

Registration and Quality Assurance of ARVs and other essential Medicines in Namibia

October 2014 - September 2015



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Registration and Quality Assurance of ARVs and Other essential Medicines in Namibia

Nasser Mbaziira

September 2015



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About SIAPS

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

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Key Words

Medicine regulation, medicines registration, dossiers, Post market surveillance

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I acknowledge the management, technical and operations /administration staff of SIAPS in Namibia for the support rendered in implementation of the activities in this report.

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ACRONYMS AND ABBREVIATIONS

3TC	Lamivudine
ADE	Adverse Drug Events
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARVs	Antiretrovirals
AZT	Zidovudine
FTC	Emtricitabine
EFV	Efavirenz
GMP	Good Manufacturing Practices
HIV	Human Immunodeficiency Virus
MoHSS	Ministry of Health and Social Services
NMRC	Namibia Medicines Regulatory Council
NVP	Nevirapine
PMS	Post Market Surveillance
QSL	Quality Surveillance Laboratory
RPM	Rational Pharmaceutical Management
SIAPS	System for Improved Access to Pharmaceuticals and Services
SPS	Strengthening Pharmaceutical Systems
STA	Senior Technical Advisor
TA	Technical Assistance
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TIPC	Therapeutics Information and Pharmacovigilance Centre
USAID	United States Agency for International Development
WHO	World Health Organization

1.0 BACKGROUND

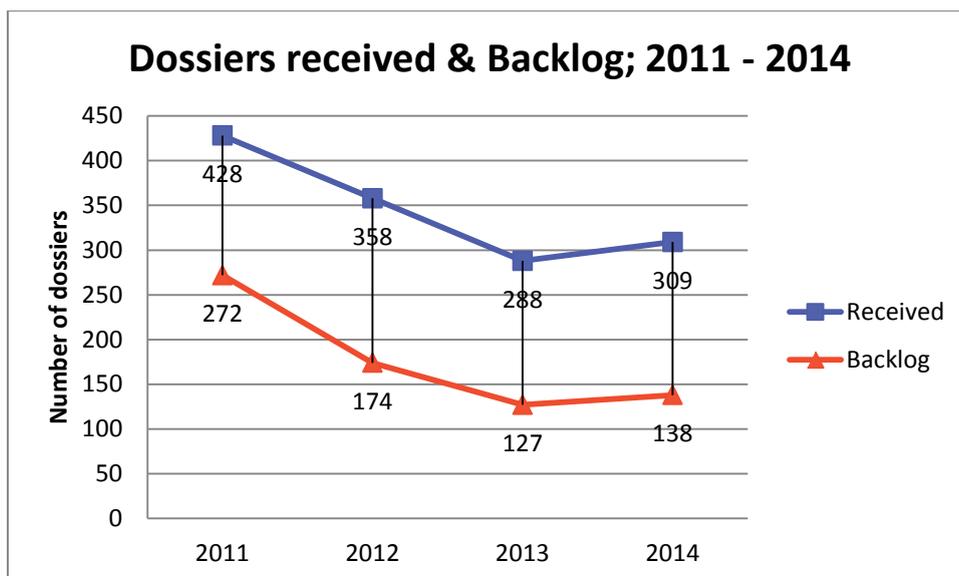
Namibia's estimated population of 2.3 million people is distributed unevenly in urban centers and rural communities and has a sparse population density of 2.6 people/square kilometers. Namibia is one of the Africa countries significantly affected by the HIV & AIDS epidemic, which is one the leading causes of morbidity and mortality in the country. The adult HIV prevalence rate is estimated at about 14.2%, and about 140,000 patients were on ART program as at March 2015.

Namibia Medicine Regulatory Council (NMRC) is mandated to ensure quality, safety and efficacy of medicines, and contribute to improving treatment outcomes; the health of Namibia's population and economy. Among the key functions of NMRC; to conduct technical assessment of medicine application prior to medicine registration and post-market surveillance to monitor quality of registered medicines in the country.

Namibia's NMRC secretariat has greatly benefited from the technical and financial support through various USAID-funded projects; Rational Pharmaceutical Management Plus (RPM plus), Strengthening Pharmaceutical Systems (SPS) and currently Systems for Improved Access to Pharmaceuticals and Services (SIAPS) project. All the projects aimed at improving and strengthening NMRC's capacity to efficiently and effectively perform its statutory regulatory functions to support the HIV&AIDS and other public health services, through ensuring quality, safety and efficacy Antiretroviral (ARV) and other essential medicines for the Antiretroviral Treatment (ART) program. The technical functions of NMRC supported over the years included; registration, inspection and licensing, quality surveillance and therapeutic information and pharmacovigilance.

For a long time, the effectiveness of NMRC's functionality was greatly limited largely due human and technical resource constraints. The challenges largely contributed to the rapid growth of the number of unassessed medicine applications/dossiers to 746 dossiers by March 2014 and the longer periods between receipt of a dossier and responding to clients on the review outcomes. This had a big impact on the HIV commodities supply chain since new ARVs, which were not yet registered could not easily be procured and stocked by the central medical stores, and the quality, safety & efficacy of those that got waivers could not be guaranteed.

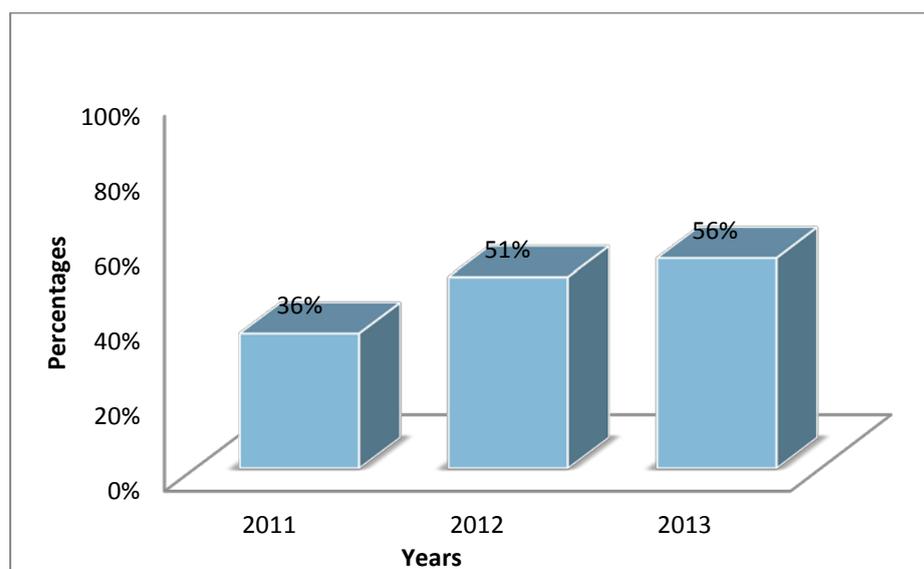
Figure1 below illustrates the trends of the backlog over a four year period; where on average over 40% of the received dossiers were not reviewed, 64% (2011), 49% (2012), 44% (2013) and 45% by September 2014.



Source: Pharmadex database, September 2014

Figure 1: Number of received and unevaluated/backlog dossier dossiers at NMRC 2011-2014.

Through SIAPS support in the previous years, an improvement in the proportion of application dossiers reviewed on annual basis has been realized as shown in figure 2.



Source: Medicine registration database, Pharmadex. Namibia MoHSS, March 2014.

Figure 2: Percentage of dossiers evaluated against those received by NMRC.

The SIAPS supported interventions in FY14 included capacity building through training and mentoring, also priority was given to applications that constituted the three year (2010 - 2013) backlog of over 550 applications.

At NMRC, the Therapeutics Information and Pharmacovigilance Centre (TIPC) relatively performs well to maintain an effective pharmacovigilance system especially in the domains of Adverse drug reactions/events (ADR) monitoring and disseminating information on medicines usage to Namibian health care providers for patient safety. However, the domain of monitoring quality of medicines in the public healthcare medicines supply chain to rule out counterfeit and substandard medicines was still a challenge, which could pose a risk of

circulation of substandard and counterfeit pharmaceuticals that may negatively affect treatment outcomes for HIV and AIDS, tuberculosis (TB) and other diseases

2.0 INTERVENTIONS

TA for expedited registration and introduction of newly recommended ARV formulations (including pediatric formulations):

In FY15, SIAPS continued to provide TA to facilitate the expedited assessment and registration of new and other ARV formulations to support the implementation of the revised Namibian ART guidelines (dated January 2014). The TA targeted improving the efficiency of the regulatory system so that the recommend new first-line fixed-dose combination (FDC) ARVs that contain tenofovir and emtricitabine for adults; and optimized ARV formulations for pediatric use, other medicines for HIV and AIDS, TB, maternal newborn and child health (MNCH), and other public health diseases are assessed and considered for registration and made available for public procurement in a timely manner to the benefit of patients on the ART program.

SIAPS provided technical assistance (TA) in the form of mentoring and on-going on-the-job training to five new staff at NMRC and other personnel engaged in evaluation of dossiers for registration of ARV medicines, including new pediatric formulations and other essential medicines. This was conducted under organized dossier evaluation sessions, which was gradually transition to NMRC for sustainability and continued improvement of institution's efficiency in its operations.

To further ensure quality, safe and efficacy of HIV&AIDS, TB, and MNCH and other essential medicines post registration, NMRC with support of the USAID-funded SIAPS project developed medicines quality monitoring guidelines, and in FY15, NMRC in collaboration with SIAPS conducted a baseline survey on the quality of ARVs, tuberculosis and other essential medicines in public health facilities using the newly developed guidelines. The activity benefitted eight (57%) of the 14 regions (Kavango East & West considered as one region) in the country, and samples were tested by the national quality surveillance laboratory (QSL) and those failing the pharmacopoeial tests were forwarded to a WHO prequalified laboratory for confirmatory testing. Table 1 shows the scope of samples collected

Table 1: Category of medicine samples targeted

#	Category	Generic Name	Strength	Dosage form
1	ARV	Abacavir/ Lamivudine (ABC/3TC)	60mg/30mg	Tablets
2	OI	Amoxicillin	250mg	Capsules
3	OI	Amoxicillin	125mg/ml	Suspension
4	OI	Amoxicillin/Clavulanic Acid	1000mg	Tablets
5	OI	Cefuroxime Axetil	125mg/5ml	Suspension
6	OI	Cefuroxime Axetil	250mg	Tablets
7	OI	Co-trimoxazole	240mg/5ml	Suspension
8	OI	Co-trimoxazole	480mg	Tablets
9	ARV	Lamivudine/Zidovudine (3TC/AZT)	150mg/300mg	Tablets
10	ARV	Lamivudine/Zidovudine (3TC/AZT)	30mg/60mg	Tablets
11	Others	Metformin	500mg	Tablets
12	ARV	Nevirapine (NVP)	50mg/ml	Oral solution
13	ARV	Nevirapine (NVP)	200mg	Tablets
14	Others	Perindopril	4mg	Tablets

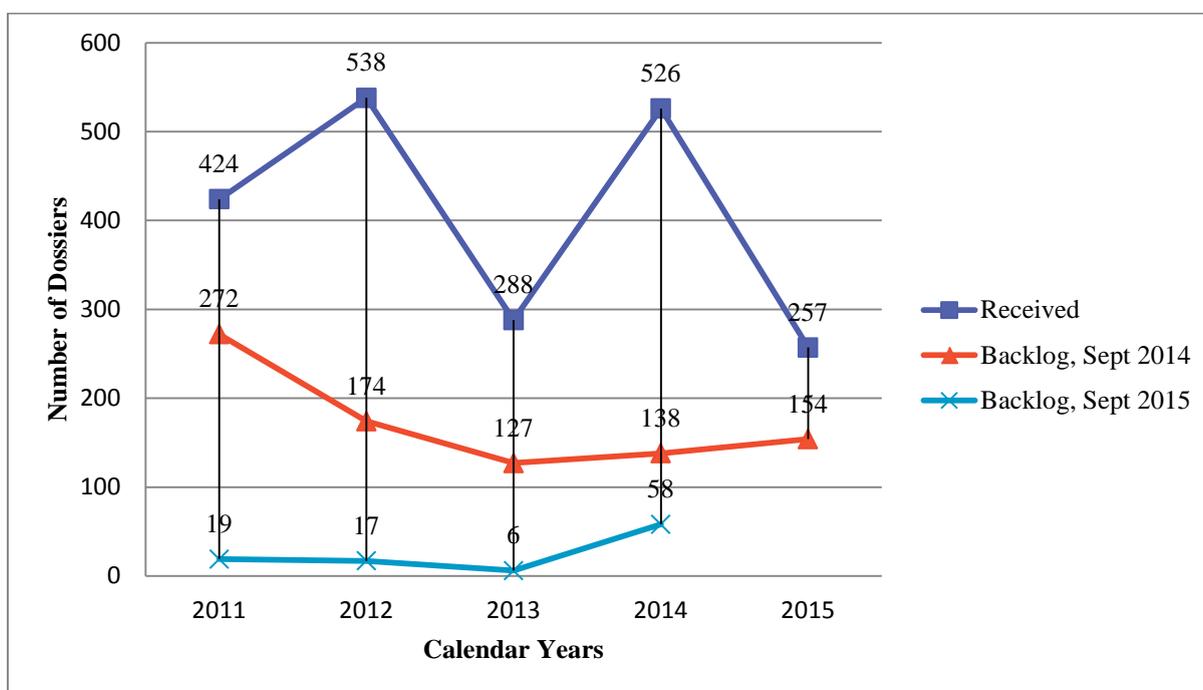
15	TB	RHZE	150/75/400/275mg	Tablets
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3.0 RESULTS/OUTCOMES

Performance of NMRC medicine registration function.

In October 2014, SIAPS continued to support NMRC and organized a dossier evaluation session primarily aimed at mentoring and improving dossier evaluation skills for the newly recruited NMRC staff and reduce the dossier backlog. A total of 132 medicine registration applications received in 2012 and part of 2011 were reviewed. This activity has been successfully transitioned to NMRC, and in FY15 four evaluation sessions (February, June and September 2015) were solely organized by NMRC and this has greatly contributed to a remarkable reduction in the numbers and age of the backlog.

Figure 3: Trends in medicine registration application backlog



There has been a significant reduction in the number and age of the dossier backlog at NMRC as shown in figure 3. A total of 711 applications received in 2011 to 2014 had not been evaluated for registration by September 2014 (FY14) compared to 100 applications as at September 2015 (FY15), reflecting an 86% reduction of the backlog up to September 2014. The age of the backlog has also reduced significantly; > three years (38%→3%), > two years (24%→2%), > one year (18%→1%) and < one year (19%→8%). And 40% of the dossiers received in running year, 2015 were reviewed.

As of August 2015, a total of 6064 pharmaceutical products were registered for use and the average number of days taken to review and approve a medicine registration application reduced from over 53 days to 48 days in 2014.

Post Market Surveillance – Medicine quality monitoring

A total of 171 samples of ARVs, TB and other essential medicines were collected from 24 public health facilities in eight regions. The facilities included seven primary healthcare clinics, six health centers, six district hospitals and one intermediate hospital. Figures 4 & 5 show the total number of samples collected categorized by generic name and region respectively.

Figure 4: Number of samples collected by generic name categories

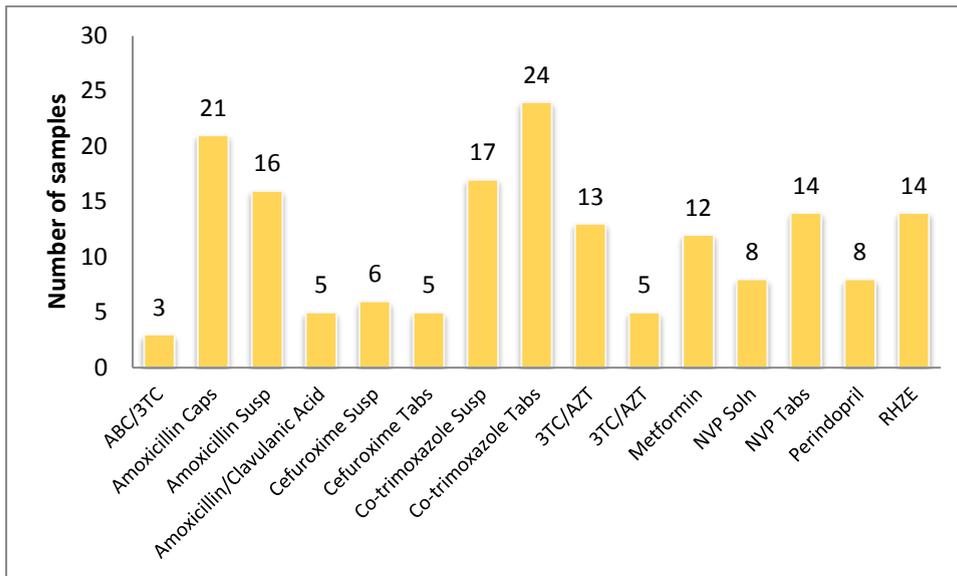


Figure 5: Number of samples collected by region.

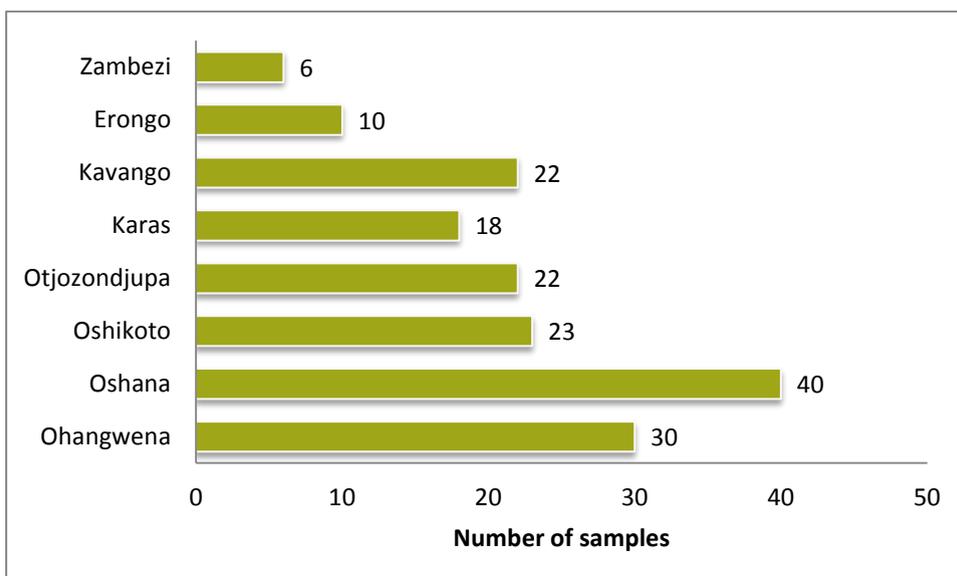


Table 3 shows the improved capacity of QSL to test medicine samples. The laboratory was able to test and release results of 88% (151) of the samples collected. This may be partly attributed to SAIPS support towards human capacity development for NMRC in FY14. Also there was a challenge of availability of reference standards for samples with zero percent rate

Table 2: Percentage of samples with results from NMRC Quality Surveillance Laboratory

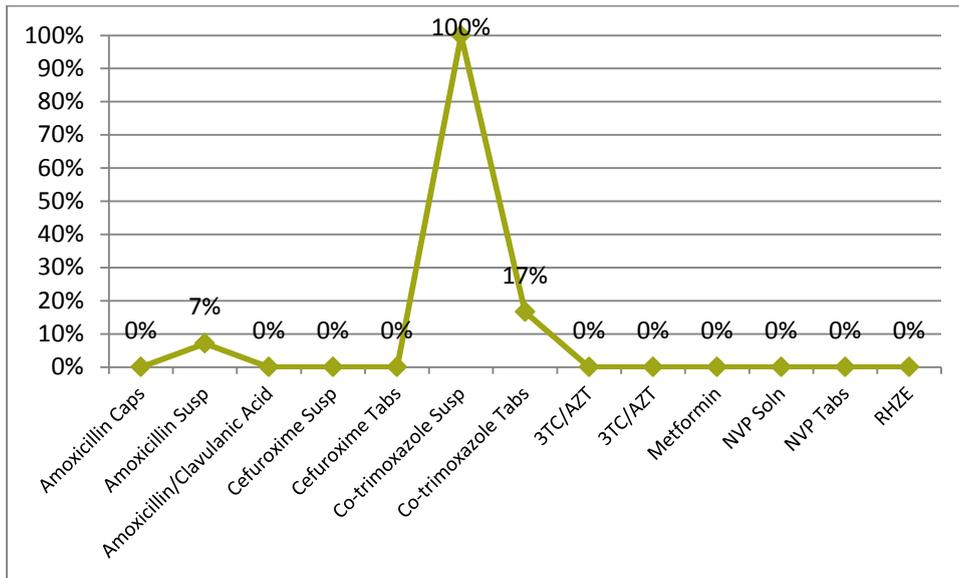
#	Generic Name	Strength	Dosage form	# of samples	% results received
1	ABC/3TC	60mg/30mg	Tablets	3	0%
2	Amoxicillin	250mg	Capsules	21	95%
3	Amoxicillin	125mg/ml	Suspension	16	88%
4	Amoxicillin/Clavulanic Acid	1000mg	Tablets	5	100%
5	Cefuroxime Axetil	125mg/5ml	Suspension	6	100%
6	Cefuroxime Axetil	250mg	Tablets	5	100%
7	Co-trimoxazole	240mg/5ml	Suspension	17	94%
8	Co-trimoxazole	480mg	Tablets	24	100%
9	3TC/AZT	150mg/300mg	Tablets	13	77%
10	3TC/AZT	30mg/60mg	Tablets	5	100%
11	Metformin	500mg	Tablets	12	100%
12	NVP	50mg/ml	Oral solution	8	100%
13	NVP	200mg	Tablets	14	86%
14	Perindopril	4mg	Tablets	8	0%
15	RHZE	150/75/400/275mg	Tablets	14	100%
Total				171	88%

Of the 151 samples tested, 13.9% (21) did not conform to pharmacopoeial specifications and Table 4 illustrates the results of the samples by region. Notably, 36.8% of the samples were unregistered, of which 1.9% were sub-standard according to the results from QSL and a WHO prequalified laboratory.

Table 3: Sample results by region

Regions	Passed	Failed	Not tested	Grand Total
Erongo	8	1 (11%)	3	12
Karas	14	3 (18%)	1	18
Kavango	12	4 (25%)	7	23
Ohangwena	24	1 (4%)	3	28
Oshana	33	6 (15%)	1	40
Oshikoto	16	3 (16%)	4	23
Otjozondjupa	19	2 (10%)	1	22
Zambezi	4	1 (20%)	1	6
Grand Total	130	21	22	172

Figure 6: Percentage of failures by product category



From figure 6 above, Co-tromoxazole suspension registered the highest percent of failures (100%), followed by Co-trimoxazole tablets (17%) and Amoxicillin suspension (7%). All the other others products had no failures registered.

Figure 7: Number of sample failures by analytical parameters.

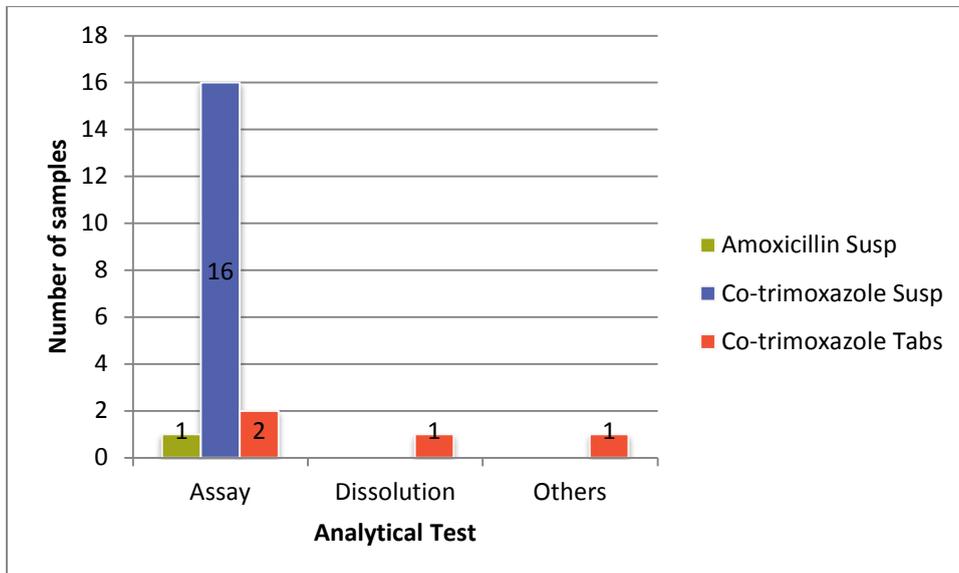


Figure 7 shows the nature of failures for the failed samples; 90% (19) failed assay, dissolution and other tests were at 5% (1) each.

5.0 CONCLUSIONS

SIAPS continued TA to NMRC has strengthened the capacity, improved the efficiency and significantly reduced the longtime backlog of medicine registration applications at NMRC. NMRC has taken up financial support for intensified medicines dossier reviews to accelerate the process and shorten the time taken to evaluate applications and register medicines, three of the four (75%) of the dossier review sessions held in FY15 were organized and financed by NMRC, which shows their commitment and sustainability of the interventions supported by the USAID-funded SIAPS project.

NMRC has also taken great strides towards post registration medicine quality monitoring and regulatory decisions are taken based on the outcomes to recall all products that do not conform to specifications, which may lack efficacy and thus impact on treatment outcomes and risk of developing microbial resistance to medicines.

5.0 REFERENCES

1. Systems for Improved Access to Pharmaceuticals and Services Namibia Work Plan: October 1, 2014–September 30, 2015.
2. Anisfeld M, An L, Mbaziira N, Kagoya H, Sagwa E. 2014. Strengthening the Capacity of the Namibia Medicines Regulatory Council in the Regulation of Antiretroviral Medicines and Other Essential Pharmaceuticals in Namibia
3. Namibian Medicines and Related Substances and Control Act of 2003
4. National Guidelines for Antiretroviral Therapy, fourth Edition, January 2014, MoHSS, Namibia.

6.0 APPENDICES

Appendix I: Official Invitation letter for Participants of Dossier review sessions



Received 9 - 0/0001
15/08/2014
Eisells

REPUBLIC OF NAMIBIA

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Windhoek

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Fax: (061) 225048
(International 264 61 225048)

Enquiry: Rite

Ref: 10/2/4

Date: 12.08.2014

NAMIBIA MEDICINES REGULATORY COUNCIL OFFICE OF THE REGISTRAR OF MEDICINES

To:

.....
.....
.....

Dear Sir / Madam

INVITATION TO A DOSSIER EVALUATION RETREAT 19TH – 24TH OCTOBER 2014

The Namibia Medicines Regulatory Council (NMRC) in collaboration with the MoHSS development partner MSH / SIAPS is organizing another dossier evaluation retreat which will be held at *the Okahanja Country Hotel* at the mentioned dates. The aim of this retreat is to further build the capacity of the attendants to enable them self evaluate and make a decision on quality of submitted dossiers and is on voluntary basis.

This retreat is a follow up on the dossier evaluation training that was held in Windhoek, 12 – 16th May 2014 (which you attended) and the subsequent successful follow up dossier evaluation retreat conducted in Windhoek on 21 – 25th July 2014.

I am inviting you to attend this important retreat. All expenses, i.e. accommodation and meals, will be covered. All that will be required from you is to be able to bring yourself to and from Okahanja.

If you are interested, please submit your name before or on 15th October 2014 preferably by e-mail to Ms. Saren Kauhondamwa, e-mail drugreg@nmrc.com.na, tel: 061 2032402, fax 061 225 048

"Health for All"

Yours Faithfully

Johannes #Gaeseb
REGISTRAR OF MEDICINES



Appendix II: Sample photographs taken during NMRC dossier review sessions in FY15



Medicine application dossiers lined up for review during a dossier evaluation session, October 2014. Photo by MSH/Namibia



A new staff of NMRC; Ms. Wubijig Legesse (on the right) reviewing a dossier, October 2014. Photo by MSH/Namibia