

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY



Tanzania Medicines & Medical Devices Authority

**ANNUAL POST MARKETING SURVEILLANCE REPORT FOR
SELECTED HUMAN AND VETERINARY MEDICINES CIRCU-
LATING IN TANZANIA**

2020/2021



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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 |
| PIR | - Product Information Review |
| PMS | - Post Marketing Surveillance |
| QA | - Quality Assurance |
| QC | - Quality Control |
| SOPs | - Standard Operating Procedures |
| SPC | - Summary of Product Characteristics |
| TMDA | - Tanzania Medicines and Medical Devices Authority |
| TLC | - Thin Layer Chromatography |
| WHO | - World Health Organization |

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Dr. Yonah H. Mwalwisi
DIRECTOR HUMAN AND VETERINARY MEDICINES
TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

FOREWORD

Monitoring the quality, safety and efficacy of medicines circulating in the market is fundamental in protecting public health. Routine surveillance of medicines after registration (Post Marketing Surveillance - PMS) is one of the key responsibilities of a functional national medicine's regulatory authority. PMS helps medicines users, especially patients, who are key stakeholders in the pharmaceutical industry, to build confidence in the medicines they use that they will meet the expected standards for quality, safety and ultimately treat the intended diseases.

PMS also helps to timely detect and remove falsified and substandard medicines from the market thus protecting the public against the possible hazards associated with their use.

In view of this importance, Tanzania Medicines and Medical Devices Authority has developed and maintained a PMS system since 2009. The Authority has been developing a three-year PMS program where selected registered medicines are monitored based on a variety of criteria including reports of complaints from various stakeholders. The implementation of the plan was divided into six phases (I - VI), and in each phase, a sampling plan was set based on various risk criteria.

In this report we present methodology and detailed results for PMS of selected medicines for year 2020/21.

Overall, the PMS exercise was excellently planned and the execution was well coordinated. Implementation was carried out by various dedicated stakeholders within and outside TMDA. Key lessons learned from the PMS exercise will be used to improve the quality, safety and ultimately efficacy of medicines circulating in Tanzanian market. Moreover, it will assist TMDA to improve the subsequent PMS programs and ultimately protect public health.

I would like to commend all esteemed stakeholders involved including our collaborators and partners for making the 2020/2021 PMS program a success.



Adam Mitangu Fimbo
DIRECTOR GENERAL
TANZANIA MEDICINES AND MEDICAL DEVICES
AUTHORITY

Executive Summary

In the financial year 2020/2021, TMDA assessed the quality of selected human and veterinary medicines circulating on the market as part of implementation of the three years (2020 - 2023) PMS program. The selected human medicines included Metronidazole solution, Metformin tablet, Azithromycin tablet, and Telmisartan+Hydrochlorothiazide. The selected veterinary medicines were Levamisole injection and Sulfadiazine+Trimethoprim powder for oral solution.

Systematic method for sample collection was used where by samples were collected from public and private hospitals, pharmacies, dispensaries, accredited drugs dispensing outlets (ADDOs), Medical Stores Department (MSD) and veterinary medicines outlets. A total of 445 medicine samples were taken from 16 regions of Tanzania Mainland; Dar es Salaam, Morogoro, Dodoma, Singida, Geita, Mwanza, Shinyanga, Simiyu, Arusha, Manyara, Mbeya, Tanga, Iringa, Katavi, Tabora and Mtwara. Of all the selected medicine samples 349(78.4%) were human medicine and, 96 (21.6%) veterinary medicines.

Results for PIR indicated that 296 (66.5%) medicine samples did not comply with regulatory requirements. Human and veterinary medicine samples with various deficiencies were 233 (66.7%) and 63(65.6%) respectively. The Marketing Authorization Holders of the samples failed PIR were directed to comply with labeling requirements.

In the PMS programme 2020/2023 which was implemented for phase I and II in 2020/2021, a total of 445 medicine samples were collected from the market. The samples were taken from representative regions countrywide using a carefully designed sampling plan. After collection, product information review (PIR) was performed followed by laboratory testing based on selected critical parameters. The whole exercise was conducted by the qualified personnel who were well versed with the PMS protocol. Out of the selected samples, 349(78.4%) were human and, 96 (21.6%) were veterinary medicines. Results for PIR indicated that 296 (66.5%) medicine samples had various deficiencies. Human and veterinary medicine samples with various deficiencies were 233 (66.7%) and 63(65.6%) respectively.

The common deficiencies observed during PIR were lack of list excipients on the labels, labels not complying to the storage condition of Zone IVb, lack of product description

and not indicating excipients of safety concerns on either the external packaging or package inserts.

Of all samples which were subjected to confirmatory laboratory testing, only one sample (Metformin tablet) failed the dissolution test.

A total of 53 samples (47 Human Medicines and 11 from Veterinary Medicines) were selected for Tier II confirmatory testing at TMDAWHO prequalified laboratory. One human medicine sample (metformin) failed the test (2.1%, 1/47) and was withdrawn from the market. All the veterinary medicine samples passed the tests.

Generally, laboratory test results of the selected medicines with exception of Metformin tablets complied to the specifications which indicate functioning of regulatory systems in the country.

1. Introduction

Globally, substandard, and falsified medicines pose a serious public health problem due to increased risk of morbidity and mortality. It is estimated that, about 1million people worldwide die annually from substandard and falsified medicines. The World Health Organization estimates about 10% of medicines circulating in the market in low- and middle-income countries are either falsified or substandard¹. The extent of falsified and substandard medicines is not well known due to limited research, methodological hurdles, and surveillance methods².

In order to protect the public health against substandard and falsified medicines, Tanzania Medicines and Medical Devices Authority (TMDA) conducts a regular and structured Post Marketing Surveillance (PMS) of selected registered medicines in Tanzanian market. PMS, as one of TMDA's regulatory mandates is a systematic quality assurance measure to monitor quality of registered medicines and it aims at establishing the status of quality of medicines circulating in Tanzanian market and protects the public against substandard and falsified medicines. It provides valuable information on the quality of medicines once the drug enters the market, the information which is often unavailable prior and during registration process.

The PMS is implemented through systematic and meticulous planning using a pre-defined sampling of medicines circulating in the market. The focus is to ensure representation of medicines for human and veterinary priority diseases in the country. Sample collection for selected medicines was conducted by trained and qualified sample collectors in line with the pre-determined sampling plan.

Sampling of human and veterinary medicines was conducted in 2020/2021 in 16 regions of Tanzania Mainland; Dar es Salaam, Morogoro, Dodoma, Singida, Geita, Mwanza, Shinyanga, Simiyu, Arusha, Manyara, Mbeya, Tanga, Iringa, Katavi, Tabora and Mtwara. The samples were collected from Medical Stores Department (MSD) the supplier of medicines and medical products to public health facilities in Tanzania. The exercise equally covered public and private health facilities, wholesale and retail pharmacy outlets; accredited drug dispensing outlets (ADDO), the lowest access point of medicines in Tanzania and from veterinary setting outlets.

The collected human medicines included Metronidazole solution, Metformin tablet, Azithromycin tablet, and Telmisartan Hydrochlorothiazide tablets whereas veterinary medicines studied were Levamisole injection and Sulfadiazine+Trimethoprim powder for oral solutions.

The scope of the PMS included screening by reviewing product information (summary of product characteristics, package leaflet and labelling) as well as preliminary laboratory tests such as appearance, disintegration and identification. Of these, 10% of the medicines which passed screening procedures, sample with doubtful results and all medicines which didn't pass screening were subjected to laboratory confirmatory tests (i.e. assay, dissolution, related substances and content of uniformity of dosage units).

All sampled human and veterinary medicines were analysed at a World Health Organization (WHO) pre-qualified Laboratory located at TMDA, Dar es Salaam to ascertain compliance to quality standards. This report highlights results obtained and regulatory actions taken by TMDA.

2. OBJECTIVES

2.1. Broad Objective

To determine quality of selected human and veterinary medicines circulating on Tanzanian market in the year 2020/2021.

2.2. Specific Objectives

The specific objectives of the surveillance were: -

- i. To determine compliance of collected medicines samples to labelling requirements by conducting PIR.
- ii. To establish quality of selected medicines samples by conducting laboratory quality control tests.
- iii. To take relevant regulatory action(s) and propose strategies to address the problems identified by the survey.

3. METHODOLOGY

3.1. Medicines Selection

Medicines for quality monitoring in these phases were selected based on the following criteria:

- i. Reports on quality, safety and efficacy of medicines received by TMDA from various sources
- ii. Changes in disease pattern and management
- iii. Experience gained in previous PMS programmes
- iv. Medicines containing active ingredients known to have stability problems
- v. Medicines from manufacturers whose products were previously reported to have high incidences of being counterfeited and substandard

3.2. Sampling

3.2.1 Sampling sites

Samples were collected from randomly selected sites which included Medical Stores Department (MSD), public and private hospitals, health centres, dispensaries, importers, wholesale and retail pharmacies in selected regions of the country.

The regions were selected based on the following criteria:-

- a) Regions bordering other countries
- b) Regions that are not frequently inspected
- c) Areas reported to have medicines quality problems
- d) Regions not involved in the previous PMS programme phase
- e) Disease endemicity.

3.2.2 Collection of Samples

Collection of samples at various levels of supply chain was based on the developed sampling plans. Sampling plans were prepared and contained detailed information on sampling sites at regional and district levels, product name, number of brands to be collected, dosage forms, strength and pack size. Sampling plans are attached as **Annex II**. Samples were collected according to Standard Operating Procedure No. TMDA/DMC/CTPV/SOP/012 by trained medicine inspectors from TMDA and Local Government Authorities. Samples were collected in their original containers and/or packages together with their package insert. Details of the collected samples were recorded in the sample collection form attached as **Annex I**.

3.2.3 Sample handling and transportation

Each collected sample was coded according to prescribed coding format. Coding was done to identify samples collected from different sampling sites and thus helped to differentiate and avoid mix up. Coded samples with respective sampling form were kept in the labelled sampling bags and sealed. The samples were transported to TMDA zonal offices for data entry in Regulatory Information Management System (RIMS).

On completion, samples were transported to TMDA HQ Sub Office for screening and confirmatory testing. Before and after transportation of samples, measures were taken to ensure that samples were stored according to manufacturers' recommended storage conditions as prescribed in the product labels.

4 Sample Analysis

4.1 Screening

Screening testing involved Product Information Review (PIR), physical/visual inspection, disintegration test and identification test by Thin Layer Chromatography (TLC) or UV - Vis spectrophotometer.

4.1.1 Product Information Review (PIR)

All samples were subjected to product information review (PIR). This involved the review of information contained on the primary and secondary packaging, package inserts and label of each sample of medicine for conformity to the TMDA approved product information and labelling requirement. Apart from appropriateness and legibility of the information on the label and associated insert, appropriateness of the type of container used, stickiness and printing on the label were also checked..

4.1.2 Physical/visual inspections

Visual inspections were conducted so as to give information about product quality prior to further laboratory testing of samples in comparison with registration information. Injectable solutions were examined for leakage, particles, homogeneity, fill volume and

colour change. For the case of oral solid dosage forms colour change, spots, moulds, abrasions, and dour were checked.

4.1.3 Simple disintegration Test

Disintegration test was used to test the possibility of solid dosage form to break into small particles that 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 in which dissolution test were conducted as per their respective compendial monographs.

4.1.4 Qualitative and semi - quantitative determination of API by using Thin layer Chromatography

TLC method was used for qualitative and semi - quantitative determination of Active Pharmaceutical Ingredient (API) and related degradants present in the dosage form. This method employs the principle of comparing spots obtained between test and reference standard solutions. The principal spot obtained with the test solution must correspond with the spot of the higher reference standard solutions in terms of colour, shape, size, intensity and retardation factor (Rf) value.

4.1.5 Qualitative determination by using UV - Vis Spectrophotometer

UV - Vis Spectrophotometry is an analytical method used for qualitative and quantitative determination of API in pharmaceutical dosage form. In qualitative determination, method employs spectrophotometry principle whereby maxima absorption wavelength of the sample (test solution) is compared with maxima absorption of the standard solution.

4.2 Laboratory Confirmatory Testing by using compendial or manufacturer methods

All samples that failed screening test, all those with doubtful screening results and 10% of all passed samples were selected for confirmatory testing. The confirmatory testing was performed by analysing each product as per their respective pharmacopoeial monograph requirements. The parameters investigated were identification, assay, dissolution, related substance and sterility as summarized in **Table 1** below.

Table 1: Parameters investigated during confirmatory testing of selected samples

| Medicine Category | Product | Parameter |
|-------------------|---|-------------------|
| Human Medicines | Telmisartan + Hydrochlorothiazide Tablets | Identification |
| | | Assay |
| | | Dissolution |
| | | Related substance |
| | Metformin Tablets | Identification |
| | | Assay |

| | | |
|----------------------|--|-------------------|
| | | Dissolution |
| | | Related substance |
| | Azithromycin Tablets | Identification |
| | | Assay |
| | | Dissolution |
| | | Uniformity |
| | Metronidazole Suspension | Identification |
| | | Assay |
| Sterility | | |
| Veterinary Medicines | Sulfadiazine + Trimethoprim water soluble powder | Identification |
| | | Assay |
| | Levamisole Injection | Identification |
| | | Assay |

5 Results

5.1 Sample collection

A total of 445 human and veterinary medicine samples were collected. More than three-quarter of the collected samples were human medicines 349 (78.4%).

5.1.1 Human Medicine Samples

Samples were collected from 12 regions of Tanzania Mainland. Most of the collected samples were from Dar es Salaam (14.9%) and Arusha (13.5%) region followed by Mwanza (10.9%), Dodoma (10.6%), Tanga (9.2%), Mtwara (8.3%), Geita (8.0%) and Tabora (8.0%) region. About 29.5% of the collected samples were metformin followed by Telmisartan+ Hydrochlorothiazide (25.2%) and metronidazole (22.9%). **Table 2.**

Table 2: The number and type of Human Medicines samples collected per region

| S/N | Regions | Telmisartan+ Hydrochlorothiazide | Metronidazole | Azithromycin | Metformin | Total |
|-----|---------------|-------------------------------------|---------------|--------------|-----------|-------|
| 1. | Arusha | 23 | 0 | 0 | 24 | 47 |
| 2. | Dodoma | 23 | 0 | 0 | 15 | 38 |
| 3. | Dar Es Salaam | 20 | 0 | 0 | 32 | 52 |
| 4. | Geita | 0 | 16 | 12 | 0 | 28 |
| 5. | Katavi | 0 | 9 | 8 | 0 | 17 |
| 6. | Manyara | 0 | 6 | 6 | 0 | 12 |

| | | | | | | |
|-----|--------------|-----------|-----------|-----------|------------|------------|
| 7. | Mbeya | 6 | 0 | 0 | 10 | 16 |
| 8. | Mtwara | 0 | 12 | 17 | 0 | 29 |
| 9. | Mwanza | 16 | 0 | 0 | 22 | 38 |
| 10. | Singida | 0 | 10 | 2 | 0 | 12 |
| 11. | Tabora | 0 | 13 | 15 | 0 | 28 |
| 12. | Tanga | 0 | 14 | 18 | 0 | 32 |
| | Total | 88 | 80 | 78 | 103 | 349 |

5.1.2 Veterinary Medicine Samples

The samples were collected from 10 regions. Most of the samples were from Iringa (16.7%) and Arusha (14.6%) region followed by Mwanza (11.5%) region. Morogoro, Shinyanga and Simiyu region had similar contribution (all 10.4%) to the total number of samples (n=96). More than half (61.5%) of the collected veterinary medicine samples were fixed dose combination of Sulfadiazine + Trimethoprim. **Table 3.**

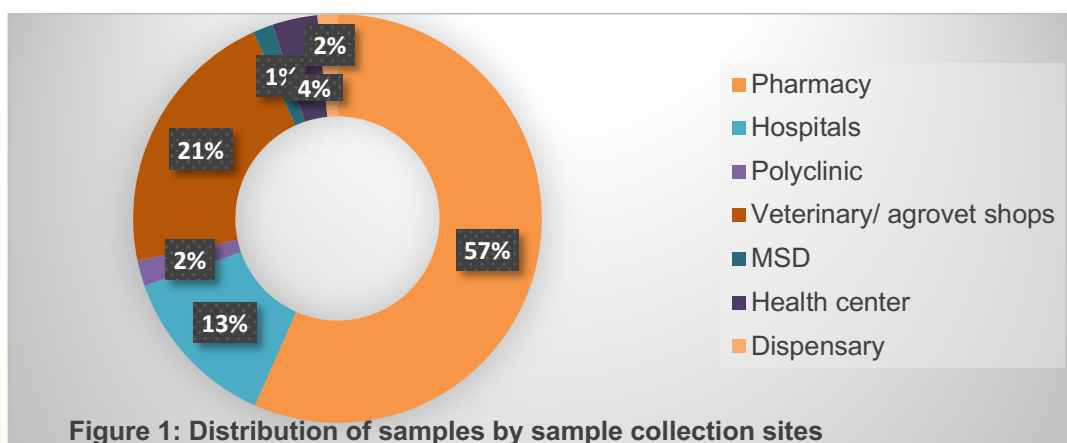
Table 3: The number and type of Veterinary Medicines samples collected per region

| Regions | Sulfadiazine + Trimethoprim | Levamisole | Total |
|---------------|--------------------------------|------------|-----------|
| Arusha | 14 | 0 | 14 |
| Dar Es Salaam | 0 | 7 | 7 |
| Geita | 0 | 2 | 2 |
| Iringa | 0 | 16 | 16 |
| Manyara | 14 | 0 | 14 |
| Morogoro | 10 | 0 | 10 |
| Mwanza | 11 | 0 | 11 |
| Shinyanga | 10 | 0 | 10 |
| Simiyu | 0 | 10 | 10 |
| Singida | 0 | 2 | 2 |
| Total | 59 | 37 | 96 |

5.1.3 Samples Collection Sites

Samples were collected from public and private facilities. These included pharmacies (retails and wholesales), hospitals such as regional referral and district hospitals and faith-based organization. Also, samples were collected from private polyclinics as well as public and private health centers and dispensaries. Additionally, medicine samples (1.5%) were collected from MSD warehouses and MSD community outlets. Overall,

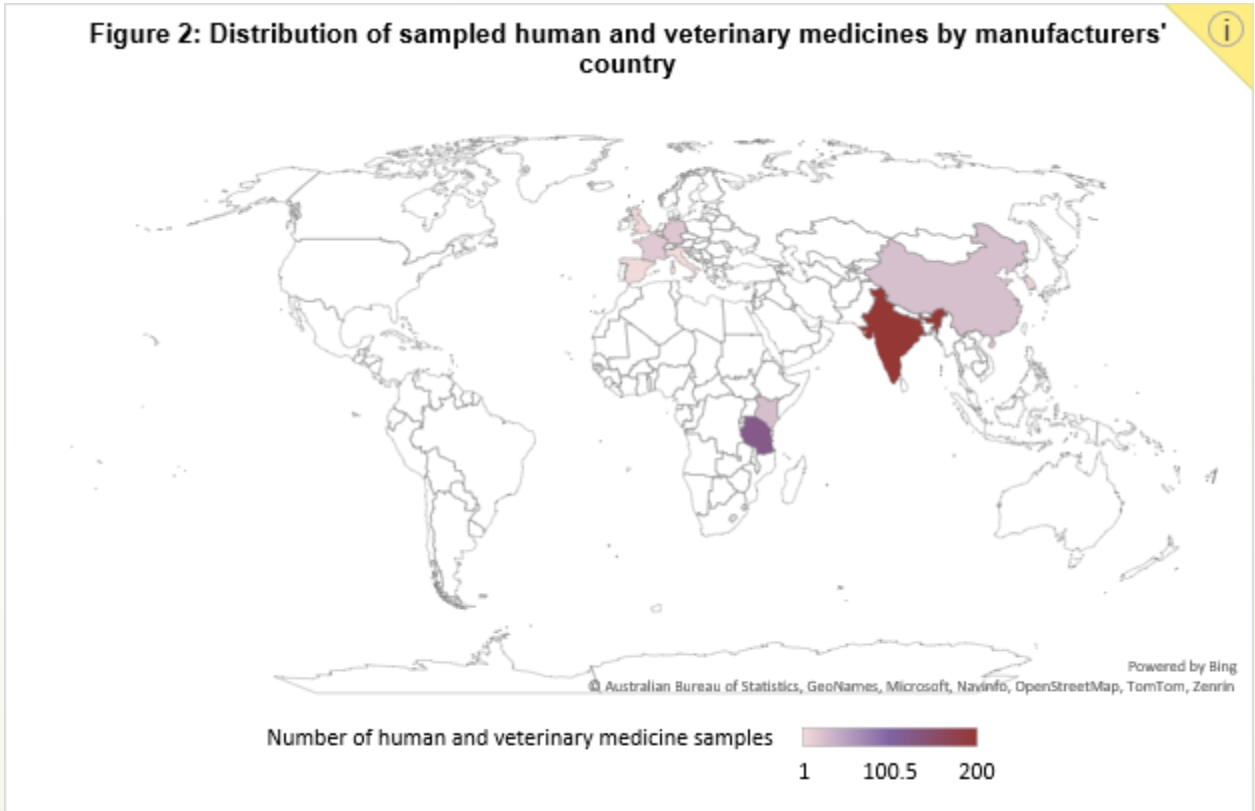
high proportion of all samples were collected from pharmacies (57.0%) and hospitals (13.0%). **Figure 1.**



5.1.4 Distribution of sampled human and veterinary medicines by manufacturers' country

The samples used in this PMS were from manufactures in Asia (56.2%), Africa (33.0%) and Europe (10.8%). Majority of the collected samples were from Indian manufacturers (45.2%) followed by Tanzanian manufacturers (27.2%). Other Asian countries were China (5.4%), Cyprus (4.0%) and South Korea (1.6%) while African countries were Kenya (5.6%) and Egypt (0.2%). Products from seven European countries were sampled from the Tanzania market. European countries were Belgium (0.2%), France (3.6%), Germany (4.3%), Italy (0.2%), Slovenia (0.2%), Spain (0.5%) and The Netherlands (1.8%). **Figure 2**

Figure 2: Distribution of sampled human and veterinary medicines by manufacturers' country



5.1.5 Distribution of sampled human medicines by country

More than half (52.7%) of the sampled human medicines were from India followed by Tanzania (28.1%). Medicines from Kenya manufacturers contributed 7.2% of the samples whereas Germany and Cyprus was 5.4% and 5.2% respectively. All (n=88) the sampled Telmisartan+Hydrochlorothiazide were from India manufacturers. Additionally, all the sampled Azithromycin and Metronidazole were from India, Tanzania and Kenya manufacturers. **Figure 3.**

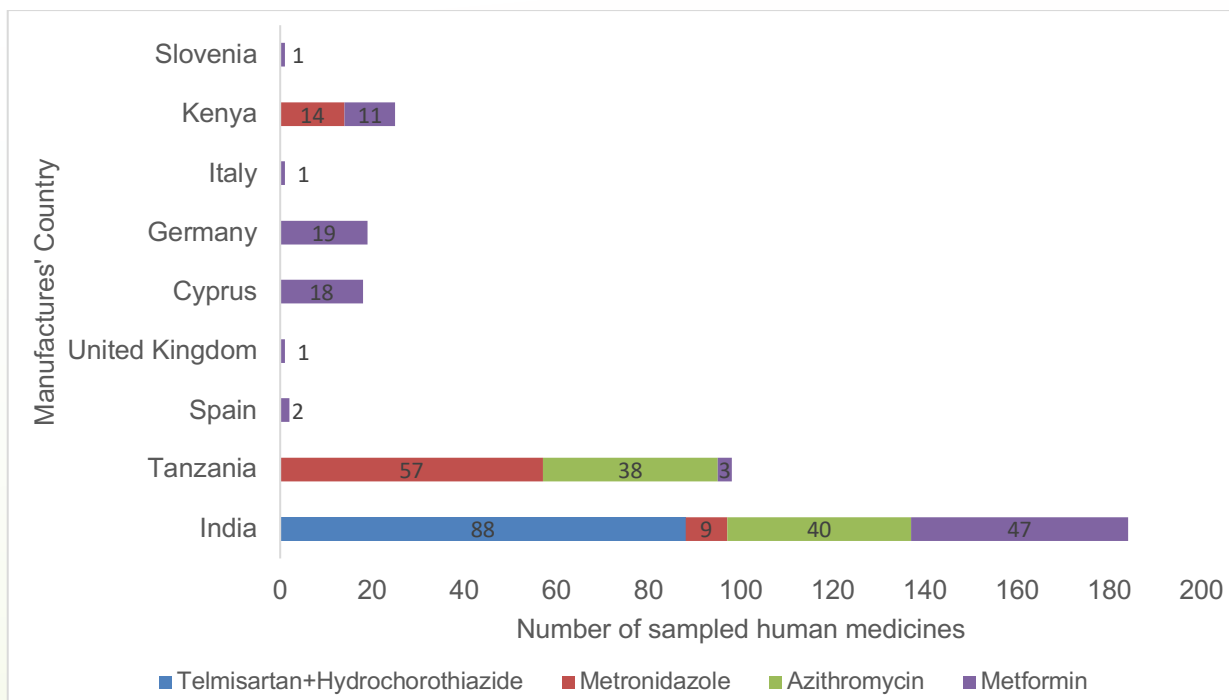


Figure 3: Number of sampled human medicines by country

5.1.6 Distribution of sampled veterinary medicine by country

Most of the collected veterinary medicines were from China (25.0%) and Tanzania (24.0%). Sampled veterinary medicines from India and France contributed equally (16.7%) to the PMS followed by The Netherlands (8.3%) and South Korea (7.3%).

Figure4

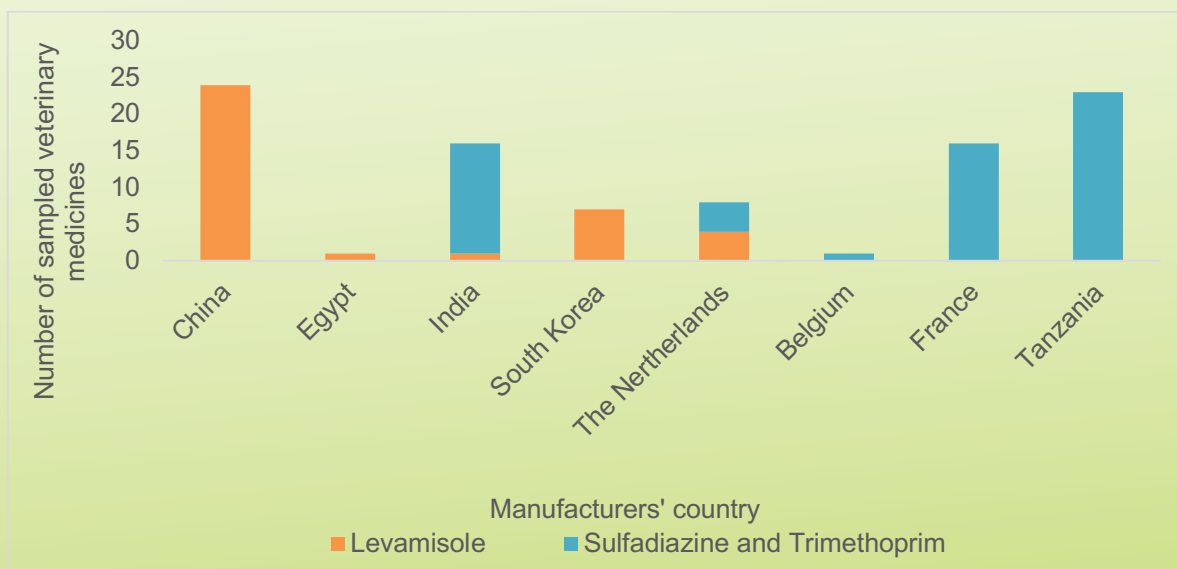


Figure No 4: Number of veterinary medicines sampled with respect to manufacturer's countries

5.1.7 Tier I: Screening

5.1.8 Product Information Review

All the collected samples were screened for PIR. The total of 296 (66.5%) medicine samples (human and veterinary medicine) had deficiencies. Human medicine samples with various deficiencies were 233 (66.7%). Seven deficiencies were observed to human medicine samples. The common deficiency was lack of list excipients on the PIL (41.4%). About 20.5% of the collected samples had labels that do not comply to the storage condition of zone IVb, as they indicated storage condition of 25°C instead of 30°C. Some samples (10.1%) had excipient of safety concern not indicated on the external packaging or PIL. Most (35.8%) of the deficiencies were observed to metformin samples followed by metronidazole samples (22.7%). Few samples of metronidazole (1.6%) and metformin (3.1%) lacked pharmacological information (pharmacodynamic and pharmacokinetic) whereas telmisartan hydrochlorothiazide (1.9%) and metformin (5.2%) lacked manufacturing date on the primary packaging. **Table 4.**

Table 4: Frequency distribution table of human with observed deficiencies during the product information review in Tanzania

| Observed deficiencies | Frequency (%) of medicine samples with deficiencies | | | | |
|--|---|----------------------|---------------------|-------------------|-------------|
| | Telmisartan+ Hydrochlorothiazide (n=88) | Metronidazole (n=80) | Azithromycin (n=78) | Metformin (n=103) | Total |
| Storage conditions on labels do not comply with zone IVb | 1 (1.9%) | 8 (13.1%) | 28 (47.5%) | 18 (18.8%) | 55 (20.5%) |
| The excipient of safety concern not indicated on the external packaging or PIL | 12 (23.1%) | 10 (16.4%) | 2 (3.4%) | 3 (3.1%) | 27 (10.1%) |
| Shelf life not specified in the PIL | 3 (5.8%) | 1 (1.6%) | 3 (5.1%) | 12 (12.5%) | 19 (7.1%) |
| List of excipients not specified in the PIL or external packaging | 22 (42.3%) | 38 (62.3%) | 17 (28.8%) | 34 (35.4%) | 111 (41.4%) |
| Description of FPP not provided in the PIL | 13 (25.0%) | 3 (4.9%) | 9 (15.3%) | 21 (21.9%) | 46 (17.2%) |
| Manufacturing date was not written on Primary packaging | 1 (1.9%) | 0 (0.0%) | 0 (0.0%) | 5 (5.2%) | 6 (2.2%) |
| No Pharmacokinetic and pharmacodynamic | 0 (0.0%) | 1 (1.6%) | 0 (0.0%) | 3 (3.1%) | 4 (1.5%) |

| | | | | | |
|------------------------|-------------|-------------|----------|----------|---------|
| information on the PIL | | | 59 | 96 | 268 |
| Total | 52 (100.0%) | 61 (100.0%) | (100.0%) | (100.0%) | (100.0) |

Sixty-three (65.6%) of the collected veterinary medicine samples had five deficiencies observed during PIR. Most (71.7%) of the deficiencies were detected from levamisole injection samples. The common (40.0%) deficiency was labels not complying to the storage condition of zone IVb. More than quarter (26.7%) of the observed deficiencies were labels not indicating the list of excipients (26.7%) and lack of description of the product (13.3%). Some the sulfadiazine + trimethoprim samples had labels different from the registered labels such as different alignment of animals. **Table 5.**

Table 5: Frequency distribution table of veterinary medicines with observed deficiencies during the product information review in Tanzania

| Observed deficiencies | Frequency Medicine samples with deficiencies | | Total |
|---|--|-------------------|-------------|
| | Sulfadiazine + Trimethoprim (n=59) | Levamisole (n=37) | |
| Storage conditions on labels do not comply with zone IVb | 11 (64.7%) | 13 (30.2%) | 24 (40.0%) |
| Product label is different from the one approved initially. | 6 (35.3) | 0 (0.0%) | 6 (10.0%) |
| List of excipients used was not indicated | 0 (0.0%) | 16 (37.2%) | 16 (26.7%) |
| No description of the product | 0 (0.0%) | 8 (18.6%) | 8 (13.3) |
| Shelf life of the product not specified or different from the approved shelf life | 0 (0.0%) | 6 (14.0%) | 6 (10.0%) |
| Total | 17 (100.0) | 43 (100.0%) | 60 (100.0%) |

5.1.9 Visual Inspection Test

All the samples (445) passed the visual inspection test which included examination for leakage, particles, homogeneity, fill volume and colour change of injectable solutions and colour change, spots, moulds, abrasions and odour for tablets.

5.1.10 Disintegration and Identification Test

All the collected samples (445) passed Identification and Disintegration test.

5.1.11 Confirmatory Testing

A total of 53 samples of which 47 Human Medicines and 11 from Veterinary Medicines which include sample that failed screening test, all those with doubtful results and 10% of all passed screening test were selected for confirmatory testing. One human medicine sample (metformin) failed the dissolution test (2.1%, 1/47). Three of selected sample of levamisole injection and two samples of Sulfadiazine+Trimethoprim powder for oral solution had doubtful assay and pH results. All samples with doubtful findings were subjected to the out of specification (OOS) investigation and passed. (**Table 6**).

Table 6: Confirmatory testing

| Summary | Dosage | Monograph | Screening Test | Qty Received | Qty Screened | | | Confirmatory | | | Remark |
|----------------------------------|--------------------------|-----------|---|--------------|--------------|------------|------------|--------------|-----------|----------|-------------------------|
| | | | | | Qty Screened | Pass | Fail | Qty selected | Pass | Fail | Remarks |
| Telmisartan+ Hydrochlorothiazide | Tablets | BP | Appearance, Identification TLC and Disintegration | 88 | 88 | 37 | 51 | 8 | 8 | 0 | |
| Metronidazole | Suspension | BP | Appearance, Identification TLC and Disintegration | 80 | 80 | 19 | 61 | 9 | 9 | 0 | |
| Azithromycin | Tablets | BP | Appearance, Identification UV and Disintegration | 78 | 78 | 16 | 62 | 8 | 8 | 0 | |
| Metformin | Solution | USP | Appearance, Identification UV | 103 | 103 | 44 | 59 | 11 | 10 | 1 | Failed Dissolution test |
| Levamisole | Injection | BP | Appearance, Identification TLC | 37 | 37 | 2 | 35 | 5 | 5 | 0 | |
| Sulfadiazine+ Trimethoprim | Powder For Oral Solution | IOC | Appearance, Identification UV | 59 | 59 | 31 | 28 | 6 | 6 | 0 | |
| Total | | | | 445 | 445 | 149 | 296 | 53 | 51 | 1 | |

6 DISCUSSION

The phase I and II of PMS programme 2020/23 was implemented in 2020-2021 to determine the quality of selected human and veterinary medicines circulating in the Tanzanian market. The total of 445 human and veterinary samples were selected. About 66.7% and 65.6% of human and veterinary medicine samples did not comply with the labelling requirement. The proportion of non-compliance on labelling requirement was high than the previously reported PMS, and almost similar the study conducted in India³ and less than the study conducted in Nepal⁴ which examined compliance to labelling requirement. The high non-compliance observed in this PMS could be a signal to strengthen reinforcement of inspection and monitoring activities at the ports of entry as well as involvement of Market Authorization Holders as one of the key stakeholders in regulating the quality, safety and efficacy of their medicines.

Most of the sampled medicines were imported, and only few of them were sourced from domestic manufacturers. The imported human medicines were mainly from Asia; India being the leading exporter. These findings are in line with the findings of the systematic analysis of data for pharmaceutical imports that reported India as the leading exporter of highest value of pharmaceuticals in Tanzania⁵. However, medicines from Tanzania manufacturers were the second leading contributors of the sampled medicines. This is contrary to the previous PMS which could be the reflection of increasing pharmaceutical industries in recent years. Veterinary medicine was also highly imported from Asia; China (25.0%) being the leading exporter followed by Tanzania manufacturers (24.0%). The agriculture industry is growing fast in Tanzania with emphasis being put to support local manufacturers⁶.

Additionally, lack of precautionary statement on the product label was observed in 10.1% of all deficiencies. This was less than the previous PMS phase conducted in 2019/2020 which reported 15.7% of labels lacking precautionary statements. Also, the current PMS has high proportional of samples with lack of precautionary statements especially for excipients with safety concerns compared to the previous report by Hiiti et al, who found 2.0% of the package inserts collected in the East African countries did not have a statement with regard to the warning and precautions⁷. The difference could be attributed to the few numbers of samples (n=93) in their study compared to the current survey (n=445). Lacking precautionary and warning statements especially for products with excipients of safety concern can be a potential source adverse event.

List of excipients and description of product not being indicated on the label as well as labeling not complying to the storage condition of zone IVb were the commonest observed deficiencies. These findings are contrary to the study conducted in Nepal

which reported deficiencies to the started parameters by 0.1%⁸. The difference in findings is attributed to the fact that, the Nepalese study surveyed only human medicines sampled from one site (teaching hospital) and produced by Nepalese pharmaceutical industries, of which cannot provide representation of all the medicines circulating in the market. Two-third of the medicine samples used in the current PMS were imported and selected from various outlets to give representation of the medicines circulating in the market.

Almost all of the collected medicine samples passed the quality parameter tests such as visual inspection, identification test, disintegration test and assay. Only one (1) sample of metformin failed dissolution tests. One (1) levamisole injection and two (2) Sulfadiazine+Trimethoprim powder oral for solution had doubtful results on pH and assay. The samples with doubtful results were subjected to out of specification investigation and passed. These findings are similar to the study that tested 869 medicine samples from Africa and Asia; about 2.4% of samples were either falsified or substandard ⁹. In their study, no medicine samples from either India or Kenya were falsified or substandard ⁹. Considering that, our study had most samples imported from India our confidence is increased that medicines circulating in Tanzania are of good quality.

Despite the deficiencies observed in PIR and the one sample that failed the quality control test, this is a clear indication of successful role of TMDA in ensuring the quality of medicines circulating in the market.

7 REGULATORY ACTION TAKEN

The following regulatory actions have been taken by TMDA:

- i. All manufactures whom their medicines failed product information review (PIR) have been directed to rectify the anomalies which were found during the PIR evaluation.
- ii. Metformin batch number JR0014 manufactured by Lincoln (India) which was confirmed to have poor quality was recalled.

8 CONCLUSION

More than half of the selected medicine samples did not comply with the regulatory labelling requirement. There was equal proportion of human (66.7%) and veterinary (65.6%) medicine samples that failed PIR. Therefore, more effort is required to enforce Marketing Authorization Holder and local manufacturers to ensure that their products meet product information requirements before being imported and supplied to the market. In addition, inspection activities need to be strengthened especially at ports of entry to identify medicines which are not labelled in the

manner that conform to the labelling requirements before being allowed into the country.

Of all selected medicines, only one human medicine sample (metformin batch number JR0014) failed confirmatory test. This indicates adequate compliance of post registration enforcement. Nevertheless, it is recommended for continuous monitoring of quality of medicines circulating on the market and reminding distributors and sellers of medicines on the importance of adhering to good distribution practices, storage, labelling and proper handling of human and veterinary medicines.

9 RECOMMENDATIONS

The following are recommended.

- i. Marketing authorization holders should be reminded to comply with labelling requirements.
- ii. Reviewers of product information should be trained regularly to improve the recording of deficiencies observed during product information review.
- iii. Regular training to the sample collectors on the proper data entry by using RIMS before sample collection process start.

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11 ANNEXES

| | | |
|--|---|---|
|  <p>TMDA Tanzania Medicines & Medical Services Authority</p> | <p align="center">MEDICINES POST MARKETING SURVEILLANCE SAMPLE COLLECTION FORM</p> | <p align="right">TMDA/DMC/CTP/F/002 Rev #:1</p> |
|--|---|---|

1. Sample code:
(Region/product/sequence number/sampling date dd/mm/yy)***
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/n | Name | Organization | Signature | Date |
|-----|------|--------------|-----------|------|
| | | | | |
| | | | | |
| | | | | |

Note: Samples collected must remain in their original containers.

Approved by MCTP (Signature)  Effective Date: 25/03/2020



ANNEX 2: SAMPLING PLAN PHASE I&II

PHASE I: HUMAN MEDICINE; AZITHROMYCIN TABLETS AND METRONIDAZOLE SUSPENSION FROM PUBLIC AND PRIVATE FACILITIES IN FIVE (5) REGIONS (TANGA, GEITA, MTWARA, SINGIDA, KATAVI)

| Sampling levels | Sampling site | 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 to be collected | Total Number of units to be collected per 2 brand | |
|--------------------------|--------------------------------|------------------|-------------|--------------|---------------------------------|---|-----------|---|---|--|
| LEVEL 1: NATIONAL | | | | | | | | | | |
| National level | MSD HQ warehouse | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg / 5mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | National Hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Sub Total | | | | | | | | | |
| LEVEL 2: REGIONAL | | | | | | | | | | |
| Regional level | MSD warehouse/ retail pharmacy | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Private Importer | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Wholesaler | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Regional/referral hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Retail pharmacy | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Government hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Private hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | | Sub Total | | | | | | | | |
| | LEVEL 3: DISTRICTS | | | | | | | | | |
| Districts level | DISTRICT 1 | | | | | | | | | |

| District hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
|---|--|-----------------------------|----------------------------|---------------|---------------------------------|---|----------------|---|---|
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| Retail pharmacy | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| Private hospital / Faith based organisation | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| DISTRICT 2 | | | | | | | | | |
| District hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| Retail pharmacy | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| Private hospital / Faith based organisation | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| Sub Total | | | | | | | | | |
| Expected number of batches/samples to be collected from districts and region level | | | | | | | 30 | | |
| Expected number of samples to be collected from 5 region | | | | | | | 150 | | |
| PHASE I: VETERINARY MEDICINES: SULFADIAZINE + TRIMETHOPRIM POWDER FOR ORAL SUSPENSION IN 5 REGIONS (SHINYANGA, MWANZA, ARUSHA, MOROGORO AND MANYARA) | | | | | | | | | |
| Sampling levels | Sampling site | 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 to be collected | Total Number of units to be collected per 2 brand |
| LEVEL 1: REGIONAL LEVEL | | | | | | | | | |
| Regional level | Importer/wholesale veterinary pharmacy | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 |
| | Retail pharmacy/veterinary shops | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 |
| | Private veterinary clinics | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 |

| | Open market/auctions | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
|---|--|-----------------------------------|----------------------------|---------------|---------------------------------|---|----------------|---|---|--|
| LEVEL 2: DISTRICTS | | | | | | | | | | |
| | District: 1 | | | | | | | | | |
| Districts level | Retail pharmacy | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | ADDO Veterinary shop | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | Open market/auctions | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | District :2 | | | | | | | | | |
| | Retail pharmacy | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | ADDO Veterinary shop | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | Open market/auctions | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | Sub Total | | | | | | | | | |
| | Expected number of batches/samples to be collected from districts and region level | | | | | | | 20 | | |
| | Expected number of samples to be collected from 5 region | | | | | | | 100 | | |
| PHASE II: HUMAN MEDICINAL PRODUCTS; METFORMIN TABLETS AND TELMISARTAN + HYDROCHLOROTHIAZIDE FROM PUBLIC AND PRIVATE FACILITIES IN FIVE (5) REGIONS (DAR, DODOMA, IMWANZA, MBEYA, ARUSHA) | | | | | | | | | | |
| Sampling levels | Sampling site | 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 to be collected | Total Number of units to be collected per 2 brand | |
| LEVEL 1: NATIONAL | | | | | | | | | | |
| National level | MSD HQ warehouse | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | National Hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |

| | | | | | | | | | | |
|--------------------------|-----------------------------------|-----------------------------------|------------------|------------|---|---|-------|---|---|--|
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | | Sub total | | | | | | | | |
| LEVEL 2: REGIONAL | | | | | | | | | | |
| Regional level | MSD warehouse/ retail pharmacy | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Private Importer | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Wholesaler | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Regional/referral hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Retail pharmacy | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Government hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Private hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | | | Sub total | | | | | | | |
| | LEVEL 3: DISTRICTS | | | | | | | | | |
| Districts level | DISTRICT 1 | | | | | | | | | |
| | District hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Retail pharmacy | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |

| Private hospital / Faith based organisation | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
|---|--|------------------|-------------|-----------|---------------------------------|--|---------------|---|---|
| | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| DISTRICT 2 | | | | | | | | | |
| District hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| Retail pharmacy | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| Private hospital / Faith based organisation | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | | Sub total | | | | | | | |
| | | | | | | Expected number of batches/samples to be collected from districts and region level | 30 | | |
| | | | | | | Expected number of samples to be collected from 5 region | 150 | | |
| PHASE II VETERINARY MEDICINES: LEVAMIZOLE INJECTION IN 5 REGIONS (DAR ES SALAAM, IRINGA, GEITA, SIMIYU, SINGIDA) | | | | | | | | | |
| Sampling levels | Sampling site | 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 to be collected | Total Number of units to be collected per 2 brand |
| LEVEL 1: REGIONAL LEVEL | | | | | | | | | |
| Regional level | Importer/wholesale veterinary pharmacy | Levamisole | Injection | 200 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 |
| | Retail pharmacy/veterinary shops | Levamisole | Injection | 201 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 |
| | Private veterinary clinics | Levamisole | Injection | 202 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 |
| | Open market/auctions | Levamisole | Injection | 203 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 |
| Sub Total | | | | | | | | | |
| LEVEL 2: DISTRICTS | | | | | | | | | |
| | District: 1 | | | | | | | | |

| | | | | | | | | | | |
|------------------------|--|------------|-----------|-----------|---|---|---------------|------------|----|--|
| Districts level | Importer/wholesale veterinary pharmacy | Levamisole | Injection | 200 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | Retail pharmacy/veterinary shops | Levamisole | Injection | 201 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | Open market/auctions | Levamisole | Injection | 202 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | District :2 | | | | | | | | | |
| | Importer/wholesale veterinary pharmacy | Levamisole | Injection | 200 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | Retail pharmacy/veterinary shops | Levamisole | Injection | 201 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | Open market/auctions | Levamisole | Injection | 202 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | Sub Total | | | | | | | | | |
| | Expected number of batches/samples to be collected from districts and region level | | | | | | | 20 | | |
| | Expected number of samples to be collected from 5 region | | | | | | | 100 | | |

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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 |
| PIR | - Product Information Review |
| PMS | - Post Marketing Surveillance |
| QA | - Quality Assurance |
| QC | - Quality Control |
| SOPs | - Standard Operating Procedures |
| SPC | - Summary of Product Characteristics |
| TMDA | - Tanzania Medicines and Medical Devices Authority |
| TLC | - Thin Layer Chromatography |
| WHO | - World Health Organization |

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Dr. Yonah H. Mwalwisi
DIRECTOR HUMAN AND VETERINARY MEDICINES
TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

FOREWORD

Monitoring the quality, safety and efficacy of medicines circulating in the market is fundamental in protecting public health. Routine surveillance of medicines after registration (Post Marketing Surveillance - PMS) is one of the key responsibilities of a functional national medicine's regulatory authority. PMS helps medicines users, especially patients, who are key stakeholders in the pharmaceutical industry, to build confidence in the medicines they use that they will meet the expected standards for quality, safety and ultimately treat the intended diseases.

PMS also helps to timely detect and remove falsified and substandard medicines from the market thus protecting the public against the possible hazards associated with their use.

In view of this importance, Tanzania Medicines and Medical Devices Authority has developed and maintained a PMS system since 2009. The Authority has been developing a three-year PMS program where selected registered medicines are monitored based on a variety of criteria including reports of complaints from various stakeholders. The implementation of the plan was divided into six phases (I - VI), and in each phase, a sampling plan was set based on various risk criteria.

In this report we present methodology and detailed results for PMS of selected medicines for year 2020/21.

Overall, the PMS exercise was excellently planned and the execution was well coordinated. Implementation was carried out by various dedicated stakeholders within and outside TMDA. Key lessons learned from the PMS exercise will be used to improve the quality, safety and ultimately efficacy of medicines circulating in Tanzanian market. Moreover, it will assist TMDA to improve the subsequent PMS programs and ultimately protect public health.

I would like to commend all esteemed stakeholders involved including our collaborators and partners for making the 2020/2021 PMS program a success.

Adam Mitangu Fimbo
DIRECTOR GENERAL
TANZANIA MEDICINES AND MEDICAL DEVICES
AUTHORITY

Executive Summary

In the financial year 2020/2021, TMDA assessed the quality of selected human and veterinary medicines circulating on the market as part of implementation of the three years (2020 - 2023) PMS program. The selected human medicines included Metronidazole solution, Metformin tablet, Azithromycin tablet, and Telmisartan+Hydrochlorothiazide. The selected veterinary medicines were Levamisole injection and Sulfadiazine+Trimethoprim powder for oral solution.

Systematic method for sample collection was used where by samples were collected from public and private hospitals, pharmacies, dispensaries, accredited drugs dispensing outlets (ADDOs), Medical Stores Department (MSD) and veterinary medicines outlets. A total of 445 medicine samples were taken from 16 regions of Tanzania Mainland; Dar es Salaam, Morogoro, Dodoma, Singida, Geita, Mwanza, Shinyanga, Simiyu, Arusha, Manyara, Mbeya, Tanga, Iringa, Katavi, Tabora and Mtwara. Of all the selected medicine samples 349(78.4%) were human medicine and, 96 (21.6%) veterinary medicines.

Results for PIR indicated that 296 (66.5%) medicine samples did not comply with regulatory requirements. Human and veterinary medicine samples with various deficiencies were 233 (66.7%) and 63(65.6%) respectively. The Marketing Authorization Holders of the samples failed PIR were directed to comply with labeling requirements.

In the PMS programme 2020/2023 which was implemented for phase I and II in 2020/2021, a total of 445 medicine samples were collected from the market. The samples were taken from representative regions countrywide using a carefully designed sampling plan. After collection, product information review (PIR) was performed followed by laboratory testing based on selected critical parameters. The whole exercise was conducted by the qualified personnel who were well versed with the PMS protocol. Out of the selected samples, 349(78.4%) were human and, 96 (21.6%) were veterinary medicines. Results for PIR indicated that 296 (66.5%) medicine samples had various deficiencies. Human and veterinary medicine samples with various deficiencies were 233 (66.7%) and 63(65.6%) respectively.

The common deficiencies observed during PIR were lack of list excipients on the labels, labels not complying to the storage condition of Zone IVb, lack of product description

and not indicating excipients of safety concerns on either the external packaging or package inserts.

Of all samples which were subjected to confirmatory laboratory testing, only one sample (Metformin tablet) failed the dissolution test.

A total of 53 samples (47 Human Medicines and 11 from Veterinary Medicines) were selected for Tier II confirmatory testing at TMDAWHO prequalified laboratory. One human medicine sample (metformin) failed the test (2.1%, 1/47) and was withdrawn from the market. All the veterinary medicine samples passed the tests.

Generally, laboratory test results of the selected medicines with exception of Metformin tablets complied to the specifications which indicate functioning of regulatory systems in the country.

1. Introduction

Globally, substandard, and falsified medicines pose a serious public health problem due to increased risk of morbidity and mortality. It is estimated that, about 1million people worldwide die annually from substandard and falsified medicines. The World Health Organization estimates about 10% of medicines circulating in the market in low- and middle-income countries are either falsified or substandard¹. The extent of falsified and substandard medicines is not well known due to limited research, methodological hurdles, and surveillance methods².

In order to protect the public health against substandard and falsified medicines, Tanzania Medicines and Medical Devices Authority (TMDA) conducts a regular and structured Post Marketing Surveillance (PMS) of selected registered medicines in Tanzanian market. PMS, as one of TMDA's regulatory mandates is a systematic quality assurance measure to monitor quality of registered medicines and it aims at establishing the status of quality of medicines circulating in Tanzanian market and protects the public against substandard and falsified medicines. It provides valuable information on the quality of medicines once the drug enters the market, the information which is often unavailable prior and during registration process.

The PMS is implemented through systematic and meticulous planning using a pre-defined sampling of medicines circulating in the market. The focus is to ensure representation of medicines for human and veterinary priority diseases in the country. Sample collection for selected medicines was conducted by trained and qualified sample collectors in line with the pre-determined sampling plan.

Sampling of human and veterinary medicines was conducted in 2020/2021 in 16 regions of Tanzania Mainland; Dar es Salaam, Morogoro, Dodoma, Singida, Geita, Mwanza, Shinyanga, Simiyu, Arusha, Manyara, Mbeya, Tanga, Iringa, Katavi, Tabora and Mtwara. The samples were collected from Medical Stores Department (MSD) the supplier of medicines and medical products to public health facilities in Tanzania. The exercise equally covered public and private health facilities, wholesale and retail pharmacy outlets; accredited drug dispensing outlets (ADDO), the lowest access point of medicines in Tanzania and from veterinary setting outlets.

The collected human medicines included Metronidazole solution, Metformin tablet, Azithromycin tablet, and Telmisartan Hydrochlorothiazide tablets whereas veterinary medicines studied were Levamisole injection and Sulfadiazine+Trimethoprim powder for oral solutions.

The scope of the PMS included screening by reviewing product information (summary of product characteristics, package leaflet and labelling) as well as preliminary laboratory tests such as appearance, disintegration and identification. Of these, 10% of the medicines which passed screening procedures, sample with doubtful results and all medicines which didn't pass screening were subjected to laboratory confirmatory tests (i.e. assay, dissolution, related substances and content of uniformity of dosage units).

All sampled human and veterinary medicines were analysed at a World Health Organization (WHO) pre-qualified Laboratory located at TMDA, Dar es Salaam to ascertain compliance to quality standards. This report highlights results obtained and regulatory actions taken by TMDA.

2. OBJECTIVES

2.1. Broad Objective

To determine quality of selected human and veterinary medicines circulating on Tanzanian market in the year 2020/2021.

2.2. Specific Objectives

The specific objectives of the surveillance were: -

- i. To determine compliance of collected medicines samples to labelling requirements by conducting PIR.
- ii. To establish quality of selected medicines samples by conducting laboratory quality control tests.
- iii. To take relevant regulatory action(s) and propose strategies to address the problems identified by the survey.

3. METHODOLOGY

3.1. Medicines Selection

Medicines for quality monitoring in these phases were selected based on the following criteria:

- i. Reports on quality, safety and efficacy of medicines received by TMDA from various sources
- ii. Changes in disease pattern and management
- iii. Experience gained in previous PMS programmes
- iv. Medicines containing active ingredients known to have stability problems
- v. Medicines from manufacturers whose products were previously reported to have high incidences of being counterfeited and substandard

3.2. Sampling

3.2.1 Sampling sites

Samples were collected from randomly selected sites which included Medical Stores Department (MSD), public and private hospitals, health centres, dispensaries, importers, wholesale and retail pharmacies in selected regions of the country.

The regions were selected based on the following criteria:-

- a) Regions bordering other countries
- b) Regions that are not frequently inspected
- c) Areas reported to have medicines quality problems
- d) Regions not involved in the previous PMS programme phase
- e) Disease endemicity.

3.2.2 Collection of Samples

Collection of samples at various levels of supply chain was based on the developed sampling plans. Sampling plans were prepared and contained detailed information on sampling sites at regional and district levels, product name, number of brands to be collected, dosage forms, strength and pack size. Sampling plans are attached as **Annex II**. Samples were collected according to Standard Operating Procedure No. TMDA/DMC/CTPV/SOP/012 by trained medicine inspectors from TMDA and Local Government Authorities. Samples were collected in their original containers and/or packages together with their package insert. Details of the collected samples were recorded in the sample collection form attached as **Annex I**.

3.2.3 Sample handling and transportation

Each collected sample was coded according to prescribed coding format. Coding was done to identify samples collected from different sampling sites and thus helped to differentiate and avoid mix up. Coded samples with respective sampling form were kept in the labelled sampling bags and sealed. The samples were transported to TMDA zonal offices for data entry in Regulatory Information Management System (RIMS).

On completion, samples were transported to TMDA HQ Sub Office for screening and confirmatory testing. Before and after transportation of samples, measures were taken to ensure that samples were stored according to manufacturers' recommended storage conditions as prescribed in the product labels.

4 Sample Analysis

4.1 Screening

Screening testing involved Product Information Review (PIR), physical/visual inspection, disintegration test and identification test by Thin Layer Chromatography (TLC) or UV - Vis spectrophotometer.

4.1.1 Product Information Review (PIR)

All samples were subjected to product information review (PIR). This involved the review of information contained on the primary and secondary packaging, package inserts and label of each sample of medicine for conformity to the TMDA approved product information and labelling requirement. Apart from appropriateness and legibility of the information on the label and associated insert, appropriateness of the type of container used, stickiness and printing on the label were also checked..

4.1.2 Physical/visual inspections

Visual inspections were conducted so as to give information about product quality prior to further laboratory testing of samples in comparison with registration information. Injectable solutions were examined for leakage, particles, homogeneity, fill volume and

colour change. For the case of oral solid dosage forms colour change, spots, moulds, abrasions, and dour were checked.

4.1.3 Simple disintegration Test

Disintegration test was used to test the possibility of solid dosage form to break into small particles that 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 in which dissolution test were conducted as per their respective compendial monographs.

4.1.4 Qualitative and semi - quantitative determination of API by using Thin layer Chromatography

TLC method was used for qualitative and semi - quantitative determination of Active Pharmaceutical Ingredient (API) and related degradants present in the dosage form. This method employs the principle of comparing spots obtained between test and reference standard solutions. The principal spot obtained with the test solution must correspond with the spot of the higher reference standard solutions in terms of colour, shape, size, intensity and retardation factor (Rf) value.

4.1.5 Qualitative determination by using UV - Vis Spectrophotometer

UV - Vis Spectrophotometry is an analytical method used for qualitative and quantitative determination of API in pharmaceutical dosage form. In qualitative determination, method employs spectrophotometry principle whereby maxima absorption wavelength of the sample (test solution) is compared with maxima absorption of the standard solution.

4.2 Laboratory Confirmatory Testing by using compendial or manufacturer methods

All samples that failed screening test, all those with doubtful screening results and 10% of all passed samples were selected for confirmatory testing. The confirmatory testing was performed by analysing each product as per their respective pharmacopoeial monograph requirements. The parameters investigated were identification, assay, dissolution, related substance and sterility as summarized in **Table 1** below.

Table 1: Parameters investigated during confirmatory testing of selected samples

| Medicine Category | Product | Parameter |
|-------------------|---|-------------------|
| Human Medicines | Telmisartan + Hydrochlorothiazide Tablets | Identification |
| | | Assay |
| | | Dissolution |
| | | Related substance |
| | Metformin Tablets | Identification |
| | | Assay |

| | | |
|----------------------|--|-------------------|
| | | Dissolution |
| | | Related substance |
| | Azithromycin Tablets | Identification |
| | | Assay |
| | | Dissolution |
| | | Uniformity |
| | Metronidazole Suspension | Identification |
| | | Assay |
| Sterility | | |
| Veterinary Medicines | Sulfadiazine + Trimethoprim water soluble powder | Identification |
| | | Assay |
| | Levamisole Injection | Identification |
| | | Assay |

5 Results

5.1 Sample collection

A total of 445 human and veterinary medicine samples were collected. More than three-quarter of the collected samples were human medicines 349 (78.4%).

5.1.1 Human Medicine Samples

Samples were collected from 12 regions of Tanzania Mainland. Most of the collected samples were from Dar es Salaam (14.9%) and Arusha (13.5%) region followed by Mwanza (10.9%), Dodoma (10.6%), Tanga (9.2%), Mtwara (8.3%), Geita (8.0%) and Tabora (8.0%) region. About 29.5% of the collected samples were metformin followed by Telmisartan+ Hydrochlorothiazide (25.2%) and metronidazole (22.9%). **Table 2.**

Table 2: The number and type of Human Medicines samples collected per region

| S/N | Regions | Telmisartan+ Hydrochlorothiazide | Metronidazole | Azithromycin | Metformin | Total |
|-----|---------------|-------------------------------------|---------------|--------------|-----------|-------|
| 1. | Arusha | 23 | 0 | 0 | 24 | 47 |
| 2. | Dodoma | 23 | 0 | 0 | 15 | 38 |
| 3. | Dar Es Salaam | 20 | 0 | 0 | 32 | 52 |
| 4. | Geita | 0 | 16 | 12 | 0 | 28 |
| 5. | Katavi | 0 | 9 | 8 | 0 | 17 |
| 6. | Manyara | 0 | 6 | 6 | 0 | 12 |

| | | | | | | |
|-----|--------------|-----------|-----------|-----------|------------|------------|
| 7. | Mbeya | 6 | 0 | 0 | 10 | 16 |
| 8. | Mtwara | 0 | 12 | 17 | 0 | 29 |
| 9. | Mwanza | 16 | 0 | 0 | 22 | 38 |
| 10. | Singida | 0 | 10 | 2 | 0 | 12 |
| 11. | Tabora | 0 | 13 | 15 | 0 | 28 |
| 12. | Tanga | 0 | 14 | 18 | 0 | 32 |
| | Total | 88 | 80 | 78 | 103 | 349 |

5.1.2 Veterinary Medicine Samples

The samples were collected from 10 regions. Most of the samples were from Iringa (16.7%) and Arusha (14.6%) region followed by Mwanza (11.5%) region. Morogoro, Shinyanga and Simiyu region had similar contribution (all 10.4%) to the total number of samples (n=96). More than half (61.5%) of the collected veterinary medicine samples were fixed dose combination of Sulfadiazine + Trimethoprim. **Table 3.**

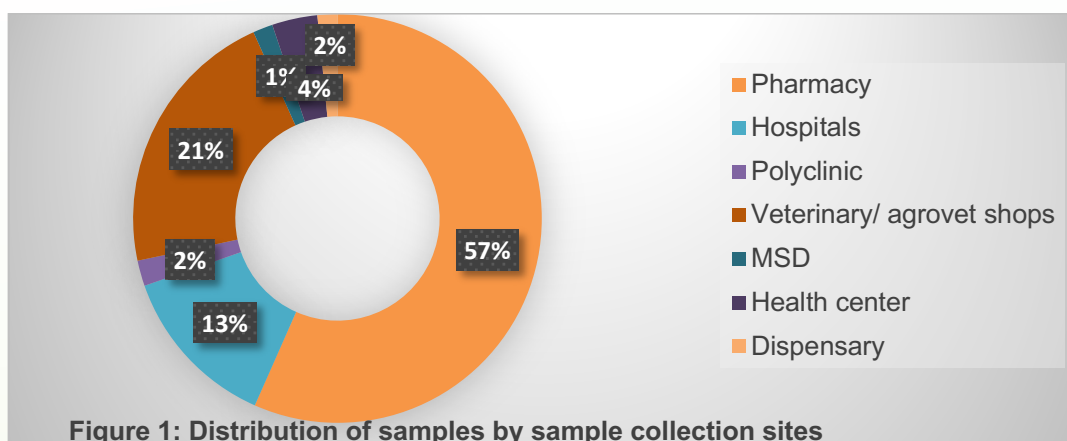
Table 3: The number and type of Veterinary Medicines samples collected per region

| Regions | Sulfadiazine + Trimethoprim | Levamisole | Total |
|---------------|--------------------------------|------------|-----------|
| Arusha | 14 | 0 | 14 |
| Dar Es Salaam | 0 | 7 | 7 |
| Geita | 0 | 2 | 2 |
| Iringa | 0 | 16 | 16 |
| Manyara | 14 | 0 | 14 |
| Morogoro | 10 | 0 | 10 |
| Mwanza | 11 | 0 | 11 |
| Shinyanga | 10 | 0 | 10 |
| Simiyu | 0 | 10 | 10 |
| Singida | 0 | 2 | 2 |
| Total | 59 | 37 | 96 |

5.1.3 Samples Collection Sites

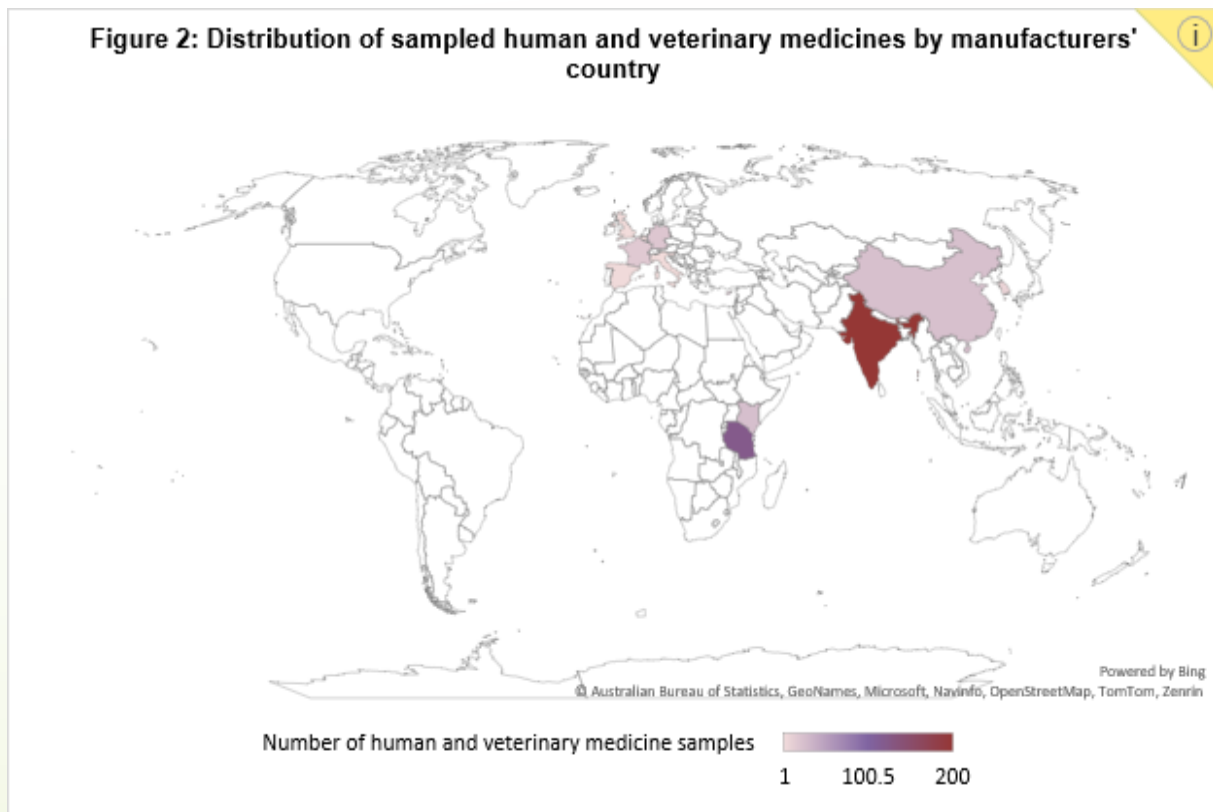
Samples were collected from public and private facilities. These included pharmacies (retails and wholesales), hospitals such as regional referral and district hospitals and faith-based organization. Also, samples were collected from private polyclinics as well as public and private health centers and dispensaries. Additionally, medicine samples (1.5%) were collected from MSD warehouses and MSD community outlets. Overall,

high proportion of all samples were collected from pharmacies (57.0%) and hospitals (13.0%). **Figure 1.**



5.1.4 Distribution of sampled human and veterinary medicines by manufacturers' country

The samples used in this PMS were from manufactures in Asia (56.2%), Africa (33.0%) and Europe (10.8%). Majority of the collected samples were from Indian manufacturers (45.2%) followed by Tanzanian manufacturers (27.2%). Other Asian countries were China (5.4%), Cyprus (4.0%) and South Korea (1.6%) while African countries were Kenya (5.6%) and Egypt (0.2%). Products from seven European countries were sampled from the Tanzania market. European countries were Belgium (0.2%), France (3.6%), Germany (4.3%), Italy (0.2%), Slovenia (0.2%), Spain (0.5%) and The Netherlands (1.8%). **Figure 2**



5.1.5 Distribution of sampled human medicines by country

More than half (52.7%) of the sampled human medicines were from India followed by Tanzania (28.1%). Medicines from Kenya manufacturers contributed 7.2% of the samples whereas Germany and Cyprus was 5.4% and 5.2% respectively. All (n=88) the sampled Telmisartan+Hydrochlorothiazide were from India manufacturers. Additionally, all the sampled Azithromycin and Metronidazole were from India, Tanzania and Kenya manufacturers. **Figure 3.**

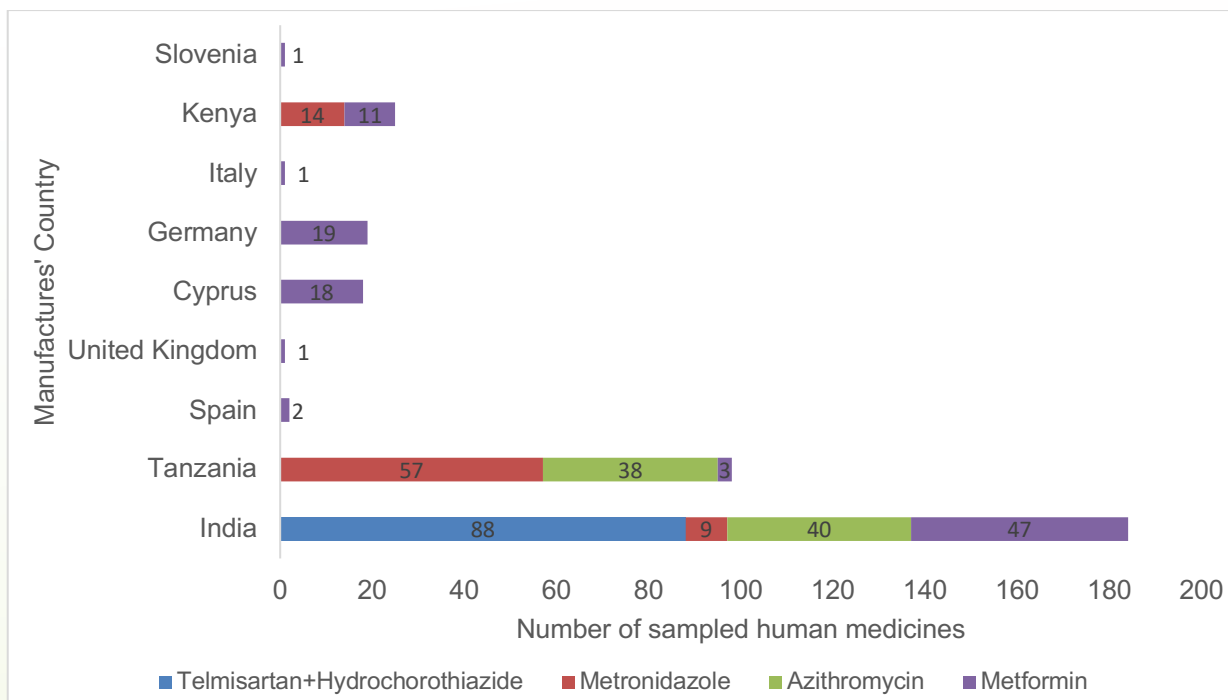


Figure 3: Number of sampled human medicines by country

5.1.6 Distribution of sampled veterinary medicine by country

Most of the collected veterinary medicines were from China (25.0%) and Tanzania (24.0%). Sampled veterinary medicines from India and France contributed equally (16.7%) to the PMS followed by The Netherlands (8.3%) and South Korea (7.3%).

Figure4

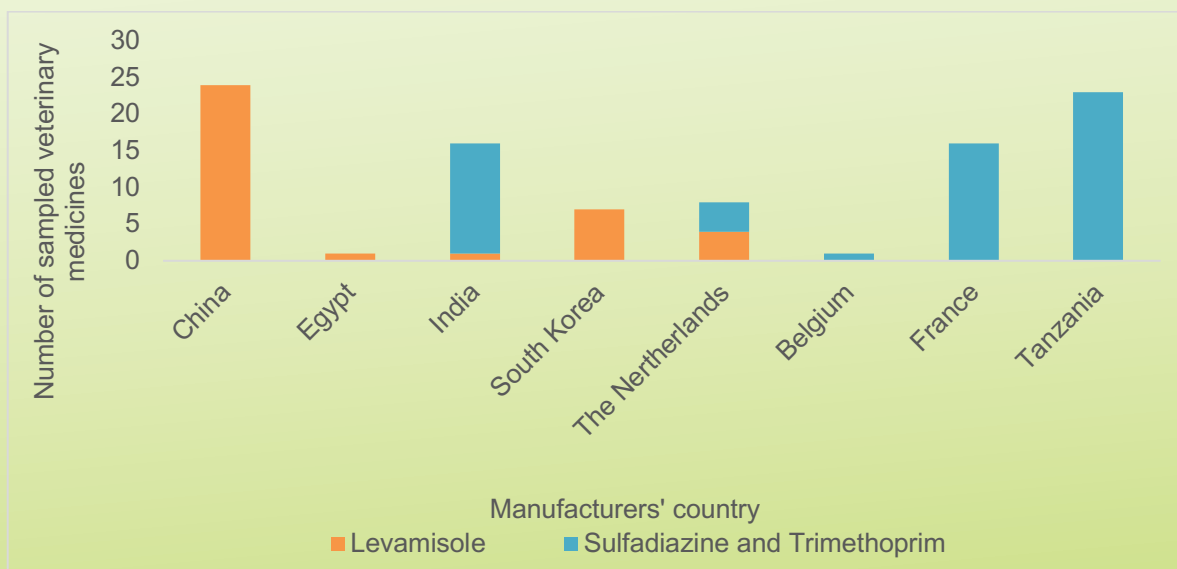


Figure No 4: Number of veterinary medicines sampled with respect to manufacturer's countries

5.1.7 Tier I: Screening

5.1.8 Product Information Review

All the collected samples were screened for PIR. The total of 296 (66.5%) medicine samples (human and veterinary medicine) had deficiencies. Human medicine samples with various deficiencies were 233 (66.7%). Seven deficiencies were observed to human medicine samples. The common deficiency was lack of list excipients on the PIL (41.4%). About 20.5% of the collected samples had labels that do not comply to the storage condition of zone IVb, as they indicated storage condition of 25°C instead of 30°C. Some samples (10.1%) had excipient of safety concern not indicated on the external packaging or PIL. Most (35.8%) of the deficiencies were observed to metformin samples followed by metronidazole samples (22.7%). Few samples of metronidazole (1.6%) and metformin (3.1%) lacked pharmacological information (pharmacodynamic and pharmacokinetic) whereas telmisartan hydrochlorothiazide (1.9%) and metformin (5.2%) lacked manufacturing date on the primary packaging. **Table 4.**

Table 4: Frequency distribution table of human with observed deficiencies during the product information review in Tanzania

| Observed deficiencies | Frequency (%) of medicine samples with deficiencies | | | | |
|--|---|----------------------|---------------------|-------------------|-------------|
| | Telmisartan+ Hydrochlorothiazide (n=88) | Metronidazole (n=80) | Azithromycin (n=78) | Metformin (n=103) | Total |
| Storage conditions on labels do not comply with zone IVb | 1 (1.9%) | 8 (13.1%) | 28 (47.5%) | 18 (18.8%) | 55 (20.5%) |
| The excipient of safety concern not indicated on the external packaging or PIL | 12 (23.1%) | 10 (16.4%) | 2 (3.4%) | 3 (3.1%) | 27 (10.1%) |
| Shelf life not specified in the PIL | 3 (5.8%) | 1 (1.6%) | 3 (5.1%) | 12 (12.5%) | 19 (7.1%) |
| List of excipients not specified in the PIL or external packaging | 22 (42.3%) | 38 (62.3%) | 17 (28.8%) | 34 (35.4%) | 111 (41.4%) |
| Description of FPP not provided in the PIL | 13 (25.0%) | 3 (4.9%) | 9 (15.3%) | 21 (21.9%) | 46 (17.2%) |
| Manufacturing date was not written on Primary packaging | 1 (1.9%) | 0 (0.0%) | 0 (0.0%) | 5 (5.2%) | 6 (2.2%) |
| No Pharmacokinetic and pharmacodynamic | 0 (0.0%) | 1 (1.6%) | 0 (0.0%) | 3 (3.1%) | 4 (1.5%) |

| | | | | | |
|------------------------|-------------|-------------|-------------|-------------|-------------|
| information on the PIL | | | | | |
| Total | 52 (100.0%) | 61 (100.0%) | 59 (100.0%) | 96 (100.0%) | 268 (100.0) |

Sixty-three (65.6%) of the collected veterinary medicine samples had five deficiencies observed during PIR. Most (71.7%) of the deficiencies were detected from levamisole injection samples. The common (40.0%) deficiency was labels not complying to the storage condition of zone IVb. More than quarter (26.7%) of the observed deficiencies were labels not indicating the list of excipients (26.7%) and lack of description of the product (13.3%). Some the sulfadiazine + trimethoprim samples had labels different from the registered labels such as different alignment of animals. **Table 5.**

Table 5: Frequency distribution table of veterinary medicines with observed deficiencies during the product information review in Tanzania

| Observed deficiencies | Frequency Medicine samples with deficiencies | | Total |
|---|--|-------------------|-------------|
| | Sulfadiazine + Trimethoprim (n=59) | Levamisole (n=37) | |
| Storage conditions on labels do not comply with zone IVb | 11 (64.7%) | 13 (30.2%) | 24 (40.0%) |
| Product label is different from the one approved initially. | 6 (35.3) | 0 (0.0%) | 6 (10.0%) |
| List of excipients used was not indicated | 0 (0.0%) | 16 (37.2%) | 16 (26.7%) |
| No description of the product | 0 (0.0%) | 8 (18.6%) | 8 (13.3) |
| Shelf life of the product not specified or different from the approved shelf life | 0 (0.0%) | 6 (14.0%) | 6 (10.0%) |
| Total | 17 (100.0) | 43 (100.0%) | 60 (100.0%) |

5.1.9 Visual Inspection Test

All the samples (445) passed the visual inspection test which included examination for leakage, particles, homogeneity, fill volume and colour change of injectable solutions and colour change, spots, moulds, abrasions and odour for tablets.

5.1.10 Disintegration and Identification Test

All the collected samples (445) passed Identification and Disintegration test.

5.1.11 Confirmatory Testing

A total of 53 samples of which 47 Human Medicines and 11 from Veterinary Medicines which include sample that failed screening test, all those with doubtful results and 10% of all passed screening test were selected for confirmatory testing. One human medicine sample (metformin) failed the dissolution test (2.1%, 1/47). Three of selected sample of levamisole injection and two samples of Sulfadiazine+Trimethoprim powder for oral solution had doubtful assay and pH results. All samples with doubtful findings were subjected to the out of specification (OOS) investigation and passed. (**Table 6**).

Table 6: Confirmatory testing

| Summary | Dosage | Monograph | Screening Test | Qty Received | Qty Screened | | | Confirmatory | | | Remark |
|----------------------------------|--------------------------|-----------|---|--------------|--------------|------------|------------|--------------|-----------|----------|-------------------------|
| | | | | | Qty Screened | Pass | Fail | Qty selected | Pass | Fail | Remarks |
| Telmisartan+ Hydrochlorothiazide | Tablets | BP | Appearance, Identification TLC and Disintegration | 88 | 88 | 37 | 51 | 8 | 8 | 0 | |
| Metronidazole | Suspension | BP | Appearance, Identification TLC and Disintegration | 80 | 80 | 19 | 61 | 9 | 9 | 0 | |
| Azithromycin | Tablets | BP | Appearance, Identification UV and Disintegration | 78 | 78 | 16 | 62 | 8 | 8 | 0 | |
| Metformin | Solution | USP | Appearance, Identification UV | 103 | 103 | 44 | 59 | 11 | 10 | 1 | Failed Dissolution test |
| Levamisole | Injection | BP | Appearance, Identification TLC | 37 | 37 | 2 | 35 | 5 | 5 | 0 | |
| Sulfadiazine+ Trimethoprim | Powder For Oral Solution | IOC | Appearance, Identification UV | 59 | 59 | 31 | 28 | 6 | 6 | 0 | |
| Total | | | | 445 | 445 | 149 | 296 | 53 | 51 | 1 | |

6 DISCUSSION

The phase I and II of PMS programme 2020/23 was implemented in 2020-2021 to determine the quality of selected human and veterinary medicines circulating in the Tanzanian market. The total of 445 human and veterinary samples were selected. About 66.7% and 65.6% of human and veterinary medicine samples did not comply with the labelling requirement. The proportion of non-compliance on labelling requirement was high than the previously reported PMS, and almost similar the study conducted in India³ and less than the study conducted in Nepal⁴ which examined compliance to labelling requirement. The high non-compliance observed in this PMS could be a signal to strengthen reinforcement of inspection and monitoring activities at the ports of entry as well as involvement of Market Authorization Holders as one of the key stakeholders in regulating the quality, safety and efficacy of their medicines.

Most of the sampled medicines were imported, and only few of them were sourced from domestic manufacturers. The imported human medicines were mainly from Asia; India being the leading exporter. These findings are in line with the findings of the systematic analysis of data for pharmaceutical imports that reported India as the leading exporter of highest value of pharmaceuticals in Tanzania⁵. However, medicines from Tanzania manufacturers were the second leading contributors of the sampled medicines. This is contrary to the previous PMS which could be the reflection of increasing pharmaceutical industries in recent years. Veterinary medicine was also highly imported from Asia; China (25.0%) being the leading exporter followed by Tanzania manufacturers (24.0%). The agriculture industry is growing fast in Tanzania with emphasis being put to support local manufacturers⁶.

Additionally, lack of precautionary statement on the product label was observed in 10.1% of all deficiencies. This was less than the previous PMS phase conducted in 2019/2020 which reported 15.7% of labels lacking precautionary statements. Also, the current PMS has high proportional of samples with lack of precautionary statements especially for excipients with safety concerns compared to the previous report by Hiiti et al, who found 2.0% of the package inserts collected in the East African countries did not have a statement with regard to the warning and precautions⁷. The difference could be attributed to the few numbers of samples (n=93) in their study compared to the current survey (n=445). Lacking precautionary and warning statements especially for products with excipients of safety concern can be a potential source adverse event.

List of excipients and description of product not being indicated on the label as well as labeling not complying to the storage condition of zone IVb were the commonest observed deficiencies. These findings are contrary to the study conducted in Nepal

which reported deficiencies to the started parameters by 0.1%⁸. The difference in findings is attributed to the fact that, the Nepalese study surveyed only human medicines sampled from one site (teaching hospital) and produced by Nepalese pharmaceutical industries, of which cannot provide representation of all the medicines circulating in the market. Two-third of the medicine samples used in the current PMS were imported and selected from various outlets to give representation of the medicines circulating in the market.

Almost all of the collected medicine samples passed the quality parameter tests such as visual inspection, identification test, disintegration test and assay. Only one (1) sample of metformin failed dissolution tests. One (1) levamisole injection and two (2) Sulfadiazine+Trimethoprim powder oral for solution had doubtful results on pH and assay. The samples with doubtful results were subjected to out of specification investigation and passed. These findings are similar to the study that tested 869 medicine samples from Africa and Asia; about 2.4% of samples were either falsified or substandard ⁹. In their study, no medicine samples from either India or Kenya were falsified or substandard ⁹. Considering that, our study had most samples imported from India our confidence is increased that medicines circulating in Tanzania are of good quality.

Despite the deficiencies observed in PIR and the one sample that failed the quality control test, this is a clear indication of successful role of TMDA in ensuring the quality of medicines circulating in the market.

7 REGULATORY ACTION TAKEN

The following regulatory actions have been taken by TMDA:

- i.** All manufactures whom their medicines failed product information review (PIR) have been directed to rectify the anomalies which were found during the PIR evaluation.
- ii.** Metformin batch number JR0014 manufactured by Lincoln (India) which was confirmed to have poor quality was recalled.

8 CONCLUSION

More than half of the selected medicine samples did not comply with the regulatory labelling requirement. There was equal proportion of human (66.7%) and veterinary (65.6%) medicine samples that failed PIR. Therefore, more effort is required to enforce Marketing Authorization Holder and local manufacturers to ensure that their products meet product information requirements before being imported and supplied to the market. In addition, inspection activities need to be strengthened especially at ports of entry to identify medicines which are not labelled in the

manner that conform to the labelling requirements before being allowed into the country.

Of all selected medicines, only one human medicine sample (metformin batch number JR0014) failed confirmatory test. This indicates adequate compliance of post registration enforcement. Nevertheless, it is recommended for continuous monitoring of quality of medicines circulating on the market and reminding distributors and sellers of medicines on the importance of adhering to good distribution practices, storage, labelling and proper handling of human and veterinary medicines.

9 RECOMMENDATIONS

The following are recommended.

- i. Marketing authorization holders should be reminded to comply with labelling requirements.
- ii. Reviewers of product information should be trained regularly to improve the recording of deficiencies observed during product information review.
- iii. Regular training to the sample collectors on the proper data entry by using RIMS before sample collection process start.

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11 ANNEXES

| | | |
|--|---|---|
|  <p>TMDA Tanzania Medicines & Medical Services Authority</p> | <p align="center">MEDICINES POST MARKETING SURVEILLANCE SAMPLE COLLECTION FORM</p> | <p align="right">TMDA/DMC/CTP/F/002 Rev #:1</p> |
|--|---|---|

1. Sample code:
(Region/product/sequence number/sampling date dd/mm/yy)***
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/n | Name | Organization | Signature | Date |
|-----|------|--------------|-----------|------|
| | | | | |
| | | | | |
| | | | | |

Note: Samples collected must remain in their original containers.

Approved by MCTP (Signature)  Effective Date: 25/03/2020



ANNEX 2: SAMPLING PLAN PHASE I&II

PHASE I: HUMAN MEDICINE; AZITHROMYCIN TABLETS AND METRONIDAZOLE SUSPENSION FROM PUBLIC AND PRIVATE FACILITIES IN FIVE (5) REGIONS (TANGA, GEITA, MTWARA, SINGIDA, KATAVI)

| Sampling levels | Sampling site | 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 to be collected | Total Number of units to be collected per 2 brand | |
|--------------------------|--------------------------------|------------------|-------------|--------------|---------------------------------|---|-----------|---|---|--|
| LEVEL 1: NATIONAL | | | | | | | | | | |
| National level | MSD HQ warehouse | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg / 5mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | National Hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Sub Total | | | | | | | | | |
| LEVEL 2: REGIONAL | | | | | | | | | | |
| Regional level | MSD warehouse/ retail pharmacy | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Private Importer | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Wholesaler | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Regional/referral hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Retail pharmacy | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Government hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | Private hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| | | Sub Total | | | | | | | | |
| | LEVEL 3: DISTRICTS | | | | | | | | | |
| Districts level | DISTRICT 1 | | | | | | | | | |

| District hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
|---|--|-----------------------------|----------------------------|---------------|---------------------------------|---|----------------|---|---|
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| Retail pharmacy | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| Private hospital / Faith based organisation | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| DISTRICT 2 | | | | | | | | | |
| District hospital | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| Retail pharmacy | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| Private hospital / Faith based organisation | Azithromycin | Tablet | 250mg | 2 | 1 | P/6 tab | 17 | 34 | |
| | Metronidazole | Suspension | 200mg/5 mls | 2 | 1 | 1 bottle | 10 | 20 | |
| Sub Total | | | | | | | | | |
| Expected number of batches/samples to be collected from districts and region level | | | | | | | 30 | | |
| Expected number of samples to be collected from 5 region | | | | | | | 150 | | |
| PHASE I: VETERINARY MEDICINES: SULFADIAZINE + TRIMETHOPRIM POWDER FOR ORAL SUSPENSION IN 5 REGIONS (SHINYANGA, MWANZA, ARUSHA, MOROGORO AND MANYARA) | | | | | | | | | |
| Sampling levels | Sampling site | 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 to be collected | Total Number of units to be collected per 2 brand |
| LEVEL 1: REGIONAL LEVEL | | | | | | | | | |
| Regional level | Importer/wholesale veterinary pharmacy | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 |
| | Retail pharmacy/veterinary shops | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 |
| | Private veterinary clinics | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 |

| | Open market/auctions | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
|---|--|-----------------------------------|----------------------------|---------------|---------------------------------|---|----------------|---|---|--|
| LEVEL 2: DISTRICTS | | | | | | | | | | |
| | District: 1 | | | | | | | | | |
| Districts level | Retail pharmacy | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | ADDO Veterinary shop | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | Open market/auctions | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | District :2 | | | | | | | | | |
| | Retail pharmacy | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | ADDO Veterinary shop | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | Open market/auctions | Sulfadiazine + Trimethoprim | Powder for Oral suspension | 250mg + 50 mg | 2 | 1 | Sachet of 100g | 10 | 20 | |
| | Sub Total | | | | | | | | | |
| | Expected number of batches/samples to be collected from districts and region level | | | | | | | 20 | | |
| | Expected number of samples to be collected from 5 region | | | | | | | 100 | | |
| PHASE II: HUMAN MEDICINAL PRODUCTS; METFORMIN TABLETS AND TELMISARTAN + HYDROCHLOROTHIAZIDE FROM PUBLIC AND PRIVATE FACILITIES IN FIVE (5) REGIONS (DAR, DODOMA, IMWANZA, MBEYA, ARUSHA) | | | | | | | | | | |
| Sampling levels | Sampling site | 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 to be collected | Total Number of units to be collected per 2 brand | |
| LEVEL 1: NATIONAL | | | | | | | | | | |
| National level | MSD HQ warehouse | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | National Hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |

| | | | | | | | | | | |
|--------------------------|-----------------------------------|-----------------------------------|------------------|------------|---|---|-------|---|---|--|
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | | Sub total | | | | | | | | |
| LEVEL 2: REGIONAL | | | | | | | | | | |
| Regional level | MSD warehouse/ retail pharmacy | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Private Importer | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Wholesaler | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Regional/referral hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Retail pharmacy | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Government hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Private hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | | | Sub total | | | | | | | |
| | LEVEL 3: DISTRICTS | | | | | | | | | |
| Districts level | DISTRICT 1 | | | | | | | | | |
| | District hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| | Retail pharmacy | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |

| Private hospital / Faith based organisation | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
|---|--|------------|-------------|-----------|---------------------------------|---|---------------|---|---|
| | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| DISTRICT 2 | | | | | | | | | |
| District hospital | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| Retail pharmacy | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| Private hospital / Faith based organisation | Metformin | Tablets | 500mg | 2 | 1 | P/100 | 1 | 2 | |
| | Telmisartan + Hydrochlorothiazide | Tablets | 80+12.5 mg | 2 | 1 | p/30 | 4 | 8 | |
| Sub total | | | | | | | | | |
| Expected number of batches/samples to be collected from districts and region level | | | | | | 30 | | | |
| Expected number of samples to be collected from 5 region | | | | | | 150 | | | |
| PHASE II VETERINARY MEDICINES: LEVAMIZOLE INJECTION IN 5 REGIONS (DAR ES SALAAM, IRINGA, GEITA, SIMIYU, SINGIDA) | | | | | | | | | |
| Sampling levels | Sampling site | 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 to be collected | Total Number of units to be collected per 2 brand |
| LEVEL 1: REGIONAL LEVEL | | | | | | | | | |
| Regional level | Importer/wholesale veterinary pharmacy | Levamisole | Injection | 200 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 |
| | Retail pharmacy/veterinary shops | Levamisole | Injection | 201 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 |
| | Private veterinary clinics | Levamisole | Injection | 202 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 |
| | Open market/auctions | Levamisole | Injection | 203 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 |
| Sub Total | | | | | | | | | |
| LEVEL 2: DISTRICTS | | | | | | | | | |
| District: 1 | | | | | | | | | |

| | | | | | | | | | | |
|------------------------|--|------------|-----------|-----------|---|---|---------------|------------|----|--|
| Districts level | Importer/wholesale veterinary pharmacy | Levamisole | Injection | 200 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | Retail pharmacy/veterinary shops | Levamisole | Injection | 201 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | Open market/auctions | Levamisole | Injection | 202 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | District :2 | | | | | | | | | |
| | Importer/wholesale veterinary pharmacy | Levamisole | Injection | 200 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | Retail pharmacy/veterinary shops | Levamisole | Injection | 201 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | Open market/auctions | Levamisole | Injection | 202 mg/ml | 2 | 1 | 100mls bottle | 10 | 20 | |
| | Sub Total | | | | | | | | | |
| | Expected number of batches/samples to be collected from districts and region level | | | | | | | 20 | | |
| | Expected number of samples to be collected from 5 region | | | | | | | 100 | | |