

Rational Pharmaceutical Management Plus Quality Assurance of Medicines in Zambia – An Assessment Visit to the Zambia Pharmaceutical Regulatory Authority: Trip Report

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Strategic Objective 5

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About RPM Plus

The Rational Pharmaceutical Management Plus (RPM Plus) Program, funded by the U.S. Agency for International Development (cooperative agreement HRN-A-00-00-00016-00), works in more than 20 developing countries to provide technical assistance to strengthen drug and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning and in promoting the appropriate use of health commodities in the public and private sectors.

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Abstract

Dat Tran and Peter Risha traveled to Lusaka June 19-23, 2006 to assess the regulatory environment of pharmaceuticals in Zambia. They met with the Zambia Pharmaceutical Regulatory Authority and other partners to discuss strategies to strengthen the pharmaceutical quality assurance system in Zambia.

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Key Words

Quality assurance, Minilab, Zambia, PRA, TFDA

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ACRONYMS

| | |
|----------|--|
| ACT | Artemisinin-based Combination Therapy |
| AMR | Antimicrobial Resistance |
| API | Active Pharmaceutical Ingredient |
| MSH | Management Sciences for Health |
| PRA | Pharmaceutical Regulatory Authority (Zambia) |
| QA | Quality Assurance |
| RPM Plus | Rational Pharmaceutical Management Plus |
| TFDA | Tanzania Food and Drugs Authority |
| TLC | Thin Layer Chromatography |
| USAID | United States Agency for International Development |
| WHO | World Health Organization |

BACKGROUND

The circulation of low quality medicines – lacking or having none or the wrong active pharmaceutical ingredient (API) – is a major public health concern worldwide. This is especially a problem with antimicrobials, as they play a key role in the treatment of major infectious diseases such as malaria, tuberculosis, and HIV/AIDS. Poor quality antimicrobials present a substantial barrier to providing proper clinical care, often leading to decreased treatment effectiveness, increased morbidity and even mortality, and the development of antimicrobial resistance (AMR).

The primary factor contributing to poor quality medicines is the lack of regulation. Therefore, Drug Regulatory Authorities (DRAs) must play a leading role in any quality assurance (QA) effort. A good QA system has many interlinked components, which must be applied in concert to be effective. The major challenge for many resource-limited countries is priority – how best to allocate limited resources to accommodate the greatest needs in both technical (e.g., registration, laboratory testing, inspection, etc.) and managerial (e.g., laboratory management, documentation, training, etc.) areas of regulation.

RPM Plus/Management Sciences for Health (MSH) has extensive experience in pharmaceutical management worldwide, including Africa. Since 2001, MSH has been collaborating with the Tanzanian Food and Drugs Authority (TFDA) to develop a cost-effective QA system, based on product testing at ports of entry (using portable testing kits called Minilab), coupled with standardized and structured inspection.

The effort in Tanzania has led to the improvement of quality control of medicines. Now, with support from USAID (RPM Plus core funds SO5/AMR), the MSH/TFDA partnership seeks to use the successes and key lessons learned in Tanzania to improve medicine QA in other countries in the region, including Zambia. To facilitate this process, MSH/TFDA began by sharing a concept paper with the Pharmaceutical Regulatory Authority (PRA) of Zambia, outlining the key details of program implementation in Tanzania. In response, PRA showed great interest and enthusiasm in working with MSH.

Purpose of Trip

To further push the collaboration forward, Drs. Peter Risha and Dat Tran, both Senior Program Associates of RPM Plus, traveled to Lusaka the week of June 19-23, 2006 to learn of the pharmaceutical environment of Zambia and discuss with the Zambia Pharmaceutical Regulatory Authority (PRA) an implementation plan consistent with the physical and human resources of Zambia.

In addition to meeting with PRA senior staff, the RPM Plus team also visited other relevant QA partners in Zambia, including: WHO country office; Food and Drugs Laboratory; University of Zambia Department of Pharmacy; Zambia MOH (Director of Clinical Services and Diagnostics); Churches Health Association of Zambia (CHAZ); National Council for Scientific and Industrial

Research (NCSIR); Medical Store Ltd; Pharco Ltd (analytical services); Melcome Pharmaceuticals Ltd (wholesale outlet).

Scope of Work

The scope of work for Drs. Tran and Risha on this trip was to:

- Meet with PRA Director General and other key staff, as well as other relevant members of MOH to discuss project implementation
- Meet with the antimicrobial resistance (AMR) working group of Zambia and World Health Organization (WHO) country office to introduce QA project
- Visit the Food and Drug Control laboratory and the University of Zambia to learn about current laboratory testing methods
- Visit other relevant QA partners, including key private health provider Churches Health Association of Zambia
- Provide a briefing and/or debriefing to USAID/Zambia, as needed.

Under this scope of work, the specific objectives included:

- To learn about the structure and functions of PRA and its system of regulating pharmaceuticals in Zambia, including inspection
- To learn about pharmaceutical quality testing capacity of PRA and its food and drug control laboratory
- To prepare a visit for PRA and MOH of Zambia to Dar es Salaam, Tanzania to i) formalize partnership, ii) learn about TFDA QA program implementation and iii) visit Minilab zonal centers in Tanzania

ACTIVITIES

Visits to relevant QA partners in Lusaka

The Zambia Pharmaceutical Regulatory Authority assisted the RPM Plus team in identifying key QA stakeholders and arranging visits to the respective individual institutions. These include both government agencies at the Ministry of Health (MOH), as well as private organizations that are key links in the pharmaceutical chain in Zambia.

WHO Country Office

Dr. Chipayeni Mtonga, Health Officer in charge of Health Systems

The key points from the discussion with Dr. Mtonga include:

- Pharmaceutical quality is a big problem of health system in Zambia.
- Lack of border control leads to flow of poor quality medicines from other countries, including HIV, TB, malaria medicines. (Democratic Republic of Congo was mentioned as a suspected entry point for many poor quality medicines.)
- Under the recent new law, PRA is now strengthened by a new mandate and more structured organization compared to its previous form (see PRA section for more information).
- Even in its current form, PRA is still not fully functional and lacks personnel on the ground, especially pharmacists and pharmacy assistants. Added to the human resource problem is the difficulty of retaining trained pharmacists in Zambia; many pursue employment opportunities in other countries, where salaries and benefits are more competitive.
- The post-marketing monitoring of product quality is very limited. A regulatory response usually only occurs when there is an adverse reaction reported. For example, in one case, patients were reported to be worse after being treated with poor quality acyclovir for ophthalmic herpes zoster. In this case, PRA recommend that patients bought a specific brand name, which was known to be of good quality.
- There is a functional registration system in place, including a licensing process for importers, but customs inspection is weak – inspectors do not know how to interpret and understand scope of import authorization, e.g. products not registered by companies that have been approved for other products.
- In the past, the WHO country office has provided technical assistance to PRA, in the form of training in analytical methods. Dr. Mtonga also sees a future role for the WHO country office in assisting PRA in establishing its national quality control laboratory, both in terms of TA and providing equipment (the establishment of a national drug quality laboratory has been approved by MOH).

Food and Drug Laboratory (FDL)

Mrs. Margaret Sakala Mazhamo, Director

The Food and Drug Laboratory (FDL) is part of the MOH, but does not function as part of PRA. With the change in mandate in 2004, FDL will focus solely on food testing, while all drug-related testing will be done by the National Drug Quality Control Laboratory (NDQC) of PRA.

The key features and discussion points of the visit include:

- Mandate originates from Food and Drug Act in 1978, covering food, drugs, cosmetics, and medical devices
- FDL is organized according to the following departments: forensic, chemistry, microbiology, and instrumental
- FDL has a total staff of 24 (2 Masters of Science, 3 Bachelor of Science, 1 pharmacist, 10 technicians), which includes 3 senior-level “public analysts,” who are responsible certifying test results
- FDL provides analytical services to many agencies within the government: inspectorate (responsible for field sampling); police (blood, alcohol, rape cases); hospitals (common requests from UTH for suspected cases poor quality medicines (e.g., patients not responding to a specific batch of quinine from Kenya); drug enforcement commission (psychotropics, narcotics)
- It also provides analysis for as a fee for service to manufacturers
- Majority of samples tested by FDL involve psychotropics, microbiology tests of disinfectants, IV solutions, etc. The rest involves testing of water samples (E coli etc.)
- FDL performs ca. 2000 samples/year, but very few for quality of pharmaceuticals
- FDL is equipped with only basic instruments: TLC, GC, UV/vis and IR (not working). It has provided TLC training on some occasions to pharmacy students

Department of Pharmacy, University Teaching Hospital (UTH) – University of Zambia

Dr. Lungwani Muungo, Head, Department of Pharmacy

The team discussed with Dr. Muungo, among other things, training experience of the school of pharmacy. UTH is viewed as potential partner for training/certifying pharmacists or pharmacy assistants. Key features and discussion points of visit include:

- The pharmacy degree program officially started 6 years ago and is still being restructured
- There are 8 full-time faculty responsible for teaching core courses
- The degree program has 2 phases: pre-clinical (2 years) covering basic sciences (physiology, biochemistry, anatomy, etc. on medical campus) and practical (3 years) which is patient-based training, working with med students in UTH. The program also includes an internship requirement which provides hands-on training at pharmaceutical companies
- To date, the school has produced 10 graduates. Currently there are 37 students in the practical phase, 29 doing internships and 40 more expected next year. The program, once in full operation, is expected to produce an average of 35 pharmacists/year

- Graduates require certification to be employed – this is provided by the pharmacy professional body
- Currently, pharmacy students are not very familiar with quality assurance and other regulatory issues in general, in part due the newness of PRA

Churches Health Association of Zambia (CHAZ)

Mr. Chipupu Kandeke, Manager Pharmaceutical Services

Key features and discussion points from visit to CHAZ include:

- CHAZ is a private NGO, providing health services to approximately 30% of the population in Zambia and almost 50% when considering only rural areas
- It has 126 members, including health centers in rural areas
- It has a staff of 8 responsible for pharmaceutical services
- CHAZ procures medicines and stores and distributes them from its own warehouse in Lusaka (part of the administrative building complex), including all essential medicines, including TB, malaria, and HIV
- CHAZ has a need for technical assistance in different areas of QA, especially for the use of Standard Operating Procedures (SOPs). For examples, efforts are being made to provide clear guidelines and protocols for storage and distribution practices. A typical problem mentioned is inspection, where products come from non-prequalified manufacturing facilities (in some cases, the same companies have been approved for pre-qualification, but for different manufacturing facilities)
- With regarding to QA, CHAZ relies on WHO-prequalification and Global Fund to procure medicines. Currently, there is not product testing being done.
- According to Mr. Kandeke, the integrity of APIs of many medicines are uncertain; CHAZ needs quick way to screen for APIs at critical points and has begun to explore the use of Minilab for this purpose

AMR working group of Zambia

The RPM Plus team met with the AMR working group to brief them of RPM Plus planned QA activities in Zambia and quality-related implications for AMR.

Prof. Chinfumbe Chintu, Chair

Dr. Ray Handema, National Council for Scientific and Industrial Research (NCISIR)

Dr. JCK Chisanga, President, Faculty of General Practitioners

Dr. Veleri C Mtunga, Director Technical Support Services, MOH

Dr. James C. Mwansa, Microbiology, University Teaching Hospital (UTH)

Dr. Ruth Mudondo, Pharmacist, Unicare Pharmacy

- Prof. Chintu gave overview of AMR working group activities. The focus of the group is tracking resistance pattern in various microbes (virus, parasite, bacteria, etc.)
- The resistance work is supported by a good microbiology laboratory

- A key activity involves medical school curriculum review, specifically how to increase emphasis on AMR
- Other activities include i) using mass media campaign, i.e. radio spots, to raise public awareness about AMR ii) disseminate standard treatment guidelines (STGs), with a focus on antiretrovirals (ARVs)
- The group members were supportive of the planned QA project and agreed that there is a crucial need to improve the quality screening of medicines

Zambia Pharmaceutical Regulatory Authority (PRA)

Ms. Esnat Mwape, Acting Director General

Mr. Felix Chizu, Senior Pharmacist and QA project liaison

Mr. P. Mangisha, Product Registration

The RPM Plus discussed with senior staff of PRA to learn (i) more about PRA regulatory functions and (ii) other relevant background information relevant implementation QA system in Zambia. The pertinent information about PRA includes:

- The Food and Drug act was revised in 2004 to establish PRA; it was launched in 2005
- The PRA board, the decision making body, has 21 members from diverse background: pharmaceutical association members, consumers, traditional healers, academics, etc.
- PRA is organized into 4 major departments: Administration & Finance; Inspectorate; Registration; Quality Control
- With the new mandate, the – soon to be established – National Drug Quality Control Laboratory (NDQCL) will take over the testing of all medicines from Food and Drug lab, which will solely focus on foods
- There is no current post marketing surveillance in place in Zambia
- PRA's current professional staff includes: 3 pharmacists and 3 pharmacy technicians, including 1 posted at Lusaka airport for inspection
- When fully operational, the new mandate from recent legislation calls for an increase in inspectorate staffing, with 3 inspectors at central level, plus an additional 4 inspectors and 2 technicians at regional level
- Inspection network is divided into 4 regions, each headed by a senior officer, who coordinates with the Registration Department of PRA and reports to Director of Inspectorate of PRA
- The current registration was started formulated in 1989 and implemented in 1993. Currently there are 6 evaluators for registration; future plan will include use 3 additional external experts from medicine committee to increase technical expertise base in areas such as microbiology, clinical studies, etc.
- Zambia is an active participant in Southern African Development Community (SADC) harmonization effort in registration. The long-term goal is to integrate SADC standards into PRA, but this not possible at the moment due to SADC countries being at drastically different levels of regulatory development. Currently, there are no exemptions to SADC members for product evaluation and registration
- The current registration system provides guidelines to applicants and requires an annual fee for retaining license once approved

- Starting in 1999, the policy was changed to make a license valid for 5 years instead of 1 year. By law, the revenue generated from registration fees stays within the PRA
- Starting in July 2006, PRA will start to monitor the importing of pharmaceuticals, although the system is not yet capable of checking the validity of certificate of analysis submitted by applicant, i.e. there is no product testing
- PRA carries out pre-licensing inspection of local manufacturers according to WHO GMP standards, but this function is weak due to the lack of inspectors
- Strong consideration for approval is granted to foreign products that have been approved by other reputable DRAs
- Other factors considered for registration of foreign products include: registration status in other countries; WHO pre-qualification scheme; new chemical entities; BA/BE requirements for generics
- Since 1999, about 2500 products have been registered in Zambia, with the majority being generics, especially antibiotics and antimalarials. Currently, there is a registration surge for ACTs and herbal products
- The registration system is currently being upgraded and computerized. That has resulted in increased efficiency, with evaluation backlog reduced to the current number of less than 300 applications
- The average time required for generics to be approved is approximately 3 months

Discussion of QA implementation plan in Zambia

With the regulatory background in place, PRA and the RPM Plus team discussed how best to adapt the QA system developed in Tanzania, based on use of Minilab and standardized inspection, for Zambia. Specifically, the partners discussed key entry points of pharmaceuticals in Zambia for Minilab screening, as well as how to integrate the inspection training component into existing training programs already planned in Zambia. The discussion also touched on how best to leverage resources for the QA implementation. The key points of the discussion are:

- The major entry points for pharmaceuticals in Zambia, in order of quantity are: (1) Lusaka airport; (2) Nakonde; (3) Livingston; (4) Kasumbalesa; (5) Chirundu
- PRA estimates that top 2 locations are responsible for almost 60% of pharmaceuticals that enter country
- The partners will work, if possible, to integrate a WHO-sponsored training program for inspectors (planned for September 2006). This depends, in part, on the nature of the training is not clear to PRA at this point
- PRA pointed out some key indicators a strong momentum and commitment are in place to implement QA: (i) there is a strong commitment from MOH, whose permanent Secretary of Health is a chairman of the PRA board (ii) by law, revenue generated from product registration stays within PRA and therefore, can be used to improve its regulatory functions (iii) the Minilab and inspection components are already included in the proposed plan to establish a new NDQCL.

National Council for Scientific and Industrial Research (NCSIR)

Dr. Lewanika, Executive Director

Dr. Ray Handema, Senior Scientist and Assistant to Dr. Lewanika

The team paid a brief visit to NCSIR, part of the Ministry of Science and Technology (MST). It serves as an advisory body to the government on issues related to science and technology, especially in identifying gaps in research and development.

NCSIR is involved in a broad range of basic and applied research areas, including those in the biological sciences. Their activities range from genetically modified food, food and drink formulation, pharmaceutical analysis, etc. to information management systems. It has well-equipped laboratories, with standard modern instruments such as High Performance Liquid Chromatography (HPLC), UV/vis, IR, calorimetry, etc.

NCSIR also has capacity, i.e. clean room, for microbiological analyses such as sterility tests. It provides analytical services to government agencies, as well as fee-for-service to private industries. In addition, it also provides training in analytical methods to university students and industry laboratory personnel.

PRA inspection office – Lusaka Airport

Mr. Osborne Kamwale, inspector

The team met briefly with Mr. Kamwale, who gave an overview of the inspection process at the Lusaka Airport. He is the sole staff responsible for inspection pharmaceutical consignments that arrive via the airport. The activities at this office are limited to physical inspection, checking for registration status of products, expiry and manufacturing dates, etc. Currently, Mr. Kamwale has no access to PRA computerized registration database and relies on phone calls and faxes to check product registration. However, according to him, this situation is being changed so he will have direct access to the database.

Medical Stores Ltd. (MSL)

Ms. Anne Zulu, Director of Pharmaceutical Standards

Mr. Davy Simonga, QA Manager

MSL is the central warehouse, responsible for storage and distribution of pharmaceuticals to all sites at the regional and local level. It is worth noting that it has no role in the procurement process. It has a staff of 6, including 2 pharmacists, 2 pharmacy technicians, and 2 others. Currently, the majority of pharmaceuticals in the warehouse is antiretrovirals (ARVs), most manufactured in India.

Upon receipt, MSL performs visual inspection (labeling, manufacturing and expiry date, etc.). Next, products are quarantined and sampled by batch for quality testing at Pharco, a private laboratory service located next door to MSL (see next section). Microbiological tests are sent to

University of Zambia teaching hospital for analysis. Once products have passed quality testing, they are then stored for distribution.

MSL is in the process of revising their standards, which includes developing guidelines and standard operating procedures (SOPs) for all warehouse workers. Dr. Zulu said there will be a training to apply these new standards. A quality manual is also being developed and is scheduled to be completed by August 2006.

Pharco Analytical Services

Pharco was, at one time, a manufacturing facility but now is no longer operational (for reasons that are not clear). It now provides analytical services to both government and private industry. It provides quality control for about 80-90% of products from MSL. Its laboratory consists of 3 analysts, who perform tests according to USP or BP standards, using dissolution, HPLC, UV/vis, and IR. (if monographs are not available, they are provided by manufacturers).

Director of Clinical Care and Diagnostics, MOH

Dr. James Simpungwe

On the last day of the visit, the team had a meeting with Dr. James Simpungwe at MOH to formally present an overview of the QA project and discussed the partnership with PRA. Dr. Simpungwe was enthusiastic and indicated that he would be supportive of the planned activities. He gave his approval and said he would recommend to senior MOH officials to push the initiative ahead.

Melcome Pharmaceuticals Ltd., wholesale outlet

Dr. A. K. Sharma, Chief Executive Officer

The team paid a short visit to Melcome, a private wholesale outlet which distributes medicines to multiple locations in and around Dar es Salaam. Dr. Sharma gave a short tour of the storage facilities, which appeared to be in good condition. Medicines were stored off the floor, with proper shelving and labeling. According to Dr. Sharma, SOPs are in place for all workers involved with handling of medicines. Typically, upon receipt, workers perform physical inspection of products (breakage, expiry and manufacturing dates, etc.) and check certificate of analysis for quality.

Collaborators and Partners

The key collaborators and partners on this visit were:

- Ms. Esnat Mwape, Acting Director General, PRA
- Mr. Felix Chizu, Senior Pharmacist, PRA and project liaison

NEXT STEPS

Immediate Follow-up Activities

- MSH and PRA will explore how best to coordinate inspection training programs by sharing training materials to identify common training objectives
- MSH will discuss with TFDA to arrange a visit to Dar es Salaam for PRA. The key objectives of the trip include: (1) to learn first-hand of the QA system in Tanzania, including its registration and inspection systems; (2) to visit the Minilab center at Dar es Salaam harbor to see how inspectors carry out their duties and (3) to discuss with TFDA and MSH about the next steps of project implementation, including agreement on key terms of collaboration