Non-adherence to sampling methodology	Resistance from sampling sites
What is the step/activity?	Dispatching samples	Screening	Identifying samples for full analysis	Evaluating results

How is the activity done?	By courier. Special instruction are given for sample handling	Product information review Disintegration and TLC	<ol style="list-style-type: none"> 1. Samples that have failed screening 2. Samples with doubtful results 3. 10% of all screened samples but representing sampling sites and regions 	Meeting and reviewing the entire process – sample collection and testing. Linking results with source of samples, literature search.
With what?	By courier	<ol style="list-style-type: none"> 1. Dossier 2. Registration sample 3. Minilab kit 		Test results Sampling reports Reference books
Who is responsible for performing the activity?	Sample Collector	<ol style="list-style-type: none"> 1. Team of inspectors, analysts and evaluators perform the product information review by comparing information given during registration and those found on the sample. Also visual inspection of sample. 2. Analysts perform the disintegration and TLC tests 	Manager for analysis	PMS Task Force
Who is ultimately accountable to the management for the activity?	Zonal Manager	Manager for Inspection and enforcement	Manager inspection and enforcement	Manager inspection and enforcement
Who (if any) provides direct support to the person discharging the activity?			PMS Task Force	PMS coordinator
Who (if any) should be consulted for the performance of the activity?		Manager for analysis		Academic institutions
Who (if any) should be informed of any aspect of the activity?		Director of Laboratory Services Director of Medicines and Complementary Products		
What are the performance indicators for the activity?		Timeframe		
What challenges are expected/encountered and how do you manage them?		Unavailability of reference sample (some may have been damaged or lost)		Inadequate samples for statistical analysis

Table 10. Secondary procedures contributing to PMS activities in Tanzania

Name of procedure	Procedure for provision of lab consumables	Laboratory analysis procedure	Procedure for publishing and dissemination	
Aim of the procedure	To timely avail lab consumables ready for analysis of PMS samples	To analyze PMS samples	To inform all stakeholders the quality status of products in the market	
Inputs used	Sampling plan	PMS samples Lab consumables Analytical equipment Lab QMS (Work instructions)	Evaluation report	
Activities of the procedure	List products involved as per sampling plan Identify test parameters Identify consumables required for each test parameter Checking stocks Prepare order Send to Procurement unit Receive consumables Verify Enter into register Store	<ol style="list-style-type: none"> 1. Receive and register samples (provide unique code) 2. Store 3. Fill sample Analysis Request Form 4. Issue and register in sample issue book and database 5. Handling and testing of sample 6. Reporting test results 7. Reviewing test results (including OOS results) 	Approval of report by management Send to procurement unit for printing Send to IT Manager for placing on website Receive printed copies Distribute to stakeholders	
Outputs	Lab consumables procured	Test reports	Disseminated PMS report	
Outcomes	Availability of consumables at the time active PMS is undertaken	Laboratory analysis reports	Public informed of status of safety of medicines circulating in the market	

(b) Tanzania (Zanzibar)

The Zanzibar Food and drugs Board is the National Medicine Regulatory Authority established in 2006 by an Act of parliament, the Zanzibar Food Drugs and Cosmetics Act. No. 2.

4.9 Legal and regulatory framework

Framework for Pharmaceutical regulation

The legal and regulatory framework for the control of medicines in Zanzibar is provided under the Zanzibar Food Drugs and Cosmetics Act. No. 2 of 2006. It has been based on the Tanzanian Food Drugs and Cosmetics Act 2003 and with regards to medicines regulation contains the same Regulatory controls. It therefore contains the following regulatory Authorities:-

- The licensing of manufacturers, wholesale dealers, and retail premises
- The regulation of premises for the storage and distribution of drugs
- The approval and registration of products manufactured in Zanzibar
- The registration of importers of medicines into Zanzibar
- The approval and registration of products imported into Zanzibar.
- The maintenance of the Drugs, Medical Devices, and Herbal Drugs Register. The establishment of the Zanzibar Food and Drugs Board(ZFDB) Laboratory
- The analysis of drugs, herbal drugs and raw materials.
- The quarantine, recall, and destruction of adulterated or defective products
- Inspectors rights of access and powers of seizure
- The analysis of samples

Regulation of products manufactured inside country

There are no manufacturers of medicines inside Zanzibar.

Regulation of imported products

There is a register of wholesale dealers authorised to import into Zanzibar. There are 7 wholesale dealers licensed in Zanzibar. Inspections were performed prior to registration but there is no programme of inspection after registration.

Medicines should be registered before they can be imported. For each consignment an import permit is required. The product should be registered, the premises registered, and certificates of analysis (C of A) provided.

There is an *ad hoc* process for physical inspection at the port of entry, although this is sometimes not done due to shortage of staff. Imports from Tanzania Mainland are not inspected. A special programme is in place for anti-malarials. No samples of imports are taken.

There is no system or procedure to identify unregistered imported products although inspection guidelines are available.

Regulation of defective medicines

Reports of defective products are received from end users (doctors, healthcare workers and patients) although there is no formal procedure for the reporting of suspicious or defective medicines.

Defect reports to the Central Medical Store are investigated. Samples are tested and a report generated. The TFDA and MSD are informed.

Legal and regulatory framework for Post-marketing surveillance

There is no post-marketing surveillance in Zanzibar. There is no sampling plan. There is no sampling programme. The malaria program (Global Fund sponsored) covered PV and PMS. There was no structured sampling program but samples of ACTs were taken every quarter and tested using the Minilab.

There is a programme of inspections for community pharmacies which focuses on the appearance of the premises, good dispensing practice, and the qualification of the staff. These do not contribute to a PMS programme.

Supplementary laws

(a) Destruction

No information was provided regarding the control of destruction of defective medicines.

(b) Litigation

No information was provided regarding the prosecution of offenders.

4.10 Planning and approach

Not applicable since there is no active PMS.

4.11 Technical capacity for PMS activities

Organization structure

Not applicable since there is no active PMS.

Internal collaboration

Not applicable since there is no active PMS.

External collaboration

Not applicable since there is no active PMS.

PMS procedure

There are no procedures for active postmarket surveillance at the moment.

Field support

Not applicable since there is no active PMS.

Laboratory support

The ZFDB Laboratory is not operational. It is a single room with one HPLC and assorted glassware for wet chemical analysis (see Table 1). The HPLC was non-functional and in need of maintenance.

ZFDB records show the following annual workloads:

Table 11: Annual analytical workload at ZFDB

	2012	2013	2014
Herbal products	24	22	42
Medicines	0	0	4
Pre-authorization assessment		4	

The laboratory has no quality management procedures and no management or operating procedures.

Administrative support

Not applicable since there is no active PMS.

4.12 Implementation

This section does not apply since there is no active PMS.

4.13 PMS scope and cost

This section does not apply since there is no active PMS.

4.14 Visibility of PMS activities

This section does not apply since there is no active PMS.

4.15 PMS outcomes

This section does not apply since there is no active PMS.

4.16 Quality assurance by importing organizations

Medical Stores

The operations of the Medical Store are subject to controls under the Public Procurement Act No. 2. Procedures for procurement are established under the Act. All procurement is handled by the procurement management unit and tender board based at the Ministry of Health Headquarters. The Medical Store compiles the list of products it requires to be procured together with their specifications and submits them to the procurement management unit. Staff from the Medical Stores participate in the evaluation committee; the Director of the Medical Stores chairs the evaluation committee.

The tender process is an open and competitive process. Importers must be registered and only registered products are allowed. An evaluation committee evaluates the bids and is responsible for confirming the registration details. There is an approved list of suppliers for restricted tenders (DN: When are these used) but this is not possible for open tenders. Purchases from the MSD on the mainland are not tendered.

When goods arrive at the Medical Stores they are quarantined and checked by Procurement Officers from the PMU alongside staff from the store. Quality verification is only physical (visual inspection of the packaging, checks on the quantity and expiry date, and confirming agreement with the tender details). No samples are taken.

240 lines of medicines and medical supplies are carried in the store. In 2014 the Ministry of Health reviewed and published new editions of the Standard Treatment Guidelines and the List of Essential Medicines in order to guide treatment and medicines procurement in public health facilities. All the products on the essential medicines list are available through the Medical Store. At the time of the visit there were a number of medicines that were out of stock.

Appendix 5: Uganda situational report

The National Drug Authority (NDA) is the National Medicine Regulatory Authority established under the National Drug Policy and Authority Act, (CAP 206).

5.1 Legal and regulatory framework

Regulatory framework for Post-marketing surveillance

The Regulatory framework for the control of medicines in Uganda is the National Drug Policy and Authority Act, (CAP 206) and its associated Statutory Instruments (SI). This Act and its regulations provide the following regulatory functions:-

- The licensing of manufacturers, wholesale dealers, and retail premises
- The regulation of premises for the storage and distribution of drugs
- The approval and registration of products manufactured in Uganda
- The registration of importers of medicines into Uganda
- The approval and registration of products imported into Uganda.
- The maintenance of a register for drugs and preparations for human and veterinary use.
- The quarantine, recall, and destruction of counterfeit products
- Inspectors rights of access and powers of seizure

There is no provision for the establishment of the National Drug Authority (NDA) Laboratory nor is there for the sampling and analysis of medicines. There is no requirement or legal obligation for manufacturers, importers or distributors to report quality defects to the NDA. There is legal provision for the inspection of manufacturers, importers, or distributors.

Regulation of products manufactured inside country

Manufacturers are required to apply and be granted a licence for the manufacture of medicines. The application should include a list of the products to be manufactured and confirmation of their registration. When a product is manufactured for the first time three validation batches must be submitted to the NDA for evaluation.

Applications for product registration should be accompanied by reference samples. These are retained and used as reference samples for complaints investigations. When expired they are replaced with new reference samples.

Regulation of Imported Medicines

Importers of medicines must hold an import licence issued by the NDA. The imported products should be registered by NDA. Manufacturing sites for products on the import register are inspected and approved. Section 8(4) of the Act allows importation of unregistered medicines. Import consignments must be notified to the NDA. A pro-forma invoice listing the products to be imported is supplied to NDA before the consignment is shipped. Checks are made that the products are registered; that the medicine name, brand, strength, and pack size are correct; and that the manufacturing site is approved. If the checks are satisfactory, a verification certificate is issued which is the permit to import. Imports come through designated ports of entry. Inspectors based at the ports verify the paperwork for the consignment – registration, verification certificate, pro-forma invoice, Certificates of Analysis (C of As), and physical attributes of the sample. Samples are taken and checked against the retained samples. If satisfactory, the products are released for distribution.

It was formerly the procedure that all imported batches of anti-malarials, anti-retrovirals and anti-tuberculosis medicines were sampled and tested. This was discontinued in 2011 because all samples were

found to be compliant and so the testing was considered to be of no value. A new risk-based approach has been adopted.

Suspicious samples that are identified by inspectors are cross-checked with the registration department against the respective registration sample.

Regulation of defective medicines

There is an SOP for handling market complaints. This covers defective medicines and conduct of staff. There is a market complaint form which is available to all healthcare workers and can be downloaded from the website. The complaint is acknowledged and investigated by the relevant committee. The SOP defines the process and there are terms of reference for the committee which comprises of staff from the inspectorate, product registration, the laboratory, the drug information unit, and the quality management unit. The investigation including any analysis of samples is the responsibility of the committee. They produce a report of the investigation and document the actions taken.

Legal and regulatory framework for Post-marketing surveillance

There is no legal obligation for manufacturers, importers, or distributors to report information about known quality defects to the NDA. Under section 36 of the Act it is provided that the drug authority shall advise the Minister on measures to be taken to ensure the quality of drugs imported into or held in stock in the country and that the execution of the measures prescribed shall be entrusted to bodies charged with the importation and distribution of drugs. The Act further provides that the inspection of drugs and measures prescribed may be delegated to the chief of pharmaceuticals and health supplies or any other person properly qualified in pharmaceuticals and health supplies. Furthermore sections 50 – 53 provide explicit powers to inspectors to enter pharmaceutical premises, investigate, and take samples. For this reason PMS is conducted in Uganda in order to test registered products sampled from the market against product quality standards, to investigate complaints received pertaining to a registered product and to examine product labels and inserts to ensure compliance to approved indications and labelling requirements. The following PMS sampling statistics were provided during the interview:

Table 12: Number of PMS samples analysed by NDA between 2011 and 2014

Financial Year	PMS	From Local manufacturers	From Import consignments
2011/2012	432	107	663
2012/2013	308	56	762
2013/2014	212	37	1115

Supplementary laws

(a) Destruction of defective medicines

Section 60(1)(c) of the Act states that a person contravening a provision of the Act commits an offence and, where no punishment is provided, is liable to cause the items in contravention to be impounded, forfeited, destroyed or disposed of in a manner prescribed by the Minister. The Authority issued “Guidelines for Disposal of Pharmaceutical Wastes Supervised by National Drug Authority” in 2000. The guidelines recognised the need to regulate disposal of pharmaceutical waste and lays down a procedure through which service providers are appointed to undertake the disposal, presumably using environmentally acceptable methods.

(b) Prosecution of offenders

Offenders are handed over to the Uganda Police Force for further investigations and prosecution and NDA serves as witness in court.

5.2 Planning and approach

There is no formal procedure for postmarket surveillance. There is no annual plan and no annual sampling strategy. There is an informal meeting whereby staff from the inspectorate, medical information, and the laboratory, meet to agree the sampling protocol and requirements for the next 3-6 months.

5.3 Technical capacity for active PMS

Organizational structure

No information was provided on the organization of PMS functions.

Internal collaboration

Staff from the inspectorate, medical information and the laboratory meet to write an informal protocol and to agree on sampling requirements for the next 3-6 months.

External collaboration

Collaboration with other stakeholders

No information was provided on how other stakeholders are involved in PMS activities.

PMS Procedure

(a) Active PMS

There is no formal written procedure or step-by step process map for PMS but there are protocols that define it. During the interview with PMS staff the following steps became evident:-

- Step 1: Planning
- Step 2: Preparing protocol
- Step 3: Training inspectors on sampling protocol
- Step 4: Sampling
- Step 5: Screening (for products that can be screened on site)
- Step 6: Dispatching samples to Hqs.
- Step 7: Coding
- Step 8: Discussing results
- Step 9: Writing report

A process map was developed during the interview (Figure 4) linking these steps to inputs and outputs as well as secondary procedures associated with the inputs/outputs. Detailed descriptions of the steps, evaluation of responsibility assignment along the RASCI model and secondary processes supporting the PMS process are appended (Tables 15 and 16).

A sampling protocol contains the following sections:-

1. Introduction
2. Categories of medicines to be sampled for quality assessment
3. Main activities
4. Sampling
5. Sampling Plan
6. Sample collection sites/sources of drugs
7. Sampling frame (Number samples/ units per sample)
8. Sampling period /Duration
9. Precautions for sample collection
10. Sample transportation
11. Payment for Samples
12. Handling and storing of samples
13. Sample Analysis and Reporting

(b) Program-initiated active PMS

There is no clear distinction between NDA and program initiated PMS activities. The report provided by NDA officials for the PMS done between July and December 2012 shows that funds were provided by a donor (Affordable Medicines Facility for Malaria) but the activity was conducted by NDA. It is assumed that the same applies to the February – April 2011 survey (only the protocol was given to the consultants). There is no evidence of sustained PMS activities undertaken by NDA.

(c) Survey of the quality of medicines identified by the United Nations Commission on Life-Saving Commodities for Women and Children, 2013

This survey, conducted in 2013/2014, aimed at identifying products which were of good quality or the quality of which could be improved in short period of time. The study, designed and supervised by the WHO, was conducted in 10 countries across the world including Kenya, Uganda and Tanzania. It was not a programmed active PMS survey aimed at regulatory enforcement.

Passive PMS

(a) Defective reports

Through the media, the public is encouraged to report suspected cases of defective products. There is a hotline established for the purpose.

(b) International operations

NDA also participates in Interpol coordinated operations to disrupt the activities of transnational organized criminals involved in the trafficking of counterfeit medical products in Eastern Africa. It also aims to raise awareness, resources, educational efforts and capacity building on the issue. Operation Mamba I took place between 29 September and 5 October 2008. Participating countries were Tanzania and Uganda. The results were 1) 226 pharmacies, wholesalers, hospitals and market stalls were inspected 2) 82 police cases were opened and 3) more than 100 different products were seized. Operation Mamba II took place in August 2009. Participating countries were Kenya, Tanzania and Uganda. The results were 1) more than 270 premises were raided 2) 83 police cases were opened 3) the prosecution of several individuals suspected of being involved in the illicit trafficking of medical products and 4) at least 4 convictions. Thousands of tablets were seized. Operation Mamba III took place in July and August 2010. Participating countries on this occasion were Burundi, Kenya, Rwanda, Tanzania (+ Zanzibar) and Uganda. The results from this operation were 1) more than 375 premises were targeted 2) nearly 200,000 pills were seized 3) over 120 police cases were opened and 4) 78 cases were sent to court with over 34 convictions pronounced. The operation led to the adoption of the Declaration of Zanzibar by participating agencies and other organizations supporting the activities. This significant step will lead to enhanced partnerships, an increased sharing of information, more intelligence-led operations, and greater public awareness of the dangers posed by counterfeit medical products.

Field support

NDA inspectors are responsible for the sampling program.

Laboratory Support

The National Drug QC Laboratory (NDQL) is a department of National Drug Authority. Following a WHO pre-qualification inspection in September 2014 it was approved as a WHO pre-qualified laboratory for a range of analytical techniques in December 2014.

A summary of the laboratory resources is provided in Table 1.

The laboratory receives samples from the NDA only. There is an SOP for sample receipt. Samples are received from NDA with a sample request form. They are coded and entered into the laboratory management system database. The inspectorate code is not used at this stage but the analytical request form accompanies the sample and contains the inspectorate code as a cross reference. The laboratory supervisor reviews the analytical request form and generates a worksheet which contains the laboratory

code. The analysis is performed and the results of the analysis and calculation sheet are sent to the laboratory data analyst who calculates all results for the laboratory. The final result is entered on the worksheet which is reviewed by the supervisor. The final report is approved by the head of laboratory and sent to the head of the inspectorate.

In 2014 the laboratory outsourced the testing of 22 veterinary vaccine samples to the government laboratory in Ethiopia.

Administrative support

PMS activities fit within the organizational structure of NDA. The staff for PMS receive funds from the Finance Department, they are bound by the organization’s human resource manual and fall under the overall administration of the Executive Director.

5.4 Implementation

From reports, protocols and requests given to the consultants during the visit, the following PMS implementation scenario was constructed:

Table 13: PMS Activities undertaken by NDA between 2011 and 2014

Year	Source	Category	Planned by	Funded by
2011	Protocol	Anti malarials, Analgesic	NDA	AMFm
2012	Report	Anti malarials	NDA	AMFm
2014	Request	Antibiotics	NDA	NDA

The request to conduct PMS in 2014³⁷ gave the following for the special surveillance:

- The quality of Ceftriaxone powder for injection in Uganda had been the subject of an article published in an international journal after some researchers discovered that a certain brand was found to be substandard, and was allegedly the cause of death of a meningitis patient in Mulago Hospital. Furthermore the NDA had received several complaints in the past about the lack of efficacy of some brands of Ceftriaxone yet it is one of the top most used drugs in systemic infections.
- Amoxicillin on the other hand, has also had a significant number of informal and formal complaints regarding efficacy from patients and clinicians. It is also the most commonly used oral antibiotic in Uganda.

The department planned to take 450 samples collected from all 10 regions of Uganda costing Uganda Shillings 23,310,000 for purchasing the samples and a further UGX 9,800,000 as per diem to 1 inspector and 1 driver for each region.

These “special” reasons, and the fact that the antimalarial PMS surveys of 2011 and 2012 were funded externally led the consultants to conclude that there is no regular active PMS conducted by the NDA.

5.5 PMS scope and cost

Scope

As discussed above, evidence provided by NDA limits PMS activities to antimalarials and antibiotics

³⁷ Request for funds for sampling of selected medicines. Memo to Executive Secretary NDA from Ag. Head NQCL, 17th April 2014.

Cost

NDA relies on its inspectors to collect samples during PMS activities. If the request referred to in section 5.4 above is to be taken as the norm 450 samples would be collected by 7 inspectors in a 10 day countrywide operation. This averages at 6.4 samples per person-day. The exercise would also cost NDA Uganda Shillings 140,000 per person-day.

The above calculations do not reflect the reality of an active surveillance program where reference standards and other laboratory consumables have to be procured, training conducted, screening undertaken and a very comprehensive report written.

Another survey of anti-malarials whose protocol was prepared in February 2013 targeted 350 samples across Uganda. The main motivation for the study was to update and expand the knowledge and information about the quality of ACT anti-malarial medicines in Uganda following results of QAMSA study which reported that approximately 26% of the anti-malarial medicine samples from Uganda were found to be of poor quality. The exercise was to use 186 person-days (51 person days for drivers are excluded) and cost US\$ 47,201.64.

Table 14: Breakdown of cost in NDA's 2013 PMS protocol

Item	Person days	Budget (US\$)	Expense category	Budget (US\$)	%
Prepare sampling protocol (per diem)	20	916.60	Allowances	10,451.64	22.1%
Discuss with inspectors (per diem)	12	825.00			
Subsistence allowance during sampling	90	2,041.70			
Level 1 testing (per diem)	70	4,491.34			
Monitoring and evaluation supervision	10	572.90			
Data entry of level 2 test results	10	229.20			
Review and approval of level 2 results	10	458.30			
Preparing the 1 st draft report	5	458.30			
Review of draft report	10	458.30			
Purchase chemicals and reagents		14,583.30	Procurement	29,166.60	61.8%
Purchase reference standards		14,583.30			
Hiring testing premises		437.50	Analysis	437.50	0.9%
Sample purchase		2,916.70	Sampling costs	3,208.40	6.8%
Sampling logistics/tools		291.70			
Fuel		3,062.50	Travelling	3,937.50	8.3%
Fuel during planning and discussions		875.00			
Total budget	237	47,201.64		47,201.64	100.0%

5.6 Visibility of PMS activities

Final reports of post-marketing surveillance are usually published for distribution to the Ministry of Health and other stakeholders.

5.7 PMS outcomes

During the study we were shown the report for the PMS for antimalarials conducted in 2012. During the activity 436 samples were collected of which 104 samples were sent to the laboratory for level II testing. Out of the 92 samples there were ultimately tested, 5 samples failed which include 4 samples of quinine

bisulphate tablets and 1 sample of quinine sulphate tablets. The report concluded that “the quality of anti-malarial medicines in all regions of Uganda was found to be good but with 1.2% failure”. It recommended that sampling for the second round be adjusted for sample prices to cater for samples in the ACT categories where few samples were collected namely Artesunate/Amodiaquine, Dihydroartemisinin/Piperaquine sulphate and Artemisinin/Naphthoquine in order to assess their quality on a large scale.

There was no information provided on the regulatory action or follow up of the failed samples.

5.8 Quality assurance by importing organizations

National Medical Stores (NMS)

(a) General Activities

The NMS is a government agency. Its stock list covers the Uganda essential medicines list only but includes specialisations such as the National Cancer Institute and the National Heart Institute recommended medicines.

(b) Quality Assurance at NMS

The NMS operates in compliance with the Public Procurement Act, which has specific provisions for medicines. The tender process is therefore a public tender. Only suppliers that are on the NDA register are invited to tender. Tenders are managed by the NMS procurement unit (PDU). When the need for a tender is identified the PDU prepare the tender documents and invites tenders from those suppliers registered with the NDA for that product. If the product has not been tendered previously, samples will be requested. These are checked against NDA reference samples and, if these are satisfactory, no further checks are done. Otherwise the samples are sent to the laboratory for analysis. Tenders are awarded on price alone

Imported consignments are checked at the port of entry by NDA inspectors in the same way as all imports. When the verification certificate has been issued by NDA, the goods are taken into stock at the NMS warehouse. Warehouse staff perform a visual check of the packaging and expiry date, which must be >75%. No others checks are done. For all consignments three samples are taken from the batch and these are screened using the TruScan. One of these packs is retained for 1 year as a reference sample. Customer complaints are handled by the customer care officer in the sales and marketing department. Customers complete a complaint form with details of the product and the complaint. If it is identified as a quality problem, the NDA is informed and the sample and paperwork passed to the NDA for investigation. Warehouse stocks are quarantined pending the outcome of the NDA investigation. When the investigation is concluded, the NMS take action as advised by NDA.

The Joint Medical Stores

(a) General Activities

The Joint Medical Store (JMS) is a private organisation working on behalf of Christian churches in Uganda. It is a not for profit body that supplies to hospitals and clinics run by the churches or that operate on a not for profit basis. It operates on the same principles as MEDS in Kenya and uses the MEDS laboratory for its analyses.

(b) Quality Assurance at JMS

For procurement it uses the WHO pre-qualification model for anti-malarials, anti-retrovirals, and anti-tuberculosis medicines to identify potential suppliers. A questionnaire is sent to all potential suppliers and assessed on their responses and their abilities to meet the conditions of supply. Decisions are based on the following criteria:-

Compliance level (with WHO model)

95%
80%
60 -80%
< 60 %

Approval level

general supply
added to approved list of suppliers for specified products
Supplier audited, samples tested
not considered.

As a result of this process each product has a defined list of approved suppliers. The tenders for those products are only sent to those on this list. Products submitted for tender must have an NDA registration.

Successful tenderers are awarded the contract to supply. A purchase order is issued for quarterly supply based on annual requirements is issued. Suppliers provide the pro-forma invoice which is submitted to the NDA for the import certificate which is sent to the supplier.

Goods delivered into the store are verified at the point of entry. Once verified they are released into the store for distribution. Those products that can be screened by the minilab are tested. The store receives about 30 batches a month which are screened by this procedure.

Complaints are handled by the customer relations manager who receives the complaint report form. Other customers are contacted to verify the complaint. If validated by multiple complaints it is followed up. Products are sent to MEDS for testing and suppliers are informed. If the defect is confirmed the NDA are informed.

The Store has its own program of product quality surveillance. The sampling program is based on product history, complaint history, and manufacturer history. An annual sampling list is created. Approximately 100 samples per annum are sampled and tested. A 2% failure rate is observed. The store blacklists the supplier for this product. When necessary, the product will be recalled by the manufacturer or the NDA. NDA are not always informed of quality defects by the store.

Fig. 4: PMS Process Map in Uganda

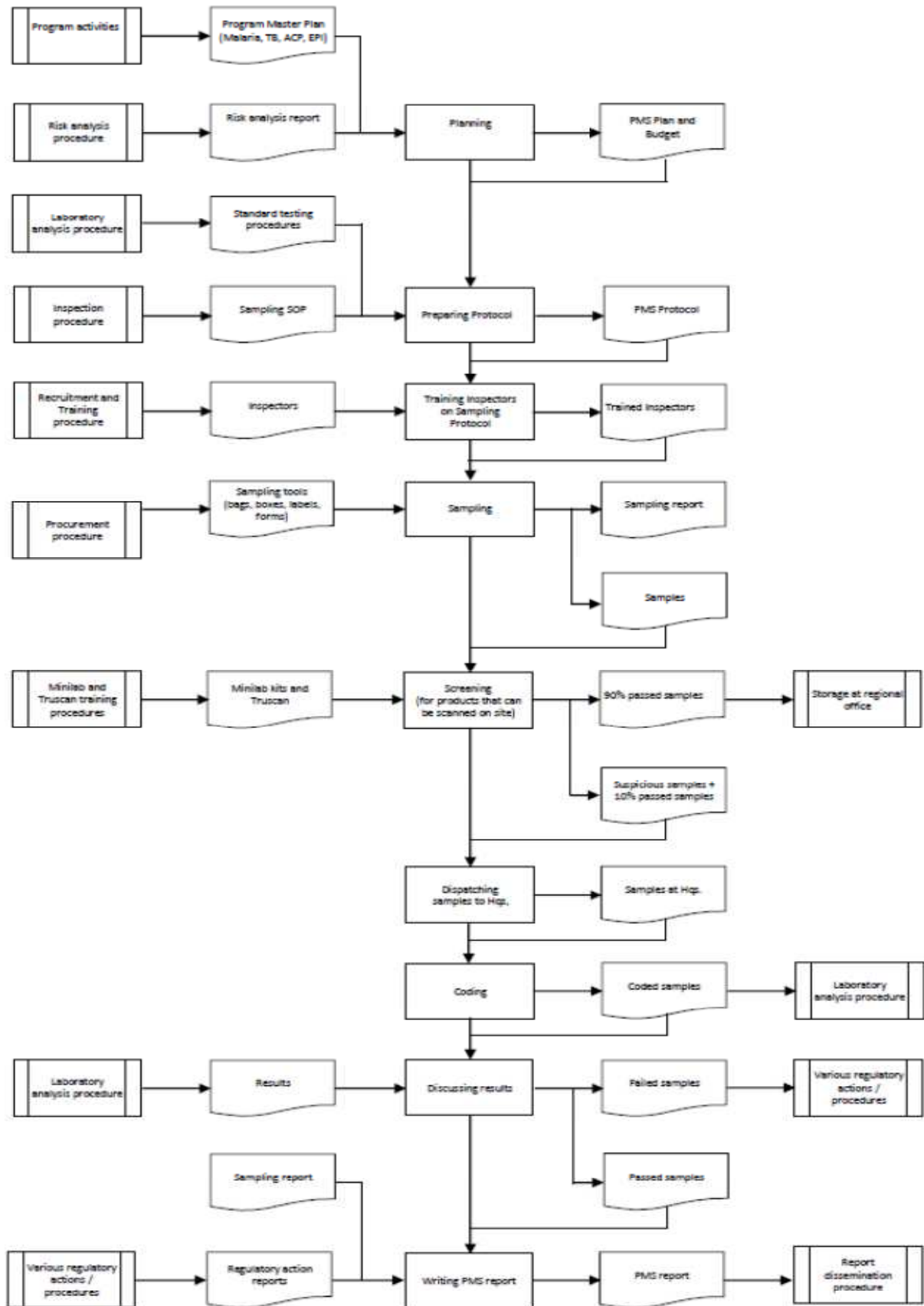


Table 15. Table of PMS responsibilities and outcomes in Uganda

What is the step/activity?	Planning	Preparing the protocol	Training inspectors on sampling protocol	Sampling
How is the activity done?	<p>The regular activity is initiated by a meeting of:</p> <ol style="list-style-type: none"> 1. Head of Drug Inspectorate Services 2. Head NDQC Lab 3. Head Drug Information Department 4. Senior Inspector LME 5. Senior Inspector Imports and Exports 6. Senior Inspector GMP <p>The activity can also be initiated by the Manager of a vertical program who communicates through the Executive Director</p>	<p>Drafted by an inspector and reviewed in a meeting of the Head Drug Inspectorate Services with Head NDQC Lab, Head Drug Information Department, Senior Inspector LME, Senior Inspector Imports and Exports and Senior Inspector GMP</p>	<p>An explanation by the Head Drug Inspectorate Services on details of the protocol especially on which medicines to sample, the techniques of sampling, sample management and record keeping</p>	<p>According to protocol</p>
With what?	<ol style="list-style-type: none"> 1. Program master plan 2. Pharmacovigilance reports 	<ol style="list-style-type: none"> 1. Standard testing procedures 2. Sampling SOP 	<p>PMS protocol</p>	<p>Sampling tools (bags, boxes, labels, forms)</p>
Who is responsible for performing the activity?	<p>Head Drug Inspectorate Services</p>	<p>Head Drug Inspectorate Services</p>	<p>Senior Inspector Licensing, Market Surveillance and Enforcement (LME)</p>	<p>Inspectors</p>
Who is ultimately accountable to the management for the activity?	<p>Head Drug Inspectorate Services</p>	<p>Head Drug Inspectorate Services</p>	<p>Senior Inspector Licensing, Market Surveillance and Enforcement (LME)</p>	<p>Senior Inspector Licensing, Market Surveillance and Enforcement (LME)</p>
Who (if any) provides direct support to the person discharging the activity?	<ol style="list-style-type: none"> 1. Head NDQC Lab 2. Head Drug Information Department 3. Senior Inspector LME 4. Senior Inspector Imports and Exports 5. Senior Inspector GMP 	<p>Inspectors and laboratory staff</p>		<p>Logistics staff</p>
Who (if any) should be consulted for the performance of the activity?				
Who (if any) should be informed of any aspect of the activity?	<p>Head of Procurement Unit Head Finance Department</p>		<p>Head Finance Department</p>	
What are the performance indicators for the activity?			<p>Attendance</p>	<p>No. of sites sampled as per protocol No. of samples collected as per protocol</p>
What internal controls are used?	<p>Approval by Executive Director</p>	<p>Approved by the team that reviews it</p>	<p>Attendance register</p>	
What challenges are expected/encountered and how do you manage them?	<p>Limited financial, human and logistical resources</p>			<p>Long traveling distances Logistics No cooperation at sampling sites</p>

What is the step/activity?	Screening	Dispatch to Hqs	Coding	Discussing results
How is the activity done?	Subject samples to screening test	Using NDA vehicles	(To be filled later)	Meeting of the following to review various reports. 1. Head of Drug Inspectorate Services 2. Head NDQC Lab 3. Head Drug Information Department 4. Senior Inspector LME 5. Senior Inspector Imports and Exports 6. Senior Inspector GMP
With what?	Using Minilab kits and Truscan equipment	Vehicles	Computer	Laboratory results
Who is responsible for performing the activity?	Laboratory personnel and inspectors	Regional inspectors	Inspectorate technician	Head of Drug Inspectorate Services
Who is ultimately accountable to the management for the activity?	Laboratory personnel	Regional inspectors	Senior Inspector LME	Head of Drug Inspectorate Services
Who (if any) provides direct support to the person discharging the activity?				This is a team activity
Who (if any) should be consulted for the performance of the activity?				
Who (if any) should be informed of any aspect of the activity?		Senior Inspector LME		
What are the performance indicators for the activity?	100% samples screened (for products that need to be screened)	Timely dispatch of samples	100% samples coded Timely coding	
What internal controls are used?	Test records	Checked and signed for at arrival	Analysis request form containing codes of products to be analysed is printed and signed by H,DIS	Results of 100% of samples sent for analysis received
What challenges are expected/encountered and how do you manage them?	Delays in procurement of reference standards and reagents			Delay in analysis

What is the step/activity?	Writing report			
How is the activity done?	Drafted by Senior LME and reviewed by Head Drug Inspectorate Services			
With what?	Sampling report Screening report Laboratory analysis report Regulatory actions reports			
Who is responsible for performing the activity?	Senior Inspector LME			
Who is ultimately accountable to the management for the activity?	Head, DIS			
Who (if any) provides direct support to the person discharging the activity?	Other Inspectors			
Who (if any) should be consulted for the performance of the activity?	Head NDQC Lab, Head Drug Information Department, Senior Inspector LME, Senior Inspector Imports and Exports and Senior Inspector GMP			
Who (if any) should be informed of any aspect of the activity?				
What are the performance indicators for the activity?				
What internal controls are used?	Signed by ED			
What challenges are expected/encountered and how do you manage them?				

Table 16. Secondary procedures contributing to PMS activities in Uganda

Name of procedure	Risk analysis procedure	Laboratory analysis procedure	Minilab and Truscan Training procedure	Storage at regional offices
Aim of the procedure	Identify high priority medicines for surveillance	Analyse samples for the field	To train inspectors how to use Minilab kits and Truscan scanners	To store samples according to manufacturers' specifications
Inputs used	Defective product complaints Inspection reports PV reports Previous PMS reports	Samples Equipment Reagents Standards Trained personnel	Minilab kits Truscan scanners	Samples, appropriate store room, inventory control facilities
Activities of the procedure	Using an approved risk analysis method	Sample receipt and registration, sample issue, analysis, reporting	Preparation, identifying trainees, identifying trainers, Preparing training materials, Training (workshop, seminar etc).	Receive samples, register, store, maintain inventory records
Outputs	List of priority products for surveillance	Certificate of analysis	Trained operators	Appropriately stored samples
Outcomes	List of priority products for surveillance	Analytical results	Trained operators	PMS samples appropriately stored in regional offices

Name of procedure	Various regulatory actions and procedures	Report dissemination procedure		
Aim of the procedure	To take action on failed products	To disseminate the report within the organization and to the Ministry of Health		
Inputs used	Analytical reports	Final report		
Activities of the procedure	Various	Printing hard copies and distributing to all departments Sending report to MOH		
Outputs	Product recall, product suspension, prosecution	Disseminated report		
Outcomes	Product recall, product suspension, prosecution	Disseminated report		

Appendix 6: Mission Team

Dr. Michael Gerard Lee, Lead Consultant, is a pharmacist who trained at the School of Pharmacy, University of London. His experience covers manufacturing, quality assurance and control, quality audits, procurement, and medicines regulation. He has 25 years of experience in NHS hospitals in a range of quality control management positions. This was followed by 13 years at the MHRA, the UK Medicines Regulator where he was a Group manager responsible at various times for laboratory services, the defective medicines reporting service, licensing of manufacturers and distributors, and the British Pharmacopoeia (BP). Dr Lee retired in 2012 from his position as Head of Laboratory Services and Secretary and Scientific Director of the BP Commission.

Dr. Joseph Robert Mhando, Regional Consultant, is a pharmacist trained in Tanzania and the United Kingdom, a trained manager and is also an IRCA Certified ISO 9000:2008 QMS Lead Auditor. His experience spans pharmaceutical manufacturing, quality management in API production, pharmaceutical representation and marketing and academics. Dr. Mhando has undertaken numerous assignments as a consultant primarily in local pharmaceutical production, pharmaceutical procurement, quality management and capacity building. He is also a consultant for the World Bank in pharmaceutical procurement. He is currently engaged as a Senior Lecturer in Pharmacy at St. John's University of Tanzania and as a Quality Assurance Consultant at Rijk Zwaan Tanzania. He is also a member of the Ministerial Advisory Board of the Tanzania Food and Drugs Authority.

Appendix 7: Persons met during the assessment visits

Burundi

Ph. SINDAYIGAYA Salvator, DPML;
Ph. BAHIZI Jean Nestor, DPML;
Mr. NDIKUMAZAMBO Innocent, DPML;
Ph. BARAYANDEMA Raphael, DPML;
Dr Alexis NIYOMWUNGERE, Manager (Pharmacist) in charge of quality management, DQCL; Ms. NDIHOKUBWAYO Godeberthe, Head of Drug Quality Control Laboratory;
Ph. ARAKAZA Larissa, Supply Chain Services, CAMEBU

Kenya

Dr Kipkerich Koskei, Chief Pharmacist and Registrar (PPB);
Dr Felictas Chebwogen, EAC (PPB);
Mr George Muthuri, Pharmacovigilance Officer (PPB);
Mr Patrick Kipiego, Drug Evaluation and Registration Officer (PPB);
Dr Hezekiah Chepkwony, Director (NQCL);
Dr Ernest Mbae, Deputy Director (NQCL);
Mrs Beatrice Rosana, Quality Assurance Officer (KEMSA);
Dr Wycliffe M Nandama, Senior Manager, Operations (MEDS).

Rwanda

Frederic Muhoza, Pharmaceutical Services Supervisor;
Theogene Ndayambaje, Medicines Registration Officer;
Joseph Kabatende, Head of Pharmaceutical Services;
Immaculee Mukankubito, Medical Procurement and Production Division.

Tanzania (Mainland)

Mrs Grace Shimwela, Medicines PMS Coordinator, TFDA;
Mr David Matle, National Medicines Registration Officer, EAC – MRH Project, TFDA;
Mr Yonah Hebron, Manager for Medicines and Cosmetics Analysis, TFDA;
Mr Heri Mchungu, Director of Procurement, MSD.

Tanzania (Zanzibar)

Zahran A. Hamad, Director Central Medical Stores;
Bora Lichanda, Pharmacist ZFDB;
Sharifa Y. Ali, Pharmacist ZFDB;
Nasir S. Buheti, Pharmacist ZFDB;
Haji J. Hamis, Pharmacist ZFDB;
Emmanuel Temu, Pharmacist ZFDB;
Salma H. Ali, Biotechnologist ZFDB;
Hidaya Juma, NMRO ZFDB;
Abraham H. Musa, QMS ZFDB.

Uganda

Mohammed Lukwago, Inspectorate Department;
Peter Ssali, Head, Quality Management;

Huldah Nassali, Drug Information Department;
Eunice Nakimuli Lukakamwa, Drug Registration Department;
David Nahamya, Inspectorate Department;
Annette Bukirwa Ssenkindu, Head, National Drug Quality Control Laboratory (NDQCL);
Kamat Lutaaya, NDQCL Quality Management System Co-ordinator;
Joanita Lwanyaga, Joint Medical Store.