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Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda

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TABLE OF CONTENTS

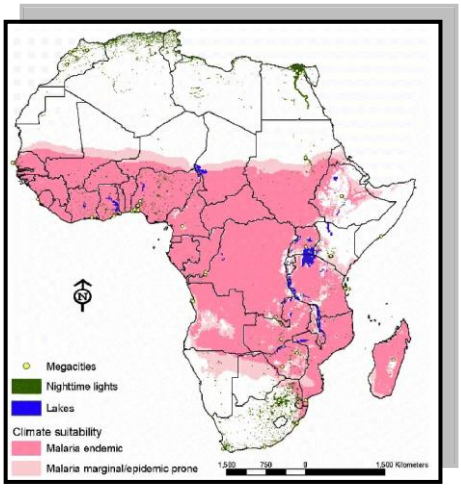
LIST OF ACRONYMS

ACT	Artemisinin-based Combination Therapy
DQI	Drug Quality and Information Program implemented by USP
FDC	Fixed-dose Combination
GPHF	Global Pharma Health Fund
IPTp	Intermittent preventive treatment in pregnancy
QAMSA	Quality of Antimalarials in Sub-Saharan Africa
QA	Quality Assurance
QC	Quality Control
SP	Sulfadoxine/Pyrimethamine fixed-dose combination
TLC	Thin-Layer Chromatography
USAID	United States Agency for International Development
USP	United States Pharmacopeia
USP-NF	United States Pharmacopeia-National Formulary
WHO	World Health Organization

SURVEY OF THE QUALITY OF SELECTED ANTIMALARIAL MEDICINES CIRCULATING IN MADAGASCAR, SENEGAL, AND UGANDA

EXECUTIVE SUMMARY

This report presents the first findings from a collaborative study by the World Health Organization and the Drug Quality and Information (DQI) Program, supported by the United States Agency for International Development (USAID) and implemented by the U.S. Pharmacopeia (USP), on the quality of key antimalarial medicines in Sub-Saharan African countries (QAMSA Study). The QAMSA Study stands out from other studies for several reasons: the large number of medicines sampled based on a field-tested protocol; the large number of samples that were submitted to full-scale confirmatory quality control (QC) testing; and the different levels of the distribution chain from which the samples were obtained. The QAMSA Study covers 10 countries in total; the findings in this subject report focus on the three countries for which DQI was responsible—Madagascar, Senegal, and Uganda.



Above: Map of endemic malaria from *The Intolerable Burden of Malaria: What's New, What's Needed*, © 2004 The American Society of Tropical Medicine and Hygiene. Below: Countries involved in QAMSA Study, Part 1

In total, 491 antimalarial samples were collected in these three countries. The samples included both artemisinin-based combination therapy (ACT) and sulfadoxine-pyrimethamine (SP) products. The samples were acquired from the public sector, the

regulated private sector, as well as from the informal market. Basic testing, using the Global Pharma Health Fund (GPHF) Minilab[1] kit, was performed on most collected samples, i.e., on 444/491 samples or 90.4%; no Minilab procedures existed for the remaining 47 samples, which underwent full-scale laboratory testing. In total, full-scale laboratory testing was performed on 197 samples at the United States Pharmacopeia Headquarters (Rockville, Maryland, USA).

The QAMSA Study reveals a high failure rate among sampled antimalarials in all three countries, based both on Minilab and full-compendial or quality control (QC) laboratory testing, with the latter method carrying the most weight. The basic Minilab tests—performed by the respective country partners—showed that approximately **43% of the samples from Senegal** did not meet the requirements for visual inspection, identification, drug content, or disintegration. The corresponding failure rates for **Uganda and Madagascar were 12% and 6%**, respectively.

The full quality control (QC) laboratory testing of 197 samples by USP provides a more complete evaluation of the quality of the antimalarials under study (focusing on the medicinal products, not including the packaging and labeling): approximately **44% of samples from Senegal failed** the QC tests; the corresponding failure rates for **Madagascar and Uganda were 30% and 26%**, respectively. Across the three countries, SP products were most likely to fail dissolution tests (35% of sampled SPs). Twenty percent (20%) of sampled ACTs also failed dissolution tests and 29% failed the impurity tests. The differences observed in overall failure rates between the basic Minilab testing and the full-scale QC laboratory testing are primarily due to the fact that the Minilab, as a screening tool, lacks the same capacity to identify dissolution and impurity test failures as full-scale QC laboratory testing. The information obtained through the QAMSA Study has now provided an evidence base for further fine-tuning the screening protocols for specific antimalarials in the context of postmarketing surveillance.

The picture of "failed" vs. "passed" QC laboratory tests for both ACT and SP products varied among the three countries. The failure rate of ACT samples, for example, was lowest in Madagascar (16%), while Uganda posted the lowest failure rate of SP samples (16%). In

[1] The Minilab® is a trademark-registered portable laboratory designed by the Global Pharma Health Foundation. It will be referred to as "Minilab" in this document.

Senegal, the failure rates of ACTs in the private and informal sector were almost comparable (5/9 or 56% samples from the informal sector failed; 7/16 or 44% samples failed in the private sector). In Uganda, all samples (11 total) taken from the public sector passed the quality tests. In all three countries, problem samples were found across the different regions in the country.

Significant differences were observed in the quality of ACTs across various brands. Some brands were consistently of good quality, while others were consistently substandard. The results also showed that, as a general rule, when a brand passed or failed in one country, it would also pass or fail in other countries. This indicates that the problem of quality is created at the source, in that case, rather than during passage through the distribution chain.

The Study did not look for evidence of counterfeiting. It is noteworthy that all the samples (ACTs and SPs) passed their respective identification test requirements and no products lacking the active ingredients were identified.

These findings present an opportunity for the countries to take targeted corrective actions, to continue to strengthen their quality assurance systems, and to close loopholes that may exist in their current regulatory framework.

I. INTRODUCTION

This report forms part of a collaborative study – Quality of Antimalarials in Sub-Saharan Africa (QAMSA) – by the World Health Organization (WHO) and the Drug Quality and Information (DQI) Program, which is supported by the U.S. Agency for International Development (USAID) and implemented by the United States Pharmacopeia (USP).

In 2007, WHO and the DQI Program agreed to undertake a survey to evaluate the quality of key antimalarials—i.e., artemisinin-based combination therapy (ACT) and sulfadoxine-pyrimethamine (SP) products—in ten countries in Sub-Saharan Africa: Cameroon, Ethiopia, Ghana, Kenya, Madagascar, Malawi, Nigeria, Senegal, Tanzania, and Uganda.

The main motivation for the Study was to update and expand the knowledge about the prevalence of substandard and counterfeit antimalarial medicines in Sub-Saharan Africa, which are believed to contribute to antimicrobial resistance of the *Plasmodium falciparum*, the most virulent form of malaria. *Plasmodium falciparum* is known to have already become resistant to traditional monotherapy medicines such as chloroquine and quinine and, more recently, sulfadoxine/pyrimethamine. As a result, many malaria-endemic countries in Africa have adopted artemisinin-based combination therapy (ACTs) as first-line treatment of uncomplicated malaria; SP products continue to be used for intermittent preventive treatment in pregnancy (IPTp). The sustainability of treatment success depends to a large extent on preventing *Plasmodium falciparum's* long exposure to sub-lethal doses of these medicines to minimize the possibility of the emergence of drug resistance. This requires promoting the rational use of these medicines as well as stringent quality control of the products, both of which can represent a formidable challenge in countries with weak regulatory systems.

The QAMSA Study adds to the existing knowledge base in two ways:

1) It provides information about the quality of ACTs currently used in Sub-Saharan countries; and,

2) It uses a unique two-step methodological approach, whereby a large number of samples are initially screened using the Minilab, followed by full-scale quality control analysis of a large sub-sample from each country.

A previous WHO study on the quality of antimalarials from selected African countries [5] had focused on chloroquine and SP products, similar to many other reports that have appeared in scientific literature. One report, published in 2007, reviewed 21 peer-reviewed articles and three reports on the quality of antimalarials in Africa [1]. All but one of the reviewed articles studied chloroquine, quinine, and SP products. Given that the recommended treatment for uncomplicated malaria in almost every national treatment policy in Sub-Saharan Africa is now ACTs, it was important to gather evidence about the quality of the ACTs currently used in Sub-Saharan Africa. The QAMSA Study was also intended to update information about the quality of SPs, which are recommended by WHO in combination with other interventions for IPTp.

The results in the reviewed articles were mostly based on simple qualitative color reaction tests, disintegration, and semi-quantitative thin-layer chromatography (TLC). These are effective screening tools but, in order to have any confidence in the data obtained with these tools, it is essential to confirm the quality attributes of identity, release rate, drug content, and purity with full-scale compendial (QC) testing. Even the more recent publications which do include ACTs [2], [3], [4] tend to be based on either semi-quantitative TLC and disintegration tests, without any confirmatory testing, or incomplete compendial testing. Without additional confirmatory tests, drug quality data obtained with basic analytical techniques can only be speculative. A few of the reviewed studies used high performance liquid chromatography (HPLC) analysis or ultraviolet-visible spectrophotometry to determine drug content, but none performed full-scale compendial analysis to confirm the drug quality data obtained, as in the context of the QAMSA Study.

This first report under the QAMSA Study covers data for samples collected from the three countries supported by the DQI Program: Madagascar, Senegal, and Uganda. A separate report, covering data from the seven countries supported by WHO, is expected to be issued at a later date by that organization.

Prior to publication of this report, each of the three countries involved received a full accounting of information on the quality of the sampled medicines in their respective supply chains that was gained in the course of this Study. It is hoped that the national regulatory authorities involved will use the information and evidence provided to undertake corrective actions where products have been found to be substandard.

II. METHODOLOGY

This section outlines the methodology followed in the course of the QAMSA Study. The full text of the Study protocol is attached in **Appendix I**.

The Study protocol was developed based on lessons learned from the previously-mentioned WHO study published in 1999 [5]. Joint meetings and trainings were organized to ensure the study protocol was uniformly applied in all participating countries:

- DQI and WHO met with the ten participating countries in Tanzania and discussed the implementation of the Study protocol [July 2007].
- Sampling strategies were discussed jointly with all participating countries to ensure national sampling plans were based on guidelines provided in the Study protocol [February 2008].
- Analysts were given hands-on training on Minilab basic tests [February 2008].

1. Sampling

The sampling plan involved sampling drugs at various levels of the distribution chain, in various parts of the countries, and from various outlets, with a focus on ACT and SP tablet products that were prescribed or purchased the most in each respective country. The countries were divided into geographic zones (regions) based on the prevalence of malaria and the national malaria control strategy. Samples were collected from both wholesale and retail outlets, in the regulated private and public sectors, as well as from the informal market (distribution sectors). A breakdown of the total samples collected for each country by product type, distribution sector, and region of sample collection, is shown in **Table 1** below. All samples were collected over the period of April–June 2008.

Table 1. Distribution of Antimalarial Products Collected for the QAMSA Study

Total Products	Product Type		Sector			Region*						
	SPs	ACTs	Informal	Private	Public	1	2	3	4	5	6	7
Madagascar												
120	40	80	30	57	33	67	34	19				
100%	33%	67%	25%	48%	27%	56%	28%	16%				
Uganda												
230	91	139	51	142	37	53	50	55	48	24		
100%	39%	61%	22%	62%	16%	23%	22%	24%	21%	10%		
Senegal												
141	61	80	38	61	42	49	12	15	3	14	18	30
100%	43%	57%	27%	43%	30%	35%	8%	11%	2%	10%	13%	21%

*Each country was separated into regions (sites) for sample collection purposes.

Madagascar: 1 = Analamanga; 2 = Atsinanana; 3 = Alaotra Mangoro
Uganda: 1 = Eastern; 2 = Northern; 3 = Southwestern; 4 = Western; 5 = Central
Senegal: 1 = Dakar; 2 = Kaolack; 3 = Kolda; 4 = Tambacounda; 5 = Ziguinchor; 6 = St. Louis; 7 = Diourbel & Touba

All collected samples were submitted to an initial screening using the Minilab kit. (For further detail on the analytical methods used, see Section 2 below.) A breakdown of the samples tested with Minilab is provided in **Table 2**. Of the total 491 samples collected, 47 samples did not have Minilab procedures (mainly dihydroartemisinin-piperaquine phosphate tablets and sulfamethoxypyrazine-pyrimethamine tablets). The 47 samples without Minilab procedures were tested at the confirmatory testing stage, except those that had already expired.

Subsequent testing using compendial procedures (QC laboratory testing), was performed on a sub-sample for each country from the total collected samples based on the following criteria:

- Samples of the product should have been collected in more than one country;
- Samples should not have expired;
- Number of dosage units collected for the sample should ideally be more than 40;
- Samples selected for each country should ideally cover all sectors (public, private, and informal) and represent all regions;

- Samples should have failed Minilab testing for disintegration or thin-layer chromatography (TLC);
- Samples should represent as many manufacturers as possible; and,
- Total number of samples submitted to compendial testing should amount to approximately one-third of the total sample (i.e., ± 50).

Table 2. Distribution of Antimalarial products Subjected to Minilab Testing

Total Products[#]	Product Type		Sector			Region*						
	SPs	ACTs	Informal	Private	Public	1	2	3	4	5	6	7
Madagascar												
118[a]	39	79	30	57	31	65	34	19				
100%	33%	67%	26%	48%	26%	55%	29%	16%				
Uganda												
190[b]	91	99	42	114	34	44	42	43	40	21		
100%	48%	52%	22%	60%	18%	23%	22%	23%	21%	11%		
Senegal												
136[c]	61	75	38	56	42	47	12	15	3	14	16	29
100%	45%	55%	28%	41%	31%	35%	9%	11%	2%	10%	12%	21%

[#] Collected products without Minilab procedures were not tested at this stage
[a] A total of 120 samples were collected for Madagascar, no Minilab procedures for 2 samples.
[b] A total of 230 samples were colleted for Uganda, no Minilab procedures for 40 samples.
[c] A total of 141 samples were collected for Senegal, no Minilab procedures for 5 samples .

Table 3 shows the sub-samples submitted for QC laboratory testing per country, as well as a breakdown of the samples by product type, distribution sector, region, and total number of brands (manufacturers). Additional details on the sub-samples, regarding the types of antimalarial medicines and manufacturer brands, are provided in **Table 4 and Table 5**.

The samples were stored under ambient conditions in the respective countries until the Minilab testing was completed. After that, all the samples were shipped for QC laboratory testing to USP Headquarters in the United States, where the samples were again stored under ambient conditions.

Table 3. Distribution of Antimalarial Products Selected for QC Laboratory Testing

Total # of Products	Product Type		Distribution Sector			Region*							Brands Tested	
	SPs	ACTs	Informal	Private	Public	1	2	3	4	5	6	7	SPs	ACTs
Madagascar														
53	21	32	12	30	11	30	14	9					10	7
100%	40%	60%	22%	57%	21%	57%	26%	17%						
Uganda														
82	43	39	22	49	11	16	21	18	14	13			17	8
100%	52%	48%	27%	60%	13%	19%	26%	22%	17%	16%				
Senegal														
62	27	35	19	31	12	21	8	7	1	4	7	14	9	10
100%	44%	56%	31%	50%	19%	34%	13%	11%	2%	6%	11%	23%		

*Each country was separated into regions (sites) for sample collection purposes.

Table 4. Antimalarial Medicines Selected for QC Laboratory Testing

Country	Product	Total	
		Number	Percentage[3]
Madagsacar	Amodiaquine and Artesunate Tablets (FDC)[1]	11	21%
	Amodiaquine Tablets + Artesunate Tablets (Co-packaged)	8	15%
	Lumefantrine and Artemether Tablets	12	22%
	Sulfadoxine and Pyrimethamine Tablets	20	38%
	Other Products[2]	2	4%
Uganda	Amodiaquine Tablets + Artesunate Tablets (Co-packaged)	8	10%
	Lumefantrine and Artemether Tablets	23	28%
	Sulfadoxine and Pyrimethamine Tablets	43	52%
	Other Products[2]	8	10%
Senegal	Amodiaquine and Artesunate Tablets (FDC)[1]	3	5%
	Amodiaquine Tablets + Artesunate Tablets (Co-packaged)	18	29%
	Lumefantrine and Artemether Tablets	7	11%
	Sulfadoxine and Pyrimethamine Tablets	26	42%
	Other Products[2]	8	13%
Total - All Countries	Amodiaquine and Artesunate Tablets (FDC)[1]	14	7%
	Amodiaquine Tablets + Artesunate Tablets (Co-packaged)	34	17%
	Lumefantrine and Artemether Tablets	42	21%
	Sulfadoxine and Pyrimethamine Tablets	89	45%
	Other Products[2]	18	9%

[1] FDC = Fixed dose combination

[2] These include Mefloquine Tablets + Artesunate Tablets; Dihydroartemisinin and Piperaquine Phosphate Tablets (FDC); Sulfamethoxypyrazine and Pyrimethamine Tablets (FDC)

[3] As percentage of total antimalarial drugs collected for the country

Table 5. Brands of Antimalarial Medicines Selected for QC Laboratory Testing

Product	Brands Tested		
	Madagascar	**Uganda**	**Senegal**
Amodiaquine and Artesunate Tablets (FDC)[1]	Coarsucam	--	Coarsucam
Amodiaquine Tablets + Artesunate Tablets (Co-packaged)	Amosunate, Arsuamoon, Falcimon	Duact, Larimal, Lumartem	Camoquin, Falcimon, Larimal
Lumefantrine and Artemether Tablets (FDC)	Artefan, Coartem	Artefan, Coartem, Lonart	Artefan, Coartem, Lufanter
Mefloquine Tablets + Artesunate Tablets (Co-packaged)	--	Artequin	Artequin
Dihydroartemisinin and Piperaquine Phosphate Tablets (FDC)	Duo-Cotecxin	Duo-Cotecxin	Duo-Cotecxin
Sulfamethoxypyrazine and Pyrimethamine Tablets (FDC) + Artesunate Tablets (Co-packaged)	--	--	Co-Arinate
Sulfadoxine and Pyrimethamine Tablets (FDC)	Combimal, Fansidar, Fastidar, Medodar, Paloxine, Paludamine, Paludar, Paludoxine, Sulfodoxine-Pyrimethamine	Agosidar, Amalar, Falcistat, Fansidar, Kamsidar, Laridox, L-Kelfin, Malagon, Malarest, Malostat, Malwin, Meldar, Neosidar, Nopyrin, Orodar, Rimodar, Stridar	Combimal, Doximine, Fansidar, Madar, Malastop, Maloxine, Melaxime, Sulfodoxine-Pyrimethamine
Sulfamethoxypyrazine and Pyrimethamine Tablets (FDC)	Malafin	--	Metakelfin

[1] FDC = Fixed dose combination

2. Analytical Methods

The quality of the collected samples was evaluated using a two-stage testing approach:

- Initial screening, using the Minilab's (1) semi-quantitative TLC procedure for identity and estimation of drug content, and (2) a basic disintegration test as a predictor of drug release rate.
- Confirmatory testing that used full-scale compendial analysis, including identification, drug release rate, assay, uniformity of dosage units, and impurity tests, in order to determine the quality.

A. Minilab Testing

Minilab (basic) testing was performed at the National Medicine Control Laboratory in Madagascar and Uganda, respectively, and at the University of Dakar Laboratory in Senegal. All samples (except for those without Minilab procedures) were analyzed using Minilab procedures [6], [7] for:

- Visual inspection of the dosage form and packaging, including labeling;
- Thin-layer chromatography (TLC) identification test;
- TLC estimation of drug content; and,
- Disintegration.

A detailed outline of the report generated for each sample tested with the Minilab can be found in *Annex 3* of the Protocol in **Appendix I**.

Dihydroartemisinin and piperaquine phosphate tablets and sulfamethoxypyrazine and pyrimethamine tablets did not have Minilab procedures, so samples of those medicines were not tested at this stage, but at the QC stage.

B. QC Laboratory Testing

The full-scale quality control testing, as mentioned, included identification, drug release rate, assay, uniformity of dosage units, and impurity tests to determine the quality.

The sub-samples selected for full-scale testing (**Table 3**) were tested in laboratories at USP Headquarters. During the QC laboratory testing, all failed tests were repeated to confirm their results. All the tests provided in the appropriate specification (analytical standard) were performed on each sample. However, if a sample is confirmed to have failed any of the requirements in the specification, additional testing was not done. Also, uniformity of dosage units was determined by weight variation in all cases and dissolution testing decisions were made at the S2 stage (that is, after two sets of six tablets failed the test).

Table 6. Source of Analytical Specifications Used for QC Laboratory Testing

Product	Source of Analytical Tests	Specified Tests
Amodiaquine and Artesunate Tablets (FDC)	i. The International Pharmacopeia 4th Edn., First Supplement (Artesunate) ii. USP32–NF27 First Supplement (Amodiaquine)	ID; UDU; Assay
Amodiaquine Tablets	USP32–NF27 First Supplement	ID; Dissolution[1]; UDU; Assay
Artesunate Tablets	The International Pharmacopeia 4th Edn., First Supplement	ID; UDU; Related substances; Assay
Lumefantrine and Artemether Tablets (FDC)	USP Non-U.S. monograph, Authorized version 1, posted date: Feb. 27, 2009	ID; Dissolution; UDU; Related compounds; Assay
Mefloquine Tablets	USP Non-U.S. monograph, Draft 1, posted date: Dec. 29, 2008	ID; Dissolution; UDU; Organic impurities; Assay
Dihydroartemisinin and Piperaquine Phosphate Tablets (FDC)	i. The International Pharmacopeia 4th Ed., First Supplement (Artenimol) ii. Piperaquine phosphate Assay procedure from literature[2]	ID; UDU; Assay
Sulfamethoxypyrazine and Pyrimethamine Tablets (FDC)	In-house specifications from manufacturer	ID; UDU; Assay
Sulfadoxine and Pyrimethamine Tablets (FDC)	USP32–NF27 First Supplement	ID; Dissolution; UDU; Assay

FDC = Fixed dose combination ID = Identification test UDU = Uniformity of dosage units, determined by weight variation
[1]Dissolution rate decisions were made at the S2 stage (that is, after two sets of six tablets failed the test).
[2]British Journal of Clinical Pharmacology 57:3 (2004), pages 253–262

The analytical standards or specifications used to evaluate the respective antimalarial medicine types are provided in **Table 6**. These consist of monographs from the *United States Pharmacopeia* and the *International Pharmacopeia*, an assay procedure taken from published literature, and an in-house specification from a manufacturer (the innovator).

3. Discussion: Pros and Cons of the Two-Stage Testing Approach

When the decision was taken to adopt a two-stage testing approach, it was understood that this would yield different failure rates for the respective phases. Concretely, it can be fully expected that the more stringent compendial tests can identify more substandard products compared to the visual inspection and Minilab screening procedures.

This is unavoidable because the capabilities of these two testing schemes (basic Minilab testing vs. QC laboratory testing) are not the same in terms of identifying poor quality drugs. The Minilab procedures use semi-quantitative TLC for estimation of drug content and identification, and disintegration tests to predict drug release rates. There are no impurity limit requirements using the Minilab screening procedure. Compendial tests, on the other hand, provide identification, drug release rates using dissolution tests, impurity limit tests, and assay acceptance criteria that are narrower than those required for passing the Minilab screening requirements.

In other words, basic Minilab testing is, by design, a screening tool. Minilab testing essentially identifies severe cases of poor quality; in the non-severe cases, Minilab testing data can, at best, indicate that the quality of a product is "doubtful," and such data necessarily needs to be confirmed by full QC laboratory testing, which provides a more complete evaluation of the quality of a drug product. [Note: A certain reasonable proportion of samples that passed Minilab testing, however, were confirmed in the QC laboratory testing].

The dilemma about whether to use a screening tool or compendial testing in order to document the extent of medicine quality problems in the supply chain is not new, and it is intrinsically

related to questions with regard to sample selection and sample size. A screening tool like the Minilab enables researchers to survey a larger sample of medicines in the supply chain, but it does not provide a "complete picture" of the quality of the sample. On the other hand, it is impractical to perform full compendial testing on all the collected samples.

Given the limitations of basic Minilab testing in providing a "complete" picture of the quality of the samples, on the one hand, and the impracticality of submitting all collected samples to QC laboratory testing, the sampling protocol needs to carefully outline sample selection and size.

In the case of the QAMSA Study, the criteria for the selection of samples for full-scale QC laboratory testing were determined to ensure that the sub-samples were representative of the total collected samples in each country. The selection criteria outlined in the "Sampling**"** section above ensure that there is a balance between ACTs and SPs; that proportions of samples from public, private, and informal sectors are maintained; and that proportions of samples from different sampling sites (regions) is generally preserved. The QC laboratory testing data is therefore expected to be a good reflection of the quality of the antimalarial medicine samples collected for this Study. One of the selection criteria—inclusion of all samples failing basic Minilab TLC and disintegration tests—would appear to bias the QC laboratory testing data, in that it appears to selectively choose samples that have a greater probability of failing the QC tests. However, of the 197 total samples selected for QC laboratory testing, only 17 samples were included based on this criterion, hence, any bias introduced by this selection criterion can be considered minimal[2]. It is noteworthy that the information obtained through the QAMSA Study has now provided an evidence base for further fine-tuning of screening protocols for specific antimalarials in the context of postmarketing surveillance.

[2] A total of 27 samples failed basic Minilab TLC and disintegration tests (detailed in Table 7), but only 17 of the 27 samples had not yet expired by the time they reached USP and had sufficient units for full QC laboratory testing.

III. RESULTS AND DISCUSSION

1. Minilab Test Results

The results of the Minilab testing of products sampled from Madagascar, Senegal, and Uganda is summarized in **Table 7.**

Approximately 43% of the samples from Senegal did not meet the requirements for visual inspection, identification, drug content, or disintegration. The corresponding failure rates for Uganda and Madagascar were 12% and 6%, respectively. Samples from Senegal had a significantly higher visual inspection failure rate (35%) compared to the 4% visual inspection failure rate each for Uganda and Madagascar. Most of the visual inspection failures were associated with missing important information in the packaging/labeling. Experience shows that visual inspection is generally a good indicator of intrinsic quality problems with the product.

The TLC and disintegration test results show less dramatic differences among countries. The data on failed TLC tests in **Table 7** reflect the samples that failed or gave inconclusive (doubtful) identification results and samples that failed drug content test. The TLC failure rate (identification and content combined) ranged from 2% (Madagascar) to 5% (Senegal) to 7% (Uganda).

Approximately 3% of the Senegal samples failed the basic Minilab disintegration test, but none of the samples from Madagascar or Uganda failed this test. The disintegration test is expected to be a predictor of the dissolution performance of the sample; hence, these results were an indication that some of the Senegal samples would likely not meet requirements for dissolution rate when tested at the full QC stage.

2. QC Laboratory Test Results

The results of the compendial testing (including assay, identification, dissolution, uniformity of dosage units, and purity tests) of products sampled from Madagascar, Senegal, and Uganda are summarized in **Table 8.**

Table 7. Results of the Minilab Testing of Antimalarial Products from Madagascar, Uganda, and Senegal

Total Products	Total Passed	Total Failed	Failed Test			Total Product Type		Failed by Product Type	
			TLC	Disintegration	Visual Inspection	SPs	ACTs	SPs	ACTs
Madagascar									
118 100%	111 94%	7 6%	2* 2%	0 0%	5 4%	39 33%	79 67%	4 10%[#]	3 4%[#]
Uganda									
190 100%	168 88%	22 12%	14[+] 7%	0 0%	8 4%	91 48%	99 52%	9 10%[#]	13 13%[#]
Senegal									
136 100%	78 57%	58 43%	7[+] 5%	4 3%	47 35%	61 45%	75 55%	15 25%[#]	43 57%[#]

* Failed TLC drug content
[+] Doubtful (inconclusive) TLC identification test results
[#] As percentage of total SPs or total ACTs tested

Table 8. Summary of the Results of the QC Laboratory Testing of Antimalarial Products from Madagascar, Uganda, and Senegal

				Identification		Dissolution			Impurity			Assay			UDU[#]		
		Pass[+]	Fail[+]	Pass	Fail	Pass	Fail	NT*	Pass	Fail	NT*	Pass	Fail	NT*	Pass	Fail	NT*
Madagascar N(53)	**ACTs N(32)**	27(84)	5(16)	32	0	16	1	15	16	4	12	30	2	0	30	0	2
	SPs N(21)	10(48)	11 (52)	21	0	9	11	1	--	--	--	10	0	11	9	0	12
Uganda N(82)	**ACTs N(39)**	25(64)	14(36)	39	0	15	6	18	20	12	7	39	0	0	37	0	2
	SPs N(43)	36(84)	7(16)	43	0	36	7	0	--	--	--	40	3	0	40	0	3
Senegal N(62)	**ACTs N(35)**	21(60)	14(40)	35	0	18	5	12	22	8	5	33	1	1	34	0	1
	SPs N(27)	14(52)	13(48)	27	0	13	13	1	--	--	--	27	0	0	21	1	5

[+] Percentages are provided in parenthesis
[#] UDU = Uniformity of dosage units
NT* - Number of samples not tested by a specific QC method. These are samples that had already failed another QC method, or samples that could not be tested due to an insufficient number of units.
-- There are no impurity test requirements in the SP monograph.

A. Overall Results

The percentages of the analyzed samples from each of the three countries that failed the QC laboratory testing are also provided in **Figure 1**. Approximately 26% of the antimalarial medicine samples from Uganda were found to be of poor quality; the corresponding percentages for samples from Madagascar and Senegal were 30% and 44%, respectively. The result is further detailed in terms of the failure rates for SP and ACT samples per country in **Figure 2**. The country data showed that the failure rate among ACT samples was significantly lower in Madagascar than in the other two countries (16% vs. 36% and 40%); the failure rate among SP samples was comparable between Madagascar and Senegal (52% and 48% respectively) and significantly higher than the failure rate in Uganda (16%).

Figure 1. Quality of Antimalarial Medicines Sampled from Madagascar, Uganda, and Senegal

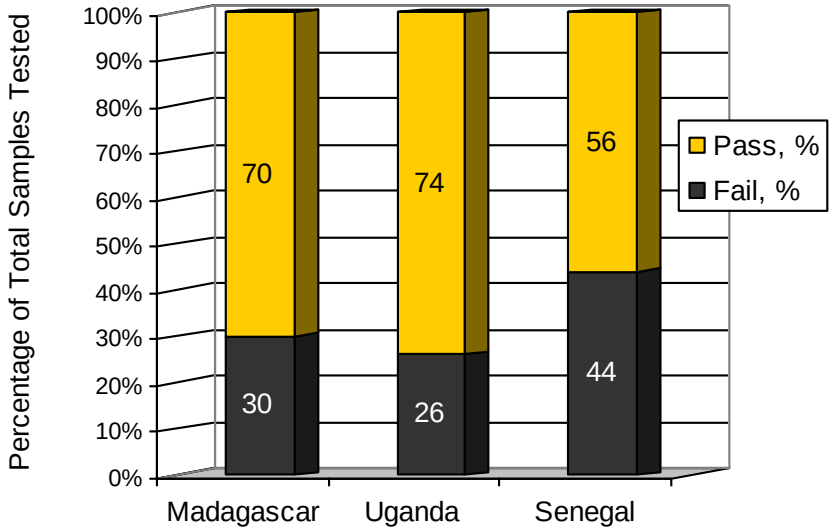
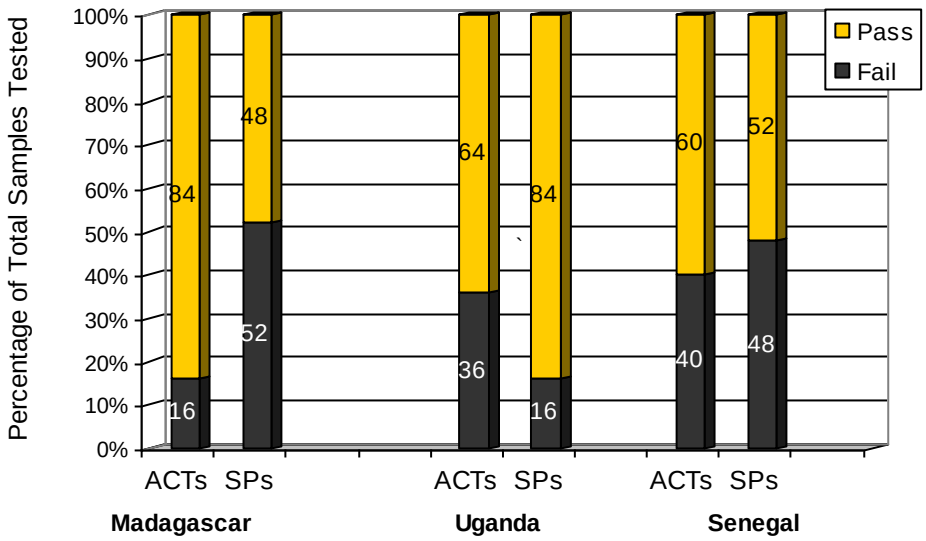


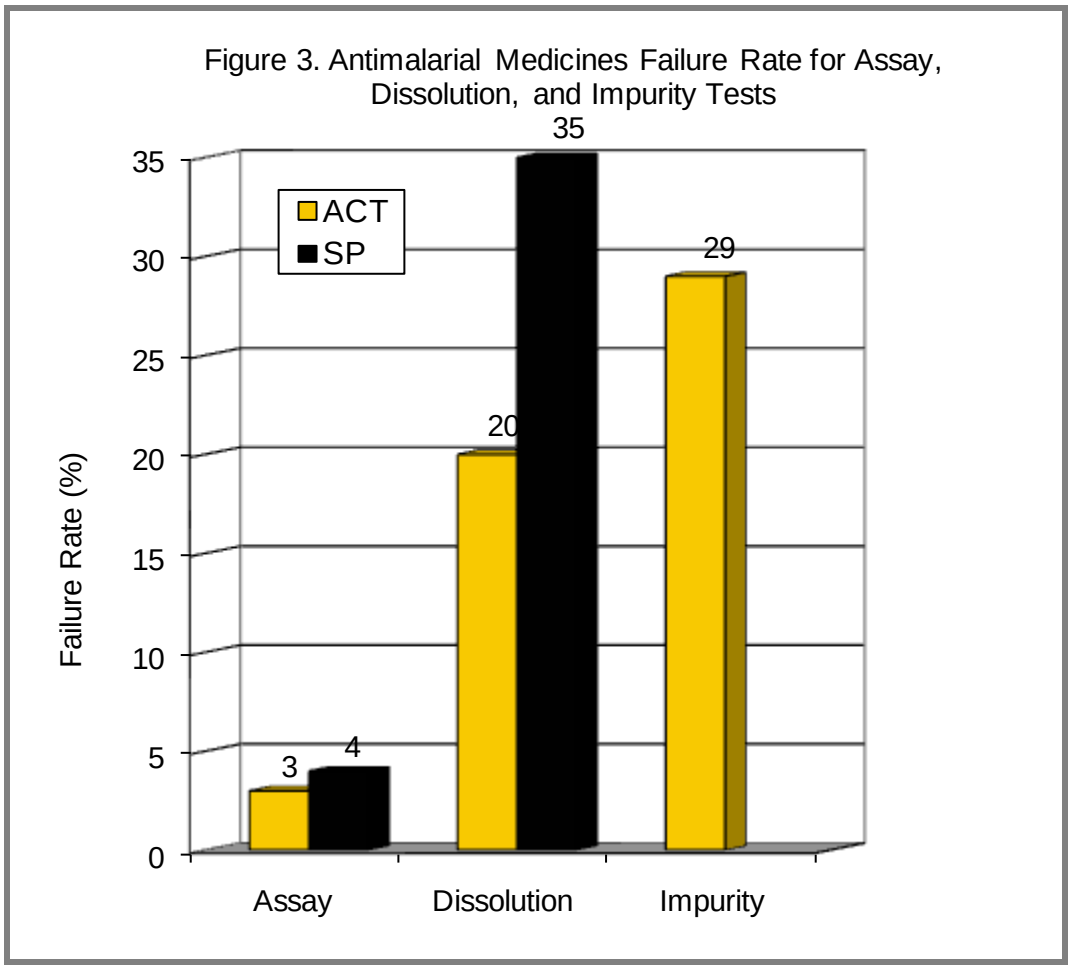
Figure 2. Quality of ACT and SP Antimalarial Medicines Sampled from Madagascar, Uganda, and Senegal



B. Results by Type of QC Test

All of the samples (ACTs and SPs) passed their respective identification test requirements and no products lacking active ingredient were identified. The basic Minilab tests also confirmed the identities of 100% of the samples collected from Madagascar. Approximately 5% and 7% of the samples collected from Senegal and Uganda, respectively, provided inconclusive (doubtful) identification test results (**Table 7**), but the identities of these samples were confirmed by the QC tests. Also, all of the samples passed the requirements of the uniformity of dosage units test, determined by weight variation. This indicates that drug content variation from tablet to tablet, for each sample tested, was within the acceptable limits.

Figure 3 illustrates the percentages of ACT and SP products that failed the other specific QC tests—assay, dissolution, and impurity. The figure indicates that SP samples were more likely to fail dissolution tests (35%) than ACTs (20%); on the other hand, approximately 29% of the ACT samples failed impurity tests. No impurity data are available for the SP products as there was no impurity test in the specifications that could have been used. The failure rates for assay were low and were similar for both the SP and ACT samples.



C. Results by Distribution Sectors and Geographical Regions

One of the main objectives of the Study was to compare the proportion of poor quality or counterfeit ACTs and SPs at different points in the regulated and informal distribution systems in the selected countries. For each of the three countries, the findings were plotted per sector (public, private, informal) and per geographic region for both ACTs and SPs. **Figure 4** and **Figure 5** represent the findings for Madagascar; **Figure 6** and **Figure 7** for Uganda; and, finally, **Figure 8** and **Figure 9** for Senegal.

Figure 4. Quality of Antimalarial Medicines Sampled from Different Distribution Sectors in Madagascar

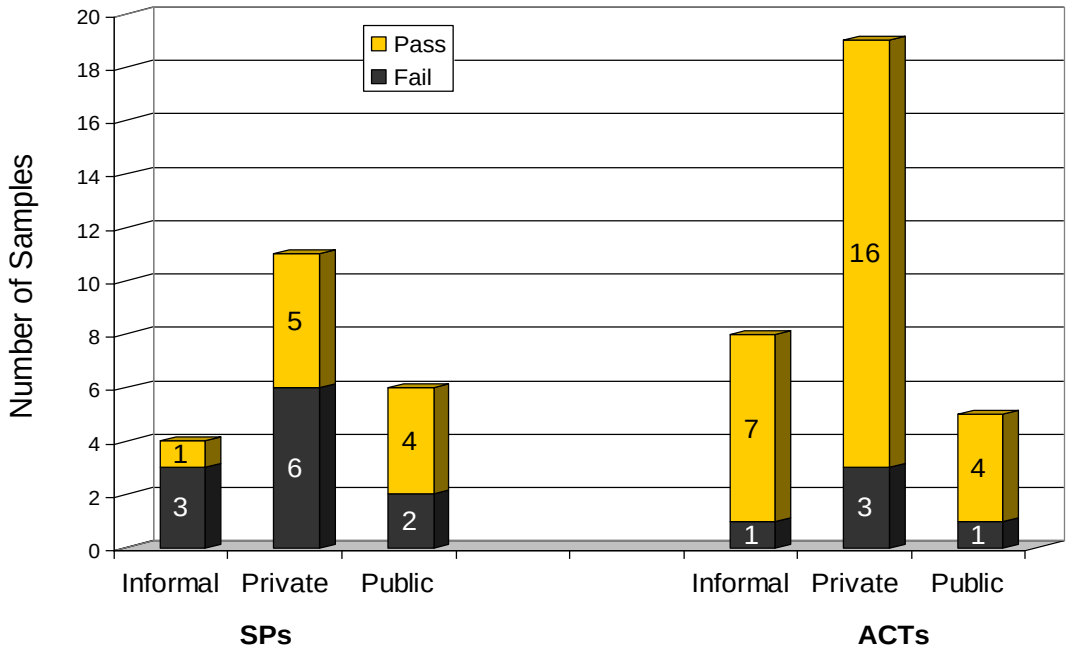


Figure 5. Quality of Antimalarial Medicines Sampled from Three Regions in Madagascar

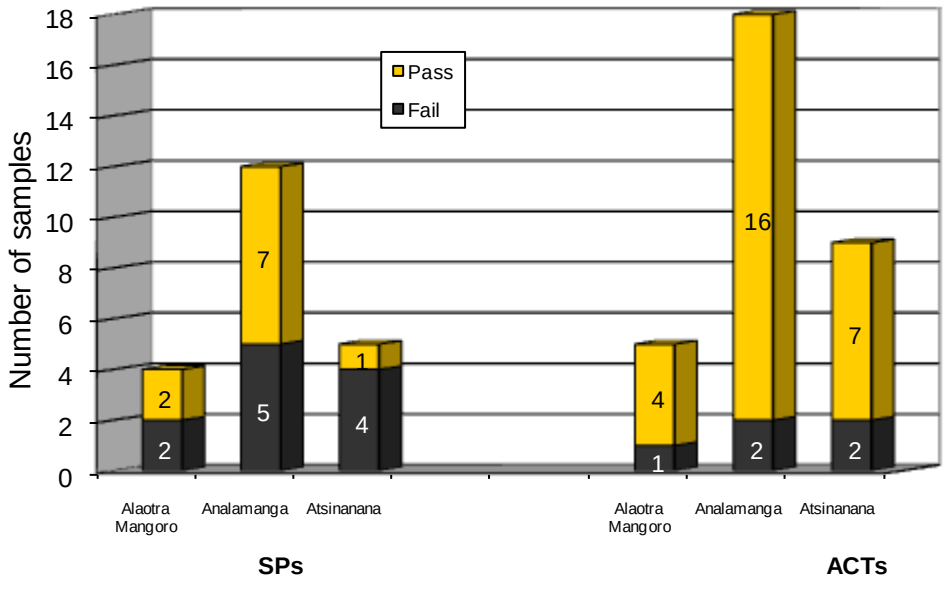


Figure 4 shows the proportion of poor quality SPs and ACTs in the samples collected from the informal, private, and public distribution sectors in Madagascar. The proportion of poor quality SPs and ACTs in the samples collected from three regions in Madagascar is also shown in **Figure 5**. The data shown in these figures seem to suggest that the issue of poor quality SPs and ACTs may be widespread in Madagascar and, most likely, is not limited to any particular distribution sector(s) or geographical region(s).

The Uganda samples reflected well on the public sector, where all ACT and SP samples passed the quality tests. In contrast, poor quality SPs and ACTs were found in the private sector as well as in the informal market (**Figure 6**). At the regional level, no poor quality SP was found among the samples from the Central and Eastern regions that were tested. Poor quality SPs, however, were found in the other three regions; poor quality ACTs were found in all five regions (**Figure 7**).

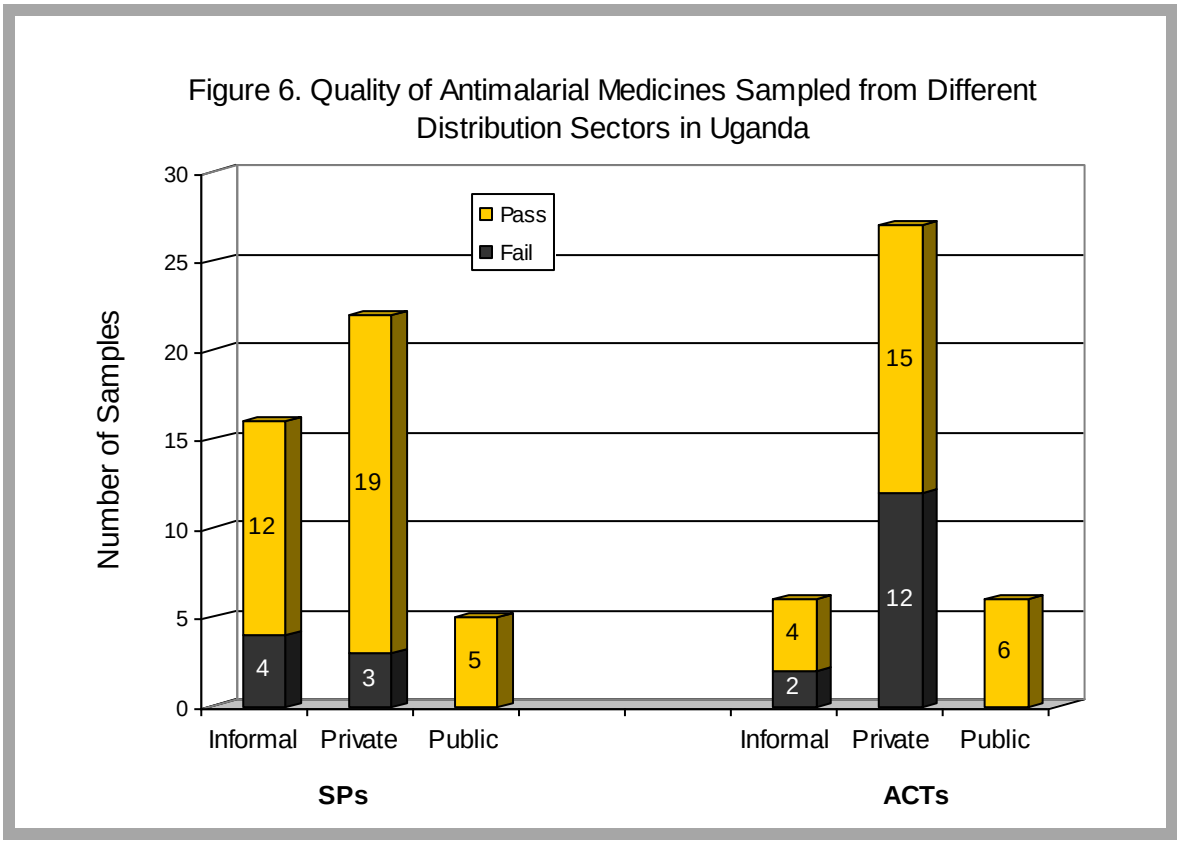
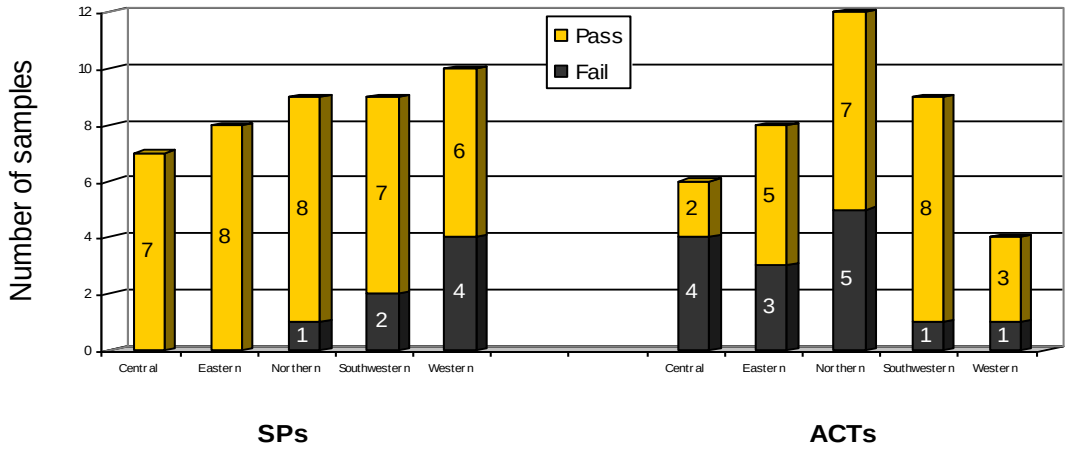
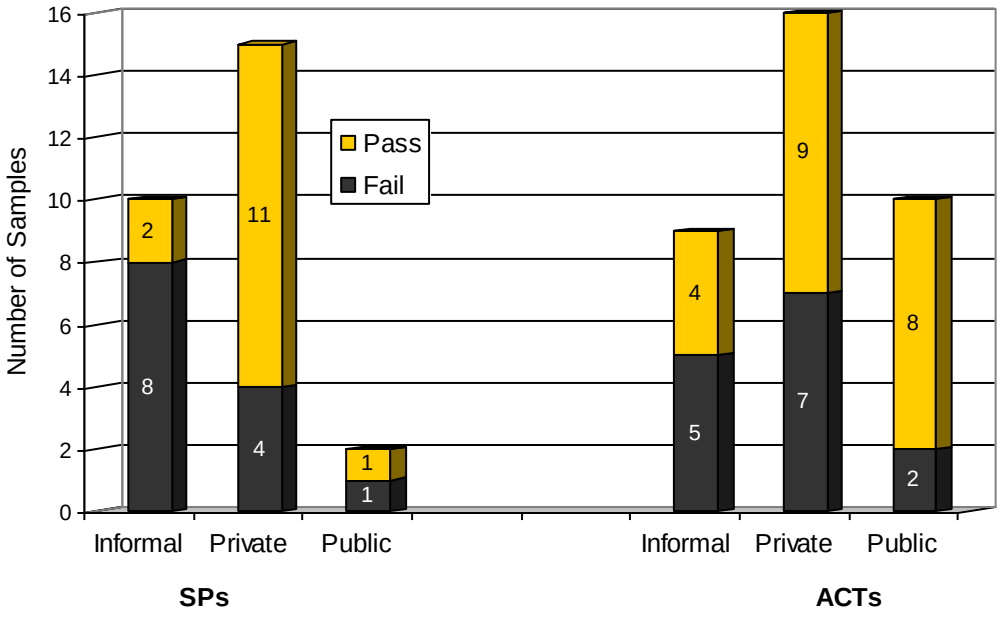


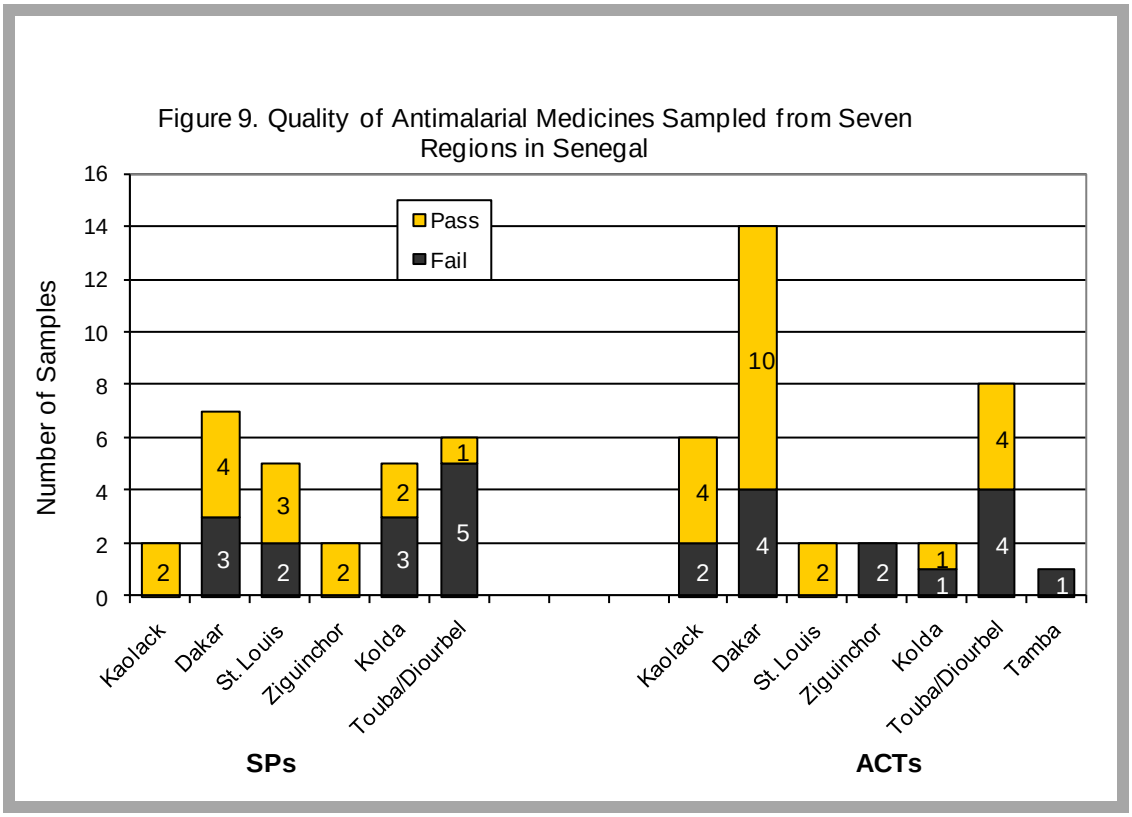
Figure 7. Quality of Antimalarial Medicines Sampled from Five Regions in Uganda



The Senegal samples suggest the presence of poor quality SPs and ACTs especially in both the private and the informal sector, throughout the geographical region(s) (**Figure 8** and **Figure 9**).

Figure 8. Quality of Antimalarial Medicines Sampled from Different Distribution Sectors in Senegal





D. Results by Brand

The QC laboratory testing data for individual brands of SPs and ACTs from each country were analyzed. **Figures 10A, 11A,** and **12A** present the data for SP samples from Madagascar, Uganda, and Senegal, respectively. **Figures 10B, 11B,** and **12B** provide the corresponding QC laboratory testing data for ACT brands.

Figure 10A. Quality of Manufacturer Brands of SP Tablets Sampled from Madagascar

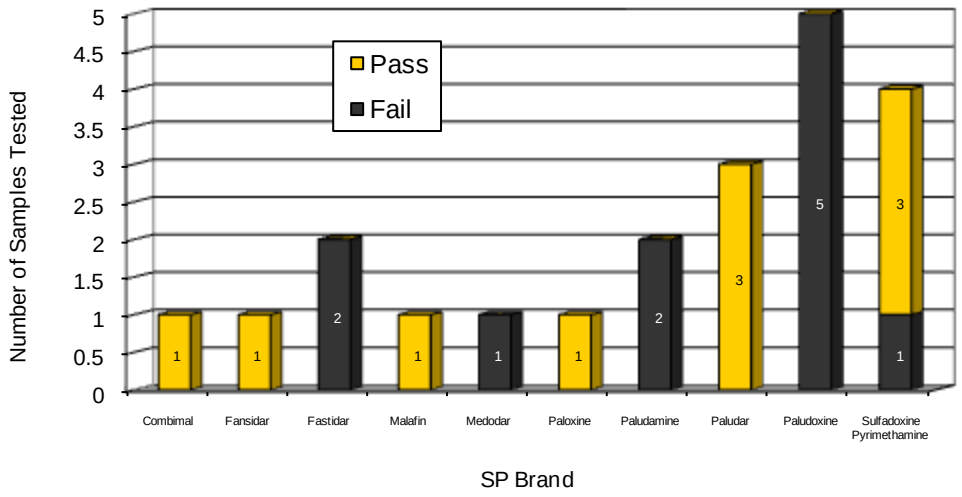
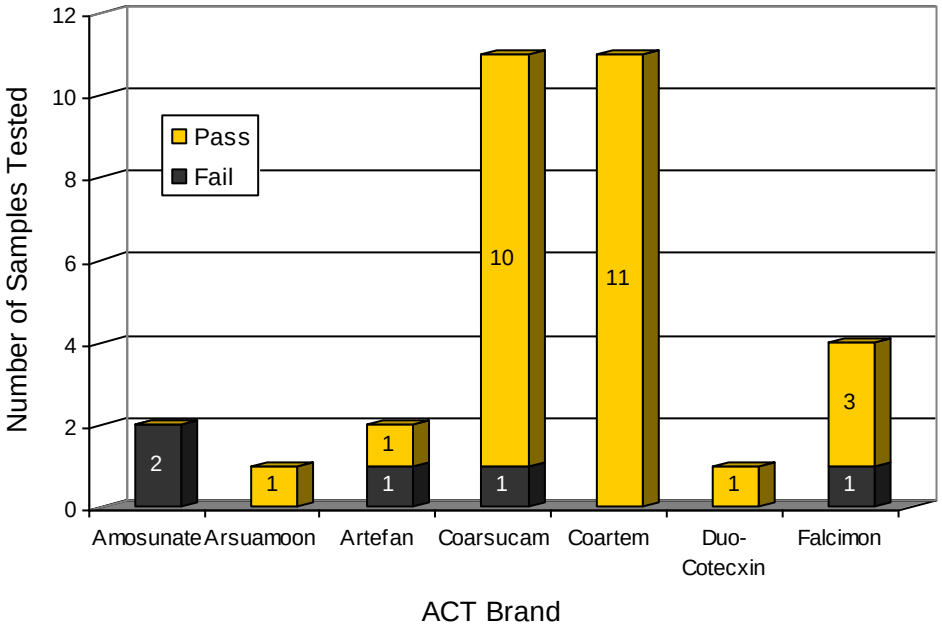


Figure 10B. Quality of Manufacturer Brands of ACT Tablets Sampled from Madagascar



For most of the SP products, the results indicate all the samples collected for any given brand either passed or failed the QC test requirements. Some brands were consistently of good quality, while others were consistently substandard. Examples include the *Melaxime* brand collected from Senegal (all eight samples tested failed), and the *Paludoxine* brand collected from Madagascar (all five samples tested failed). Another example is the *Malagon* brand sampled from Uganda for which 4 out of 5 samples tested failed. On the other hand, all 10 samples of the *Kamsidar* brand from Uganda passed the requirements. Furthermore, samples of the *Fansidar* brand were collected from all three countries, and every one of the tested *Fansidar* samples passed the required standards.

The results were similar for the ACT products, that is, samples of most of the brands either all passed or all failed the QC test requirements, with only a few exceptions. One example is the *Larimal* brand, sampled from both Uganda and Senegal. All six *Larimal* samples tested failed the QC test requirements. *Coartem* and *Duo-Cotecxin* brands, on the other hand, were found in all three countries, and all samples of these brands passed the testing requirements. Also, all samples of the *Lonart* brand sampled from Uganda passed the QC test requirements.

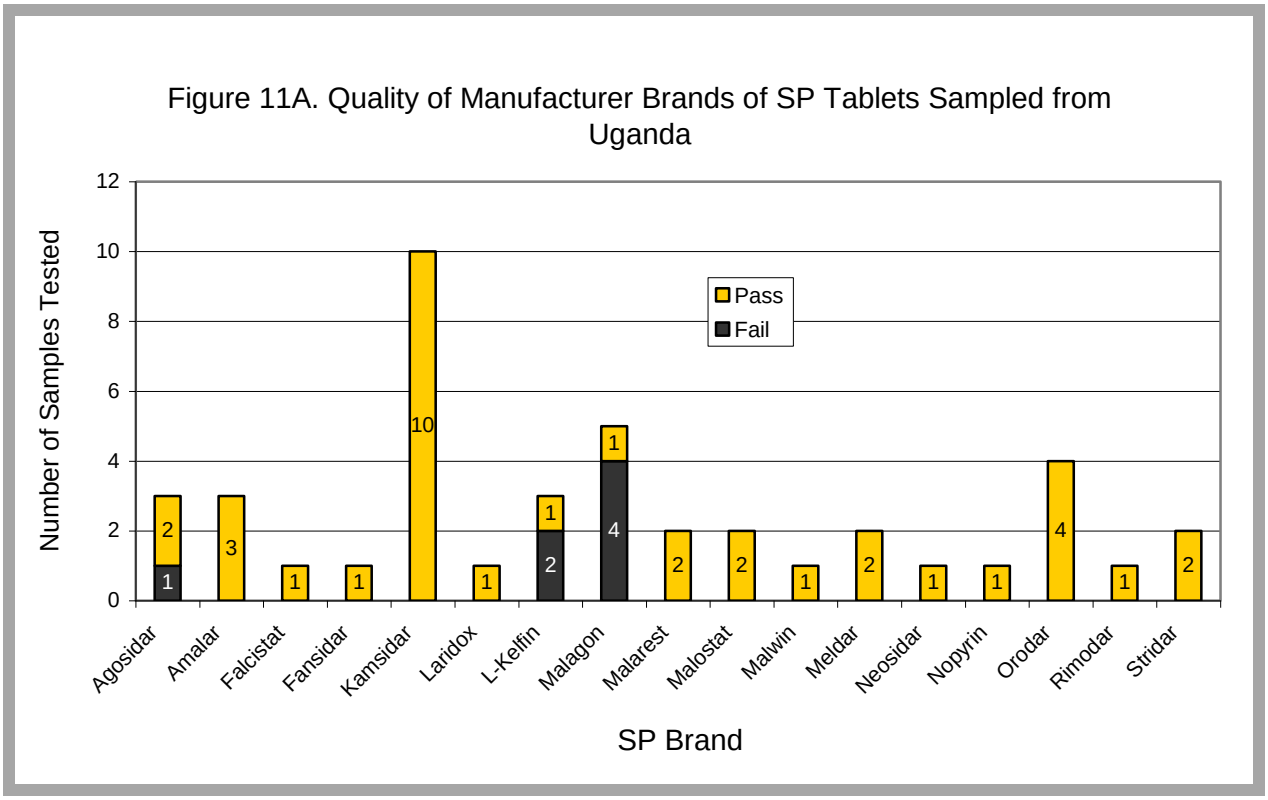


Figure 11B. Quality of Manufacturer Brands of ACT Tablets Sampled from Uganda

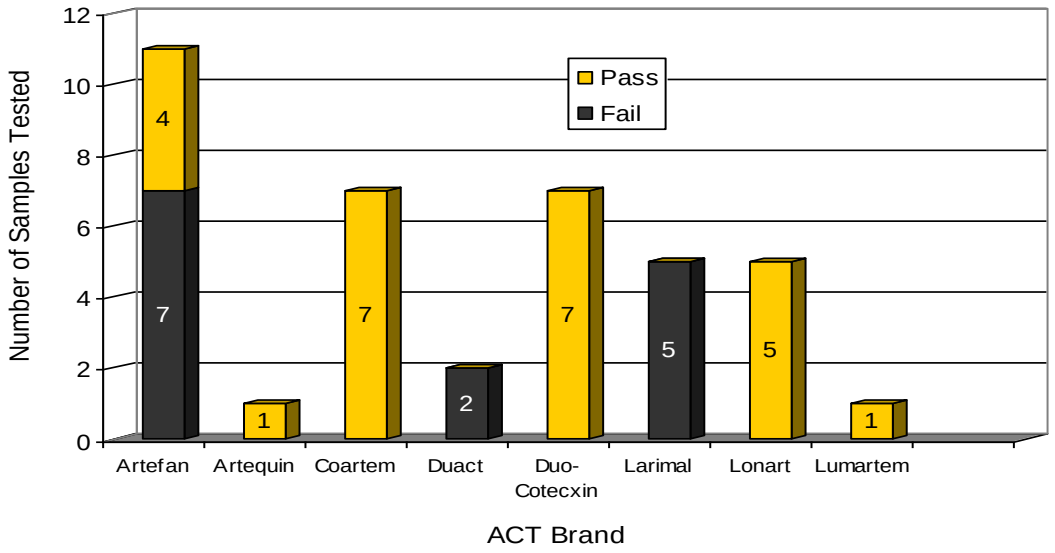
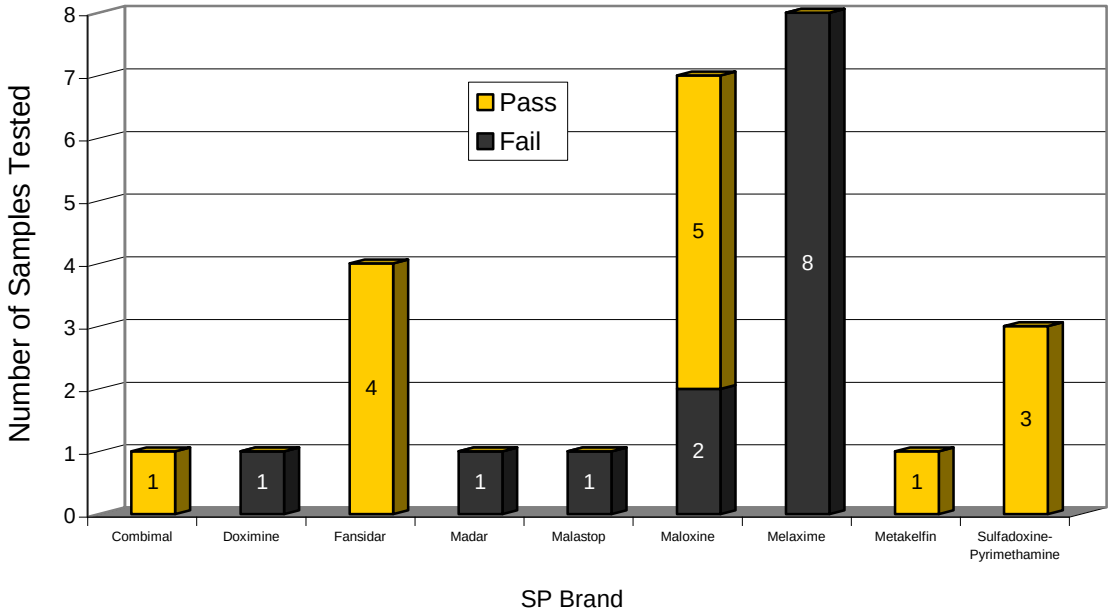
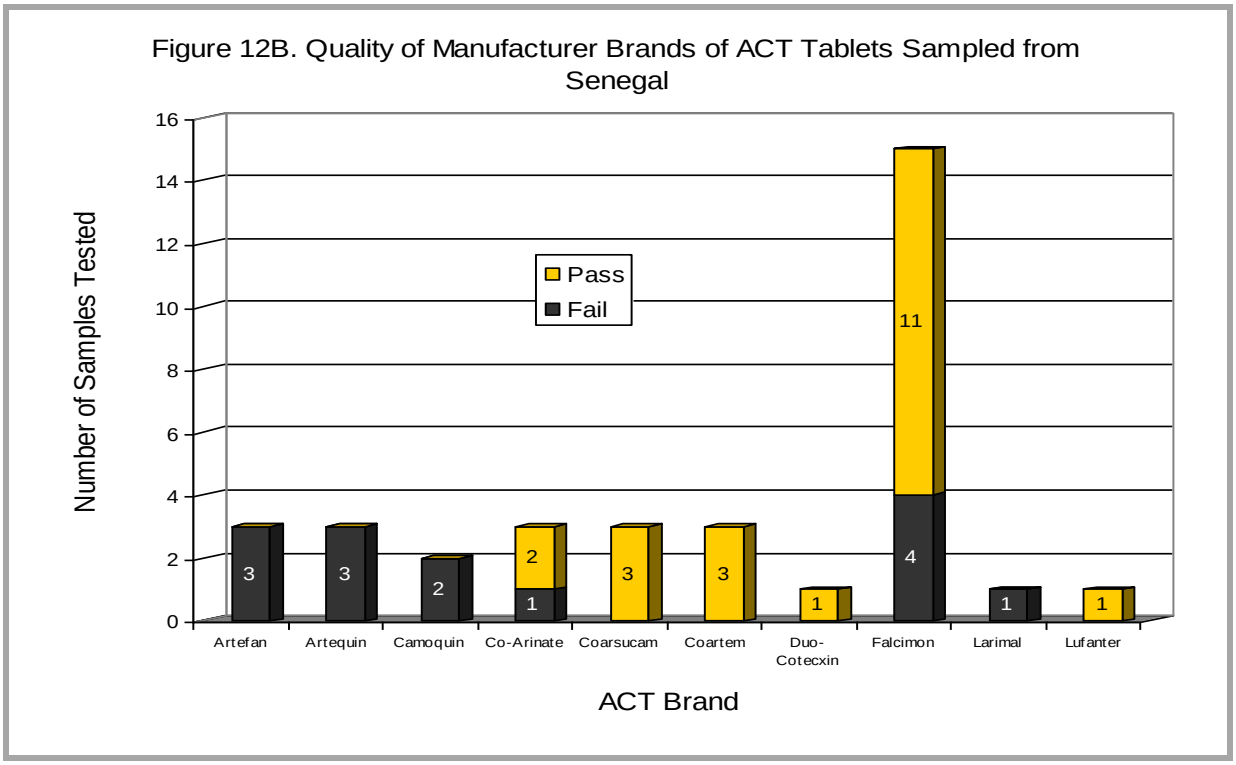


Figure 12A. Quality of Different Manufacturer Brands of SP Tablets Sampled from Senegal





E. Additional Significant Observations

There was no evidence to confirm counterfeits among any of the products tested, but issues like differences in the color intensity of packaging materials were observed in samples from the same brand but from different lots. In some of the brands, there was a direct correlation between sample-packaging color intensity and results of the dissolution test. In the case of the SP brand *Maloxine* from Senegal, samples packaged in darker blue boxes passed the dissolution test requirements, whereas samples with lighter blue packaging failed the dissolution test. For the SP brand *Melaxime,* also from Senegal, all samples failed the dissolution test, but samples packaged in darker green boxes had higher dissolution results than those in lighter green packaging.

A few of the SP samples from Uganda had small colored "spots" on the tablets (for example, the *Agosidar* and *Malarest* brands), but the samples passed the QC test requirements. One sample of the ACT brand, *Artefan,* had brown-colored spots on the tablets; that sample failed the QC test requirements.

This suggests that, at a very basic level, a careful visual inspection of the packaging and product can be useful in identifying products for further testing and confirmation of the product quality.

IV. PRELIMINARY CONCLUSION

Overall, the QAMSA Study in Senegal, Madagascar, and Uganda documented a sizeable proportion of sampled antimalarial medicines failing to meet quality tests: 44% of samples in Senegal failed to meet specific quality standards. The corresponding failure rates in Madagascar and Uganda were 30% and 26% respectively.

This Study also provides more specific data on which types of antimalarial are more or less problematic, as well as which brand, in which region, and in which sector. It is the firm hope of the authors of this report that the data provided will be used by the regulatory authorities in each country to determine where to focus attention in combating the availability of substandard medicines in the supply chain. Within this context, it is recommended that priority be given to the brands of antimalarials that failed quality standard tests irrespective of where they were collected, especially if the products are present in more than one country.

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Appendix 1

Study Protocol

SURVEY OF THE QUALITY OF SELECTED ANTIMALARIAL MEDICINES CIRCULATING IN SELECTED AFRICAN COUNTRIES

Version: Final 3

1. Introduction

WHO identified fighting malaria as a first priority for action. Antimalarial medicines are central to any strategy aimed at effectively reducing mortality caused by malaria. Quality, efficacy and safety of antimalarials are therefore essential and should be assured.

2. Objective/purpose

The present study aims to evaluate the quality of selected antimalarials in a defined number of African countries.

Specific objectives are:

1. To estimate the proportion[1] of Artemisinin-based combination therapy (ACT) products and Sulfadoxine pyrimethamine (SP) products meeting specific quality standards in the selected countries at different points of the regulated and informal distribution system;
2. To estimate the proportion of counterfeit ACT and SP products in the selected countries at different points of the regulated and informal distribution system;
3. To identify possible causes of the above findings; and,
4. To propose possible strategies and implementation plans to address the problems identified by the study.

3. Antimalarial products to be surveyed

This study aims at studying oral solid preparations of artemisinin-based combination therapy products (ACT) (co-packed and fixed dose combinations products) and products containing the combination Sulfadoxine-Pyrimethamine (SP).[2]

In the regular sector, sampling will be based on the products most sold and/or recommended by national guidelines. In the informal sector, the Focal Person for Sampling (FPS) will ask for the "best ACT and the best SP."

4. Main activities

- Collect and test samples of selected antimalarials from selected sites of the regulated private and public sector as well as from the informal market.
- Analyse findings and write a report describing overall results and country-specific results
- Identify the elements of a strategy aimed at addressing the problems identified by this study

[1] Proportion refers to the percentage of the total sample collected.
[2] Since policies on and use of specific products varies, a separate list of products to be included in the study will be drawn for each participating country.

5. Countries participating in the study

The first phase of the study will be carried out in **Cameroon, Ethiopia, Ghana, Kenya, Madagascar, Malawi, Nigeria, Senegal, Tanzania and Uganda.**

The second phase of the study will include **Angola, Guinea, Liberia, Mali, Mozambique and Sudan**.

6. Sampling

A defined amount of all branded and/or generic presentations (which means same product name, manufacturer, dosage form, package size, packaging material and strength) of selected ACTs and SP products available at each sample collection site will be collected.

Items collected for each presentation at the same collection site will be called a sample. All administration units (e.g., tablet, capsule) of one sample must be of the same batch or the same dispensing container in the case of loose items in the informal sector.

7. Items to sample and sample collection sites

- The selection of products and sites will be determined through a national plan. For this reason, malaria control program staff as well as staff from the drug registration authority and the national quality control lab should be involved in sampling selection from different sectors (public, private and informal).
- Sampling should be practical and feasible and reflect the reality of the geographical area. Sampling should also be balanced between budget availability for testing and for reaching all levels for drug distribution
- Selection should take in consideration the following criteria (for the template see Annex 1).

Steps to developing sampling strategy

Sampling level 1

7.1. Identify the **sources** of medicines in each participating country. Sources include: importers, central medical store, manufacturers, and NGO central stores. These categories are referred to as "sources" or "the highest level of the distribution system."

7.2. List sample collection sites for each source. Identify the **sources** that, in the concerned country, provide the medicines that will be sampled (see 7.7 below). Collect the samples from these sites.

Sampling level 2

7.3. Identify at least 3 study **regions** of high malaria prevalence on the basis of epidemiological information drawn from the national malaria strategy and other elements, as appropriate.

7.4. Within each region: **map** types of facilities for each level of the distribution chain (excluding the highest level identified above at point 7.1), e.g., wholesalers (both public

and private sector, including NGOs), regulated retailers (including all dispensing facilities) and informal sector.[3]

7.5. **List all facilities** at each level within this map in order to identify potential sample collection sites for each one of the distribution chain levels identified above.

7.6. For each level, **randomize** a number of sampling sites on the basis of the following criteria: a) take at least 3 sites for the higher levels within the region (public and private medical stores, wholesalers), b) ensure that there is a larger number of sites among those facilities of the distribution system that are closer to the point where patients obtain their medicines.

7.7. The purpose of this step is to identify the products that most patients use. **List all the products** on the market, or potentially on the market, that contain ACTs or SP and group them by INNs. Then, indicate the most-sold[4] ACT (by INNs) and the most-sold SP at the national level and, if doable, at the regional level in the regions identified above (see point 7.3).

7.8. **Allocate** the budget in a way that the largest number of samples is drawn from the lowest levels of the distribution system. The following breakdown can be used as guidance:

- **Level 1**
  - 5% each to most sold ACT (nationally, by INNs), recommended ACT (according to national guidelines) and most sold S/P (nationally) at the highest level of the distribution system (e.g., importer, central medical store, manufacturer, NGO central store).[5]
- **Level 2**
  - 20% to the most sold (according to region-specific information) ACT* (by INNs),
  - 20% to the recommended ACT (according to national guidelines),[6]
  - 20% to the most sold S/P,*
  - 25% to the informal market (buyers should ask for the "best medicine for malaria" as recommended by the seller). At least every attempt should be made to collect both ACTs and SP in the informal market. If an expired product is found, purchase one presentation and take notes after visual identification, in this case sample only one package to fill Annex 3. If other drugs are used instead of ACTs or SPs, take a note of the drug and ask why it is sold to treat malaria.**

*Remark: If the most-sold ACT (by INNs) and the most-sold SP are not available in a site, select a new site in replacement. If they also are not available in the new selected site, then sample the product available in this new selected site.
** Questions can address why it is sold (affordable, available, more known to the public, doesn't have side effects, others, etc.).

[3] The actual classification of levels will be decided at the national level on the basis of what is relevant in each country.
[4] Determine which ACT is "most sold" according to the best available information from central medical stores, importers, market studies, price surveys, or other sources. Countries may request WHO assistance in order to improve their capacity to produce or obtain the necessary information.
[5] If the most sold and the recommended are the same, 10% should be allocated to this ACT (by INNs).
[6] If the most sold and the recommended are the same, 40% should be allocated to this ACT (by INNs).

8. The focal person for sampling

In every country the Medicines Regulatory Authority (MRA) will communicate to WHO[7] the name and CV of a candidate to be designated as focal person for sampling (FPS). This candidate must have pharmacy background and, preferably, work as inspector. The FPS will, in collaboration with other national counterparts, as appropriate:

- Ensure the development of the national sampling plan as established at §7 and provide reasons of this choice (Annex 1).
- Supervise the implementation of the sampling strategy and the completion of sample collection.
- Complete or supervise the completion of Annexes 2 and 3 for each sample collected and ensure all the package leaflets are copied.
- Conduct or supervise testing with the Minilab.

During August 2007 a period of time will be identified when sampling will be carried out in all countries to enable the laboratory to test samples in series. **The common deadline for sending the last sample has to be adhered to.**

9. Sample collection techniques

- Ensure the use of sampling check list prior departure to the collecting site (see Annex 5)
- Whenever possible, the technique of "mystery client" shall be adopted to collect samples. This will be essential at informal market and private collection sites. Arrangements should be made to ensure replacement of samples collected in government and other facilities as appropriate.
- Practice key questions to be used at informal market in order to get to ACTs and SPs.

10. Number of units per sample

The number of units/sample at Level 1 will be 40. For Level 2 it is fixed at 30. Ideally for the informal sector the number of units/sample is fixed at 30, if it is not possible to find this amount in the informal sector consider sample until a limit of 5 units.

11. Additional precautions for sample collection

11.1. Every effort must be made to collect samples and send them for testing in the original package, including the package leaflet.

11.2. When the original package cannot be collected, the sample will be collected using ad hoc packaging provided by WHO.

11.3. For each sample collected the FPS will fill and sign the sample collection form (Annex 2) and insert samples and form in a dedicated envelope. This should be done after leaving the sampling site in order to avoid triggering unnecessary questions.

11.4. In order to avoid confusion each sample will be identified by a unique code number (A/B/C/D/E as indicated below) consisting of the name of the country, type of the product, sampling level, sampling date and a sequential number of the sample.
A: Country name - CM for Cameroon, ET for Ethiopia, GH for Ghana, KE for Kenya, MW for Malawi, MG for Madagascar, NG for Nigeria, SN for Senegal, TZ for Tanzania, and UG for Uganda

[7] Focal point: Dr Amor Toumi, toumia@who.int.

B. Type of the product - ACT or SP
C: Sampling level - 1 or 2
D: Sampling date DD-MM-YY
E: Sample sequential number - from 01 to 99.

11.5. When it is necessary to collect more than one original package in order to obtain the required number of units, all original packages will be marked with the appropriate sample code number.

11.6. Sample envelops should be labelled mentioning sample code number, INN and trade name of each product.

11.7. Packages which have been opened in order to collect units to be used for Minilab testing will be clearly indicated.

11.8. Package leaflets, where available, will be taken out of the original package, photocopied (or scanned) and reinserted in the original package. Photocopies (or electronic copies) will be marked with the appropriate sample code number and sent to WHO.[8]

12. Information collected

The following product details will be indicated for each sample collected. The details are important not only for writing the final reports but also to help differentiate one sample from another:

- Sample code number
- Product name (as applicable brand/trade name, generic name)
- Names of active ingredients
- List of excipients (when available)
- Dosage form
- Strength per administration unit
- Type and packaging material of primary container
- Package size (number of administration units per package)
- Batch number
- Manufacturing date
- Expiry date
- Name of manufacturer
- Country and address of manufacturing site
- Regulatory status in the country according to the national MRA, i.e. authorized for marketing, not-authorized for marketing, other status (if authorized, provide name of marketing authorization holder and number)

At the end of sampling the NFP informs WHO or USP. Validation of sampling will be organized in each country by WHO and/or USP.

13. Sample analysis

After validation of the sampling each sample collected will be first tested using GPHF-Minilab. In order to evaluate the compliance with the basic requirements on information accompanying products (on external and primary packaging, as well as in the package leaflet) the form in Annex 3 should be filled in. This form includes also report on the results of Minilab testing. All

[8] Focal point: Dr Amor Toumi, WHO/OMS, Avenue Appia, 1211 Geneva, Switzerland, toumia@who.int.

Minilab basic tests should be performed on collected samples, i.e., visual inspection, disintegration/ dissolution and TLC. Medicines that cannot be tested by Minilab will be tested by a method performed by USP DQI at phase I otherwise they will be tested in phase II.
The NFP will send the results and the filled Annex 3 to funding organization (WHO or USP). A meeting between the teams of these two organizations will examine the results and decide what samples have to be sent to the QC laboratory.

The selected samples for verification testing at a designated QC laboratory for 1) appearance, 2) identification, 3) dissolution or disintegration depending on the product, and, 4) assay for content of APIs. Testing will be based on either *International Pharmacopoeia 4th edition* (2006), *USP30-NF25, Pharmacopoeia of the People's Republic of China*, or validated analytical methods (in this order of preference).

Participating QC laboratories will establish communication and coordination in order to ensure comparability of results.

The Report on QC laboratory testing shall, in accordance with the Good Practices For National Pharmaceutical Control Laboratories,[9] contain the information listed in Annex 4.

14. Sample transportation and documentation for QC laboratory testing

Adequate care and measures have to be taken to ensure that samples reach the site where the tests are performed (both basic testing using the Minilab and QC lab) without any physical or chemical damage.

Appropriate care should be taken to provide adequate packaging to protect samples during transportation, e.g., by filling the container with cotton, foam, or other suitable material. All containers should be sealed and appropriately labeled.

14.1 Samples must follow the paths presented in paragraph 16.

14.2 All samples, envelops and documents are placed in a box with sufficient caution for travel and given to the WHO/NPO.

14.3 The WHO/NPO will verify that the boxes can travel without damage and send them to the designated control laboratory.

15. Payment for Samples

An invoice should be obtained for samples collected and immediate payment should be facilitated by the WHO representation in the country. An allotment number will be provided for all local costs associated with the sample collection, Minilab testing and transportation to designated QC laboratory.

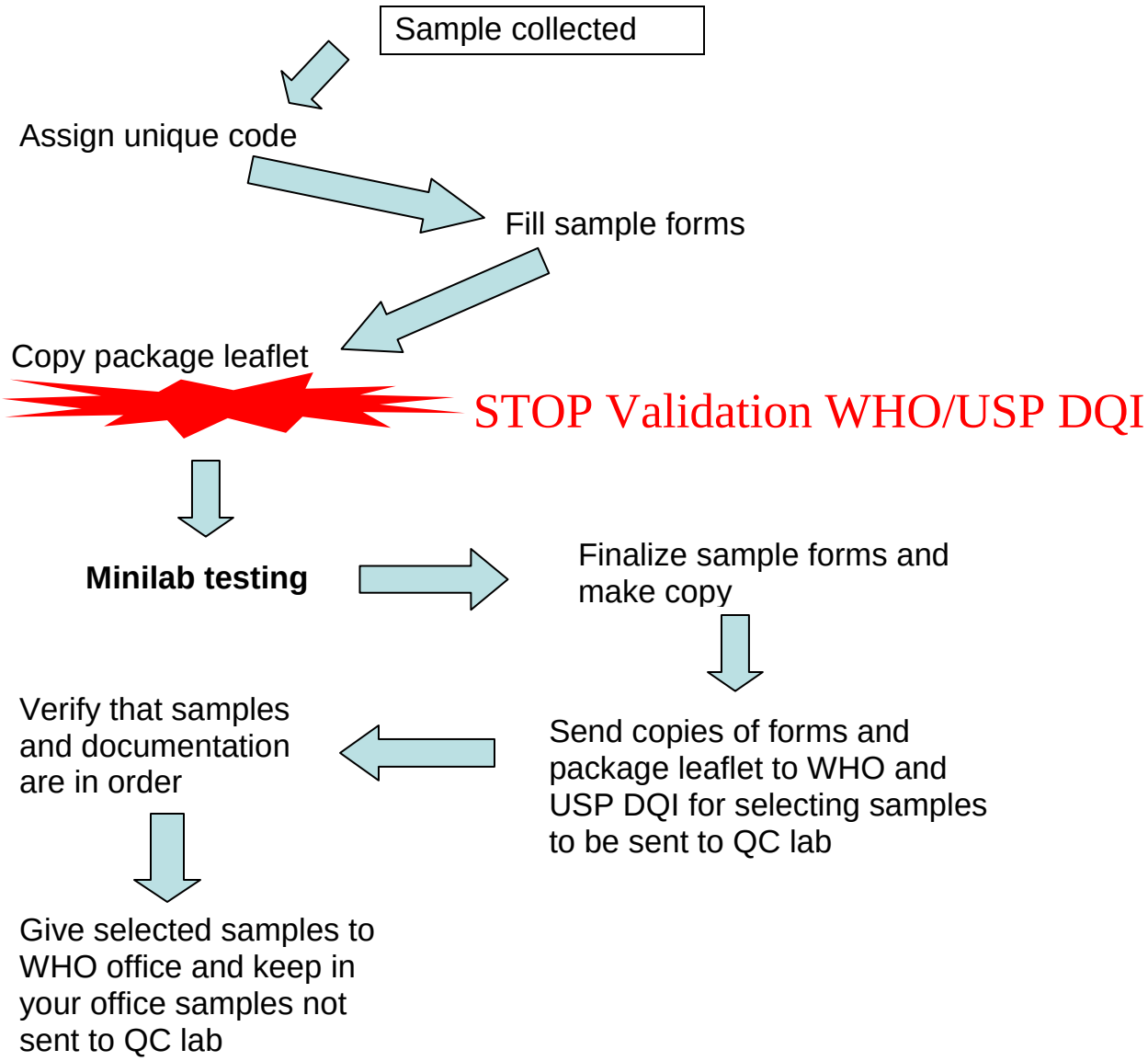
16. Handling and storing of samples

Samples collected are packed, transported, and stored in such a way to prevent any deterioration, contamination, or adulteration. Samples collected should be stored and transported in their

[9] World Health Organization. WHO Technical Report Series (TRS), No. 902 (2002). Annex 3: Good practices for national pharmaceutical control laboratories.
http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf#page=37

original sealed containers and in accordance with storage instructions for the respective product. Closures and labels should be tamper-evident, that is, of such a type that unauthorized opening can be detected. When it is necessary to open a sample container, the analyst or the person who opens it must re-seal, date, and initial the container, and complement the sample documents with a note explaining the reason for opening the container. Any product purchased without original container or when there is for any reason disclosure of the original container the sample must be stored in a plastic bottle. All information must be indicated on the new container and a note must be inserted.

The flowchart on the following page outlines the steps to be followed after sample collection. The flowchart needs to show the validation step by WHO and USP DQI between phase 1a and phase 1b. Also, reporting of the data of the Minilab should follow a template that will be prepared by USP DQI and sent to all participants.



Annex 1

National Sampling Plan

Country:

Focal person for sampling:

Products to be collected

ACTs *(oral solid preparations co-packed and/or fixed dose combinations)*	*International Non-proprietary Names*
Most-sold ACT	
ACT recommended by national guidelines	
Sulfadoxine-Pyrimethamine	*Product name and marketing authorization holder/manufacturer*
Most-sold SP	

Sample collection sites

Level 1 *(Highest level of distribution system, e.g., importers, central medical store, manufacturers, NGO central stores)*

Facility name, address, region	*Type of facility*	*Private/ Public*
1.		
2.		
3.		

Level 2 *(e.g., wholesalers, regulated retailers, dispensing facilities, informal sector)*

Facility name, address, region	*Type of facility*	*Private/ Public/ Informal*
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		

Reasons for this choice

Allocated budget	Level 1	Level 2	
		Regulated market	Informal market
(Most-sold ACT)	*(5%)*	*(20%)*	*(25%)*
(ACT recommended according to guidelines)	*(5%)*	*(20%)*	
(Most-sold SP)	*(5%)*	*(20%)*	

Date, name, and signature of the Focal Person for Sampling

Annex 2

QAMSA Study
Sample Collection Form

1. Country:_____

   Code given to the sample: _____

2. Name of survey site (e.g., region, city): _____

3. Price of the product_____

4. Name, type and address of collection site/point (please specify, if the site is private or public, as well as the type, e.g., Hospital, Clinic, Public dispensary, Wholesaler, Pharmacy, other retail outlet, NGO facility or Informal market. In cases of informal market, please describe:

_____

_____

_____

5. Commercial name of product: _____

6. INN names of active ingredients:

_____

7. List of excipients: _____

_____

_____

_____

8. Dosage form: *(e.g., tablet, capsule)*: _____

9. Strength per unit dose (*e.g., mg/tablet):* _____

10. Type and packaging material (primary container):
    (e.g., strips, PVC bottle)

_____

☐ taken in original package ☐ taken from bulk container

11. Quantity collected/per sample, with specification of the package size:

_____

_____

12. Batch number: _____

13. Manufacturing date: _____

14. Expiry date: _____

15. Name of manufacturer: _____

_____

16. Country and physical address of manufacturer:

_____

_____

_____

17. Regulatory status of the product in the country (on the basis of MRA records), i.e., registered, non-registered, and other; if registered, marketing authorization holder/ number:

_____

_____

_____

18. Any other comments, other than comments on the above-collected sample:
List drugs that are not ACTs or SPs but sold to treat Malaria and note why they are sold. Record the location and site where it was obtained, and ask why they are sold and why people request them.

_____

_____

_____

_____

Date of sample collection, name(s), and signature(s) of the person(s) who collected the samples and of the Focal Person for Sampling

_____

Note: ***Samples collected to be sent to the QC laboratory must be in their original containers, intact and unopened. Package leaflet(s) must be included. Packages that have been opened for Minilab testing will be clearly indicated and the sample should be contained in a plastic package as previously indicated.***

Annex 3

Compliance with the basic requirements for information accompanying the product and report on Minilab testing

Product name:_____

INN:_____

Code assigned to the sample (from Sample Collection Form):_____

1- External packaging	**Information present on the label**	
Product name	YES ☐	NO ☐
INN	YES ☐	NO ☐
Strength	YES ☐	NO ☐
Batch number	YES ☐	NO ☐
Expiry date	YES ☐	NO ☐
Manufacturer/Marketing authorization holder (MAH) - Name/address	……	
Storage conditions		

2- Primary packaging	**Information present on the label**	
Product name	YES ☐	NO ☐
Strength	YES ☐	NO ☐
Unit dose per blister or container stated	YES ☐	NO ☐
Batch number	YES ☐	NO ☐
Expiry date	YES ☐	NO ☐
Manufacturer/MAH name	YES ☐	NO ☐
(specify only if different from the external packaging)	……	
Inviolability system present	YES ☐	NO ☐

3- Package leaflet		
Presence of the leaflet	YES ☐	NO ☐
Language(s) of the leaflet		
Composition	YES ☐	NO ☐
Manufacturer/MAH name/address	YES ☐	NO ☐
	……	
(specify only if different from the external packaging)	……	
Storage conditions	YES ☐	NO ☐
(specify only if different from the external packaging)		

4- Observation on any discrepancies among points 1, 2, and 3 above or any non-compliance

_____

_____

_____

5- Report on Minilab testing:

PHYSICAL/VISUAL INSPECTION TEST		
Description of dosage form		
Shape (circular, oval, flat sides, other)		
Uniformity of shape		
Uniformity of color		
No physical damage (cracks, breaks, erosion, abrasion, sticky)		
Other observations (no foreign contaminant, dirty marks, proper seal (for capsule))		
DISINTEGRATION TEST		
Time of complete disintegration expected (30 minutes for uncoated tablet) ----------	Time, in minutes, of complete disintegration observed ----------	Did the drug pass disintegration test? ☐ Yes ☐ No
RESULT OF TLC TEST (see Appendix 2 for TLC results interpretation)		
Rf Standard (---): ---------- Rf Standard (---): ---------- Rf Standard (---): ---------- Rf Standard (---): ---------- Rf Sample (1): ---------- Rf Sample (2): ---------- Rf Sample (3): ---------- Rf Sample (4): ----------	Did the drug and the standard spots have the same intensity? ---------- Was there any contaminant spot on TLC? ----------	Did the sample pass quality by using the TLC Test? ☐ Yes ☐ No
FINAL COMMENTS ☐ The sample conformed to basic testing specifications. ☐ The sample was non-conforming to basic quality testing. (Reason:……..…….) ☐ The sample is doubtful for its basic quality testing (Reason:…….……..…….…….……)		

REPORT PREPARED BY: Date: …….... Name: ……..……. Signature: …….	REPORT REVIEWED BY: Date: …….. Name: …… Signature: ……..……
ACTION TO BE TAKEN BY THE PROVINCIAL FIELD DRUG TESTING FACILITY[10]	
Report the result to national disease program Date of report …….. Signature…….……	Send the remaining sample units together with this Form to the national lab for further testing Date …… Signature ……...……
Reasons given for the chosen action: ---------- ---------- ----------	

Date, name, and signature of the Focal Person for Sampling

[10] Action to be taken and communication between key agencies in the country should be dependent upon the country's rules and regulations.

Annex 4

Content of the Report on QC Laboratory Testing

The Report on QC Laboratory Testing shall, in accordance with the Good Practices For National Pharmaceutical Control Laboratories provide the following information:

1. Name and address of the QC laboratory performing the sample testing;
2. Number/code of the Report on QC Laboratory Testing;
3. Name and address of the originator of the request for testing;
4. Code given to the sample (from Sample Collection Form);
5. Date on which the sample was received;
6. Name of the country from which the sample was collected;
7. Sample product name, dosage form, active ingredient(s), strength, package size, type and packaging material of primary container;
8. Description of the sample;
9. Batch number of the sample, expiry date, and manufacturing date, if available;
10. Name and address of the manufacturer;
11. Reference to the specifications used for testing the sample, including the limits;
12. Results of all the tests performed, or the numerical results of all the tests performed (if applicable);
13. Conclusion as to whether or not the sample was found to be within the limits of the specifications used;
14. Date on which the test was performed; and,
15. Signature of the head of the laboratory or authorized person.