

Regional Training Workshop: Compendial Analysis of Lumefantrine and Artemether Tablets

Paramaribo, Suriname
April 16-27, 2012

Trip Report

Lawrence Evans III, Ph.D., M.P.H.
Global Services and Standards Manager

Mark Liddell, Ph.D.
Scientist IV, USP

Pati Gaitan
Senior Program Assistant

Promoting the Quality of Medicines
Implemented by U.S. Pharmacopeia (USP)
12601 Twinbrook Parkway
Rockville, MD 20852 USA
Tel: (+1-301-816-8389)
Email: pqm@usp.org and le@usp.org

Cooperative Agreement # GHS-A-00-09-00003-00
Funding Source: USAID/Peru (for Amazon Malaria Initiative) and USP Technical Assistance Program
Grantee: Promoting the Quality of Medicines (PQM) Program
Author(s) Name: Lawrence Evans III
Language: English
Date of Publication: June 12, 2012



USAID
FROM THE AMERICAN PEOPLE



This report is made possible by the generous support of the American people through the United States Agency for International Development (USAID), under Cooperative Agreement No. GHS-A-00-09-00003-00. The contents are the responsibility of the Promoting the Quality of Medicines Program, implemented by the U. S. Pharmacopeia, and do not necessarily reflect the views of USAID, or the United States Government

Executive Summary

PQM conducted a technical training for analysts at the Bedrijf Geneesmiddelen Voorziening Suriname (BGVS) lab in April 2012. The goal was to train participants in the analysis of lumefantrine and artemether tablets according to the *USP* monograph. The training consisted of lectures and hands-on activities in the laboratory for:

- High Performance Liquid Chromatography (HPLC)
- Dissolution including performance verification testing (PVT)
- Ultraviolet (UV) Absorption
- Thin-layer chromatography (TLC)

The lecture series also covered good laboratory practices (GLP) and good documentation practices (GDP). The training was regional, including scientists from Suriname, Brazil, Belize, Jamaica, and Trinidad and Tobago. The latter three were supported through funding provided by the USP Technical Assistance Program (TAP). A total of 21 individuals participated in the lectures and 10 in the hands-on training.

PQM staff also held a meeting with the Ministry of Health (MoH) and the Pan American Health Organization (PAHO) to discuss an awareness campaign strategy as a follow-up to the malaria medicine quality study results.

TABLE OF CONTENTS

<u>Acknowledgements</u>	4
<u>Acronyms</u>	5
<u>Background</u>	6
<u>Purpose of Trip</u>	6
<u>Source of Funding</u>	6
<u>Overview of Activities</u>	6
<u>Conclusion</u>	9
<u>Annex 1: List of Participants</u>	10
<u>Annex 2: Training Agenda</u>	11
<u>Annex 3: Participant evaluations</u>	14

About PQM

The Promoting the Quality of Medicines (PQM) program, funded by the U.S. Agency for International Development (USAID), is the successor of the Drug Quality and Information (DQI) program implemented by the United States Pharmacopeia (USP). PQM is USAID’s response to the growing challenge posed by the proliferation of counterfeit and substandard medicines. By providing technical assistance to developing countries, PQM helps build local capacity in medicine quality assurance systems, increase the supply of quality medicines to priority USAID health programs, and ensure the quality and safety of medicines globally. This document does not necessarily represent the views or opinions of USAID or the United States Government. It may be reproduced if credit is given to PQM and USP.

ACKNOWLEDGEMENTS

The authors would like to thank:

- The training participants for their high level of interest and for their feedback regarding the training
- Ms. Sheila Kort and her staff at the BGVS lab for their support in delivering a successful training
- Ms. Miriam Naarendorp, from Suriname's Medicine Regulatory Authority (MRA), for her assistance and hospitality in ensuring a highly productive visit
- Dr. Marthelise Eersel, from Suriname's MOH, and the receptive and accommodating staff at the MOH for their support during PQM's visit
- Dr. Rachel Eersel, from PAHO-Suriname, for supporting PAHO-PQM collaborations
- Dr. Ingrid May, Managing Director of BGVS, and Dr. Wilfred Balraadjsing, Assistant Director of BGVS, for allowing the use the BGVS lab facilities for the training
- PQM administrative staff and editors for their assistance with logistical arrangements and for editing the trip report
- Mr. Anthony Boni and Dr. Maria Miralles at USAID/Washington and Dr. Jaime Chang at USAID/Peru for their guidance and helpful insights

ACRONYMS

AMI	Amazon Malaria Initiative
BGVS	Bedrijf Geneesmiddelen Voorziening Suriname (Drug Supply Company Suriname)
DQI	Drug Quality and Information Program
GDP	Good Documentation Practices
GLP	Good Laboratory Practices
HPLC	High Performance Liquid Chromatography
MOH	Ministry of Health
MRA	Medicine Regulatory Authority
OMCL	Official Medicines Control Laboratory
PAHO	Pan American Health Organization
PMI	President's Malaria Initiative
PQM	Promoting the Quality of Medicines Program
PVT	Performance Verification Tests
TAP	Technical Alliance Program
TLC	Thin Layer Chromatography
UV-Vis	Ultraviolet-visible
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

Background

The U.S. Pharmacopeia (USP) has been providing technical assistance to Suriname in the context of the Amazon Malaria Initiative (AMI) since 2003. Until 2009, activities in Suriname focused solely on medicines quality monitoring with basic tests, through collaboration with the University of Suriname and the Pan American Health Organization (PAHO).

A malaria medicine quality study was performed in 2009 to determine the prevalence of poor quality medicines in the private and informal sectors. In most countries in South America, malaria medicines are available free-of-charge when obtained in the public sector. However, in the interior region of Suriname, where there are fewer public health facilities and access to them may be difficult, malaria medicines are often obtained from the private and informal sectors. PQM shared the findings of the study with the medicine regulatory authority (MRA) and is working with the country to develop corrective and preventative actions through an awareness campaign and by strengthening the technical capacity of the Bedrijf Geneesmiddelen Voorziening Suriname (BGVS) lab to analyze malaria medicines.

Purpose of Trip

The objectives of this trip were to:

- Provide a regional training in Paramaribo, Suriname on Good Laboratory Practices (GLPs), Good Documentation Practices (GDPs), and Compendial Analysis of Lumefantrine - Artemether Tablets using High Performance Liquid Chromatography (HPLC), Dissolution, Thin-Layer Chromatography (TLC), and Ultraviolet (UV) Spectroscopy
- Meet with the Ministry of Health (MoH) and PAHO to continue planning and developing the outreach/awareness campaign based on the findings of the malaria medicine quality study performed in 2009

Source of Funding

These activities were funded by the United States Agency for International Development/Peru (USAID/Peru) through AMI and by the U.S. Pharmacopeia (USP) through the Technical Assistance Program (TAP).

Overview of Activities

The training activities are summarized in the following table:

Item	Description
Specific Objectives/ Expected Outcomes	<ul style="list-style-type: none">• Perform HPLC assay, Dissolution, and TLC procedures according to pharmacopeial standards• Perform dissolution performance verification testing (PVT)• Evaluate the quality of antimalarial products using available public standards• Work in compliance with GLP guidelines
Venue/Location	<ul style="list-style-type: none">• Lectures: Suriname Ministry of Health, Paramaribo, Suriname• Lab Hands-on: BGVS Laboratory, Paramaribo, Suriname
Organizers	<ul style="list-style-type: none">• Promoting the Quality of Medicines Program• Suriname Ministry of Health

Sponsors	<ul style="list-style-type: none"> Promoting the Quality of Medicines Program United States Pharmacopeia Technical Assistance Program
Trainers and Facilitators	<ul style="list-style-type: none"> Lawrence Evans III, PQM Mark Liddell, USP Pati Gaitan, PQM
Trainees	<ul style="list-style-type: none"> Lecture (21 participants) Lab hands-on (10 participants) <p>See Participant List in <i>Annex 1</i> for detailed information</p>
Agenda	See Agenda in <i>Annex 2</i> for detailed information
Opening Ceremony	<ul style="list-style-type: none"> Dr. Malti Algoe of Suriname MOH Dr. Rachel Eersel of PAHO
Modules	<ul style="list-style-type: none"> GLP GDP HPLC (theory & hands-on) UV-Vis (theory & hands-on) Dissolution & PVT (theory & hands-on) TLC (theory & hands-on)
Closing Ceremony	<ul style="list-style-type: none"> Miriam Naarendorp of Suriname MRA Dr. Ingrid May of BGVS <p>Certificates were given to the participants</p>
Training Evaluation	See participant evaluations of each module in <i>Annex 3</i>
Outcomes/Conclusion	Participants indicated that the hands-on training was especially useful and that they would like to receive additional training

Training commentary

Prior to the training, the lab installed new cabinets, requiring the dissolution instrument to undergo and pass PVT prior to performing any analyses. After watching a demonstration on how to perform PVT, the trainees performed and passed PVT for apparatus 1 and 2.

The lab did not receive sodium 1-hexanesulfonate, a reagent required for the mobile phase in the HPLC assay procedure for artemether and lumefantrine tablets. An alternative medicine was analyzed using available reagents and USP reference standards in the lab. This deviation also allowed the PQM trainers to demonstrate how to qualify a secondary reference standard using a USP reference standard (primary standard).





Challenges were observed when dissolving the USP lumefantrine reference standard in the dissolution media containing benzalkonium chloride. Solid benzalkonium chloride, a highly hygroscopic reagent, was used to prepare the dissolution media. The humidity in this region increases water absorption, making it difficult to accurately weigh the required amount of the reagent. The PQM trainers recommended drying the reagent before use or procuring benzalkonium chloride in ethanol solution to alleviate this problem.

The training was initially developed following a request from the Guyana Food and Drug Department to demonstrate to their analysts how to analyze Coartem (the fixed-dosed

combination of artemether-lumefantrine used in that country) according to the compendial method. The scope of the training was later expanded to include Brazil and Suriname, where the fixed-dosed combination of artemether-lumefantrine is also the first-line treatment against *Plasmodium falciparum*. Unfortunately, the two analysts from Guyana were unable to attend the training due to procedural issues.



Additional Meetings

Debrief Meeting with Suriname Director of Health – Friday, April 27, 2012

Participants: Dr. Lawrence Evans III (PQM), Miriam Naarendorp (Suriname MRA), Sheila Kort (BGVS Lab), Dr. Wilfred Balraadjsing (BGVS), and Dr. Marthelise Eersel (Suriname MoH)

Summary of Discussion Topics

- 1) Ms. Naarendorp and Dr. Evans provided an update on the technical training provided to BGVS lab analysts during the visit.
- 2) Laboratory Equipment: The BGVS lab will purchase additional equipment for the lab, such as a UV-Vis spectrophotometer. PQM was informed that other essential lab equipment (balances, etc.) had been already ordered.
- 3) Staff Training: Additional technical assistance was requested to continue strengthening the lab for the analysis of medicines other than malaria.
- 4) Reference Standards supply: PQM will provide the MRA with the relevant TAP documents (“Request to Participate in USP TAP” and the TAP Factsheet).

Debrief Meeting with PAHO Suriname – Friday, April 27, 2012

Participants: Dr. Rachel Eersel (PAHO Suriname), Dr. Lawrence Evans III (PQM), Miriam Naarendorp (Suriname MRA), and Dr. Guillermo Troya (PAHO/WHO country Representative, Suriname)

Summary of Discussion Topics

- 1) Dr. Rachel Eersel, Ms. Naarendorp, and Dr. Evans briefed Dr. Troya on the training and provided an overview of the PAHO/PQM collaboration.
- 2) Awareness Campaign: Further discussions pertaining to the strategy for the awareness campaign were held. PAHO Suriname will take the lead in drafting a strategy
- 3) Dissemination of quality control results: Develop a communication strategy based on results/data from medicine quality study. The Suriname MoH will be responsible for implementing the strategy, and the next step will be to draft a project proposal. PAHO Suriname will take the lead and develop the first draft to be distributed for review and comment.

Next Steps

- PQM will provide recommendations to BGVS lab for the procurement of a new UV-Vis spectrophotometer. At the writing of this report, this activity was completed.
- PQM will follow-up with Suriname MRA regarding the status of their application to USP TAP by June 30, 2012.
- PAHO Suriname will develop a draft awareness strategy and distribute it to the Suriname MRA and PQM. At the writing of this report, this activity was completed.

Conclusion

The trip was very successful, with the training objectives met and the feedback from participants positive. The BGVS lab needs additional technical assistance in the area of quality management systems as well as in analytical techniques not covered in this training. The MOH and BGVS management are committed to sustaining the improved capacity of the lab. This is evident by their investments in new essential lab equipment and continuing education and training of staff.



List of Participants

Paramaribo, Suriname – April 16 – 27, 2012

		Name of Participant	Country
Lecture & Hands-on Laboratory	1	Chander Soerdjla	Suriname
	2	Sarda Soekhai-Ramsaroep	Suriname
	3	Maureen Djasiman	Suriname
	4	Eunike Kasanpawiro	Suriname
	5	Magda Samuel	Suriname
	6	Erskine Smith	Trinidad & Tobago
	7	Margarete Gomes Mendonca	Brazil
	8	Kamille Gibson	Belize
	9	Wilton McVoitte	Jamaica
	10	Ginny Saridjo	Suriname
Lecture Only	11	Miriam Naarendorp	Suriname
	12	Quincy Joemai	Suriname
	13	Alli Razia	Suriname
	14	Marlon Delchot	Suriname
	16	Ingrid May	Suriname
	17	Johanna Kartomenggolo	Suriname
	18	Wilfred Balraadjsing	Suriname
	19	Soekarina Ardjosentono	Suriname
	20	Sheila Kort	Suriname
	21	Malti Mangre	Suriname
	22	Rugia de Groot-Wijsman	Suriname

Training Agenda

April 16 – 27, 2012

DAY	AGENDA		
Monday, April 16, 2012	<ul style="list-style-type: none"> • Opening Session (9:00 – 9:30) <ul style="list-style-type: none"> ○ Opening Remarks & Introductions ○ Review agenda, training objectives and expected outcomes • Presentations: (9:30 – 5:00); lunch 12-1; break at 10:30 & 3 pm <ul style="list-style-type: none"> ○ Good Laboratory Practices ○ Good Documentation Practices ○ Practical HPLC and Pharmacopeial Gen. requirements 		
Tuesday, April 17, 2012	<ul style="list-style-type: none"> • Presentations: <ul style="list-style-type: none"> ○ Practical HPLC and Pharmacopeial Gen. requirements (continued) ○ Dissolution ○ UV ○ Performance Verification Testing (PVT) 		
Wednesday, April 18, 2012	<ul style="list-style-type: none"> • Hands-on: <ul style="list-style-type: none"> ○ Dissolution PVT <ol style="list-style-type: none"> 1. Set up tester 2. Perform Mechanical Calibration 3. Prepare and Deaerate Media 4. Perform PVT using Apparatus 2 5. PVT calculations 		
Thursday, April 19, 2012	<ul style="list-style-type: none"> • Hands-on: HPLC Assay and Dissolution: <ul style="list-style-type: none"> ○ Review of HPLC Assay Procedure in the Lumefantrine and Artemether Tablets Monograph ○ Review of the Dissolution of Lumefantrine Procedure in the Lumefantrine and Artemether Tablets Monograph <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top;"> Group 1 - HPLC Assay Lumefantrine and Artemether Tablets <ol style="list-style-type: none"> 1. Set-up system 2. Prepare mobile phase and standard solutions, and equilibrate column 3. Perform system suitability test 4. Prepare standard & sample solutions 5. Perform system suitability check 6. Perform sample assay 7. Perform calculations </td> <td style="width: 50%; vertical-align: top;"> Group 2 – Dissolution for Lumefantrine <ol style="list-style-type: none"> 1. Prepare media 2. Perform sample dissolution 3. Prepare standard solutions 4. Perform UV analysis of standards and samples 5. Perform calculations & discuss results </td> </tr> </table>	Group 1 - HPLC Assay Lumefantrine and Artemether Tablets <ol style="list-style-type: none"> 1. Set-up system 2. Prepare mobile phase and standard solutions, and equilibrate column 3. Perform system suitability test 4. Prepare standard & sample solutions 5. Perform system suitability check 6. Perform sample assay 7. Perform calculations 	Group 2 – Dissolution for Lumefantrine <ol style="list-style-type: none"> 1. Prepare media 2. Perform sample dissolution 3. Prepare standard solutions 4. Perform UV analysis of standards and samples 5. Perform calculations & discuss results
Group 1 - HPLC Assay Lumefantrine and Artemether Tablets <ol style="list-style-type: none"> 1. Set-up system 2. Prepare mobile phase and standard solutions, and equilibrate column 3. Perform system suitability test 4. Prepare standard & sample solutions 5. Perform system suitability check 6. Perform sample assay 7. Perform calculations 	Group 2 – Dissolution for Lumefantrine <ol style="list-style-type: none"> 1. Prepare media 2. Perform sample dissolution 3. Prepare standard solutions 4. Perform UV analysis of standards and samples 5. Perform calculations & discuss results 		

DAY	AGENDA	
DAY		
Friday, April 20, 2012	<ul style="list-style-type: none"> • Hands-on: HPLC Assay and Dissolution: 	
	<p>Group 1 - HPLC Assay Lumefantrine and Artemether Tablets</p> <ol style="list-style-type: none"> 1. Set-up system 2. Prepare mobile phase and standard solutions, and equilibrate column 3. Perform system suitability test 4. Prepare Standard & Sample solutions 5. Perform System suitability check 6. Perform sample assay 7. Perform Calculations 	<p>Group 2 – Dissolution for Lumefantrine</p> <ol style="list-style-type: none"> 1. Prepare Media 2. Perform sample dissolution 3. Prepare standard solutions 4. Perform UV analysis of standards and samples 5. Perform Calculations & discuss results
Groups Switch Training Activities		
Monday, April 23, 2012	<ul style="list-style-type: none"> • Hands-on: HPLC Assay and Dissolution: <ul style="list-style-type: none"> ○ Review of HPLC Assay Procedure in the Lumefantrine and Artemether Tablets Monograph ○ Review of the Dissolution of Lumefantrine Procedure in the Lumefantrine and Artemether Tablets Monograph 	
	<p>Group 1 – Dissolution for Lumefantrine</p> <ol style="list-style-type: none"> 1. Prepare media 2. Perform sample dissolution 3. Prepare standard solutions 4. Perform UV analysis of standards and samples 5. Perform Calculations & discuss results 	<p>Group 2 - HPLC Assay Lumefantrine and Artemether Tablets</p> <ol style="list-style-type: none"> 1. Set-up system 2. Prepare mobile phase and standard solutions, and equilibrate column 3. Perform system suitability test 4. Prepare Standard & Sample solutions 5. Perform System suitability check 6. Perform sample assay 7. Perform Calculations
Tuesday, April 24, 2012	<ul style="list-style-type: none"> • Hands-on: HPLC Assay and Dissolution: 	
	<p>Group 1 – Dissolution for Lumefantrine</p> <ol style="list-style-type: none"> 1. Prepare Media 2. Perform sample dissolution 3. Prepare standard solutions 4. Perform UV analysis of standards and samples 5. Perform Calculations & discuss results 	<p>Group 2 - HPLC Assay Lumefantrine and Artemether Tablets</p> <ol style="list-style-type: none"> 1. Set-up system 2. Prepare mobile phase and standard solutions, and equilibrate column 3. Perform system suitability test 4. Prepare Standard & Sample solutions 5. Perform System suitability check 6. Perform sample assay 7. Perform Calculations

DAY	AGENDA
Wednesday, April 25, 2012	<ul style="list-style-type: none"> • Discuss results and Q & A ▪ Presentations: <ul style="list-style-type: none"> ○ TLC
Thursday, April 26, 2012	<ul style="list-style-type: none"> ▪ Presentations: <ul style="list-style-type: none"> ○ Review of Related Compounds Test for Artemether procedure in the Lumefantrine and Artemether Tablets Monograph • Hands-on: TLC <ol style="list-style-type: none"> 1. Set-up TLC system 2. Prepare standard and test solutions 3. Perform TLC analysis of standards and samples 4. Perform Calculations 5. Discuss results
Friday, April 27, 2012	<ul style="list-style-type: none"> • Wrap-up Training and Complete Evaluations Forms • Closing Session

Participant Evaluations

Evaluation of Specific Aspects of the Training Workshop

TRAINING	EXTENT TO WHICH THE TRAINING MET YOUR OVERALL EXPECTATIONS			
	Exceeded Expectations	Met Expectations	Met Some Expectations	Unsatisfactory
Lectures				
Good laboratory/documentation practices	3	7		
Practical HPLC and Pharmacopeial General Requirements	3	7		
Dissolution and Performance Verification Testing	5	5		
UV Spectroscopy	2	8		
Thin Layer Chromatography	4	6		
Hands-on training				
HPLC	4	5	1	
Performance Verification Testing	7	3		
Dissolution	4	6		
Thin Layer Chromatography	6	4		

Overall Evaluation of the Training Workshop

	Strongly agree	Agree	Somewhat disagree
Course objectives were relevant to my needs	5	5	
The training material helped me understand and better organize my data	4	5	1
I was able to understand the content of the materials presented	5	5	
Overall, the course was useful and will help me do my job better	6	4	
There were enough practical exercises to facilitate understanding of the course	4	6	
The pacing of the various sessions was appropriate for my understanding of course materials	4	6	
The sequence in which the sessions were presented was appropriate for my understanding	4	6	
The instructors were knowledgeable on the subject	7	3	
The instructors allowed an appropriate level of participation	6	4	

Other Comments/Suggestions:

1. What did you like best about the course?
 - All of the practical hands-on (9)
2. What did you like least about the course?
 - Reagents were not available to do initial HPLC (1)
 - Fonts too small on some handouts (1)
3. What are your recommendations/suggestions for improvement of the course?
 - Provide training on more routine basis (4)
 - Make sure all reagents are at lab before training starts (2)