MINISTRY OF PUBLIC HEALTH AND SANITATION
& MINISTRY OF MEDICAL SERVICES

DIVISION OF MALARIA CONTROL & PHARMACY AND POISONS BOARD

Monitoring the Quality of Antimalarial Medicines Circulating in Kenya

November 2011

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LIST OF ACRONYMS

ACT	Artemisinin - based Combination Therapy
DOMC	Division of Malaria Control
DQI	Drug Quality and Information Program implemented by USP
FDC	Fixed - Dose Combination
GFATM	Global Fund to Fight AIDS Tuberculosis and Malaria
GPHF	Global Pharma Health Fund
HCSM	Health Commodities and Services Management program
IPTp	Intermittent Preventive Treatment in pregnancy
MSH	Management Sciences for Health
MQM	Medicines Quality Monitoring
NQCL	National Quality Control Laboratory
PMI	President's Malaria Initiative
PQM	Promoting the Quality of Medicines
PPB	Pharmacy and Poisons Board
QAMSA	Quality of Antimalarials in Sub-Saharan Africa
QA	Quality Assurance
QC	Quality Control
SP	Sulfadoxine - Pyrimethamine 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

EXECUTIVE SUMMARY

Good quality medicine is a pre requisite to prompt and effective treatment, the main objective of case management according to the current national malaria strategy. This first round of the monitoring of the quality of antimalarials was carried out in April and May 2010 in five sentinel sites representing areas with the highest malaria burden.

In total, 536 antimalarial samples were collected from the five sentinel sites according to the endemicity of Malaria. The samples included artemisinin-based combination therapy (ACT) and sulfadoxine-Pyrimethamine (SPs) among other antimalarials. The samples were collected from the public sector, the private sector and the informal sector.

Basic testing, using the Global Pharma Health Fund (GPHF) Minilab kit, was performed on most collected samples at the sentinel sites. This was followed by confirmatory analysis of 10% of the samples that passed minilab analysis, all doubtful samples and all failed samples at the National Quality Control Laboratory (NQCL) using the Minilab. The samples which failed were then subjected to full scale quality control laboratory testing using compendial methods at the same laboratory.

Of the 536 samples collected, all were assessed for registration status with PPB, 519 were analyzed using minilabs at level 1, 80 at level 2 and 44 using compendial methods in NQCL. The study findings indicate that 94% of the samples collected were registered, 92% conformed at level one, 76% conformed at level two and 84% conformed to compendial methods (level three).

CHAPTER ONE:
INTRODUCTION

1.1 Malaria in Kenya

Malaria continues to be one of the major public health problems in Africa, Asia and Latin America. ***Plasmodium falciparum*** malaria is estimated to be the direct cause of 500 million cases and over 1 million deaths per year, mostly in women and children under the age of 5 years (Guerra, Gikandi, & Tatem, 2008). In Kenya, malaria is responsible for 30 per cent of outpatient consultations, 19 per cent of hospital admissions and 3–5 per cent of inpatient deaths. Seventy per cent of Kenya's population lives in malarious areas. (Ministry of Public Health and Sanitation, 2009). It is for this reason that the government has prioritised the prevention and treatment of malaria in Kenya.

In collaboration with partners, the Division of Malaria Control (DOMC) developed an 8-year Kenya National Malaria Strategy (KNMS) 2009-2017 which was launched on 4th November 2009 (Ministry of Public Health and Sanitation, 2009). The goal on the National Malaria Strategy is to reduce morbidity and mortality associated with malaria by 30% by 2009 and to maintain it as such by 2017.

Prior to 2009, the country was stratified into 4 main malaria eco-epidemiological zones: endemic, seasonal transmission, epidemic-prone and low risk zones. A malaria indicator survey by DOMC in 2007 showed that there are variations in malaria parasite prevalence across the eco-epidemiological zones of the country among children under 5 years of age: 17 per cent in endemic areas, 1.4 per cent in areas of seasonal malaria transmission (arid and semiarid lowlands), 1 per cent in epidemic prone areas, and 0.4 per cent in low risk transmission areas. Increasing evidence shows that the epidemiology and risk of malaria in Kenya are declining. A comparison of previous malaria maps and recently updated maps on malaria prevalence shows the shrinking of malaria endemic areas and expansion of low transmission zones. It is estimated that 60-70 per cent of the Kenyan land mass has a parasite prevalence of less than 5 per cent where 78 per cent of the population of Kenya lives. On the other hand, there is also a decline in the level of malaria prevalence in endemic areas characterised by a reversal in the age group with the highest prevalence among children less than five years old and those between 5-15 years of age.

In 2009, a model-based map of the intensity of ***P. falciparum*** transmission in Kenya as defined by the proportion of infected children aged 2-9 years in the community was produced (Abdisalan, 2009). Based on the malaria risk map and the eco-epidemiology of malaria in Kenya, districts have been stratified into 4:

- Lake stable endemic & Coast seasonal stable endemic (risk class equal to or above 20 per cent);
- Highland epidemic-prone districts (risk class 5- <20 per cent);
- Seasonal low transmission including arid and Semi arid districts (risk class less than 5 per cent);
- Low risk districts (risk class less than 0.1 per cent).

1.2 The Quality of Antimalarials

Various studies have been undertaken on the quality of medicines in Kenya. These continue to inform current and future initiatives towards a comprehensive post – marketing surveillance (PMS) system. Some of the studies are highlighted below:

a) A nationwide study of antimalarials by the Pharmacy and Poisons Board in collaboration with DOMC in May 2006, found that a wide range of antimalarials existed in the market, and the majority were not in the national malaria treatment guidelines; that a large proportion (42.6%) of antimalarial medicines were not registered, and that some antimalarial medicines found in the market did not meet quality standards.The survey enabled an innovative approach to the regulation of medicines for priority conditions, with the regulator and disease control programme working collaboratively to address an issue of public health importance (Ministry of Health, 2007).

b) During 2009, NASCOP and DLTLD undertook similar studies on quality of ARVs and TB medicines respectively. The studies were modeled along the 2007 AM survey, with modifications and adaptations to suit the context of ARVs and TB medicines. The results of both studies are being finalized, and are expected to inform further strategies for post-market surveillance of HIV and TB medicines.

c) PPB and DOMC also participated collaboratively in a multi-country study on quality of antimalarials in Africa (QAMSA) in 2008. Results from the study showed that 96% of the 44 samples collected from Kenya fully conformed to quality specifications. Only two of 24 ACT samples tested failed (both on limit tests for presence of impurities), and all SP samples were found compliant (WHO, 2010).

d) Concerning ARVs, a WHO multi-country study undertaken in 2005 did not demonstrate any failures of ARVs sampled from Kenya, which comprised both imported and locally produced ARVs. A recent follow up study is yet to be published.

CHAPTER TWO:
MAIN OBJECTIVE OF THE PROGRAM

The primary objective of the program in general is to monitor the safety of medicines and conformity with established specifications for quality as declared in the registration dossier or recognized pharmacopeia specifications. It will provide regular information on the quality of medicines circulating in the country.

2.1 Specific Objectives

The specific objectives of the program include the following:

- To determine the proportion of unregistered products in the selected sites
- To determine the proportion of medicines in the selected sites that conform to quality standards
- To develop a medicine information database on the quality of medicines in circulation for trend analysis
- Disseminate information on the quality of medicines to stakeholders involved in medicines procurement, use, and regulation
- Promote communication and cooperation between stakeholders involved in medicines procurement, use, and regulation
- Provide evidence-based data for enforcement actions
- Propose possible strategies and implementation plans to address the problems identified in the study

CHAPTER THREE:
METHODOLOGY

3.1 Sampling Strategy and Training

The sampling strategy involved convenience sampling from the various levels in the distribution chain including public (KEMSA, public health facilities e.g health centers), non-governmental organizations (NGOs), faith-based organizations (such as Mission for Essential Essential Drug Supplies (MEDS), private for-profits (pharmacies), hospitals (private and public), and illicit (informal) markets. Samples were collected using "mystery shoppers" in the private sector to simulate the real life situation on how patients access medicines to avoid alerting traders who might have hidden products. For the purpose of the malaria control program, samples were collected from five sentinel sites defined in the sample site selection section. This strategy ensured that samples were obtained from all sectors where patients are likely to be exposed to medicines. The training for round 1 was facilitated by PQM with support from DOMC, PPB and NQCL.

3.2 Site Selection

For the purpose of the Division of Malarial Control, five sites were identified in collaboration with PPB, NQCL, and PQM for sample collection based on epidemiological data demonstrating prevalence of the disease, medicines availability and accessibility, medicines circulating freely originating from border towns, ports of entry, and availability of human resources. The sites where sampling was done were as follows

Figure 1: *Sentinel sites for post market surveillance*

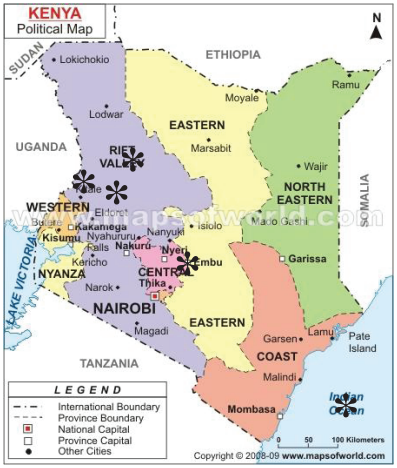
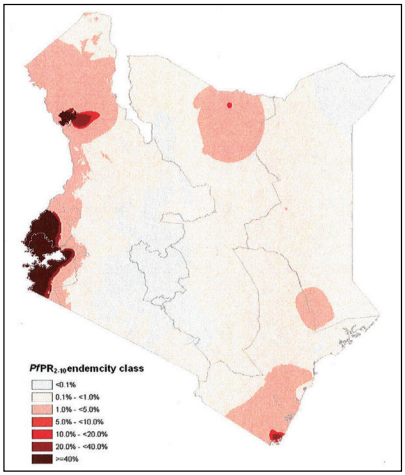


Figure 2: *Malaria endemicity map*



SENTINEL SITES: *Kisumu (Nyanza), Kakamega (Western), Eldoret (Rift valley), Mombasa (Coast), Nairobi (capital city)*

Samples were collected from importers, wholesalers, Non-Governmental Organizations (NGOs), central stores, regulated retailers, hospitals, private sources, and informal markets.

3.3 Medicines Selected for Sampling

The antimalarial medicines selected for sampling were based on the DOMC's national treatment guidelines and the availability of monographs for analysis. They include first-line treatment, second-line treatment, intermittent preventive treatment (IPT) for malaria in pregnant women, chemoprophylaxis, and treatment for severe malaria.

- **First-line treatment**
  - Artemether Lumefantrine (AL)
- **Second-line treatment**
  - Dihydroartemesinin & Piperaquine (DHAP)
- **Severe malaria**
  - Parenteral quinine
  - Oral quinine
  - Artemether/Artesunate injection
  - Rectal Artesunate
- **Intermittent Preventive Treatment (IPT)**
  - Sulphadoxine & Pyrimethamine (SP)
- **Chemoprophylaxis**
  - Doxycycline
  - Atovaquone/proguanil
- **Other ACTs**
  - Artesunate Amodiaquine
- **Monotherapies**
  - Monotherapies were only collected but not tested for purposes of monitoring the shift from monotherapies to ACTs and to evaluate their availability in the market.

3.4 Sample Definition

For the purpose of this study, a sample was defined as a medicine with a given API, dosage form, strength, and lot number from a given level in the distribution chain. Samples with the same attributes above and including the same lot number were only collected if they were from a different level in the distribution chain, such as wholesaler versus retailer, etc. The same lots were not collected from similar or same level institutions (for example, two pharmacies or retailers).

3.5 Number of Units to Collect per Sample

The number of units collected per sample was determined by the types of conclusions which can be drawn regarding product quality. Refer to table below.

The following example of sample collection applied to solid dosage forms (tablets and capsules) only. Sampling of oral suspension, injectables, or other dosage forms was discussed in consultation with PQM.

Table 1: ***Field sampling strategy for tablets***

Initial Sampling		
Minimum Units	Maximum Units	Comments
20	40	If the "minimum" of 20 units is not feasible, collect what is available but no less than 5 units

Table 2: ***Re-sampling strategy for compendial testing***

Re-sampling for Compendial Testing (if necessary)		
Minimum Units	Maximum Units	Comments
50	100	If the "minimum" of **50** units is not feasible, refer to the Number of Units Needed in Table 1: Guidelines for Compendial Testing

3.6 Criteria for Prioritization of Sampling

Priority was given to the following APIs and dosage forms:

- First-line treatment in the DOMC treatment guidelines
- Most-sold medicines
- Most commonly-used medicines to reflect the reality of consumed medicines from all available sectors
- Medicines known or suspected to be counterfeit or sub-standard

3.7 Criteria for Diversification of Sampling

Attempts were made to try and diversify the samples collected from each site to reflect the availability in the market. The following characteristics to diversify the sampling were considered:

- Different brands of the same API
- Different batch/lot numbers
- Multiple dosage forms (tablets, capsules, oral suspensions, injectables, suppositories, etc.)
- Different sectors (private/public/informal)

- Different sources or outlets of the same product with same lot number
- Suspicious medicines;
- Improperly stored medicines at the sampling site (exposed to sunlight, humid/wet conditions, etc.); and,
- Different packaging of same product (i.e. blister vs. bulk).

3.8 Sample Collection

A Sampling Checklist (Annex 1) was provided to the sampling team prior to their departure to collection sites and the need for its consistent use was emphasized. Each site planned to collect approximately 100 samples although some sites collected more than this number.

Each collected sample was secured in a plastic container or sealable plastic bag and attached to its corresponding ***Sample Collection Form (Annex 2)***. The Sample Collection Form contained all traceable data that accompanied the sample from the site of the collection to the site of Minilab testing and then to the quality control laboratory for confirmatory testing. This was done in order to maintain a traceable record of the identity of the sample should it fail or be doubtful.

Samples were then packed, transported, and stored in such a way as to prevent any deterioration, contamination, or adulteration. Samples were stored and transported in their original sealed containers, according to the storage instructions for the respective product.

3.9 Sample Analysis

Once samples were collected, they were tested at three levels (Figure 1). Level 1 is the sentinel site using Minilab tests, level 2 is the verification test carried out in the lab using Minilab basic tests to verify sentinel site data and level 3 is the confirmatory testing done using full compendial testing.

***3.9.1** Level 1 Basic Tests Minilabs at Sentinel Site*

Basic tests included Physical/Visual (P/V) Inspection, Disintegration, and Thin Layer Chromatography (TLC) and this was carried out at the sentinel sites. Test results were

Safety & Environmental Considerations

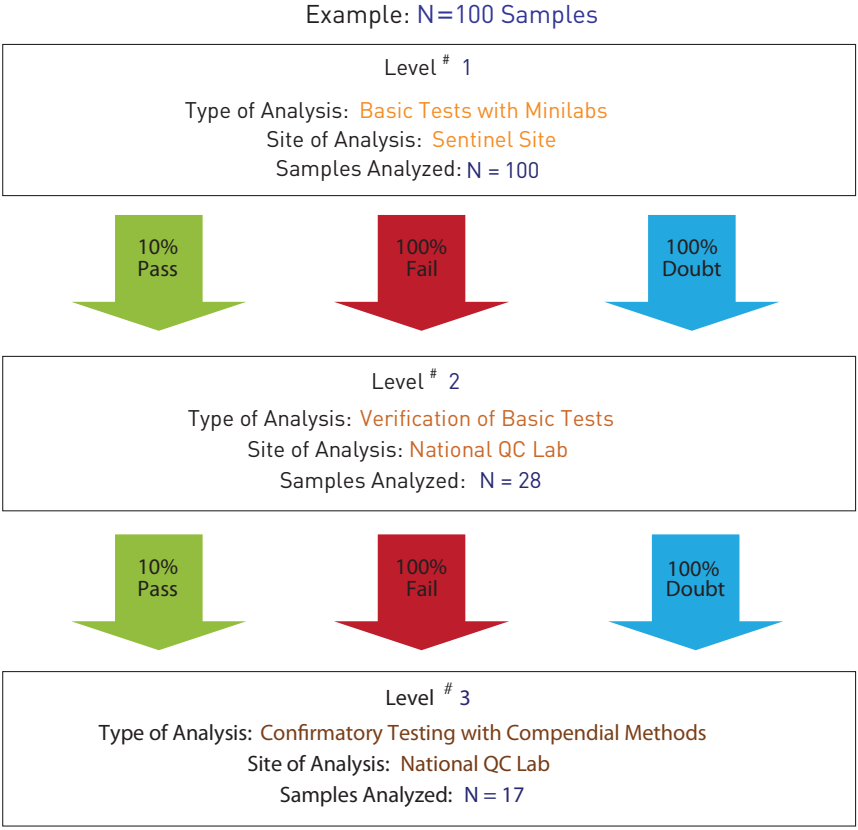
Sample analysis should be performed taking into consideration any possible safety and environmental consequences. Safety guidelines were followed as per Part Four of the WHO Technical Report Series, No. 902, Annex 3. Waste disposal was followed as per the country's national legislation.

clearly recorded for each sample on the Basic Tests Analysis Form for Sentinel Site Staff (Annex 3). A subset of samples was sent to the NQCL for verification testing, as follows: (Refer to Figure 1—MQM Analysis Flow Chart.)

- 10% of samples that passed*
- 100% of samples that failed**
- 100% of samples that are doubtful***

This subset of samples was sent with their respective forms attached (***Sample Collection Form*** and ***Basic Tests Analysis Form for Sentinel Site Staff***) to the NQCL for verification and confirmatory testing.

Figure 1: ***MQM Analysis Flow Chart***



 # Protocols may define "stages" or "levels" differently; individual protocols should clearly indicate the terminology to be utilized and its specific meaning.

***3.9.2** Level 2: Verification of Basic Tests at NQCL*

NQCL performed verification testing by repeating basic tests on the subset of samples (as described above). Results of each sample were recorded clearly on the *Basic Tests Analysis Form for National Quality Control Laboratory Staff.*

For any samples that failed or were doubtful, they continued to the third stage of analysis for complete compendial testing.

Compendial testing was performed on the following samples: (Refer to Figure 1—MQM Analysis Flow Chart.)

- 10% of samples that pass verification testing*
- 100% of samples that fail verification testing**
- 100% of samples that are doubtful for verification testing***
- 50-100% of sulfadoxine-pyrimethamine(S/P)tablets/capsules and other medicines with known dissolution failures.

* Pass: Conforms to all three (3) tests
** Fail: Does NOT conform to at least one (1) of the three (3) tests
*** Doubtful: Conflicting or inconclusive results for at least one (1) of the three (3) tests

***3.9.3** Stage/Level 3: Confirmatory Testing with Compendial Methods at NQCL*

If compendial testing was to be conducted and there were insufficient units, more units of the same sample were collected to ensure full compendial testing took place as per Table 4.

CHAPTER FOUR:
RESULTS AND DISCUSSION

4.1 Sample Description

A total of 536 samples were collected from 126 facilities across the three sectors (public, private and informal).

4.1.1 Sampling by Sector

Sampling was highest at the private sector followed by the public sector and least at the informal sector. This was because the range of antimalarials was highest in the private and public sectors respectively. This is demonstrated in figure 4

Table 3 Sampling by Sector

Sector	Number of Samples	Percentage
INFORMAL	55	10.3%
PRIVATE	312	58.2%
PUBLIC	169	31.5%
Grand Total	**536**	**100%**

4.1.2 Sampling by API

The most sampled medicines were AL, SPs and quinine according to the availability across the sectors

Table 4 Distribution of samples by API

API	Number of Samples	Percentage
ARTESUNATE AMODIAQUINE	14	2.6%
DIHYDROARTEMESININ PIPERAQUINE	19	3.5%
OTHER	29	5.4%
QUININE	83	15.5%
SULFADOXINE PYRIMETHAMINE	101	18.8%
ARTEMETHER LUMEFANTRINE	290	54.1%
TOTAL	**536**	**100%**

4.1.3 Sampling by Sentinel Site

The sampling across the sentinel sites was fairly even with slightly higher sampling in Eldoret and Coast as shown in table 5 below.

Table 5 Sampling by Sentinel Site

Sentinel Site	Number of Samples	Percentage
COAST	107	20.0%
ELDORET	128	23.9%
NAIROBI	100	18.7%
NYANZA	101	18.8%
WESTERN	100	18.7%
Grand Total	**536**	**100%**

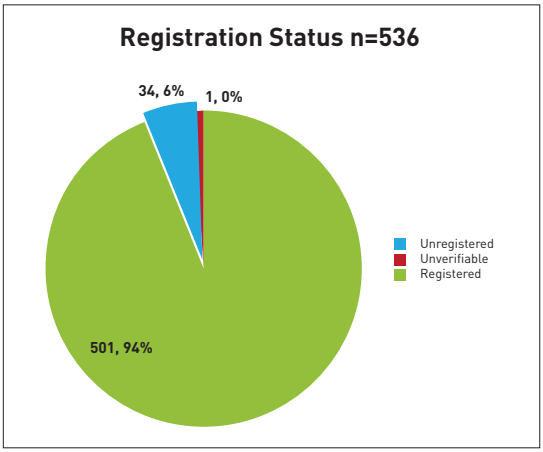
4.2 Registration with PPB

All the 536 samples collected were evaluated for registration status.

4.2.1 Registration Status of Samples

Of 536 samples collected, 501 were registered with PPB, 34 were not registered and one of the sample's registration status could not be established (Quinine sulfate). This is shown in figure 3 below

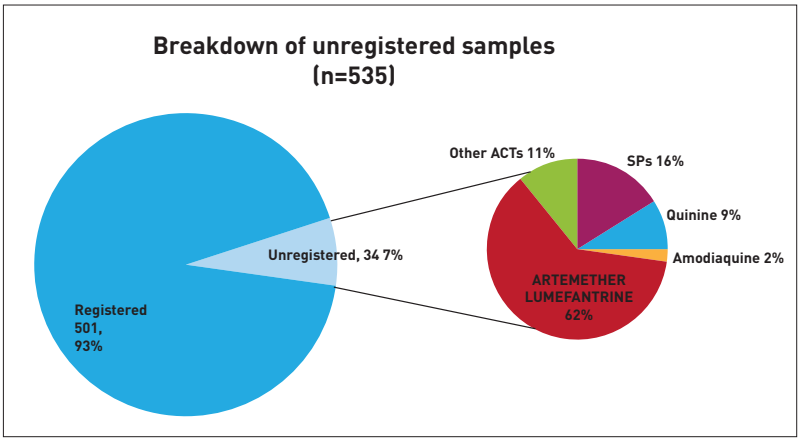
Figure 3 Registration status



4.2.2 Composition of Unregistered Samples

The breakdown of the unregistered samples had AL as the highest proportion (62%) followed bty SPs (16%) and other ACTs (11%). This is shown in figure 5 below. The unverifiable sample was excluded from this analysis hence n=535.

Figure 4 Breakdown of unregistered samples



The companies which had their products unregistered were identified and the inspectorate team instructed to take action. The products on the companies' warehouses were quarantined and a recall ordered for the ones in the market.

4.3 Basic Test Analysis

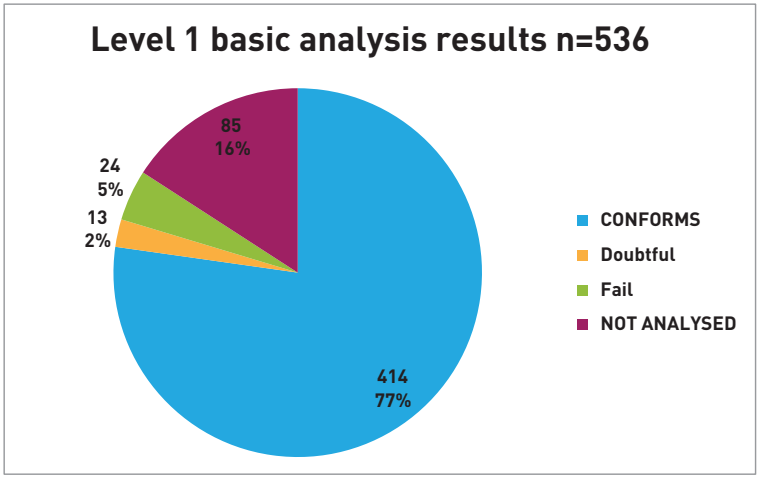
A total of 536 samples were collected from all the sentinel sites and samples were analyzed at different levels according to the protocol as follows;

Number of Samples Collected	Number of samples analyzed in the field using Minilab (Level 1)	Number of Samples analyzed using Minilab at NQCL (Level 2)	Number of Samples analyzed using compendial methods (Level 3)
536	451	80	44

4.3.1 Level One Basic Analysis Results

Of the 536 samples that were analyzed, 414 conformed to the tests, 24 failed, 13 were doubtful and 85 were not analyzed due to unavailability of monographs. This is shown in figure 5 below.

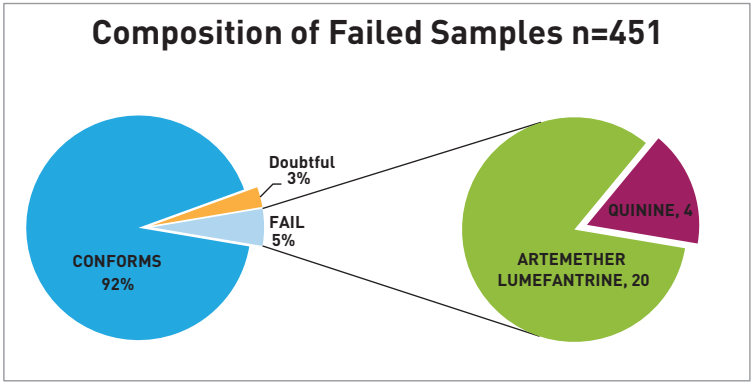
Figure 5: *Level one basic analysis results*



4.3.1.1 Composition of Failed Samples at Level One

Of the 24 samples that failed, 20 were Artemether Lumefantrine and 4 were quinine.

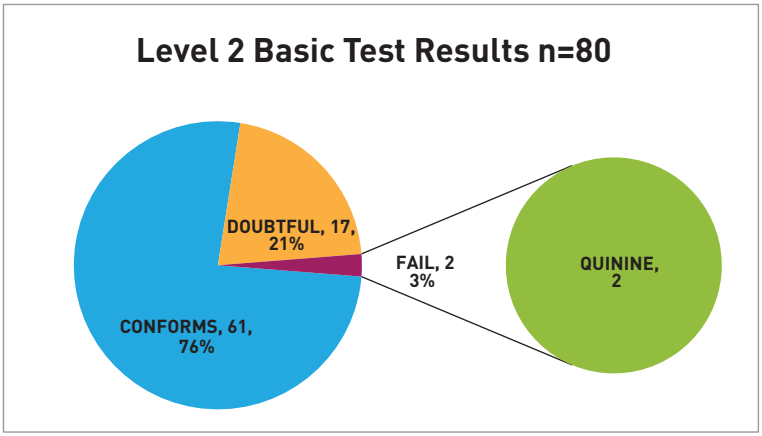
Figure 6: *Level Two Basic Analysis Results (NQCL Minilab Testing)*



4.3.2 Level Two Basic Analysis Results

A total of 80 samples were sent to NQCL for minilab testing as per the protocol. Of these, 61 conformed, 17 were doubtful and 2 failed. The 2 samples that failed were both quinine. This is shown in figure 7 below.

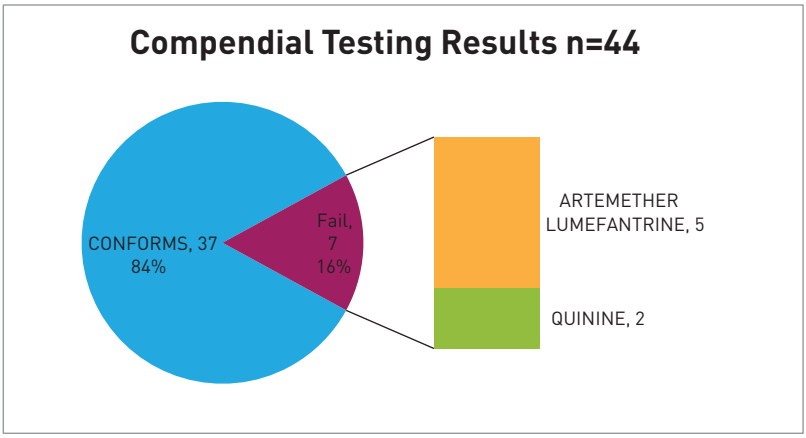
Figure 7: *Level Two Basic Test Results*



4.4 Compendial Testing Results

A total of 44 samples were sent to NQCL for confirmatory testing using compendial methods. Of these, 37 conformed and 7 failed. Those that failed consisted of 5 samples of Artemether Lumefantrine and 2 samples of quinine as shown in figure 8 below.

Figure 8: *Compendial Testing Results (level 3)*



Further analysis of the failed samples was done to determine the reasons for failure and is represented in table 6 below.

Table 6: *Reasons for Failure*

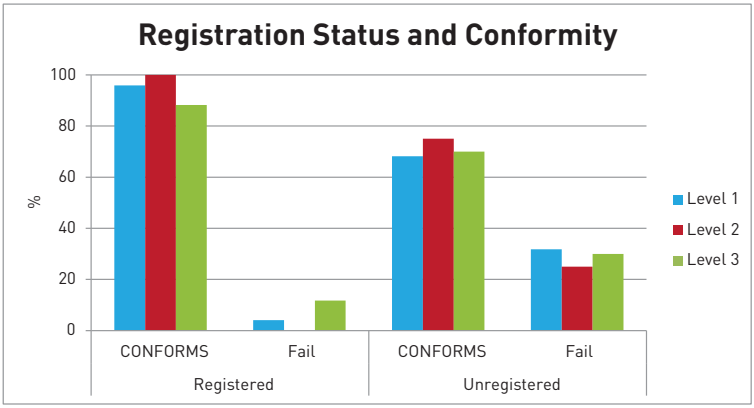
Drug	Formulation	Number of Failed Samples	Reasons For Failure
Artemether Lumefantrine	SUSPENSION	1	Assay
	TABLETS	4	Dissolution (3), Assay (1), Uniformity of Weight (1)
Quinine	TABLETS	2	Identification (2), Dissolution (2), Assay (1)
Grand Total		**7**	

Dissolution and assay were the most common causes of failure.

4.5 Registration Status and Conformity

Registration status and conformity was evaluated for all the samples analyzed and expressed as a percentage as shown on figure 9 below.

Figure 9 *: Registration status and conformity*



Registered products were more likely to conform to quality specifications than unregistered products. Conversely, unregistered products were more likely to fail quality specifications as compared to registered products.

4.6 Concordance of Test Results Across Various Levels

A comparison between the test results at NQCL (level 3) and those using minilab® (level 1 and 2) was done for tablets alone. Tablets alone were chosen because the monographs provided in the minilabs were approved for tablet formulations only. The results were as follows;

4.6.1 NQCL Results Compared with Level One Results

Table 7: *Concordance at Level 1*

Outcome	CONFORMS	Doubtful	Fail	Grand Total
CONFORMS	16	5	5	26
FAIL	2	1	3	6
Grand Total	**18**	**6**	**8**	**32**

Only 16 out of 26 test results that conformed using minilabs also conformed when compendial methods were used. 5 samples that failed minilab testing conformed to compendial tests.

Only 3 out of 6 test results that failed using minilabs also failed when compendial methods were used. Only one sample that was doubtful failed compendial testing, the rest conformed.

4.6.2 NQCL Results Compared with Level Two Results

Table 8 : *Concordance at Level 2*

Outcome	CONFORMS	DOUBTFUL	FAIL	Grand Total
CONFORMS	16	9	0	25
FAIL	3	1	2	6
6 Grand Total	**19**	**10**	**2**	**31**

Only 16 out of 25 test results that conformed using minilab analysis also conformed when compendial methods were used. However it is encouraging to note that no sample failing minilab tests conformed when compendial methods were used.

Only 2 out of 6 test results that failed using minilabs also failed when compendial methods were used. Only one doubtful sample also failed compendial testing, the rest conformed.

The minilab is a quick and fast way to conduct physical testing of medicines by visual inspection, disintegration and color reactions that can identify the presence or absence of active drug substances. The thin layer chromatography test is used to identify active ingredients or lack of, obtain semi quantitative information about the active ingredients, and to detect the presence of impurities.

Compendia testing or full monograph testing allows for detailed evaluation of the sample. With compendia testing, you can accurately determine identity, content of active ingredients, drug release characteristics, purity as well as other characteristics of the medicine.

CHAPTER FIVE:
SUMMARY AND CONCLUSION

A total of 536 samples were collected from 126 facilities across the public, private and informal sectors representative of the market segmentation. The most sampled antimalarials were AL followed by SPs and quinine. The number of samples collected by segment and API was purposive and therefore did not represent the antimalarial availability in the market. This was a slight departure from previous sampling strategies which also sought to determine the availability in the market. The primary purpose of this survey was to determine the quality status of antimalarials in the market and therefore biased the sampling towards antimalarials that were most used and the sectors in which they were most common. This sampling strategy was more likely to capture salient quality assurance issues that would otherwise not be picked in other sampling strategies.

The registration status of the samples collected was 6 percent, a dramatic improvement from 42.6 percent determined during an earlier survey done in 2006 (Ministry of Health, 2007). This is an indication that the regulation of medicines in the country is improving and therefore a good majority of antimalarials in the market have been subjected to some quality assurance system. Sustained efforts however need to be maintained to ensure all medicines in the market are registered.

The conformity results were 92, 76 and 98.4 percent at levels one two and three respectively. The decreased conformity in levels 2 and 3 can be explained by the nature of sampling which biased towards failed and doubtful samples (refer to the sampling strategy). The failure rate of antimalarials in the market has also improved from 16 percent (Ministry of Public Health and Sanitation, 2007) to 7 percent (WHO, 2010) and now 1.6 percent over the last five years (when the compendial results are represented as percentage of the total samples analyzed at all levels). It is noteworthy that efforts in improving the regulation of medicines including frequent monitoring on conformity has also increased over the same period. More than half of the samples assessed were from the private and informal sectors which are usually not required to be WHO prequalified before use.

This shows that although additional quality assurance measures are required in the public sector procurement such as WHO prequalification for AL, the quality of antimalarials in the private sector is still high. It is however alarming that most of the samples that failed analysis were AL which is the first line for the treatment of uncomplicated malaria. This could be attributed to the higher sampling of AL in all sectors. More vigilance is however required to ensure that no antimalarial fails compendial tests. This is especially so for ACTs which are already at risk of resistance going by reports from South East Asia.

Registered antimalarials are less likely to fail conformity tests as demonstrated in the survey results. This means that a stringent regulatory system that ensures no medicine

enters the market before registration could offer a quick and affordable way of ensuring quality. Stiffer and decisive actions on unregistered medicines could discourage the vice and thereby ensure 100 percent registration of all medicines in the market.

The use of Minilabs to screen antimalarials is a cost effective way of conducting post market surveillance of medicines in the market. Out of a possible 451 samples that would otherwise have required compendial testing at the reference lab, only 42 samples were subjected to full compendial testing. Considering that the average cost of testing one sample varies between Kshs 20,000 to 50,000, post market surveillance can be carried out in a cost effective way using minilabs. In addition to the time saved, the turnaround time for conducting post market surveillance can drastically be reduced when using minilabs. This will ensure that timely regulatory action is taken on samples that do not comply with quality standards.

5.1 Regulatory Action on Failed and Unregistered Samples

Appropriate regulatory action needs to be part of a post market surveillance system. Some of the regulatory actions that were taken based on the findings of this survey included quarantine of products yet to be marketed, notifications to companies on the failure of compendial testing and closure of the manufacturing plant.

Samples whose batches failed and were yet to be marketed were quarantined and later destroyed under PPB supervision. This action ensured that patients were not exposed to products whose quality was already established to be substandard. The companies were also served with warning letters thus setting a strong precedent on the need to maintain quality during the manufacturing process.

One of the factories was forced to shut down after it was noted that it had been notorious for consistently manufacturing substandard medicines. This action being unprecedented gave fresh impetus on the fight against poor quality medicines and their corresponding manufacturers.

CHAPTER SIX:
RECOMMENDATIONS

Monographs for all antimalarials circulating in the market should be availed in the minilab to ensure all samples collected are tested. Out of the 536 samples collected, only 451 samples were screened using minilabs owing to the availability of monographs. Notable among these was the unavailability of a monograph for screening Dihydroartemisinin Piperaquine which is currently the second line treatment for uncomplicated malaria. The monographs for screening suspensions should also be availed.

Regulatory action needs to include a risk based approach to ensure that manufacturers and importers of medicines that are noted to consistently fail quality tests are blacklisted or dealt with firmly. This therefore requires that post market surveillance be instituted as a routine practice rather than a one off event. By so doing temporal changes in the quality of antimalarials in the market can be established and notorious manufacturers or importers be identified.

Post market surveillance needs to be extended to other medicines and regions. So far, the only medicines that are subjected to some form of monitoring are antimalarials, antiretrovirals and anti tuberculosis medicines. This can be attributed to the resources available to these disease programs to carry out such surveys. However there is a need to ensure that all medicines in the market are monitored for quality considering that adjuvant treatment usually accompanies the management of these priority diseases. Furthermore, all newly developed counties should be equipped with a minilab for routine screening of all medicines in the various districts. Capacity building of health workers to conduct minilab testing should also be done.

Clear and well defined standard operating procedures on regulatory actions to be taken in the case of poor quality, counterfeit or unregistered medicines should be documented and institutionalized. This will serve as a deterrent for manufacturers who "test the system."

Future post market surveillance activities should be designed to capture medicines that may be of good quality standard but are not recommended by the prevailing policies. Medicines such as artemisinin monotherapies, amodiaquine and SPs which are no longer recommended for the treatment of uncomplicated malaria still continue to be available in the market thus curtaining policy implementation.

The analysis of the results should stratify the poor quality medicines by sector. This will better guide and target the regulatory activity employed by PPB.

REFERENCES

Abdisalan, M. N. (2009). Malaria endemicity map. Kenya.

Division of Malaria Control. (2010). ***Malaria Standard Treatment Guidelines.*** Ministry of Public Health and Sanitation.

Guerra, C. A., Gikandi, P., & Tatem, A. (2008). The limits and intensity of Plasmodium falciparum transmission: Implications for malaria control and elimination worldwide. 5, E38.

Ministry of Health. (2007). ***Antimalrials Medicines in Kenya***. Ministry of Health.

Ministry of Public Health and Sanitation. (2007). ***Kenya Malaria Indicator Survey.*** Kenya: Ministry of Public Health and Sanitation.

Ministry of Public Health and Sanitation. (2009). ***Kenya National Malaria Strategy 2009-2017***. Kenya: Ministry of Public Health and Sanitation.

WHO. (2010). ***THE SURVEY OF THE QUALITY OF ANTIMALARIALS IN SUBSAHARAN (QAMSA)***. WHO.

ANNEXES

***Annex 1** Guidelines for Compendial Testing (Solid Dosage Forms)*

Guidelines for Compendial Testing (Solid Dosage Forms)1					
Step	Failed Basic Test		Number of Units Needed2,3	How to Proceed	Comments
1	Physical/Visual Inspection	Physical/ Visual Inspection	10	Pass or Fail, proceed to Step 2	• Although P/V Inspection is not required by compendial tests, it is
2	ID	ID(s)	5	Pass, proceed to Step 3 Fails, STOP	• If sample Fails Step 2, you can conclude: Sample does not conform to compendial specifications
3	Content	Assay	20	Pass, proceed to Step 4 Fails, STOP	• If sample Fails Step 3, you can conclude: Sample does not conform to compendial specifications
4	Disintegration	Dissolution	24	Pass, proceed to Step 5 Fails, STOP	• If sample Fails Step 4, you can conclude: Sample does not conform to compendial specificationst
5	Impurity	Related Compund	See Comments	Pass, proceed to Step 6	• Some related compound and/ or impurity tests can be performed as part of the Assay. Other monographs may require additional units, which should be discussed on a case-by-case basis. • If sample Fails Step 5, you can conclude: Sample does not conform to compendial specifications
6	If the sample passes Steps 1-6 and there are sufficient units, proceed to remaining monograph tests.				• If sample Fails Step 6, you can conclude: Sample does not conform to compendial specifications

1. This example applies to solid dosage forms (tablets and capsules) only. Details for testing oral suspension, injectable, or other dosage forms should be discussed during protocol development on a case-by-case basis.
2. The number of units needed for each test depends on the individual monograph.
3. Use the available units and follow the sequence indicated in the table. (For example: If only 50 units are available, begin performing Steps 1-3. Do not wait for re-sampling to occur.)

Monitoring the Quality of Antimalarial Medicines Circulating in Kenya, Round 1

DOMC/PPB/PMI

Background of Quality of Antimalarials

- In 2006, a study on the availability, quality and registration status of antimalarials found that
  - 42.2% of the samples were unregistered
  - 16% of the samples did not conform with quality standards (MOH 2007)
- In 2008, a collaborative multi-country study on quality of antimalarials in Africa (QAMSA) study found that
  - 7% of the samples did not comply with quality standards (WHO, 2010)

Primary Objective

- The primary objective of the MQM (monitoring quality of anti-malarials)program is to monitor the quality and registration status of antimalarials in 5 sentinel sites in Kenya.

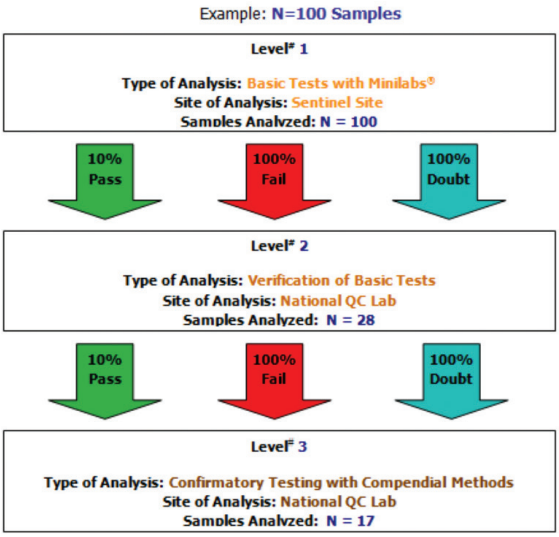
Specific Objectives

- To determine the proportion of unregistered products in the selected sites
- To determine the proportion of medicines in the selected sites that conform to quality standards
- To develop a medicine information database on the quality of medicines in circulation for trend analysis

Methodology

- A 5 day training was conducted prior to the data collection
- Data collection was carried out in April and May 2010 in five sentinel sites representing areas with the highest malaria burden and ports of entry ie Nyanza, Western, Eldoret, Coast and Nairobi
- 536 antimalarial samples were collected from the public, private and informal sectors
- Basic testing were done using Minilab kit and confirmatory tests using compendial methods

Testing



Results

Sample Description

- A total of *536* samples were collected from 126 facilities across the three sectors as follows:
  - Informal (10.3%)
  - Private (58.2%)
  - Public (31.5%)

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  - Informal (10.3%)
  - Private (58.2%)
  - Public (31.5%)

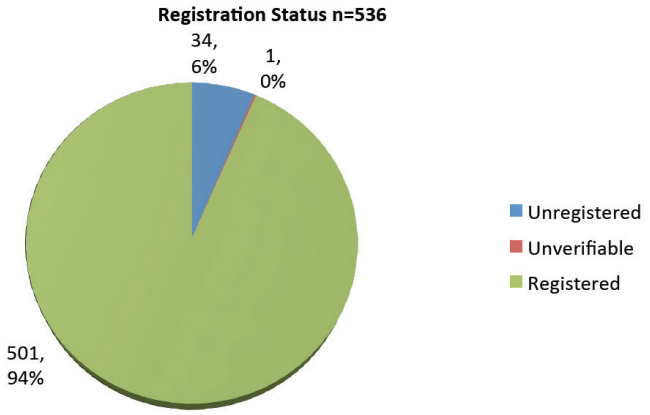
Sample Description Cont'd

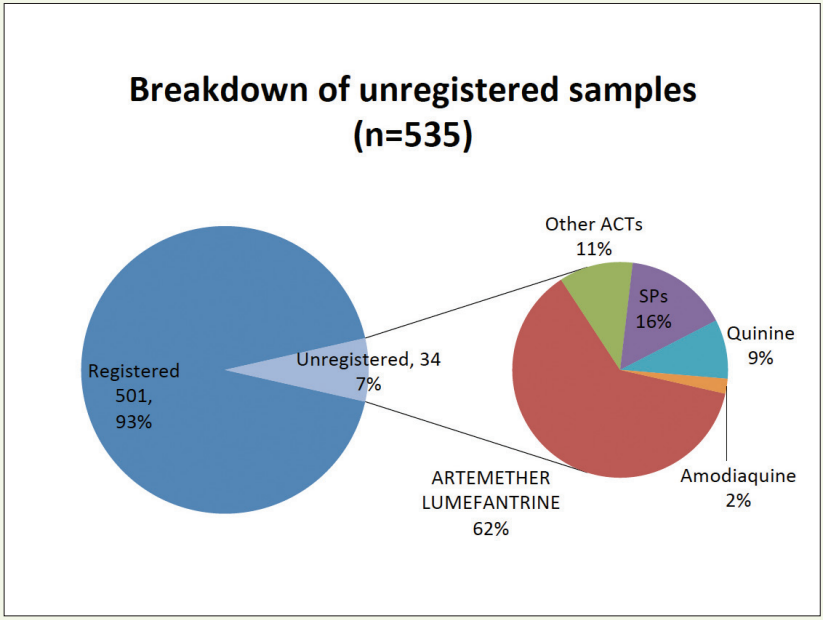
- Most sampled medicines were AL, SPs and quinine in line with the availability across the sectors
  - Artemether Lumefantrine (54.1%)
  - Sulfadoxine Pyrimethamine (18.8%)
  - Quinine (15.5%)
  - Other (5.4%)
  - Dihydroartemesinin Piperaquine (3.5%)
  - Artesunate Amodiaquine (2.6%)

Sample Description Cont'd

- The sampling across the sentinel sites was fairly even with slightly higher sampling in Eldoret and Coast as follows:
  - Coast (20.0%)
  - Eldoret (23.9%)
  - Nairobi (18.7%)
  - Nyanza (18.8%)
  - Western (18.7%)

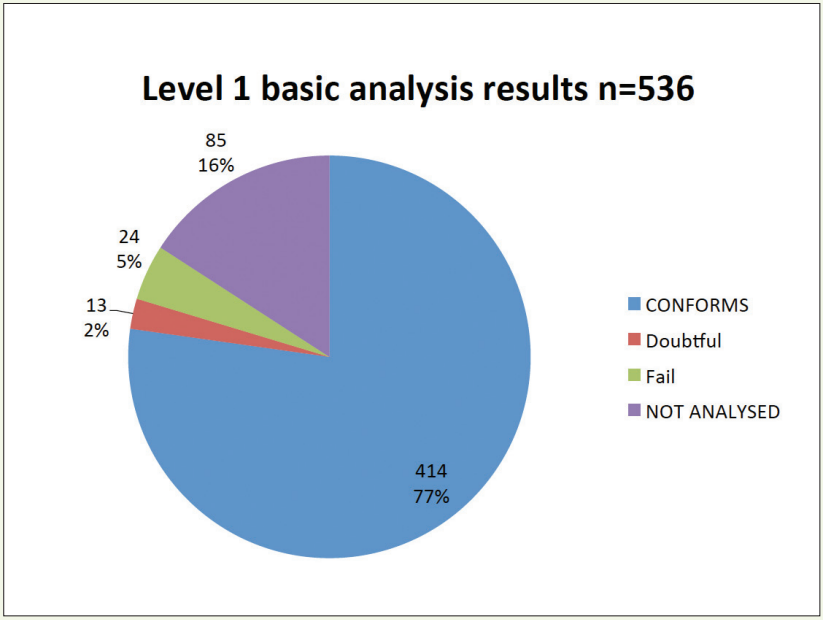
Registration with PPB

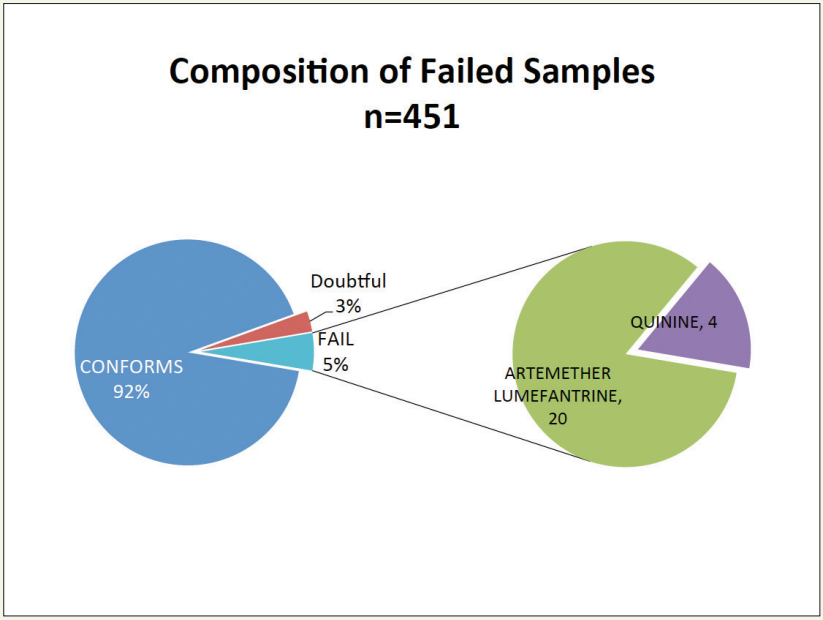


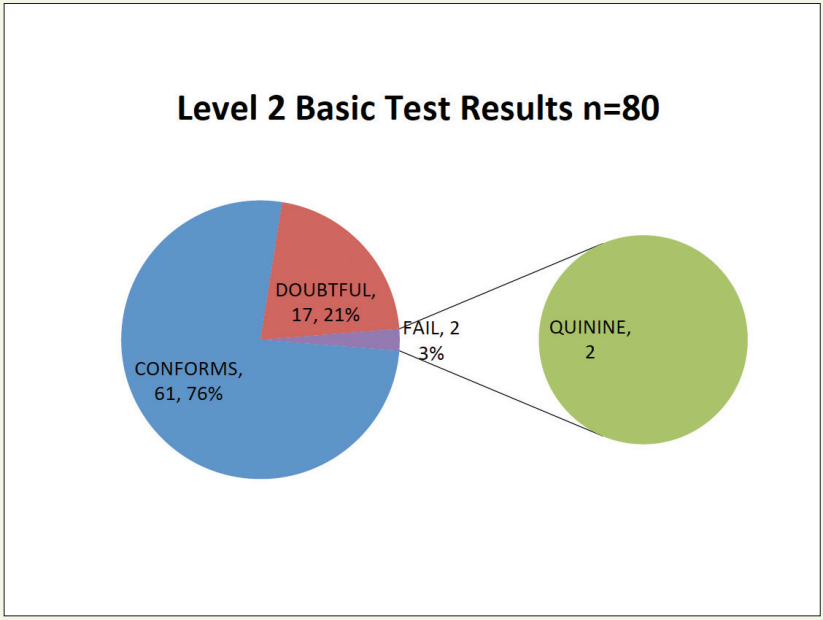


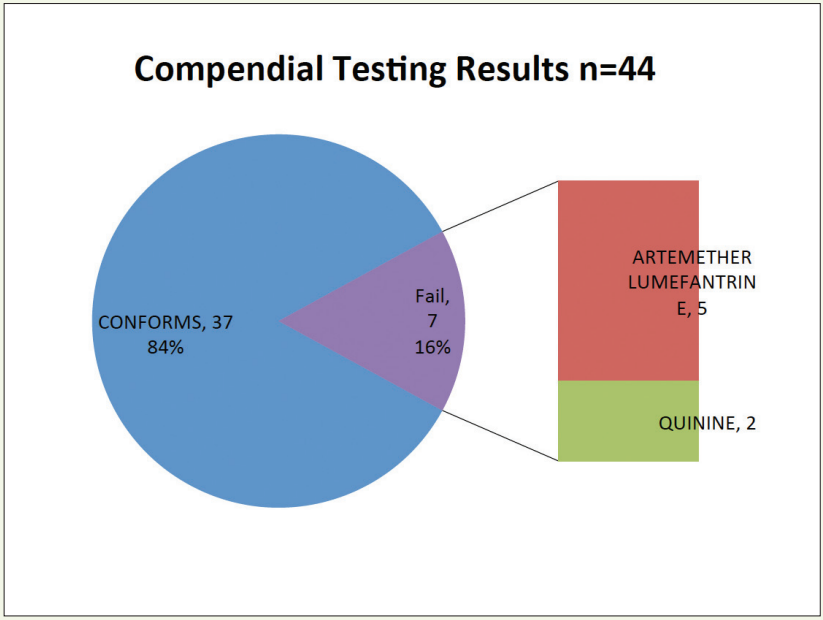
Basic test analysis

Number of Samples Collected	Number of samples analyzed in the field using Minilab (Level 1)	Number of Samples analyzed using Minilab at NQCL (Level 2)	Number of Samples analyzed using compendial methods (Level 3)
536	451	80	44


Level 1 basic analysis results n=536
85
16%
24
5%
13
2%
414
77%
CONFORMS
Doubtful
Fail
NOT ANALYSED


Composition of Failed Samples
n=451
CONFORMS
92%
Doubtful
3%
FAIL
5%
QUININE, 4
ARTEMETHER
LUMEFANTRINE,
20

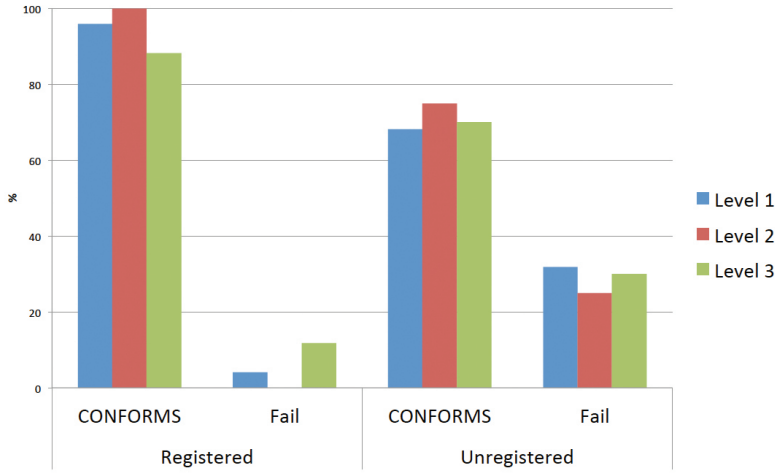

Level 2 Basic Test Results n=80
DOUBTFUL, 17, 21%
FAIL, 2 3%
QUININE, 2
CONFORMS, 61, 76%


Compendial Testing Results n=44
CONFORMS, 37 84%
Fail, 7 16%
ARTEMETHER LUMEFANTRINE, 5
QUININE, 2

Reasons for Failure

Drug	Formulation	Number of Failed Samples	Reasons For Failure
Artemether Lumefantrine	SUSPENSION	1	Assay
	TABLETS	4	Dissolution (3), Assay (1), Uniformity of Weight (1)
Quinine	TABLETS	2	Identification (2), Dissolution (2), Assay (1)
Grand Total		7	

Registration Status and Conformity



Conclusion

- Most unregistered and failed samples were ACTs
- Registered antimalarials are less likely to fail conformity tests
- Minilabs are a cost effective way of conducting post market surveillance of medicines in the market

Actions Taken

- The companies which had their products unregistered were identified after which the medicines in question were quarantined and a recall ordered for the ones in the market.
- One company was ordered to close for consistently producing poor quality medicines
- Companies whose medicines failed compendial testing were notified by the PPB

Gains in improving registration and quality

- The Registration status of antimalarials in Kenya has improved from *57.4% (2006) to 94% (2011)*
- Failure rate of anti-malarial medicines has decreased from *16% (2007) to 7% (2008) to 1.6% (2011)*

Recommendations

Sustained surveillance of quality of medicines in the market should be maintained to ensure all medicines are of good standard at all times

Even though the registration status has improved, efforts should be made to ensure all medicines in the market are registered

PMS should be extended to other regions and other medicines

Clear SOPs on the actions to be taken on companies who manufacture substandard medicines should be developed

Acknowledgements