Doc. No.: TMDA/DMC/CTP/G/005

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

TMDA

Tanzania Medicines & Medical Devices Authority

POST MARKETING SURVEILANCE REPORT FOR SELECTED HUMAN AND VETERINARY MEDICINES CIRCULATING IN TANZANIA

2016 – 2017

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2016/2017

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ABBREVIATIONS

ADDO	-	Accredited Drug Dispensing Outlet
DG	-	Director General
DLS	-	Directorate of Laboratory Services
DMC	-	Directorate of Medical Products Control
GMP	-	Good Manufacturing Practices
HC	-	Health Centre
LGAs	-	Local Government Authorities
MAH	-	Marketing Authorization Holders
MOHCDGEC	-	Ministry of Health, Community Development, Gender, Elderly and Children
MSD	-	Medical Stores Department
PMS	-	Post Marketing Surveillance
QA	-	Quality Assurance
QC	-	Quality Control
SOPs	-	Standard Operating Procedures
SPC	-	Summary of Product Characteristics
TFDA	-	Tanzania Food and Drugs Authority
TLC	-	Thin Layer Chromatography
WHO	-	World Health Organization

ACKNOWLEDGMENTS

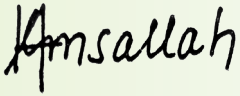
This report presents results for the quality surveillance of selected human and veterinary medicines monitored in the year 2016/17 as part of the three years structured Post Marketing Surveillance (PMS) programme from 2014/15 to 2016/17. This work would not have been possible without the commitment of TMDA staff and various stakeholders who worked tirelessly to implement the different phases of the programme.

I wish to express my heartfelt appreciation to all parties involved in this activity particularly; the section at TMDA which coordinates PMS activities, drug inspectors who took part in sample collection; evaluator's who reviewed the product information and analysts who carried out laboratory testing.

The report has been developed by the dedicated team of TMDA PMS task force after conducting a thorough assessment of analytical data. Special acknowledgement goes to Ms. Kissa Mwamwitwa, Mr. Chrispin Severe, Ms. Sophia Mziray, Mr. Emmanuel Alphonce, Ms. Siya Augustine, Mr. David Matle, Dr. Yonah Hebron, Mr. Makala Erasto, Mr. Sunday Kisoma, Mr. Seth Kisenge, Dr. Itikija Mwanga, Mr. Mujtaba Ratansi, Ms. Chimpaye Julius, Ms. Jane Jacob and Mr. Tryphone Gujema for the work well done to accomplishment. The secretarial services which

were offered by Ms. Joyce Komba are also greatly appreciated.

Last but not least, the TMDA Management team is highly acknowledged for their support and leadership which facilitated the successful implementation of the activities.



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ACTING DIRECTOR MEDICAL PRODUCTS CONTROL

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

FOREWORD

The Tanzania Medicines and Medical Devices Authority (TMDA) is mandated to monitor medicines circulating on the Tanzanian market to ensure that they are of good quality, safe and efficacious through various regulatory mechanisms including the Post Marketing Surveillance (PMS) programme.

PMS involves sampling of medicines from the market using a pre-arranged sampling plan, physical collection of samples, product information review and quality control testing in the laboratory.

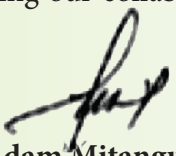
Through development of three years PMS programme, TMDA previously known as TFDA has been able to monitor the quality of different selected human and veterinary medicines randomly sampled from different levels of medicine distribution channels. In this way, substandard and falsified medicines were detected and appropriate regulatory actions taken.

The programme is implemented annually and every year different types of medicines are monitored to ascertain their quality. Results from previous years indicated low compliance on labelling and package insert requirements but high compliance for laboratory tests. Almost 83% and 92% of human and veterinary medicines failed to meet labelling and package insert

requirements respectively. However, results of confirmatory tests as per monograph requirement indicated high compliance rate of 95% and 89.2% for samples of human and veterinary medicines respectively.

In this report, result of the quality of human medicines namely; Albendazole tablets, Diclofenac/Paracetamol tablets, Dexamethasone/Neomycin ear/eye drops and Oxytetracycline 10% and 20% injection / powder for injection surveyed in the year 2016/17 are presented. Low compliance to labelling requirements as a major deficiency observed in this survey. Majority 62% (208/337) of the samples of human medicines lack list of excipients on package inserts whereas 66% (86/130) of veterinary medicines had inappropriate storage condition instructions on the label and package inserts.

Nevertheless, the PMS planned activities have been successfully completed due to the coordinated team work which involved various stakeholders within and outside TMDA. I thank all who were involved, including our collaborators and partners for the well done job.



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ACTING DIRECTOR GENERAL
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EXECUTIVE SUMMARY

During final year (2016/2017) of implementation of the three years (2014 – 2017) PMS program, TMDA through the so called TFDA assessed the quality of selected human medicines namely Albendazole tablets, Diclofenac/Paracetamol tablets, Dexamethasone/Neomycin ear/eye drops and veterinary medicines - Oxytetracycline 10% and 20% injection / powder for injection.

Samples were systematically collected from both public and private hospitals, pharmacies, dispensaries, accredited drugs dispensing outlets (ADDOs), Medical Stores Department (MSD) and veterinary clinics located in Mwanza, Dar es Salaam, Kagera, Arusha, Mtwara, Mbeya, Simiyu, Kigoma, Manyara and Shinyanga regions.

All sampled medicines were subjected to Tier I screening tests which involved product information review and laboratory testing using GPHF minilab kit. Samples which failed Tier I screening tests together with 10% of those complied were taken to Tier II confirmatory testing at WHO TFDA laboratory.

A total of 337 (78%) samples of human and 130 (68%) veterinary medicines were collected out of 432 and 192 respectively as planned. Review of information on the labels and package inserts of the collected samples revealed that, majority 62% (208/337)

of the samples of human medicines lack list of excipients on package inserts whereas 66% (86/130) of veterinary medicines had inappropriate storage condition instructions on the label and package inserts.

Notably, all samples of human and veterinary medicines passed physical appearance test except eight (8) samples of Diclofenac/ Paracetamol tablets which had brown spots on the tablets. Additionally, samples of Albendazole tablets passed identification tests by TLC and disintegration test.

Furthermore, samples for Dexamethasone/Neomycin eye/ear drops taken for confirmatory test passed identification, sterility, assay and bioassay tests. Likewise, all samples of Albendazole and Diclofenac/Paracetamol passed identification tests. However, 1.2% (9/13) samples of Albendazole and 0.7% (1/139) Diclofenac/Paracetamol failed dissolution and assay tests respectively. Similarly, 9.9% (7/71) samples of Oxytetracycline 20% failed assay test.

It is evidenced from the finding of this surveillance that, strengthening enforcement post registration of medicines is very crucial. This is because, manufactures still failed to comply with labelling requirements as observed in the previous surveys conducted. Nevertheless, substandard medicines were also found on the market.

1. INTRODUCTION

Structured Post Marketing Surveillance (PMS) programme is one of the two (2) principle approaches utilized by Tanzania Medicines and Medical Devices Authority (TMDA) to ascertain the quality of medicinal products circulating on the market. It is a systematic quality assurance measure to monitor the quality of registered medicines circulating on Tanzania market, after they have been subjected to and passed the pre-registration assessment processes.

Among the critical processes involved in PMS are proper planning and systematic sampling of medicines from the market using a pre-defined sampling plan so as to get good representation of medicines used for treatment of priority diseases. Sampling is performed by trained and qualified sample collectors. Comprehensive review of product information against the approved information, physical examination of product samples, laboratory screening and confirmatory testing of the collected samples were among other important aspects/elements of the PMS programme.

The so called TFDA, developed the third structured PMS programme for a period of three years between 2014/15 and 2016/17 after successful implementation of the two earlier programmes (2007 – 2009 and 2010 - 2013). Previous PMS programmes and the two years of this programme showed that

some of the samples of human and veterinary medicines did not meet quality standards and this calls for continuous monitoring of products circulating on Tanzania market.

The last two phases (V and VI) of the 2014/15 – 2016/17 PMS programme were implemented in 10 regions and included medicines for human and veterinary use namely Albendazole, Diclofenac/Paracetamol, Dexamethasone/Neomycin and Oxytetracycline 10% and 20% in different dosage forms.

The aforementioned medicines were sampled from different distribution points in the supply chain including public and private procurement and supplies agents, public and private hospitals and other outlets. These embraced Medical Stores Department (MSD), public and private hospitals, dispensaries, and health centres, wholesale and retail pharmacies, Accredited Drugs Distribution Outlets (ADDO) and veterinary medicines outlets in the regions namely; Mwanza, Dar es Salaam, Kagera, Arusha, Mtwara, Mbeya, Simiyu, Kigoma, Manyara and Shinyanga.

Collected samples were analysed at WHO pre-qualified TFDA laboratory to verify compliance with quality standards. This report henceforth highlights results obtained and regulatory actions taken by TFDA.

2. OBJECTIVES

2.1 Broad Objective

To determine quality of selected human and veterinary medicines circulating in Tanzanian market in the year 2016/2017.

2.2 Specific Objectives

The specific objectives of the surveillance were:-

2.2.1 To conduct laboratory quality control testing of samples of selected medicines (Albendazole tablets, Diclofenac + Paracetamol tablets, Dexamethasone + Neomysin eye drop and Oxytetracycline 10% & 20% for injection/ powder for injection solution).

2.2.2 To propose possible strategies and implementation plans to address the problems identified by the survey.

2.2.3 To inform the public on the quality status of circulating medicines.

2.3 Exploratory Objective

2.3.1 To determine availability of selected medicines (Albendazole tablets, Diclofenac + Paracetamol tablets, Dexamethasone + Neomysin eye drop and Oxytetracycline 10% & 20% for injection/powder for injection solution) on the market.

3. METHODOLOGY

3.1 Sampling Sites

Randomly selected one (1) district and city within eight (8) regions namely Arusha, Dar es Salaam, Mtwara, Mwanza, Kigoma, Kagera, Mbeya and Simiyu participated in the survey. Regions were selected based on the following criteria:-

- Regions bordering other countries
- Regions that are not frequently inspected
- Areas reported to have medicine quality problems
- Regions not involved in the previous PMS programmes

In each region samples were taken from MSD, public and private hospitals, dispensaries, health centres, wholesale and retail pharmacies, ADDO, and veterinary medicines outlets.

3.2 Sampling

3.2.1 Collection of Samples

Sampling of the selected medicines was done based on sampling plan attached as Annex I. Sampling plan highlighted detailed information on sampling sites, name of product, number of brands to be collected for each product, number of batches for each product, dosage forms, strength, pack size and number of units to be collected for each product. It also detailed specific sites of sampling at regional and district levels.

Samples were collected by using attached sampling form (Annex II) in their original containers by trained inspectors in accordance with the Standard Operating Procedure.

3.2.2 Handling of collected samples

Each collected sample was coded according to the prescribed coding format. Coding was done to identify samples collected from different regions and thus helped to differentiate and avoid mix up. Coded samples with respective sampling form were kept in the labelled sampling bag and sealed. Before and after transportation of the samples to TFDA headquarters, measures were taken to ensure that samples were stored according to manufacturers' recommended storage conditions as prescribed in the product labels.

3.3 Screening Testing (Tier I)

Samples were screened for the information provided on labels and package inserts through Product Information Review (PIR); and those with minilab screening methods were tested for disintegration test and identification test by Thin Layer Chromatography (TLC).

3.3.1 Product Information Review

Information provided on the labels of primary and secondary packaging and that in the package inserts was reviewed with the aim of verifying if they still comply with labelling requirements

and approved product information.
Information details checked during PIR included: -

- Generic and trade name (if any), dosage form and strength.
- Appearance or description of the dosage form.
- Name and address of manufacturer.
- Batch or lot number.
- Manufacturing and expiry dates.
- Packaging and pack size.
- Package inserts.
- Registration number.
- Language.
- Storage instructions.

PIR results were recorded in the designed screening form provided as Annex III.

3.3.2 Laboratory Screening

Among all samples of medicines collected in these phases only samples of Albendazole tablets were subjected to laboratory screening tests because minilab screening methods were available. They were tested for disintegration and identity by TLC methods.

3.3.2.1 Disintegration Test

Disintegration test was used to test the possibility of solid dosage

form to break into small particles and thus can dissolve and undergo dissolution to release active pharmaceutical ingredient. This was done by using disintegration test machine. The tablets which did not disintegrate within 30 minutes indicated dissolution problems necessitating confirmatory testing.

3.3.2.2 Identification Test by Thin layer Chromatography

TLC method was used for quantitative determination of active ingredients, related substances and impurities present in the dosage form. This method employs the principle of comparing spots obtained between test and reference solutions. The principal spot obtained with the test solution must correspond with the chromatographic runs of the lower and higher standard solutions in terms of colour, shape, size, intensity and retardation factor (R_f) value.

3.4 Laboratory Confirmatory Testing (Tier II)

Samples of medicines which did not have minilab screening methods were taken for laboratory tests according to their pharmacopoeia monograph or manufacturer's methods. All samples that failed screening test, all samples with doubtful screening results and 10% of all passed samples were selected for confirmatory testing. Confirmatory testing was performed by analysing each product as per pharmacopoeia monograph requirements. Parameters checked for each type of medicine were as shown in the table 1 below

Table 1: Method of analysis used for the parameters tested in each medicine

Category of medicines	Type of medicine	Parameters tested	Analytical Method used
Human Medicines	Albendazole tablets	Identification, assay, uniformity of dosage unit	USP 38NF 33, International pharmacopoeia
	Diclofenac + Paracetamol tablets	Appearance, Identification, disintegration, dissolution, related substances assay.	Manufacturer's in house methods
	Dexamethasone + Neomycin eye drop	Identification, assay, bioassay	USP 38NF 33, International pharmacopoeia
Veterinary Medicines	Oxytetracycline 10% & 20%	Identification, assay	British pharmacopoeia 2015

4. RESULTS

4.1 Samples Collected

4.1.1 Human Medicines

Samples of human medicines collected were 78% (337/432) of the planned. Many samples were from Arusha 20.2% (68/337) and few from Mtwara 7% (23/337). Of all the collected samples Diclofenac/Paracetamol amounted to 41.5% (140/337) ,Albendazole 36% (122/337) and Dexamethasone/Neomycin contributed 22% (75/337) as shown in the Table 2 below.

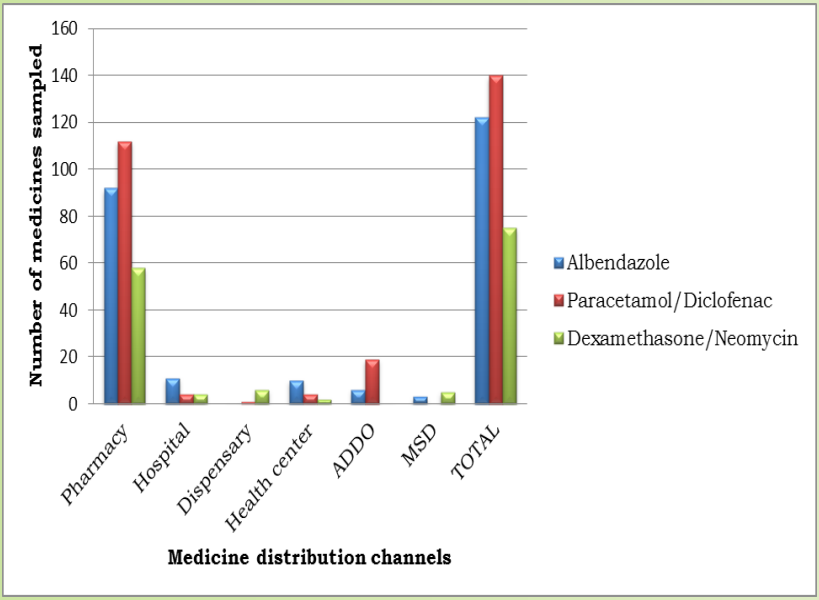
Table 2: Number of Samples of Human Medicines Collected				
Region	**Anthelminthic**	**Analgesic**	**Antibiotic and Steroid**	**Total**
	Albendazole	**Diclofenac/ Paracetamol**	**Dexamethasone/ Neomycin**	
Mwanza	14	14	10	**38**
Dar es Salaam	21	22	11	**54**
Kagera	14	11	10	**35**
Arusha	16	37	15	**68**
Simiyu	14	9	4	**27**
Mtwara	10	9	4	**23**
Mbeya	18	24	15	**57**
Kigoma	15	14	6	**35**
Total	**122**	**140**	**75**	**337**

4.1.2 Veterinary Medicines

Veterinary medicines samples collected were 68% (130/192) of the planned of which 58 were oxytetracycline 10% and 72 Oxytetracycline 20%. Most of the samples were collected from Arusha 46% (60/130) and few in Dar es Salaam (0.8% (1/130)) as shown in table 3 below.

Table 3: Samples of Veterinary Medicines Collected in the Regions			
Regions	**OXYTETRACYCLINE 20%**	**OXYTETRACYCLINE 10%**	**Number of samples collected**
ARUSHA	24	36	**60**
DAR ES SALAAM	1	0	**1**

MANYARA	5	0	**5**
MWANZA	10	10	**20**
SHINYANGA	32	12	**44**
	72	**58**	**130**



4.2 Sample Collection Sites

Figure 1 below depicts that, majority of human medicines were sampled in pharmacies - 78% (262/337) and least in dispensaries - 0.6% (2/337). Samples of Dexamethasone/Neomycin and Paracetamol/Diclofenac planned to be collected were not available in ADDOs and MSD respectively.

Fig 1: Number of human medicines sampled at different levels of distribution channel

4.3 Manufacturers and countries of origin

4.3.1 Human Medicines

As outlined in table 5 below, medicines sampled were from different manufacturers ranging from four (4) to thirteen (13) per product.

Table 5: Human medicines sampled with respective manufacturer (s)

Type of medicine	Manufacturer
Albendazole Tablets	Shelys Pharmaceuticals Limited, Tanzania
	Fourrts Laboratories Pvt-Ltd, India
	GlaxosmithKline Africa- South Africa
	Medopharm, India
	Regal Pharmaceuticals Ltd, Kenya
	Medreich,Avalahali, Bangalore, Limited-India
	Bluecross laboratories-India
	Indoco Remedies Ltd, India
	Elys Chemical Industries-Kenya
	Mercury Healthcare-India
	Lincoln Pharmaceuticals-India
	Shin Poong Pharmaceuticals-Korea
	Arlico-Korea arlico Pharm.co.,Ltd-Korea

Diclofenac/ Paracetamol Tablets	Win Medicare Pvt. Ltd, India.
	Shelys Pharmaceuticals Ltd, Tanzania
	Zenufa Laboratories Ltd, Tanzania
	Keko Pharmaceuticals Industries (1997) Limited Tanzania
	Lincoln Pharmaceuticals Ltd, India
Dexamethasone/ Neomycin Eye/Ear Drops	Nabiqasim Industries (PVT) Ltd, Pakistan
	Ivee Infusions EPZ Limited, Kenya
	Amman Pharmaceutical Industries Co., Jordan.
	Abacus Parenteral Drugs Ltd, Uganda

4.3.2 Veterinary Medicine

Likewise, samples of Oxytetracycline10% were from five (5) manufacturers and nine (9) for Oxytetracycline 20% as depicted in table 6 below.

Table 6: Veterinary medicines sampled with respective manufacturer(s)

Oxytetracycline 10% Powder for Oral and Solution for Injection	Farvet Laboratories, The Netherland
	Hebei Yuanzheng Pharmaceuticals Company Ltd, China
	Chongqing Fangtong Animal Pharmaceuticals, China
	Norbrook Laboratories Limited, Northern Ireland
	Inter Chemie Werken, Holland.

Oxytetracycline 20% Powder for Oral and Solution for Injection	Farvet Laboratories, Holland
	Hebei Yuanzheng Pharmaceuticals Company Ltd, China
	Chongqing Fangtong Animal Pharmaceuticals, -China
	Farmers Centrer Ltd, Tanzania
	NUTEC, UK.
	Alfavet Animal Healthcare Ltd, UK
	Nerix Pharma Ltd, Kenya
	Ceva Sante Animale, France
	Vetcare Africa, Kenya
	Anglian Nutrition, United Kingdom

From table 7 below, majority 54% (182/137) of the human medicines sampled were imported. About 77.1% of Diclofenac/ Paracetamol tablets sampled were from domestic manufacturer.

In addition, most of the samples of Albendazole tablets 34.4% (42/122) were imported from India and Dexamethasone/ Neomycin 42.7% (32/75) from Uganda.

Table 7: Percentage of Sampled Human Medicines that were Imported and Domestically Manufactured

Type of Product	Number of samples	Domestically Manufactured	Percentage (%)	Imported	Foreign manufactured (Country of origin)	Percentage (%)
Albendazole	122	47	(47/122) 38.5%	15	Kenya	(15/122) 12.3%
				5	S. Korea	(5/122) 4.1%
				42	India	(42/122) 34.4%
				13	S. Africa	(13/122) 10.7%

Diclofenac/ paracetamol	140	108	(108/140) 77.1%	32	India	(32/140) 22.9%
Dexamethasone/ neomycin	75	0	(0/75) 0%	32	Uganda	(32/75) 42.7%
				29	Kenya	(29/75) 38.7%
				2	Jordan	(2/75) 2.7%
				12	Pakistan	(12/75) 16.0%
Powder for solution						
Total	**337**	**155**	**(155/337) 46.0%**	**182**		**(182/337) 54%**

For veterinary medicines sampled, about 93% (122/130) were imported out of which 53% (38/72) were Oxytetracycline 20% and 76% (44/58) were Oxytetracycline 10% and these were mainly from China (table 8 below).

Table 8: Percentage of sampled veterinary medicines that were imported and domestically manufactured

Type of Product	Number of samples	Domestically Manufactured	Percentage (%)	Imported	Foreign manufactured (Country of origin)	Percentage (%)
Oxytetracycline 10%	58	0	0	3	Netherland	(3/58) 5.2%
				44	China	(44/58) 75.9%
				4	Northern Ireland	(4/58) 6.9%
				7	Holland	(7/58) 12.1%

Oxytetracycline 20%	72	7	(1/72) 1.4%	3	Holland	(3/72) 4.2%
				38	China	(38/72) 52.8%
				9	Kenya	(9/72) 12.5%
				13	United Kingdom	(13/72) 18.1%
				1	France	(1/72) 1.4%
Total	**130**	**7**	**(7/130) 5.4%**	**122**		**(122/130) 93.8%**

4.3 Screening Testing (Tier I) Results

4.3.1 Product Information

Review of information on the labels and package inserts of the samples of human and veterinary medicines was carried out against the approved labels and inserts of the respective products.

A total of 337 samples of human medicines were reviewed and found to have at least one deficiency. Eleven (11) deficiencies were observed on labelling and package inserts requirements of which the highest (208) being missing list of excipients in the package inserts, and the lowest (1) was unapproved language on the label. Among the three (3) sampled products, Diclofenac/ Paracetamol contributed highest (120) package inserts. with missing list of excipients.

The detailed results are shown in figure 2 below and annex IV.

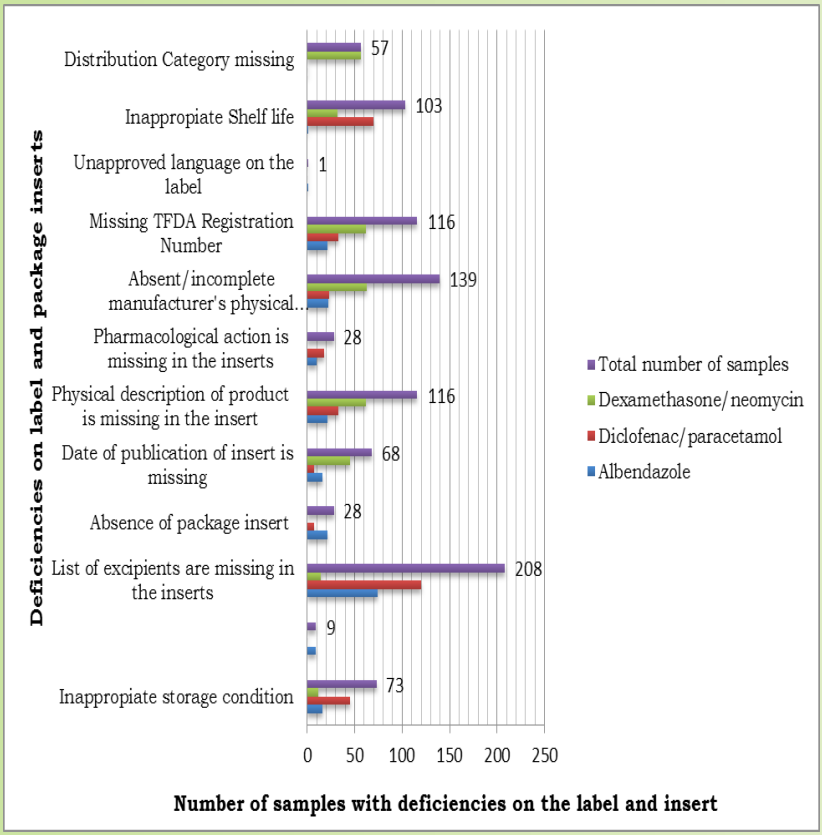


Fig 2: Number of human medicines with deficiencies on the labels and package inserts

For the veterinary medicines, a total of 130 samples were reviewed and found to have at least one (1) deficiency. Notably, 11 deficiencies were observed on the labels and package inserts of which the highest (86) was inappropriate storage condition and the least was (2) incorrect label artworks. The detailed results are shown in figure 3 below and annex V.

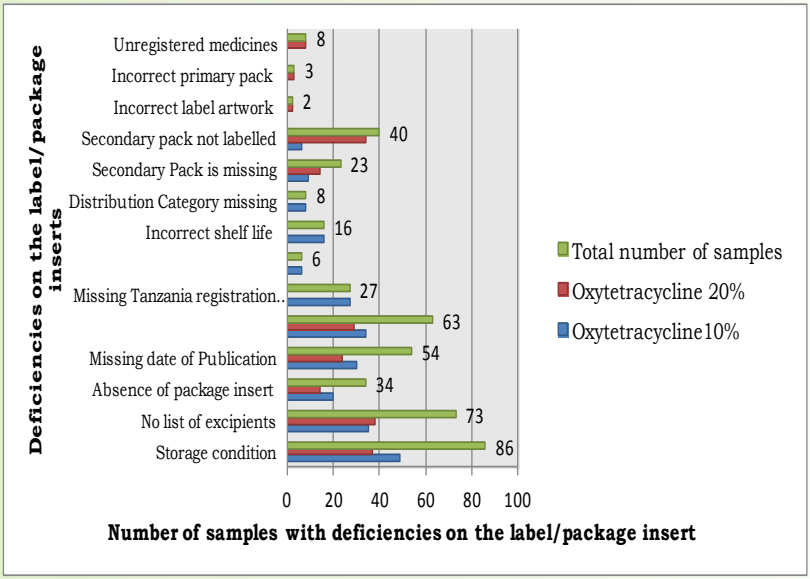


Fig 3: Number of veterinary medicines with deficiencies on the labels and package inserts

4.3.2 Visual Inspection

All samples collected for human and veterinary medicines were visually checked and results showed that most samples passed the test except eight (8) samples of Diclofenac/Paracetamol tablets which failed as they were having brown spots on the tablets.

4.3.3 Disintegration and Identification Test by TLC

A total of 122 samples of albendazole tablets were subjected to disintegration and identification tests by TLC and all samples passed the tests. Therefore, only 10% of the samples of Albendazole were taken for Tier II confirmatory testing.

Samples of human medicines namely Dexamethasone/ Neomycin eye/ear drops and Paracetamol/Diclofenac tablets and veterinary medicines namely Oxytetracycline 10% & 20% injection and powder for solution were not subjected to screening tests due to absence of GPHF minilab methods. Hence all samples were taken for Tier II confirmatory testing as shown in table 10 below.

Table 10: Number of Samples Selected for Confirmatory Testing

Category of medicine	Product name	Collected	Expired	Samples selected
Human medicines	Albendazole	122	0	13* (6%)
	Diclofenac / Paracetamol	140	1	139 (63%)
	Dexamethasone / Neomycin	75	5	70 (31%)
	Total	**337**	**6**	**222**
Veterinary medicines	Oxytetracycline 10%	58	0	58 (45%)
	Oxytetracycline 20%	72	1	71 (55%)
Total		**130**	**1**	**129**

*Note: * obtained from 10% of samples passed screening test (122)*

4.4 Confirmatory Testing (Tier II) Results

As shown in table 10 below, a total of 222 samples of human medicines were taken for confirmatory testing, of which 63% (139) were samples of Diclofenac/Paracetamol tablets, 31% (70) Dexamethasone/Neomycin eye/ear drops and 6% (13) Albendazole tablets. However, six (6) samples one (1) for Diclofenac/Paracetamol tablets and five (5) for Dexamethasone/Neomycin eye/ear drops were not tested because they had expired. A total of 222 samples comprising of Albendazole (13), Diclofenac/Paracetamol (139) and Dexamethasone/Neomycin (70) were tested, out of which 5.9% (13/222) failed to comply with compendial/manufacturer's specifications. Among the failure, dissolution test contributed 4.1% (9/222) and assay contributed 0.5% (1/222).

Table 11: Confirmatory testing results of human medicines

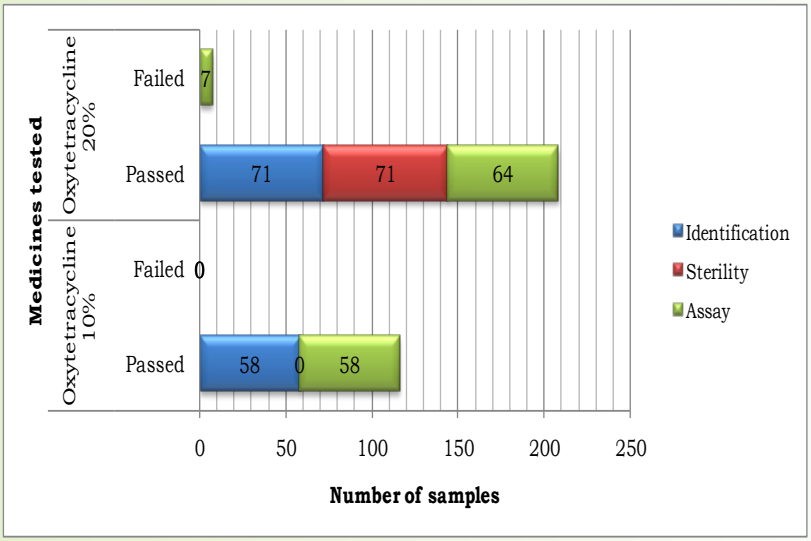
Type of Medicine	Tested	Identification (HPLC)		Disintegration		Dissolution test		Related Substance		Sterility		Assay		Bioassay	
		Passed	Failed	Passed	Failed	Passed	Failed	Passed	Failed	Passed	Failed	Passed	Failed	Passed	Failed
Albendazole chewable tablets	13	13	0	13	0	4	9	0	0	0	0	13	0	0	0
Paracetamol + Diclofenac tablets*	139	139	0	136	3	0	0	139	0	0	0	138	1	0	0
Dexamethasone + Neomycin eye/ear drops	70	70	0	0	0	0	0	0	0	70	0	70	0	70	0
Total	**222**	**222**	**0**	**149**	**3**	**4**	**9**	**139**	**0**	**70**	**0**	**221**	**1**	**70**	**0**

Note: 'x' test not applicable

Also, a total of 130 samples of veterinary medicines were collected, of which 129 samples were taken for confirmatory testing while one (1) sample of Oxytetracycline 20% was not tested because it had expired.

Samples of Oxytetracycline 10% were tested for identification and assay while oxytetracycline 20% were tested for identification, assay and sterility as shown in figure 4 below. Results shows that, all samples of Oxytetracycline 10% passed identification and assay tests whereby 7/71 (9.9%) of Oxytetracycline 20% did not comply with assay test.

Figure 4: Confirmatory test results for veterinary medicines



5. DISCUSSION

In this survey samples of human and veterinary medicines were collected in ten (10) regions as per sampling plan. About 75% of the samples were collected which is less than what was planned due to unavailability of the medicines at the time of collection. Similar findings were observed in the previous PMS programme reports [3].

It was noted that, majority of samples were collected from Dar es Salaam, Mwanza and Arusha as these are cities with high business volume and the later two with high livestock population [1].

Notably, contribution of private sector was found to be higher than public sector as observed in this survey that, large numbers (78%) of human medicines were sampled from private pharmacies. Similar findings were reported in previous surveys conducted in Kenya and Tanzania [3, 4, 5, 6]. Similarly, all veterinary medicines were from private pharmaceutical outlets since currently there is no public supply mechanism for veterinary medicines.

As noted earlier in the previous PMS survey, large quantity of the surveyed samples for both human (54%) and veterinary medicines (93%) were imported [5, 6]. This is justified by the fact that domestic manufacturing facilities in Tanzania still have low capacity (20-30%) to serve the country's medicines demand [5,6,7]. However, this was not the case for combination of Diclofenac/Paracetamol tablets where majority of the surveyed

samples were domestically manufactured.

Significant failure to adhere with labelling requirements and information presented on the package inserts observed in this survey is supported by similar findings in previous studies [6, 7]. The most notable discrepancy on the samples of human medicines was absence of list of excipients on package inserts and inappropriate storage statement for veterinary medicines [8]. This still shows that manufacturers do not comply with the labelling and package inserts requirements as provided for in the Guidelines for Submission of Documentation for Marketing Authorization of Human and Veterinary Pharmaceutical Products [1].

Unapproved shelf life was also observed for some of the samples of human and veterinary medicines. This can be explained by the reason that manufacturers make changes to the product labels, package inserts and sometimes extend shelf lives without filling variation to TFDA. Moreover, failure of manufacturers to print registration numbers on labels was also observed and this poses significant risk of introducing falsified medicines on the market.

Some samples of Diclofenac/Paracetamol tablets with brown spots were found on the market hence the products failed physical examination. Much as dissolution test was not one of the requirements for testing Albendazole at the time of approval, this parameter has been tested as per the current pharmacopoeial standards and result shows that 69.2% (9/13) of samples failed the test.

Nevertheless, since only 2.1% (3/139) of the samples tested failed dissolution and 0.2% (1/139) assay testing, this signifies that the percentage failure rate was insignificant.

6. REGULATORY ACTIONS TAKEN

The following regulatory actions were taken by TFDA:

6.1 Batches of Diclofenac/Paracetamol tablets and Oxytetracycline 20% which failed the tests were withdrawn from the market and manufacturers were directed to conduct thorough investigation to find out the root cause of the problem.

6.2 Importation of future batches of the identified poor-quality products has been suspended until after manufacturers have submitted their investigative reports.

6.3 Warning letters were issued to marketing authorization holders whose products failed to meet labelling and package inserts requirements.

6.4 MAH was requested to submit applications for variation to include dissolution test for albendazole chewable tablets as one of the parameters to be tested at release of the finished product.

7. CONCLUSION

Survey results have led to a better understanding of the quality status of the medicines on the market and facilitated detection of substandard medicines circulating on the market.

It can be inferred that the manufacturers of the human and veterinary medicines have observed the laboratory quality standards of their products with exception of some few batches of Albendazole tablets, Diclofenac/Paracetamol tablets and Oxytetracycline 20%. However, all manufacturers are argued to adhere to the Tanzania Food, Drugs and Cosmetics (Registration of Medicinal Products) Regulations 2015, due to the existence of high failure rate on the labelling and package inserts requirement.

This has also contributed towards evidence-based regulatory actions and emphasizes further the need for constant and continuous surveillance of the medicines by both the Authority and manufacturers to ensure that only good quality medicines are circulating on the Tanzanian market.

8. LIMITATIONS

Limitations encountered during implementation of the programme including writing up of the report were;

a) As results of limited capacity of TFDA Quality Control Laboratory, analysis of samples collected took long time and at the time of releasing analytical results the identified batches of substandard medicines were not available on the market.

b) Insufficient samples collected from the planned sampling sites compared to the targeted number due to unavailability of products.

c) Delays in procurement process of reagents and chemicals which contributed to stock-piling of the collected samples and hence expiration of the samples before confirmatory testing that caused decrease in the number of analysed samples and delay in completion of analysis as planned.

9. AREAS FOR IMPROVEMENT

a) Before embarking on sample collection, sample collectors should be trained appropriately on how to conduct sampling. In addition, reviewers of product information should be re-trained so as to avoid improper recording of deficiencies observed during product information review.

b) Preparation for PMS plan should take into consideration the practicability of time taken to process the collected samples and laboratory analysis.

c) Laboratory consumables and reagents should be procured/purchased in time so that PMS implementation plan is not affected.

d) The system for storing and keeping medicines registration data including variations should be updated and updated information and retained samples of the registered medicines should as well be readily available when needed.

e) The procedure for conducting screening should be revised to accommodate products which do not have minilab screening methods so as to have a clearly scientific justification for selecting samples for confirmatory testing.

f) TFDA Zone Offices should give priority on investigating and supervising recall of the identified substandard and/or falsified medicines and submit the report to DMC as requested.

g) Products that were found to have highest failure rates (more than 50% of the surveyed samples) should be included in the next programme.

10. REFERENCES

1. Guidelines for Submission of Documentation for Marketing Authorization of Human and Veterinary Pharmaceutical Products.

2. Guidelines for Good Manufacturing Practices (GMP - 2008)

3. TFDA (2016), *Post Marketing Surveillance Report of the Quality of Selected Medicines under phase III-IX of 2011-2013 PMS Program*. Tanzania Food and Drugs Authority, Dar-es-Salaam, Tanzania.

4. Mwathi Martha Wangu and Ben Onyango Osuga (2014); *Availability of essential medicines in public hospitals: A study of selected public hospitals in Nakuru Country*,

Kenya; African journal of pharmacy and pharmacology.

5. Joseph Wales, Julia Tobias, et al (2014), *Stock-out of essential medicines in Tanzania, A political economy approach to analysing problems and identifying solutions*, Twaweza report

6. Local production of pharmaceuticals in Africa and access to essential medicines: 'urban bias' in access to imported medicines in Tanzania and its policy implications.

7. TFDA (2016), *Post Marketing Surveillance Report of the Quality of Antimalarial, Anti-Retroviral and Anti-Tuberculous Medicines Circulating in Tanzania for the year 2012-2015*. Tanzania Food and Drugs Authority, Dar-es-Salaam, Tanzania.

8. ICH Stability Zones: http://www.pharmaguideline.com/2010/12/different-climatic-zones-for-stability.html accessed on 24th January 2017.

11. ANNEXES

Annex I: Sampling plan

Annex II: Sample collection form

Annex III: Screening Form

Annex IV: Detailed description of the failures on the label and package inserts of samples of veterinary medicines

Annex I: Sampling Plan

SAMPLING PLAN FOR PHASE V-VI

1.2 SAMPLING PLAN FOR CONDUCTING PMS OF OXYTETRACYCLINE 10% & 20% IN ARUSHA, MANYARA, MWANZA AND SHINYANGA REGIONS											
Sampling sites	**Product Category**	**Product**	**Dosage Form**	**Strength**	**Number of brand to be collected**	**Number of batch per brand to be collected**	**Unit Pack**	**Number of unit pack per batch be collected**	**Total number of samples to be collected**	**Unit cost**	**Cost**
Regional Level											
Level 1	**National and Private Procurement agent/ supplier**										
Importer/ Wholesale pharmacy	Antibiotic	Oxytetracycline	Injection	10%	2	1	Bottle	10	20	5000	100000
				20%	2	1	Bottle	10	20	6000	120000
			Powder	20%	2	1	Sachet	20	40	7000	280000
Veterinary clinic	Antibiotic	Oxytetracycline	Injection	10%	2	1	Bottle	10	20	5000	100000
				20%	2	1	Bottle	10	20	6000	120000
			Powder	20%	2	1	Sachet	20	40	7000	280000

Retail pharmacy	Antibiotic	Oxytetracycline	Injection	10%	2	1	Bottle	10	20	5000	100000
				20%	2	1	Bottle	10	20	6000	120000
			Powder	20%	2	1	Sachet	20	40	7000	280000
ADDO Vet.	Antibiotic	Oxytetracycline	Injection	10%	2	1	Bottle	10	20	5000	100000
				20%	2	1	Bottle	10	20	6000	120000
			Powder	20%	2	1	Sachet	20	40	7000	280000
Subtotal					**24**						**2000000**

District Level											
District 1											
Wholesale pharmacy	Antibiotic	Oxytetracycline	Injection	10%	2	1	Bottle	10	20	5000	100000
				20%	2	1	Bottle	10	20	6000	120000
			Powder	20%	2	1	Sachet	20	40	7000	280000

Veterinary clinic	Antibiotic	Oxytetracycline	Injection	10%	2	1	Bottle	10	20	5000	100000
				20%	2	1	Bottle	10	20	6000	120000
			Powder	20%	2	1	Sachet	20	40	7000	280000
Retail pharmacy	Antibiotic	Oxytetracycline	Injection	10%	2	1	Bottle	10	20	5000	100000
				20%	2	1	Bottle	10	20	6000	120000
			Powder	20%	2	1	Sachet	20	40	7000	280000
ADDO Vet.	Antibiotic	Oxytetracycline	Injection	10%	2	1	Bottle	10	20	5000	100000
				20%	2	1	Bottle	10	20	6000	120000
			Powder	20%	2	1	Sachet	20	40	7000	280000
Subtotal					**24**						**2000000**
Total cost of purchasing sample per region											**4,000,000.00**
Total cost of purchasing sample in 4 regions											**16,000,000.00**

Number of regions involved	**4**					
Expected number of batches to be collected per region	**48**					
Total number of batches to be collected in 4 regions (i.e 48x 4)	**192**					

Annex II: Sample Collection Form

MEDICINES POST MARKETING SURVEILLANCE
SAMPLE COLLECTION FORM

1. Sample code: .....

   (Region/product/sequence number/sampling date ddmmyy)***
2. Name of Premises where sample was taken: .....
3. Physical Address.....Postal address.....

   Telephone No.....Fax No .....

   Email address..... (If applicable)
4. Product name of the sample: .....
5. Name of active pharmaceutical ingredient(s) (INN) with strength: .....
6. Dosage form (tablet, oral powder, etc): .....
7. Package size & type: .....
8. Batch/lot number: ..... Date of manufacture: .....Expiry date: .....….
9. Name and physical address of the manufacturer: .....
10. Number of units collected.....
11. Is the product registered in Tanzania? Yes/ No. If Yes,

indicate the registration number: .....

12. Comment on storage condition of product at the premises: .....

13. Name and signature of the Representative of the premise where sample was collected:

Name.....

Signature.....Date.....

14. Name of Drug Inspector (s)/Sampling officer

S.No	Name	Organization	Signature	Date

Note: Samples collected must remain in their original containers.

Annex III: Screening Form

TANZANIA FOOD AND DRUGS AUTHORITY

DIRECTORATE OF LABORATORY SERVICES

MEDICINES QUALITY ASSURANCE CENTERS

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

Product name:_____

INNs:_____

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 Name & Physical 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 name (specify only if different from the external packaging under point 1)	YES NO .....

3- Package leaflet	
Presence of the leaflet	YES NO
Language(s) of the leaflet	.....
Composition	YES NO
Manufacturer name & physical address (specify only if different from the external packaging under point 1)	YES NO ....

Storage conditions (specify only if different from the external packaging under point 1)	YES NO ....

4- Observation on any discrepancy between the above points 1, 2 or 3 or non-compliance, if any

_____

_____

_____

5- Report on Minilab testing

PHYSICAL/VISUAL INSPECTION TEST	
Description of dosage form	
Shape (circular, oval, flat sides, other)	
Uniformity of shape	
Uniformity of colour	
No physical damage (cracks, breaks, erosion, abrasion, sticky)	
Other observations (no foreign contaminant, dirty marks, proper seal - for capsule)	
DISINTEGRATION TEST	

Time of complete complete Did the drug pass Disintegration expected disintegration observed disintegration test? (30 minutes for uncoated tablet) ---------- Yes No	Time in minute of	
RESULT OF TLC TEST (see Appendix 2 for TLC result 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 with basic testing specifications

The sample not-conformed with 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 SUPERVISOR OF MEDICINES QUALITY ASSURANCE CENTER1	
Report the result to TFDA Date of report ..... Signature.....	Send the remaining sample units together with this Form to the TFDA QC lab for further testing Date..... Signature.....

Reasons given for the chosen action

ANNEX IV: Result of Product Information Review of human medicine

Deficiencies on the labels and package inserts	Albendazole	Diclofenac/paracetamol	Dexamethasone/neomycin	Total number of samples	% per total number of samples
Storage condition					
Storage temperature below 25°C	6	30	12	48	14.2% (48/337)
Storage condition not specified in numerical figures	10	0	0	10	3% (10/337)
Storage condition not included on the insert	0	15	0	15	4.4% (15/337)

Manufacturing date, expiry date and batch number					
Lack of batch number, manufacturing and expiry date on secondary pack	9	0	0	9	3% (9/337)
Batch number, mfg and expiry date erasable	19	0	0	19	6% (19/337)
Package Insert information					
No list of excipients	74	120	14	208	62%(208/337)
Absence of package insert	21	7	0	28	8%(28/337)
Missing date of publication	16	7	45	68	20.2%(68/337)
Missing product physical description	21	33	62	116	34.4%(116/337)
Missing pharmacological action of product	10	18	0	28	8.3%(28/337)
Manufacturer address					
Incomplete name and physical address of the manufacturer on primary pack	0	0	1	1	0.3%(1/337)

Name & address of FPP manufacturer not included	16	0	0	16	5%(16/337)
Manufacturing plot number is missing	6	0	0	6	2%(6/337)
Street and block address missing	0	23	62	116	34.4%(116/337)
Missing Tanzania registration number	21	33	62	116	34.4%(116/337)
Unapproved language on the label	1	0	0	1	0.3%(1/337)
Inappropriate shelf life					
Shelf life 48 months is different from the one approved	1	0	0	1	0.3%(1/337)
Shelf life indicated 48 months instead of 24 months	0	57	0	57	17%(57/337)
Shelf life indicated 30 months instead of 24 months	0	0	32	32	9.5%(32/337)
Shelf life indicated 4 years instead of 2 years	0	13	0	13	4%(13/337)
Distribution Category missing	0	0	57	57	17%(57/337)

ANNEX V: Results of Product Information Review of veterinary medicine

Deficiencies on the label and package insert	OXYTETRACYCLINE 10%	OXYTETRACYCLINE 20%	Total number of samples	% per total number of samples
Storage condition				
Storage at temperature below 25°C	49	35	84	64.62% (84/130)
Storage at temperature at 15°C-25°C	0	2	2	1.54% (2/130)
Package Insert information				
No list of excipients	35	38	73	56.15% (73/130)
Absence of package insert	20	14	34	26.15% (34/130)

Missing date of Publication	30	24	54	41.54% (54/130)
Missing product physical prescription	34	29	63	48.46% (63/130)
Missing Tanzania Registration Number	27	0	27	20.77% (27/130)
Incomplete Registration Number (TAN 09, 237 J01A) instead of TAN 09,237 J01A TAN	6	0	6	4.62% (6/130)
Shelf life indicated on the label 36 & 37 months instead of 24months	16	0	16	12.31% (16/130)
Distribution Category missing	8	0	8	6.15%(8/130)
Secondary pack				
Secondary Pack is missing	9	14	23	17.69%(23/130)
Secondary pack not labelled	6	34	40	31% (40/130)

The artwork of the sample label was different from the one approved by TFDA	0	2	2	1.54% (2/130)
Primary packaging used is different from the one approved by TFDA	0	3	3	2.31% (3/130)
Product not Registered	0	8	8	6.15% (8/130)

(Footnotes)

1 Action to be taken and communication between should be dependent on country's rules and regulations.

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