Rational Pharmaceutical Management Plus
Densitometry Training and Review of Quality Assurance Activities, Dar es Salaam, Tanzania

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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.

Abstract

Dat Tran traveled to Dar es Salaam March 6-10, 2006 to participate in and monitor a 5-day training on densitometry at the central laboratory of the Tanzania Food and Drugs Authority. Discussion was also held with TFDA on the next steps for the regional rollout, an effort to adapt the quality assurance program developed in Tanzania to other regional countries.

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Key Words

Quality assurance, densitometry, level 1 testing, regional rollout, TFDA

Contents

ACRONYMS

AMR	Antimicrobial Resistance
API	Active Pharmaceutical Ingredient
CAMAG	Chemie-Erzeugnisse und Adsoprtionsterchnik AG
GFATM	Global Fund to Fight AIDS, Tuberculosis & Malaria
MSH	Management Sciences for Health
QA	Quality Assurance
RPM Plus	Rational Pharmaceutical Management Plus
TFDA	Tanzania Food and Drugs Authority
TLC	Thin Layer Chromatography
HPTLC	High Performance Thin Layer Chromatography
USAID	United States Agency for International Development
WHO	World Health Organization

BACKGROUND

The worldwide existence of substandard and/or fake medicines is a major public health problem. It presents a significant barrier to providing proper health care services, often leading to decreased treatment effectiveness, increased morbidity and even mortality, as well as the development of antimicrobial resistance (AMR).

To address drug quality concerns in Tanzania, the Tanzania Food and Drugs Authority (TFDA), part of the Tanzania Ministry of Health (MOH), with technical assistance from MSH/RPM Plus, have put in place an integrated drug quality assurance (QA) program based on the use of thin layer chromatography (TLC). The program has been successfully employed over the past 2 years to test a selective number of antibiotics at critical areas of port of entry.

However, TLC, which relies on visual quantification, presented some problems for TFDA inspectors. In some cases, the analysts were not able to detect substandard drugs. This called into question the use of TLC to detect substandard drugs and the need to improve TLC quantification. To remedy this situation, with funds from the Global Fund to Fight AIDS, Tuberculosis & Malaria (GFATM), TFDA improved its TLC capacity by purchasing a more sensitive instrument, densitometer or High Performance TLC instrument (HPTLC), for its central laboratory. Densitometry removes visual acuity as a parameter and directly measures the amount of active pharmaceutical ingredient (API) from TLC.

To further build upon this QA project, MSH/RPM Plus, with funds from USAID, has worked closely with TFDA to provide a technical training for its staff in order to validate the use of densitometry as an analytical method. The 5-day technical training session was provided by Anchrom laboratory services (Mumbai, India), a HPTLC expert contractor of the manufacturer CAMAG (Muttenz, Switzerland).

Purpose of Trip

Dat Tran, Senior Program Associate, RPM Plus, traveled to Dar es Salaam (March 6-10) to attend and monitor the 5-day densitometry technical training at TFDA. The other purpose of the trip was to discuss with Dr. Peter Risha, Senior Technical Advisor of MSH Tanzania, and TFDA senior staff about progress and next steps for several ongoing QA activities. This includes the "regional rollout," an effort to expand the Tanzania's QA program using TLC and standardized inspection to other regional countries, and, at the request of USAID, improving the operation and management of the pharmacovigilance system in Tanzania.

Scope of Work

The scope of work for Dr. Tran on this trip was to:

- Monitor and evaluate technical training on the use of densitometry
- Follow up with MSH Tanzania about progress of QA project
- Lead discussion with TFDA on progress and key next steps for QA regional rollout phase
- Provide a briefing and/or debriefing to USAID/Tanzania, as needed

Under this scope of work, the specific objectives included:

- To monitor and evaluation of densitometry training by CAMAG consultant Anchrom (Mumbai, India)
- To discuss with TFDA about densitometry validation methods and protocols for TFDA laboratory
- To discuss with TFDA about next steps for QA regional rollout, including the drafted concept paper for rollout phase
- To identify potential regional countries which might participate in this QA partnership, including key persons and contacts
- To discuss with TFDA about other related QA activities, including efforts to improve its pharmacovigilance system. This work is in support of the President's Malaria Initiative (PMI) being planned for National Malaria Control Program (NMCP) with support from MSH/RPM Plus

ACTIVITIES

Densitometry training

The 5-day densitometry training course, organized by TFDA and MSH/RPM Plus, took place at the central TFDA laboratory on March 6-10, 2006. The instructor of the course was Mr. Tukaram B. Thite of Anchrom (Mumbai, India), a contractor for CAMAG. The course focused on the use of the newly purchased CAMAG densitometer. Specifically, it covered the use and application of model *TLC Scanner 3* and sample applicator *Linomat 5*. Also included in the training was the use of the accompanied software *winCATS* for application and analysis.

The objectives of the training, agreed to by Anchrom, included:

- Installing and setting up the instrument for the use of the Tanzania Food and Drugs Authority (TFDA). This task includes installing the appropriate CAMAG software on a TFDA computer, interfacing the instrument to the PC of operation, and demonstrating routine preventive maintenance procedures and lamp replacements.
- Conducting an instruction session on the use of the integrated system for TLC applications. This task includes demonstrating HPTLC scanning procedures, routine calculations, and data analysis.
- Demonstrating the use of the instrument and methods to interpret results, including multi-component analysis applications (e.g., antimalarial sulfadoxine-pyrimethamine).
- Demonstrating data file backup procedures.
- Conducting as many practice sessions as time permits on running the TLC with the scanner, overseeing the trainees performing TLC procedures and scanning-calculations-file storage-system backups.
- On the last day, facilitating a discussion among participants regarding key lessons learned during the training.

The reports and deliverables by the trainer, Mr. Thite, included:

Documents

- Electronic and hard copies of Standard Operating Procedures for the use and maintenance of the instrument.
- Basic information sheets on Thin Layer Chromatography technique.
- Copies of the training presentations and other reference materials.

Instrument set up

- Demonstrated installation of instrument.
- An operable instrument with proper PC computer interfacing and control software installed and demonstrated.
- Instrument calibration with appropriate validation.
- Performance qualification.

- Demonstrated trouble shooting procedures.

Training session

- Five one-day theory and practice sessions conducted for participants.
- Method validation
- Quality control (assuring the quality of results)
- At the end of the training session, participants must be able to independently handle, run, and perform preventative maintenance of the installed instrument.

Summary of training activity

A total of 13 people participated in the 5-day training course at the central TFDA. They included members of TFDA, as well as faculty members of the School of Pharmacy, Muhimbili University College of Health Science (MUCHS) (see Annex 1 for list of participants). It is noteworthy to point out that the school of pharmacy has also acquired a new densitometer (same model, TLC Scanner 3) and was also getting a similar training course from Mr. Thite the following week.

During day 1 of the training, Mr. Thite explained and demonstrated the physical components of the scanner and sample applicator. He also demonstrated how to operate the data software and set up the parameters for data collection. A major problem encountered on the first day concerned the installation and application of the software winCATS. Mr. Thite was unable to operate the scanner with the installed software, which was a slightly different version than that used by the scanner. It resulted in an error message indicating the need for firmware upgrade.

Required firmware: 1:14:22
Installed Firmware: 1:14:21 update

Mr. Thite telephoned Anchrom (Mumbai, India) for assistance, but was not able to resolve this software problem the same day. Dr. Risha then made further contacts to both the manufacturer CAMAG and Anchrom by email to address this issue.

Fortunately, the software incompatibility was resolved by the second day of training. An SOP, sent from Anchrom by service engineer Vivek Maid, was able to fix the problem (see Annex 2). On the second day of training, Mr. Thite continued the training, focusing on the operation of Linomat5, including how to set optimal conditions for best quantification (e.g. using band application 6 mm).

Mr. Thite did further demonstrations with a standard caffeine sample (prepared in 8/2 toluene/acetonitrile solution by volume) at different concentrations. This was done, in part, to emphasize the need to find optimal concentration for testing. This is an important point, given that densitometry is more sensitive and requires a less concentrated sample than TLC. The demonstration using caffeine samples also focused on another important aspect of the instrument operation, establishing good linear calibration response.

Day 3, 4, and 5 were devoted to "hands-on" operation of the instrument by the trainees. During this process, Mr. Thite played a supervisory role and answered specific technical questions posed by the trainees. The questions posed were related to specific aspects of instrument operation, as well as its range of applications.

The trainees prepared different methanol/ethylacetate solutions of the drug cotrimoxazole (fixed-dosed combination of trimethoprim and sulfamethoxazole) to establish optimal concentration range for calibration.

The latter part of the training was very constructive for the trainees. By the end of the training week, everyone was able to navigate through the instrument and the software comfortably. More importantly, they were able to obtain good linear response in their calibration tests, a key to ensure that the instrument operates appropriately.

The training was concluded on the last day with a brief closing ceremony. Mr. Thite of Anchrom, Dr. Tran of MSH, and Ms. Charys Ugullum, Acting Director General of TFDA, respectively made brief remarks on behalf of their institution before each trainee was issued a certificate of training. Mr. Thite thanked TFDA and MSH for organizing the training and the trainees for their enthusiastic participation.

In his remarks, Dr. Tran expressed MSH's appreciation for the spirit of collaboration between MSH and TFDA, especially the contribution of Dr. Risha, who was the main liaison between MSH and TFDA during the planning process. Dr. Tran also thanked Mr. Thite for sharing his knowledge and experience in densitometry during the training. Finally, Ms. Ugullum concluded by expressing her appreciation to Mr. Thite for conducting the training. She also thanked MSH for supporting the training and expressed how pleased she was that TFDA was finally able to secure the densitometer as a way to improve their ability and efficiency to systematically test drugs.

Evaluation of training

In the broader context, the training did accomplish its key goal of getting the trainees well versed with the operation and applications of the instrument. However, there were problems that prevented the training from being even more effective. The key issue resided with the presentation of the trainer, Mr. Thite of Anchrom, a contractor of the manufacturer CAMAG. He appeared to be thoroughly knowledgeable and highly experienced about the use of densitometry. However, he was not as efficient in transferring this knowledge to the training group.

Training problems were found in several areas:

- Organization – there was no coherent structure or format for the training.
- Presentation of material was not appropriate for the level of the trainee. Mr. Thite did not seem to take into consideration the level of expertise of his audience. Time was wasted

unnecessarily on technical details, most of which was already familiar to a group with broad TLC and chemistry background.
- Style – Mr. Thite was somewhat impatient in listening fully to the trainees' questions. He had a tendency to cut off questions or started answering them before the questioners finished. This was a point of frustration for many trainees.
- Preparation – the software problem on day 1 was indicative of inadequate preparation. Mr. Thite did not appear to go through any pre-training checklist to make sure that things were in place. Anchrom did not respond to TFDA's offer with assistance in the pre-training preparation. Nor did it request a list of things needed from the hosting institution, as often is the case with laboratory training.

At the end of the training (day 5), the trainees were asked to evaluate the 5-day training by ranking (1-10 points) 10 different key indicators. The scores indicated that, overall, most trainees were only moderately satisfied with the training course. The individual evaluation scores, along with the trainees' most common comments, are tabulated in Annex 3.

Discussion with TFDA about QA and related activities

Participants: Dat Tran and Peter Risha (MSH); Charys Ugullum, Danstan Hipolite, and Mary Masanja (TFDA).

TFDA and MSH discussed on-going QA projects and how best to move these projects forward. The discussion touched on three key projects:

1) Implementation of level 1 testing regional rollout (TLC and standardized inspection)
2) Improving the pharmacovigilance system in Tanzania
3) Technical assistance (TA) to TFDA in densitometry and related activities

1. Regional rollout

MSH and TFDA agreed that TFDA should play a lead role in the next phase of this initiative. The partners also agreed with the goal of engaging 2-3 countries in region for this regional rollout effort. Three potential regional partners were identified: Zambia, Uganda, and Ethiopia. This was based on what is known about the countries' QA system, as well as their expressed interest thus far.

The partners agreed that it would be best engage each country individually, according to its own timeline, to take advantage of the momentum. For example, Zambia has clearly indicated its interest in this initiative and is ready to move forward, while more work has to be done to gauge Uganda and Ethiopia's interest. TFDA was very enthusiastic about taking a lead role in sharing the key lessons learned in Tanzania with other countries in the region.

From Tanzania's perspective, Ms. Ugullum said the establishment of the TLC testing centers throughout the country has been effective in enhancing TFDA's testing capacity. At the same time, has given the TFDA central laboratory much needed relief for the number of tests it had to conduct. She also indicated that thus far, 7 out of the 10 planned TLC testing centers are now in

full operation, with the rest soon to be started. She emphasized it is important for Tanzania to share with other countries both positive and negative lessons from its own implementation. Therefore, TFDA suggested that, once the country partners have been identified, a visit to Tanzania to learn first hand about the details of program implementation would be most constructive.

2. Improving pharmacovigilance

Dr. Risha started by explaining the origin of this project to provide broader context for discussion. This initiative, at the request of USAID mission in Tanzania, is set out to build upon the ADDO (accredited drug dispensing outlets) initiative. The goal is to get artemisinin combination therapy (ACT) – more effective treatment for pregnant women with malaria, especially at the early stage – to be approved as new standard treatment guidelines for malaria, and more importantly, to explore ADDOs as the potential mechanism for reporting ACT adverse drug reaction (ADR).

Ms. Masanja of TFDA provided some background information about ADR reporting in Tanzania. Currently there are some limited ADR activities going on in the country involving healthcare providers. However, there is no legal requirement for manufacturers to report ADR to TFDA. Ms. Masanja informed the group that MOH has recently completed its guidelines for ADR reporting. She said a key goal of MOH is to publicize these new guidelines, as well as sensitizing health providers to the need for ADR reporting.

At the present, there are 2 on-site drug information centers based in reference hospitals. These drug information centers play 2 major roles: to provide information to healthcare professionals and to collect ADR data. But due to lack of resources, these centers operate only on a part-tine basis. TFDA has provided some furniture and computers, as well as training for hospital workers (physicians and pharmacists). However, TFDA acknowledged that much more needs to be done. Ms. Masanja said that some recent ADR activities (e.g. training) in Tanzania have been supported by WHO.

As the discussion evolved, the partners agreed that there are too many disconnected ADR and related activities going on and there needs to be a centralized system for ADR reporting in Tanzania. A constructive first step would be to engage all stakeholders in a meeting to identify knowledge gaps and more importantly, to see if these gaps might be bridged by existing expertise within the country. For example, with regard to the potential role of ADDO in ADR reporting, some linkage between ADDO and the health centers has to be made since the health center is where most patients invest their confidence and get their information about drug use.

3. Technical assistance (TA) to TFDA in densitometry and related activities

The partners agreed that the important next step was to develop a protocol for the validation of the newly acquired densitometer. A list of drugs will be selected for testing, which includes antibiotics, antimalarials, and antiretrovirals (ARVs). It was agreed that MSH will initiate the process by coming up with the first draft. This will be then shared with TFDA for comments and

suggestions before it will be finalized. Mr. Hipolite, who has extensive experience in method validation, will be the lead person for TFDA in this effort.

As part of this discussion, TFDA also requested assistance from MSH in the area of good laboratory practices (GLP) training. TFDA has a goal of achieving accreditation ISO 17025 within 2 years. This international standard is concerned with 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.

TFDA indicated that it needs hands-on, practical technical assistance on specific activities and how to implement them systematically to achieve this accreditation. This issue is also timely for TFDA as it has plans to expand its laboratory space in the near future. The partners agreed that MSH would further look into this to clearly define if and how it might be able to play an appropriate role. The partners discussed the possibility of having a partnership with another organization, i.e. U.S. Pharmacopeia or WHO, to assist TFDA in this initiative. As the discussion ended, TFDA agreed to share a previous WHO assessment as background information.

Collaborators and Partners

The key collaborators and partners on this visit were:

- Dr. Peter Risha, Senior Technical Advisor, MSH Tanzania.
- Ms. Charys Ugullum, Director of Laboratory Services and Acting Director General, TFDA.
- Mr. Danstan Hipolite, Head, Technical Services, TFDA.
- Ms. Mary Masanja, Pharmacovigilance Program, TFDA.

NEXT STEPS

Immediate Follow-up Activities

Regional rollout (TLC/standardized inspection)

- MSH will share with a draft of a concept paper for this initiative with TFDA by early April for comments.
- MSH will initiate contact with potential partners for the regional rollout (Zambia, Uganda, and Ethiopia).

Validation of densitometry

- MSH will draft a list of drugs to be tested and develop a validation protocol before sending them to TFDA for comments.
- MSH will explore how it might able to assist TFDA with installation, operation and performance qualification (IQ, OQ, PQ) for the densitometer (this was not included in the training package provided by CAMAG).

Laboratory accreditation

- TFDA will share a previous assessment report by WHO.
- MSH will explore its role internally and how it might be able to assist TFDA with laboratory accreditation issues in general and if possible, how to achieving its goal of ISO 17025.

Important Upcoming Activities or Benchmarks in Program

Regional rollout

- The goal is to invite country partners to Dar es Salaam to learn about Tanzania's QA program implementation (TLC and standardized inspection) by July 2006.

ANNEX 1. LIST OF TRAINING PARTICIPANTS

Tanzania Food & Drugs Authority - Staff		
1	Ms. Charys Ugullum	Director, Laboratory Services
2	Mr. Danstan Hipolite	Head, Technical Services
3	Ms. Zera Msuya	Head, Chemistry
4	Ms. Anita Bitegeko	Analyst
5	Mr. Kandege Oscar	Instrumentation Technician
6	Mr. Aaron Elias	Assistant analyst
7	Mr. Rajabu Mziray	Analyst
8	Mr. Yonah Hebron	Analyst
9	Ms. Mwanamvua Ngwena	Assistant Analyst
10	Ms. Gladness Kanza	Assistant Analyst
School of Pharmacy (MUCHS) personnel		
11	Dr. Olypa Ngassapa	Senior Lecturer
12	Dr. E. Kaale	Lecturer
13	Dr. M. Chambuso	Lecturer

ANNEX 2. SOP FOR UPGRADING OF SCANNER FIRMWARE

1. **Put Scanner on & connect RS 232 Communication cable to COM 1 port of computer.**
2. **Go to windows explorer.**
3. **Click on "C" drive (Hard disk)**
4. **Select Camag Folder & open it.**
5. **Select winCATS folder & open it.**
6. **Select Firmware folder & open it.**
7. **Double click on**  Fwupdate.exe
8. **Go to Transfer > > Interface > >**
9. **New window will appear in that** Port = COM 1 & BAUDRATE = 19200 **& click ok.**
10. **Go to File > > Open**
11. **Open "C" Drive > > Camag > > winCATS >> Firmware**
12. **Select Scanner 3 Firmware file.(SC3_11422.frm) Click open.**
13. **Go to Transfer & click on start.**
14. **It will start firmware upgradation automatically. Wait for a moment.**
15. **After finishing upgradation a message will appear "FIRMWARE UPGRADATION SUCCESSFUL" & Scanner will restart automatically.**

ANNEX 3. PARTICIPANTS' EVALUATION OF TRAINING

Evaluation Criterion	Participants' Score (1-10 with 10 being best)													
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Ave	Max
C1	3	3	3	3	3	4	5	2	3	3	4	3	3.3	5
C2	4	2	2	3	3	4	4	3	3	4	3	4	3.3	5
C3	4	2	1	3	1	3	5	4	2	2	3	4	2.8	5
C4	4	2	3	3	4	3	3	4	2	3	4	4	3.3	5
C5	4	2	5	4	5	4	5	5	4	5	4	5	4.3	5
C6	2	2	3	2	3	3	2	2	2	2	2	2	2.3	3
C7	7	4	6	6	7	7	5	7	6	4	5	6	5.8	10
C8	3	3	5	4	6	6	5	7	6	2	5	3	4.6	10
C9	5	4	7	4	5	7	9	6	7	4	5	5	5.7	10
C10	6	4	4	6	3	7	9	9	7	8	5	6	6.2	10

The participants were asked to score 1-10 for each of the following these criteria:

C1: Training objectives clearly defined at the beginning of the training

C2: Defined objectives achieved by the end of the course

C3: Amount of material covered during the course

C4: Depth of coverage of the material

C5: The training was useful to my work

C6: Overall, the difficulty level of the course was

C7: The pace of the course

C8: The style and format of the course

C9: The instruction materials

C10: The length of the course

Summary of most common comments:

- The trainer should have had a training schedule and follow it up appropriately, arrange topics in sequence starting with a theoretical session
- It would have been very useful if SOP for the operation of the equipment had it been made available before hand
- The trainer did not appear to be adequately prepared for the course
- The course was very useful to TFDA laboratory, as the equipment demonstrated the potential for many different analyses