SAHPRA
South African Health Products Regulatory Authority

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Post-Marketing Surveillance (PMS) Report for Selected Human Medicines Circulating in South Africa 2022/2023

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LIST OF ABBREVIATIONS/ACRONYMS

Acronym	Definition
ABA	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
AML	Amlodipine
API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
CHC	Community Healthcare Centre
DOL	Dolutegravir
EMT	Emtricitabine
ENA	Enalapril
FC	Fixed Combination
G	Gram
GBC	Glibenclamide
HCl	Hydrochloride
HCR	Holder of the Certificate of Registration
HCT	Hydrochlorothiazide
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ID	Identification
IR	Infrared
ISO	Isoniazid
L	Litre
LAM	Lamivudine
MAH	Market Authorisation Holder
MCO	Medicines Control Officer
MET	Metformin
µg	Microgram
mg	Milligram
mL	Millilitre
NDoH	National Department of Health
nm	Nanometer
NEV	Nevirapine
NIF	Nifedipine
OOS	Out of Specification
PHC	Primary Healthcare
Ph. Int	International Pharmacopoeia
PI	Professional Information

PIL	Patient Information Leaflet
PMS	Post-Marketing Surveillance
RCU	Regulatory Compliance Unit
RIF	Rifampicin
Rf	Retardation factor
RSD	Relative Standard Deviation
SA	South Africa
SAHPRA	South African Health Products Regulatory Authority
SF	Substandard/Falsified
SOP	Standard Operating Procedure
TB	Tuberculosis
TEN	Tenofovir
THY	Thyroxine
TLC	Thin Layer Chromatography
TS	Total solids
UV	Ultraviolet
UV-DAD	Ultraviolet Diode-Array Detection
WHO	World Health Organisation
ZID	Zidovudine

SUMMARY

With limited resources, the identification and selection of medical products to be monitored and prioritised must be based on the risk of being substandard or falsified (SF).

In the 2022/2023 financial year, the South African Health Products Regulatory Authority (SAHPRA) assessed the quality of selected human medicines circulating on the South African market. The priority therapeutic classes of medicines were tuberculostatic medicines (medicines for the treatment of tuberculosis), antiviral agents (specifically anti-retroviral medicines for the treatment of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome [HIV/AIDS]); oral hypoglycaemic medicines (medicines for the treatment of diabetes mellitus); anti-hypertensive medicines (medicines for the treatment of high blood pressure) and thyroid preparations (medicines for the treatment of hypothyroidism).

A systematic method for sample collection covered the medicines supply chain from public and private facilities, including wholesalers, military hospitals, and community healthcare clinics. All outlets were in Gauteng.

All sampled medicines were subjected to screening tests, which involved the review of labelling information and analytical testing at a SAHPRA World Health Organisation (WHO) pre-qualified laboratory.

A total of 26 samples were collected. Labelling information review [label, PI (Professional Information) & PIL (Patient Information Leaflet)] was conducted on all collected samples; six (6) of the 26 samples underwent analytical testing. The results revealed that only five (5) out of the 26 (19%) samples were found without deficiencies relating to labelling, PI and PIL. The Market Authorisation Holders (MAHs) of the samples that failed the labelling information review were directed to comply with labelling requirements.

All samples of medicines passed the screening test on identification (ID) and assay analysis. In addition, oral solid dosage form medicines passed disintegration tests.

Generally, the results of the survey indicate that there is room for improvement in compliance with labelling information review requirements, with 31% of samples presenting non-conformances in terms of labelling requirements, 65% of samples presenting non-conformances in terms of requirements for the PI, and 77% of samples presenting non-conformances in terms of requirements for the PIL. Similarly, analytical testing of samples indicates that there is room for improvement.

1. INTRODUCTION

SAHPRA is the regulatory body responsible for implementing a surveillance system to continuously monitor the quality, safety and effectiveness of medicines circulating on the South African market through various regulatory mechanisms, including Post-Marketing Surveillance (PMS) sampling and testing.

PMS is fundamental to the effective regulation of medicines and includes all regulatory activities that monitor the effectiveness, safety, quality, and use of medications on the market in terms of Section 2B(1)(d) of the Medicines and Related Substances Act, 101 of 1965, as amended [hereinafter referred to as the 'Medicines Act']. PMS of medicines after product authorisation/registration will provide valuable information in terms of quality and safety based on a larger population and a wider range of individuals. Despite the requirement for post-importation testing before release, products may be subject to adverse conditions at any point within the manufacturing processes and the pharmaceutical supply chain (transportation, storage, distribution, handling and dispensing to patients).

South Africa imports a large proportion of its medicines, and this imposes a risk of SF medicines, which further necessitates the existence of a surveillance system to continuously monitor the quality, safety and effectiveness of medicines circulating on the market.

SAHPRA conducts PMS studies with the priority therapeutic classes of registered oral solid and oral liquid dosage forms identified: tuberculostatic, antiviral agents (specifically anti-retroviral treatment for HIV/AIDS, oral hypoglycaemic medicines, anti-hypertensive medicines and thyroid preparations to establish the status of the quality of these medicines circulating the South African market and in so doing, protect the public against substandard and falsified medicinal products.

Through PMS, SAHPRA inspectors, who are also Medicines Control Officers (MCOs), collect samples of medicines from the market using a prepared sampling plan to ascertain their quality. The PMS sampling and testing process involves the physical collection of samples, review of the labelling information against SAHPRA labelling, PI and PIL requirements and against SAHPRA-approved product labelling, PI and PIL. Physical examination of product samples, as well as screening and confirmatory analytical testing by a SAHPRA-designated WHO pre-qualified laboratory, is also performed as part of the PMS sampling and testing process.

Medicines circulating on the market are monitored through PMS by the National Regulator, with the annual implementation effected via planning and budgeting before the collection of medicine samples.

PMS is implemented through planning and systematic sampling of medicines from the market using a pre-defined sampling plan to ensure appropriate representation of medicines used for the treatment of priority diseases. Trained and qualified sample collectors from SAHPRA's Regulatory Compliance Unit (RCU) sampled selected medicines as per the sampling plan.

The survey was implemented in one province and included medicines for human use. The studied medicines included products containing Abacavir sulphate, Amlodipine maleate, Dolutegravir sodium, Emtricitabine, Enalapril maleate, Glibenclamide, Hydrochlorothiazide, Isoniazid, Lamivudine, Levothyroxine sodium, Metformin hydrochloride, Nifedipine, Rifampicin, Tenofovir disoproxil fumarate and Zidovudine.

Medicines were sampled from different public facilities and one private facility in the Gauteng province. These included a medical supply depot, a distributor, a Military Hospital, and Community Healthcare Centres (CHCs) in Johannesburg, Midrand, Pretoria, Laudium and Lyttleton.

SAHPRA developed and implemented the first PMS programme for a period of 12 months between 2022/2023.

A total of 26 samples were collected, with analytical testing results for six (6) samples not performed. A review of label, PI and PIL was conducted on all products sampled. Results demonstrated that 80% of the collected medicine samples had deficiencies. Not all samples of medicines passed analytical tests in terms of initial assay testing.

All sampled medicines were analysed at a SAHPRA-designated WHO pre-qualified laboratory.

Among noted deficiencies observed during labelling, PI and PIL review are that labels of some products did not contain the name and quantity of the specified sugar, no registration number included on the label, PIs not included, sugar statement, name and quantity of sugar not included, no excipients included, registration date not included and incorrect translation of the PI and/or PIL.

This report displays results of the quality of medicines, including medicines for the treatment of HIV, TB, hyperglycaemia, high blood pressure and hypothyroidism. There are several factors that may lead to medicines not fully complying with quality requirements and specifications. Those factors may include manufacturing processes, transportation, storage, distribution, handling and dispensing to patients.

The prepared report highlights the results obtained and regulatory actions taken by SAHPRA.

PMS is considered a systematic quality assurance measure to monitor the quality of registered medicines. Findings from these studies will be used to streamline and strengthen the regulatory framework of medicines in South Africa.

2. OBJECTIVES

2.1 GENERAL OBJECTIVES

To determine the quality of selected human medicines circulating on the South African market in the year 2022/2023 as per the sampling plan. Due to resource constraints, six (6) samples were to be collected per month.

2.2 SPECIFIC OBJECTIVES

The specific objectives of the surveillance were:

2.2.1 To determine compliance of collected medicines samples with labelling requirements by reviewing the labelling, PI and PIL.

2.2.2 To establish the quality of selected medicine samples by conducting laboratory analysis.

2.2.3 To determine the source of quality issues in the medicines' supply chain.

2.2.4 To liaise with Holders of Certificates of Registration (HCRs)/MAHs for any compliance matters detected during the review and testing of samples.

2.2.5 To take the relevant regulatory action(s) and propose strategies and implementation plans to address the problems identified by the survey.

2.2.6 To determine the portion of poor-quality medicines among the marketed medicines sampled and tested.

2.2.7 To compile and publish a report based on the PMS plan to inform the public about the quality status of selected circulating products sampled during the period April 2022 – March 2023.

3. METHODOLOGY

3.1 SAMPLING SITES

This PMS plan was implemented as a proof of concept; therefore, Gauteng was selected as the region to undertake the survey, and four (4) facilities participated in the survey. The facilities were selected based on the following criteria:

- Gauteng region, due to limited resources;
- Public facilities, due to the supply chain risk with only one private facility;
- Facilities closer to the patients; and
- Facilities that were willing to participate and kept the medicines as indicated per the sampling plan.

3.2 SAMPLING

3.2.1 COLLECTION OF SAMPLES

The sampling of the selected medicines was based on the sampling plan. The sampling plan includes the rationale for the inclusion of the therapeutic classes of priority diseases in South Africa.

Samples were collected in their original containers by trained SAHPRA RCU inspectors in accordance with the entity's Standard Operating Procedures (SOPs).

3.2.2 HANDLING OF COLLECTED SAMPLES

Each collected sample was recorded on a seizure form and placed in a numbered National Department of Health (NDoH) Law Enforcement Unit collection bag and sealed. Before and after the transportation of the samples to SAHPRA's head office and to the contracted testing laboratory, measures were taken to ensure that samples were stored according to manufacturers' recommended storage conditions as prescribed per the product labels.

3.3 PRODUCT INFORMATION REVIEW AND LABORATORY TESTING

Samples were screened for the information provided on labels, PI and PIL through the labelling information review.

3.3.1 PRODUCT INFORMATION REVIEW (PIR)

Information provided on the labels of primary and secondary packaging and in the PI and PIL was reviewed to verify if they comply with labelling requirements and approved product information, in accordance with the SOP based on Regulations 10, 11 and 12 relating to the label, PI and PIL, respectively. These regulations are published in terms of Section 35 of the Medicines Act.

Information details checked during the labelling information review included: -

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

Compliance or non-compliance detected during labelling information review was recorded in the designed PMS Sampling Report.

3.3.2 LABORATORY TESTING

All collected medicine samples were subjected to laboratory analytical tests for appearance, identification (ID), and assay. The disintegration of oral solid dosage forms was performed for samples available in sufficient quantity. Physical examination, ID and assay for oral liquid dosage forms were also performed as described below.

3.3.2.1 IDENTIFICATION TEST BY THIN LAYER CHROMATOGRAPHY (TLC)

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

3.3.2.2 IDENTIFICATION TEST BY ULTRAVIOLET (UV) SPECTROSCOPY

The standard and sample solutions are scanned at a specified range of wavelengths (in nm). The UV absorption spectrum of the sample solution should exhibit maxima at the same wavelength as that of the standard solution. This was performed using a spectrophotometer.

3.3.2.3 IDENTIFICATION TEST BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

The retention times of consecutive runs of each corresponding standard and sample chromatograms for API(s) were compared. The identification test complies only if the retention times observed for standard peak(s) correspond to each other.

3.3.2.4 IDENTIFICATION TEST BY ULTRAVIOLET DIODE-ARRAY DETECTION (UV-DAD)

A DAD is a type of detector used in HPLC that detects absorption in the UV to visible region. This detector has multiple photodiode arrays to obtain information over a wide range of wavelengths at one time. The wavelength maxima of the sample(s) should match the standard solution(s) for each API.

3.3.2.5 IDENTIFICATION TEST BY INFRARED (IR) SPECTROSCOPY

The IR absorption spectrum of the test specimen exhibits only at the same wavelengths as that of a similar preparation of the corresponding reference standard.

3.3.2.6 IDENTIFICATION TEST BY REACTION A OF SULPHATES

The presence of sulphate ions in the chemical structure of some medicines is determined for substances which are required to dissociate the substance to its free base *in-vivo*. A white precipitate is formed, which is practically insoluble in hydrochloric acid (~250 g/L) TS.

3.3.2.7 IDENTIFICATION TEST BY COLOUR TEST

Metformin hydrochloride is identified by triturating powdered tablets with water and filtering. Sodium hydroxide and 1-naphthol solution are added while shaking. Diluted sodium hypochlorite solution is added, which produces an orange-red colour that darkens on standing.

3.3.2.8 IDENTIFICATION TEST BY REACTION OF CHLORIDES

Metformin hydrochloride is identified by triturating powdered tablets with water and filtering. The filtrate yields Reaction A characteristics of chlorides.

3.3.2.9 DISINTEGRATION TEST

A disintegration test was used to test the possibility of a solid dosage form to break into small particles, which can thus dissolve and undergo dissolution to release the active pharmaceutical ingredient (API). This was done by using a disintegration test machine.

3.4 LABORATORY CONFIRMATORY TESTING

Laboratory testing of samples was performed according to their manufacturer's methods or the pharmacopoeia monograph for products for which the manufacturer's methods were not available. Parameters checked for each type of medicine were as per Table 1 below:

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

Category of medicine	Type of Medicine	Parameters tested	Analytical Method used
Category A (human medicines)	Anti-viral agents (oral solid dosage form)	1. Appearance 2. Identification 3. Assay 4. Disintegration	1. Visual 2. TLC / HPLC / UV-DAD HPLC / IR 3. HPLC 4. BP / Ph. Int
Category A (human medicines)	Anti-viral agents (oral liquid dosage form)	1. Appearance 2. Identification 3. Assay	1. Visual 2. HPLC / UV / Reaction A of sulphates 3. HPLC
Category A (human medicines)	Anti-hypertensive medicines (oral solid dosage form)	1. Appearance 2. Identification 3. Assay 4. Disintegration	1. Visual 2. TLC / HPLC / UV-DAD HPLC / IR 3. HPLC 4. BP / Ph. Int
Category A (human medicines)	Tuberculostatic medicines (oral solid dosage form)	1. Appearance 2. Identification 3. Assay 4. Disintegration	1. Visual 2. HPLC 3. HPLC 4. BP / Ph. Int
Category A (human medicines)	Oral hypoglycaemic medicines (oral solid dosage form)	1. Appearance 2. Identification 3. Assay 4. Disintegration	1. Visual 2. IR / Colour test / Reaction of chlorides 3. UV 4. BP / Ph. Int
Category A (human medicines)	Thyroid preparations (oral solid dosage form)	Analytical testing was not performed	Analytical testing was not performed

4. RESULTS

4.1 SAMPLE COLLECTION

Different criteria were used during the selection of human medicines to be monitored. Type of medicines and criteria were as per Table 2 below:

Table 2: Medicines selected for quality assessment

Therapeutic group	Product	Selection criteria
20.2.8 Antiviral agents	Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets	Disease treatment priorities from the NDoH based on the National Development Plan 2030 [Government of South Africa, 2012], NDoH Strategic Plan [National Department of Health, 2020] and Stats SA report (Mortality and causes of death in South Africa: Findings from death notification) [Stats SA, 2021]. Therapeutic areas selected: – Antiviral agents (specifically Anti-Retroviral treatment for HIV/AIDS)
	Lamivudine 10 mg/mL solution	
	Zidovudine 50 mg/5 mL syrup	
	Abacavir sulphate equivalent to 20 mg/mL Abacavir oral solution	
	Dolutegravir 50 mg tablets	
	Dolutegravir sodium equivalent to 50 mg Dolutegravir, Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets	
	Nevirapine 200 mg tablets	
7.1 Vasodilators, hypotensive medicines	Amlodipine maleate 5 mg tablets	Disease treatment priorities from the NDoH based on the National Development Plan 2030 [Government of South Africa, 2012], NDoH Strategic Plan [National Department of Health, 2020] and Stats SA report (Mortality and causes of death in South Africa: Findings from death notification) [Stats SA, 2021]. Therapeutic areas selected: – Anti-hypertensive medicines (for the treatment of high blood pressure)
	Nifedipine 10 mg capsules	
7.1.3 Other hypotensives	Enalapril maleate 10 mg tablets	
	Enalapril maleate 20 mg tablets	
18.1 Diuretics	Hydrochlorothiazide 25 mg tablets	
	Hydrochlorothiazide 12,5 mg tablets	

Table 2: Medicines selected for quality assessment

Therapeutic group	Product	Selection criteria
20.2.3 Tuberculostatics	Rifampicin 150 mg & Isoniazid 75 mg FC tablets	Disease treatment priorities from the NDoH based on the National Development Plan 2030 [Government of South Africa, 2012], NDoH Strategic Plan [National Department of Health, 2020] and Stats SA report (Mortality and causes of death in South Africa: Findings from death notification) [Stats SA, 2021]. Therapeutic areas selected: – Tuberculostatic medicines (for the treatment of tuberculosis)
	Rifampicin 300 mg & Isoniazid 150 mg FC tablets	
21.2 Oral Hypoglycaemics	Metformin hydrochloride 500 mg tablets	Disease treatment priorities from the NDoH based on the National Development Plan 2030 [Government of South Africa, 2012], NDoH Strategic Plan [National Department of Health, 2020] and Stats SA report (Mortality and causes of death in South Africa: Findings from death notification) [Stats SA, 2021]. Therapeutic areas selected: – Oral hypoglycaemic medicines (for the treatment of diabetes)
	Metformin hydrochloride 850 mg tablets	
	Glibenclamide 5 mg tablets	
21.3 Thyroid preparations	Levothyroxine sodium 100 µg tablets	Disease treatment priorities from the NDoH based on the National Development Plan 2030 [Government of South Africa, 2012], NDoH Strategic Plan [National Department of Health, 2020] and Stats SA report (Mortality and causes of death in South Africa: Findings from death notification) [Stats SA, 2021] and pharmacovigilance data relating to safety alerts. Therapeutic areas selected: – Thyroid preparations (for the treatment of hypothyroidism)

4.1.1 HUMAN MEDICINES SAMPLE COLLECTION

A total of 26 samples of medicines were collected during the year 2022/23. Samples were collected at the regional level from within one (1) province. Medicine samples were sourced from four (4) different regions. Out of 26 samples collected, 38% (10/26) were for the treatment of HIV/AIDS, 30% (8/26) were for the treatment of hypertension, 16% (4/26) were for the treatment of hyperglycaemia, 8% (2/26) were for the treatment of hypothyroidism and 8% (2/26) were for the treatment of tuberculosis, as summarised in Table 3 below:

Table 3: Number of human medicines samples collected

Region	Antiviral agents	TB agents	Hypo-glycaemic agents	Thyroid preparations	Hypotensive medicines	TOTAL
Midrand, Gauteng	Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets	-	-	-	-	**3**
	Lamivudine 10 mg/mL solution	-	-	-	-	
	Zidovudine 50 mg/5 mL syrup	-	-	-	-	
Thaba Tshwane, Pretoria, Gauteng	Abacavir sulphate equivalent to 20 mg/mL Abacavir oral solution	-	-	-	Amlodipine maleate 5 mg tablets	**6**
	Dolutegravir 50 mg tablets	-	-	-	Enalapril 10 mg tablets	
	Dolutegravir sodium equivalent to 50 mg Dolutegravir, Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets	-	-	-	-	
	Nevirapine 200 mg tablets	-	-	-	-	
Laudium, Gauteng	-	Rifampicin 150 mg & Isoniazid	Metformin hydrochloride 500 mg tablets	-	Nifedipine 10 mg capsules	**7**

Table 3: Number of human medicines samples collected						
Region	**Antiviral agents**	**TB agents**	**Hypo-glycaemic agents**	**Thyroid preparations**	**Hypotensive medicines**	**TOTAL**
		75 mg FC tablets				
	-	Rifampicin 300 mg & Isoniazid 150 mg FC tablets	Metformin hydrochloride 850 mg tablets	-	Hydrochloro-thiazide 25 mg tablets	
	-	-	-	-	Hydrochloro-thiazide 12,5 mg tablets	
Lyttleton, Centurion, Gauteng	Dolutegravir sodium equivalent to 50 mg Dolutegravir, Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets	-	Metformin hydrochloride 500 mg tablets	Levo-thyroxine sodium 100 µg tablets	Enalapril maleate 20 mg tablets	
	Abacavir sulphate equivalent to 20 mg/mL Abacavir oral solution	-	Glibenclamide 5 mg tablets	Levo-thyroxine sodium 50 µg tablets	Enalapril maleate 10 mg tablets	
	Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets	-	-	-	Hydrochloro-thiazide 25 mg tablets	**10**
Total:	**10**	**2**	**4**	**2**	**8**	**26**

4.2 SAMPLES COLLECTION SITES

Figure 1 below shows a total of 26 samples of human medicines which were sampled from different medicines distribution channels, namely, a wholesaler, hospital, and Community Healthcare Centres. The results indicate that the highest number of medicines samples were collected from Community Healthcare Centres (CHC), with one CHC accounting for 37 % (10/26) and another CHC accounting for 28 % (7/26), a Military Hospital Pharmacy accounting for 23 % (6/26), followed by a wholesaler with 12 % (3/26).

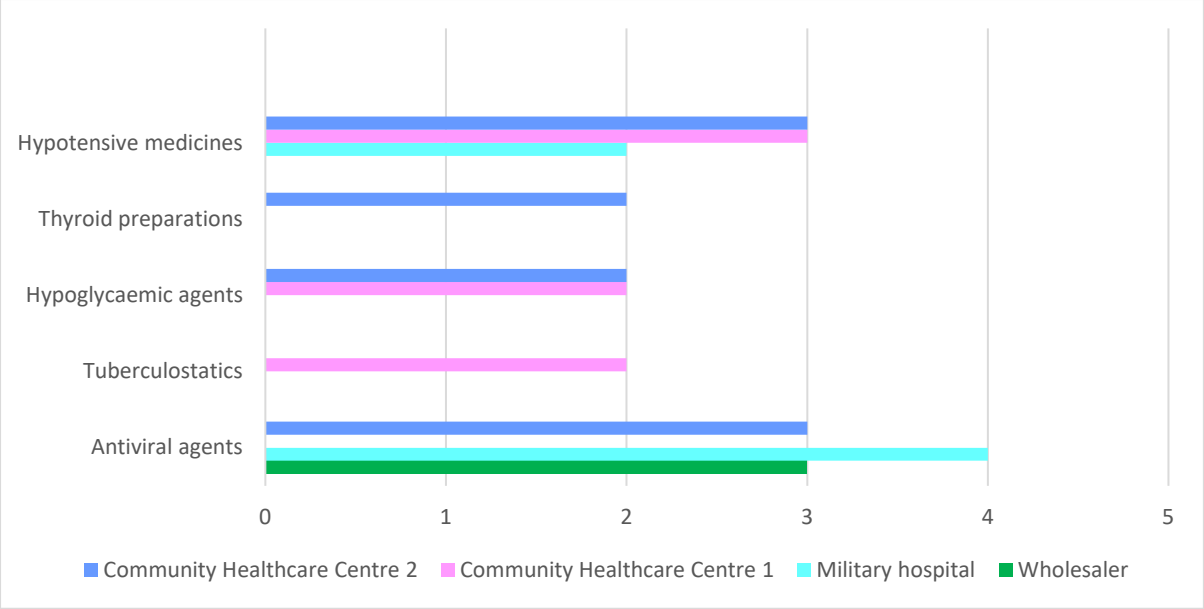

Figure 1: Number of human medicines sampled at different levels of the distribution chain.

The majority of collected samples of medicines were imported from different manufacturers, as listed in Table 4 below:

Table 4: Human medicines sampled with respective manufacturers

Product	Number of samples	Manufacturer	Country of origin
Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets	1	Adcock Ingram Healthcare (Pty) Ltd Wadeville	South Africa
Lamivudine 10 mg/mL solution	1	Adcock Ingram Healthcare (Pty) Ltd Wadeville	South Africa
Zidovudine 50 mg/5 mL syrup	1	Adcock Ingram Healthcare (Pty) Ltd Wadeville	South Africa
Amlodipine maleate 5 mg tablets	1	Unique Pharmaceutical Laboratories	India
Enalapril 10 mg tablets	1	Unique Pharmaceutical Laboratories	India
Abacavir sulphate equivalent to 20 mg/mL oral solution	1	Aurobindo Pharma Limited	India
Dolutegravir 50 mg tablets	1	Aurobindo Pharma Limited	India
Dolutegravir sodium equivalent to 50 mg Dolutegravir; Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets	1	Hetero Labs Limited	India
Nevirapine 200 mg tablets	1	Mylan Laboratories Limited, Aurangabad	India
Rifampicin 150 mg & Isoniazid 75 mg FC tablets	1	Macleods Pharmaceuticals Limited	India
Metformin 500 mg tablets	1	Ipca Laboratories Limited	India

Table 4: Human medicines sampled with respective manufacturers

Product	Number of samples	Manufacturer	Country of origin
Nifedipine 10 mg capsules	1	Ascendis Supply Chain (Pty) Ltd	South Africa
Hydrochlorothiazide 25 mg tablets	1	IPCA Laboratories Limited	India
Metformin hydrochloride 850 mg tablets	1	Rusan Pharma Limited	India
Hydrochlorothiazide 12,5 mg tablets	1	Aspen Pharmacare Port Elizabeth	South Africa
Rifampicin 300 mg & Isoniazid 150 mg FC tablets	1	Sanofi Industries, Watloo	South Africa
Levothyroxine sodium 100 µg tablets	1	Aspen Bad Oldesloe GmbH	Germany
Levothyroxine sodium 50 µg tablets	1	Merck Healthcare, Darmstadt	Germany
Dolutegravir sodium equivalent to 50 mg Dolutegravir; Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets	1	Mylan Laboratories Limited	India
Enalapril maleate 20 mg tablets	1	Sun Pharmaceutical Industries Ltd.	India
Abacavir 20 mg/mL oral solution	1	Aspen Pharmacare, East London	South Africa
Enalapril maleate 10 mg tablets	1	Qualigens Pharma Pvt. Ltd.	India
Metformin hydrochloride 500 mg tablets	1	Rusan Pharma Limited	India
Glibenclamide 5 mg tablets	1	Rusan Pharma Limited	India
Hydrochlorothiazide 25 mg tablets	1	Milan Laboratories Pvt. Ltd.	India
Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets	1	Mylan Laboratories Limited	India

Seven (7) of the 26 (27%) medicine samples were domestically manufactured, and the majority were imported from India, 65% (17/26), followed by 8% (2/26), which were imported from Germany. These results are presented in Figure 2 below.

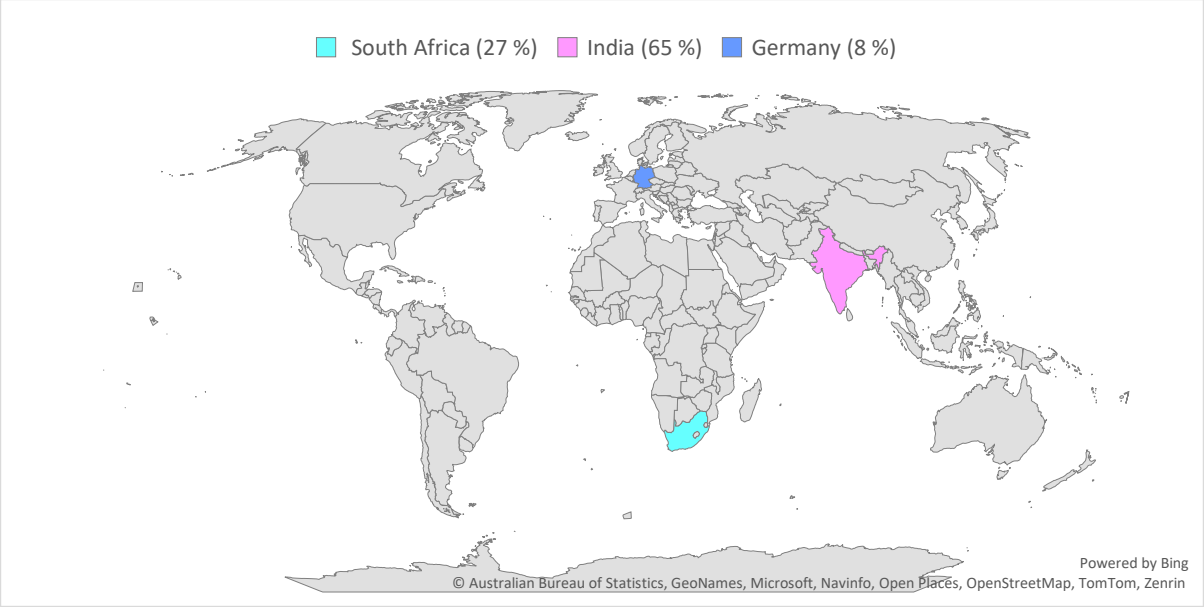

Figure 2: Number of imported and locally manufactured human medicines sampled.

4.3 PRODUCT INFORMATION REVIEW AND LABORATORY TESTING

4.3.1 PRODUCT INFORMATION REVIEW

Of the collected medicine samples, labelling information was reviewed against the SAHPRA labelling and packaging requirements and approved product information. A total of 26 samples of medicines were reviewed against Regulation 10 in terms of labelling published in terms of Section 35 of the Medicines Act.

Labels of only 19% (5/26) of the collected medicine samples had no deficiencies. Laboratory testing for three (3) out of these five (5) samples was not performed. The following deficiencies were noted:

- Some samples did not comply with Regulation 10(1) in that the particulars were only provided in English and French, which is not an official language in South Africa.
- Some samples did not comply with Regulation 10(1)(a) in that the SAHPRA-approved scheduling status of the sample was not as assigned by SAHPRA.
- Some samples did not comply with Regulation 10(1)(c)(i) in that the SAHPRA registration number was not included on the label.
- Some samples did not comply with Regulation 10(1)(e) in that the particulars of the API were only included in English and no other official language on the label.
- Some samples did not comply with Regulation 10(1)(h)(i) in that the sugar statement, name and/or quantity of the sugar was not included on the label.

- Some samples did not comply with Regulation 10(1)(h)(iii) in that the name and quantity of the sweetener and sweetener statement were not included on the label.
- Some samples did not comply with Regulation 10(1)(n) in that the lot number on the secondary packaging was not legible.
- Some samples did not comply with Regulation 10(1)(q) in that the HCR name was not updated after the name change in HCR.
- Some samples did not comply with Regulation 10(1)(t) in that the "Keep out of reach of Children" warning was only included in English on the label.
- Some samples did not comply with Regulation 10(1)(z)(aa) in that the category of the medicine was not included on the label.
- Some samples did not comply with Regulation 10(1)(z)(bb) in that the class of medicine was not included on the label.

Of the collected medicine samples, the PI was reviewed against the Regulation 11 requirements in terms of professional information published according to Section 35 of the Medicines Act.
PIs of only 31% (8/26) of the collected medicine samples had no deficiencies. Laboratory analyses were not performed on three (3) of these eight (8) samples.

- Some samples did not comply with Regulation 11(1)(a)(i)-(ii) in that no PI was provided with the sample.
- Some samples did not comply with Regulation 11(1)(b) in that the PI was available in English and French, which is not an official South African language.
- Some samples contravened Regulation 11(a)(c)(vii) in that the name and quantity of sweetener and sugar statement was not included in the PI.
- Some samples contravened Regulation 11(2)(a) in that one sample did not have the scheduling status as assigned by SAHPRA on the PI, and for the other sample, the South African registration number was not included on the PI.
- Some samples contravened Regulation 11(2)(c)(i) in that the active ingredient and quantity contained per dosage unit were incorrectly translated.
- Some samples contravened Regulation 11(2)(c)(ii) in that for three (3) of seven (7) samples, the approved names of all excipients in the formulation were not included. One of the three (3) samples did not contain the approved names of all excipients in the translation. One sample contained mannitol as part of the formulation, but it was not included in the sugar statement or contents. One of the samples had a spelling error of "excipients", for another

sample, the translation for "Other ingredients" was not included, and one sample did not include a list of excipients.

- Some samples contravened Regulation 11(1)(c)(vi) in that the "sugar statement" and name and quantity of sugar were not included for six (6) samples, with one sample having the incorrect translation of the dosage unit of sugar.
- Some samples contravened Regulation 11(2)(c)(vii) in that the sugar statement was not included for one sample, and the other sample contained mannitol, as part of the formulation, but it was not included with the sugar statement or as a sweetener.
- Some samples contravened Regulation 11(2)(d) in that the category and class of medicine were not included in the PI.
- Some samples contravened Regulation 11(2)(e)(s) in that reference was made to previous regulations with the new regulations published on 25 August 2017.
- Some samples contravened Regulation 11(2)(j) in that human production or equivalent was not included in the PI.
- Some samples contravened Regulation 11(2)(n) in that the identification was not included in the PI for one sample. The other sample contained the incorrect translation of "odour" to "kleur".
- Some samples contravened Regulation 11(2)(q) in that the registration number was not included in the PI.
- Some samples contravened Regulation 11(2)(r) in that the PI contained the previous HCR name and address after the change was approved by SAHPRA.
- Some samples contravened Regulation 11(2)(s) in that the date of registration was not included in the PI.

Of the collected medicine samples, the PIL was reviewed against the Regulation 12 requirements in terms of PIL published according to Section 35 of the Medicines Act.

PILs of only 19% (5/26) of the collected medicine samples had no deficiencies relating to their PILs.

- Some samples contravened Regulation 12(1)(a)-(c) in that no PIL was included with the sample.
- Some samples contravened Regulation 12(2)(c) in that the PIL for one sample was incompletely translated for composition. The other sample contains mannitol as part of the formulation, but it was not included with the sugar or sweetener statements.
- Some samples contravened Regulation 12(2)(d) in that the indications for use were incorrectly translated.

- Some samples contravened Regulation 12(2)(e) in that the instructions before taking were incorrectly translated.
- Some samples contravened Regulation 12(2)(g) in that the side effects were incorrectly translated.
- Some samples contravened Regulation 12(2)(k)(i) in that the registration number contained commas instead of full stops.
- Some samples contravened Regulation 12(2)(l)(i) in that "access to the corresponding Professional Information" was included under this heading instead of "Name of the holder of the certificate of registration".
- Some samples contravened Regulation 12(2)(m) in that the date of the most recent amendment for one sample was incorrectly translated. The date of registration was not included on the PIL of the other sample.
- Some samples contravened Regulation 12(2)(o)(i) in that the sugar statement, name and quantity of sugar were not included on the PIL. The other sample contains mannitol as part of the formulation, but it was not included with a sugar statement or sweetener.
- Some samples contravened Regulation 12(2)(o)(ii) in that mannitol is part of the formulation but is not included under the sugar contents or sweetener of the PIL. The results are presented in Figure 3 below:

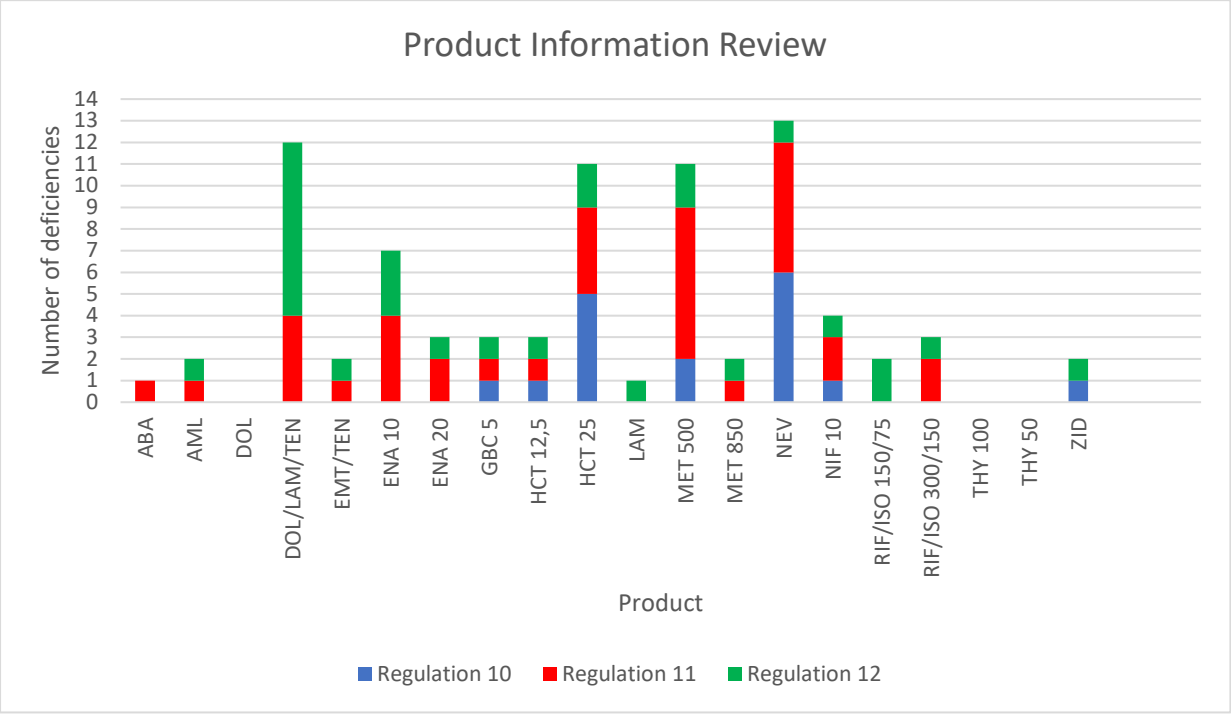

Figure 3: Number of deficiencies on the labels, PI and PIL.

ABA-Abacavir, AML-Amlodipine, DOL-Dolutegravir, EMT-Emtricitabine, ENA-Enalapril, GBC-Glibenclamide, HCT-Hydrochlorothiazide, ISO-Isoniazid, LAM-Lamivudine, MET-Metformin, NEV-Nevirapine, NIF-Nifedipine, RIF-Rifampicin, TEN-Tenofovir, THY-Thyroxine & ZID-Zidovudine.

4.3.2 VISUAL INSPECTION TEST

The results of the visual inspection test revealed that 100% (26/26) of sampled medicines passed the test. Medicine samples listed below in Table 5 were submitted for further testing.

4.3.3 DISINTEGRATION AND IDENTIFICATION TEST

All collected samples of medicines were subjected to an ID test using TLC, UV, IR, HPLC, UV-DAD and some other methods, and all passed the identification test.

For the oral solid dosage forms of medicines, Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets, Amlodipine maleate 5 mg tablets, Enalapril 10 mg tablets, Dolutegravir 50 mg tablets, Dolutegravir sodium equivalent to 50 mg Dolutegravir; Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets, Nevirapine 200 mg tablets, Rifampicin 150 mg & Isoniazid 75 mg FC tablets, Metformin 500 mg tablets, Nifedipine 10 mg capsules, Hydrochlorothiazide 25 mg tablets, Metformin hydrochloride 850 mg tablets, Hydrochlorothiazide 12,5 mg tablets, Rifampicin 300 mg & Isoniazid 150 mg FC tablets, Dolutegravir sodium equivalent to 50 mg Dolutegravir; Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets and Metformin hydrochloride 500 mg tablets were tested for disintegration.

Samples of Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets, Dolutegravir sodium equivalent to 50 mg Dolutegravir; Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets, Metformin 500 mg tablets, Metformin hydrochloride 850 mg tablets, Rifampicin 300 mg & Isoniazid 150 mg FC tablets, Dolutegravir sodium equivalent to 50 mg Dolutegravir; Lamivudine 300 mg and Tenofovir disoproxil fumarate 300 mg tablets, Metformin hydrochloride 500 mg tablets disintegrated within 30 minutes at 37 °C (between 2-18 minutes).

Samples of Enalapril 10 mg tablets, Amlodipine maleate 5 mg tablets, Dolutegravir 50 mg tablets, Nevirapine 200 mg tablets, Rifampicin 150 mg & Isoniazid 75 mg FC tablets, Nifedipine 10 mg capsules, Hydrochlorothiazide 25 mg tablets, Hydrochlorothiazide 12,5 mg tablets disintegrated within 15 minutes (between 1-12 minutes). These results indicated that there were no signs of disintegration problems that would have necessitated dissolution testing of the samples.

4.4 CONFIRMATORY TESTING

Based on selection criteria, a total of 20 samples were submitted for confirmatory testing as listed in Table 5.

Table 5: Confirmatory testing results for human medicines sampled

PRODUCT	TEST	SPECIFICATION	RESULTS	COMPLIED (YES OR NO)
Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets	ASSAY Emtricitabine	90,00 – 110,00%	Sample 1: 99,50% Sample 2: 100,70% Sample 3: 99,70% Average (% RSD): 100,00% (0,60%)	Yes
	ASSAY Tenofovir disoproxil fumarate	90,00 – 110,00%	Sample 1: 99,30% Sample 2: 100,20% Sample 3: 98,80% Average (% RSD): 99,40% (0,70%)	Yes
Lamivudine 10 mg/mL solution	ASSAY Lamivudine	90,00 – 110,00%	Sample 1: 99,80% Sample 2: 98,80% Sample 3: 99,80% Average (% RSD): 99,50% (0,60%)	Yes
Zidovudine 50 mg/5 mL syrup	ASSAY Zidovudine	90,00 – 110,00%	Sample 1: 99,00% Sample 2: 98,80% Sample 3: 98,80% Average (% RSD): 98,90% (0,10%)	Yes
Amlodipine maleate 5 mg tablets	ASSAY Amlodipine maleate equivalent to Amlodipine	90,00 – 110,00%	Sample 1: 90,50% Sample 2: 92,00% Sample 3: 90,90% Average (% RSD): 91,10% (0,90%)	Yes
* Enalapril 10 mg tablets	ASSAY Enalapril	Release specification: 93,00 – 105,00%	Sample 1: 91,20% Sample 2: 91,00% Sample 3: 91,40% Sample 4: 90,60% Sample 5: 90,60% Sample 6: 90,40% Sample 7: 90,20% Sample 8: 90,70% Sample 9: 88,70% Average (% RSD): 90,50% (0,90%)	No
		Stability specification: 90,00 – 110,00%	Sample 1: 91,20% Sample 2: 91,00% Sample 3: 91,40%	Yes

Table 5: Confirmatory testing results for human medicines sampled

PRODUCT	TEST	SPECIFICATION	RESULTS	COMPLIED (YES OR NO)
			Sample 4: 90,60% Sample 5: 90,60% Sample 6: 90,40% Sample 7: 90,20% Sample 8: 90,70% Sample 9: 88,70% Average (% RSD): 90,50% (0,90%)	
Abacavir sulphate equivalent to 20 mg/mL oral solution	ASSAY Abacavir sulphate equivalent to abacavir	90,00 – 110,00%	Sample 1: 100,50% Sample 2: 100,40% Sample 3: 100,50% Average (% RSD): 100,50% (0,10%)	Yes
Dolutegravir 50 mg tablets	ASSAY Dolutegravir	95,00 – 105,00%	Sample 1: 98,40% Sample 2: 99,00% Sample 3: 100,70% Average (% RSD): 99,40% (1,20%)	Yes
Dolutegravir sodium equivalent to 50 mg Dolutegravir; Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets	ASSAY Dolutegravir sodium equivalent to dolutegravir	95,00 – 105,00%	Sample 1: 97,40% Sample 2: 97,60% Average: 97,50%	Yes
	ASSAY Lamivudine	95,00 – 105,00%	Sample 1: 97,00% Sample 2: 97,40% Average: 97,20%	Yes
	ASSAY Tenofovir disoproxil fumarate	95,00 – 105,00%	Sample 1: 101,30% Sample 2: 101,30% Average: 101,30%	Yes
Nevirapine 200 mg tablets	ASSAY Nevirapine	90,00 – 110,00%	Sample 1: 98,80% Sample 2: 98,90% Sample 3: 98,70% Average (% RSD): 98,80% (0,10%)	Yes
Rifampicin 150 mg & Isoniazid 75 mg FC tablets	ASSAY Rifampicin	90,00 – 105,00%	Sample 1: 96,80% Sample 2: 96,10% Sample 3: 97,30% Average (% RSD): 96,70% (0,60%)	Yes
	ASSAY Isoniazid	90,00 – 105,00%	Sample 1: 97,00% Sample 2: 97,20% Sample 3: 97,70% Average (% RSD): 97,30% (0,40%)	Yes
Metformin 500 mg tablets	ASSAY Metformin	95,00 – 105,00%	Sample 1: 95,70% Sample 2: 95,00% Sample 3: 95,80%	Yes

Table 5: Confirmatory testing results for human medicines sampled

PRODUCT	TEST	SPECIFICATION	RESULTS	COMPLIED (YES OR NO)
			Average (% RSD): 95,50% (0,50%)	
Nifedipine 10 mg capsules	ASSAY Nifedipine	90,00 – 105,00%	Sample 1: 98,00% Sample 2: 96,00% Sample 3: 96,00% Average (% RSD): 97,00% (1,00%)	Yes
Hydrochlorothiazide 25 mg tablets	ASSAY Hydrochlorothiazide	92,50 – 107,50%	Sample 1: 94,10% Sample 2: 94,30% Sample 3: 93,40% Average (% RSD): 93,90% (0,50%)	Yes
Metformin hydrochloride 850 mg tablets	ASSAY Metformin HCl	95,00 – 105,00%	Sample 1: 98,10% Sample 2: 98,70% Sample 3: 98,30% Average (% RSD): 93,40% (0,30%)	Yes
Hydrochlorothiazide 12,5 mg tablets	ASSAY Hydrochlorothiazide	90,00 – 110,00%	Sample 1: 99,10% Sample 2: 102,00% Sample 3: 100,10% Average (% RSD): 100,40% (1,50%)	Yes
Rifampicin 300 mg & Isoniazid 150 mg FC tablets	ASSAY Rifampicin	90,00 – 110,00%	Sample 1: 99,10% Sample 2: 96,30% Sample 3: 94,30% Average (% RSD): 96,60% (2,50%)	Yes
	ASSAY Isoniazid	90,00 – 110,00%	Sample 1: 99,80% Sample 2: 101,90% Sample 3: 104,90% Average (% RSD): 102,20% (2,50%)	Yes
Dolutegravir sodium equivalent to 50 mg Dolutegravir; Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets	ASSAY Lamivudine	95,00 – 105,00%	Sample 1: 98,70% Sample 2: 97,60% Sample 3: 97,00% Average (% RSD): 97,80% (0,90%)	Yes
	ASSAY Tenofovir disoproxil fumarate	95,00 – 105,00%	Sample 1: 97,60% Sample 2: 99,00% Sample 3: 98,60% Average (% RSD): 98,40% (0,70%)	Yes
	ASSAY Dolutegravir	95,00 – 105,00%	Sample 1: 103,20% Sample 2: 103,80% Sample 3: 102,60%	Yes

Table 5: Confirmatory testing results for human medicines sampled

PRODUCT	TEST	SPECIFICATION	RESULTS	COMPLIED (YES OR NO)
			Average (% RSD): 103,20% (0,60%)	
Enalapril maleate 20 mg tablets	ASSAY Enalapril maleate	95,00 – 105,00%	Sample 1: 100,00% Sample 2: 99,00% Sample 3: 99,80% Average (% RSD): 99,60% (0,50%)	Yes
Metformin hydrochloride 500 mg tablets	ASSAY Metformin HCl	95,00 – 105,00%	Sample 1: 96,54% Sample 2: 96,65% Sample 3: 95,84% Average (% RSD): 96,34% (0,50%)	Yes
Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets	ASSAY Emtricitabine	95,00 – 105,00%	Average (% RSD): 99,10% (1,10%)	Yes
	ASSAY Tenofovir Disoproxil Fumarate	95,00 – 105,00%	Average (% RSD): 97,00% (1,10%)	Yes

** One sample was initially out of specification (OOS) (Enalapril 10 mg tablets)*

The results show that all medicine samples [100% (20/20)] subjected to confirmatory testing subsequently complied with the tested parameters.

However, 5% (1/20), the Enalapril 10 mg tablets sample did not comply with release specifications for the assay test, initially, having a quantity below the acceptable range of 93,00 – 105,00%. The sample did however, comply with stability specifications for the assay test within the range of 90,00 – 100,00%. Parameters tested for each medicine are provided in Table 6.

Confirmatory testing of the following samples: Levothyroxine sodium 100 µg tablets, Levothyroxine sodium 50 µg tablets, Abacavir 20 mg/mL oral solution, Enalapril maleate 10 mg tablets, Glibenclamide 5 mg tablets and Hydrochlorothiazide 25 mg tablets were not performed due to delays in the delivery of the reference standards, columns and reagents which was caused by the Transnet strike at the end of 2022.

Table 6: Parameters and method of analysis for testing of medicine samples

PRODUCT	PARAMETERS TESTED	ANALYTICAL METHOD USED
Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets	1. Appearance 2. Identification 3. Assay (Emtricitabine) Assay (Tenofovir disoproxil fumarate) 4. Disintegration	1. Visual 2. HPLC 3. HPLC HPLC 4. BP / Ph. Int

Table 6: Parameters and method of analysis for testing of medicine samples

PRODUCT	PARAMETERS TESTED	ANALYTICAL METHOD USED
Lamivudine 10 mg/mL solution	1. Appearance 2. Identification 3. Assay	1. Visual 2. HPLC 3. HPLC
Zidovudine 50 mg/5 mL syrup	1. Appearance 2. Identification A Identification B 3. Assay	1. Visual 2. HPLC UV-DAD 3. HPLC
Amlodipine maleate 5 mg tablets	1. Appearance 2. Identification A Identification B 3. Assay 4. Disintegration	1. Visual 2. UV-DAD HPLC 3. HPLC 4. BP / Ph. Int
Enalapril 10 mg tablets	1. Appearance 2. Identification A Identification B 3. Assay 4. Disintegration	1. Visual 2. TLC HPLC 3. HPLC 4. BP / Ph. Int
Abacavir sulphate equivalent to 20 mg/mL oral solution	1. Appearance 2. Identification B Identification C Identification D 3. Assay	1. Visual 2. HPLC UV Reaction A of sulphates 3. HPLC
Dolutegravir 50 mg tablets	1. Appearance 2. Identification A Identification B 3. Assay 4. Disintegration	1. Visual 2. HPLC TLC 3. HPLC 4. BP / Ph. Int
Dolutegravir sodium equivalent to 50 mg Dolutegravir; Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets	1. Appearance 2. Identification Identification 3. Assay (Dolutegravir sodium equivalent to dolutegravir) Assay (Lamivudine) Assay (Tenofovir disoproxil fumarate) 4. Disintegration	1. Visual 2. HPLC UV-DAD 3. HPLC HPLC HPLC 4. BP / Ph. Int
Nevirapine 200 mg tablets	1. Appearance 2. Identification A Identification B 3. Assay 4. Disintegration	1. Visual 2. IR HPLC 3. HPLC 4. BP / Ph. Int
Rifampicin 150 mg & Isoniazid 75 mg FC tablets	1. Appearance 2. Identification A 3. Assay (Rifampicin) Assay (Isoniazid)	1. Visual 2. HPLC 3. HPLC HPLC

Table 6: Parameters and method of analysis for testing of medicine samples

PRODUCT	PARAMETERS TESTED	ANALYTICAL METHOD USED
	4. Disintegration	4. BP / Ph. Int
Metformin 500 mg tablets	1. Appearance 2. Identification A Identification B Identification C 3. Assay 4. Disintegration	1. Visual 2. IR Colour test Reaction of chlorides 3. UV 4. BP / Ph. Int
Nifedipine 10 mg capsules	1. Appearance 2. Identification A Identification B 3. Assay 4. Disintegration	1. Visual 2. UV-DAD HPLC 3. HPLC 4. BP / Ph. Int
Hydrochlorothiazide 25 mg tablets	1. Appearance 2. Identification 3. Assay 4. Disintegration	1. Visual 2. IR 3. HPLC 4. BP / Ph. Int
Metformin hydrochloride 850 mg tablets	1. Appearance 2. Identification A Identification B Identification C 3. Assay 4. Disintegration	1. Visual 2. IR Colour test Reaction of chlorides 3. UV 4. BP / Ph. Int
Hydrochlorothiazide 12,5 mg tablets	1. Appearance 2. Identification A Identification B 3. Assay 4. Disintegration	1. Visual 2. HPLC TLC 3. HPLC 4. BP / Ph. Int
Rifampicin 300 mg & Isoniazid 150 mg FC tablets	1. Appearance 2. Identification A 3. Assay (Rifampicin) Assay (Isoniazid) 4. Disintegration	1. Visual 2. HPLC 3. HPLC HPLC 4. BP / Ph. Int
Levothyroxine sodium 100 µg tablets	No laboratory testing performed	No laboratory testing performed
Levothyroxine sodium 50 µg tablets	No laboratory testing performed	No laboratory testing performed
Dolutegravir sodium equivalent to 50 mg Dolutegravir; Lamivudine 300 mg & Tenofovir disoproxil fumarate 300 mg tablets	1. Appearance 2. Identification A Identification B 3. Assay (Dolutegravir sodium equivalent to dolutegravir) Assay (Lamivudine) Assay (Tenofovir disoproxil fumarate) 4. Disintegration	1. Visual 2. HPLC UV-DAD 3. HPLC HPLC HPLC 4. BP / Ph. Int

Table 6: Parameters and method of analysis for testing of medicine samples

PRODUCT	PARAMETERS TESTED	ANALYTICAL METHOD USED
Enalapril maleate 20 mg tablets	1. Appearance 2. Identification 3. Assay	1. Visual 2. HPLC 3. HPLC
Abacavir 20 mg/mL oral solution	No laboratory testing performed	No laboratory testing performed
Enalapril maleate 10 mg tablets	No laboratory testing performed	No laboratory testing performed
Metformin hydrochloride 500 mg tablets	1. Appearance 2. Identification A Identification B Identification C 3. Assay 4. Disintegration	1. Visual 2. IR Colour test Reaction of chlorides 3. UV 4. BP / Ph. Int
Glibenclamide 5 mg tablets	No laboratory testing performed	No laboratory testing performed
Hydrochlorothiazide 25 mg tablets	No laboratory testing performed	No laboratory testing performed
Emtricitabine 200 mg & Tenofovir disoproxil fumarate 300 mg tablets	1. Appearance 2. Identification A Identification B 3. Assay (Emtricitabine) Assay (Tenofovir disoproxil fumarate)	1. Visual 2. HPLC TLC 3. HPLC HPLC

5. DISCUSSION

Poor-quality medicines present a serious public health problem. Substandard and falsified medicines have been of great concern, particularly in developing countries like South Africa. Thus, to ensure that medicines of good quality are circulating in the South African medicines supply chain, PMS of human medicines was conducted in four (4) regions in South Africa's Gauteng province in line with the approved PMS plan for 2022-2023. Samples of medicines were collected from different levels of the pharmaceutical distribution channels, starting from national, regional and district levels.

The samples and regions were selected using criteria set in the PMS plan 2022/2023, which included anti-hypertensive medicines, anti-malarial medicines, antiviral agents (particularly anti-retroviral treatment for HIV/AIDS), oral hypoglycaemic medicines, thyroid preparations and tuberculostatic medicines based on the disease priorities as per the National Department of Health.

The number of samples collected for human medicines was 26, which comprises only about 36% (26/72) of the planned sample size. The low percentage of the collected samples could be explained by the unwillingness of facility staff to provide samples, and the unavailability of some medicines at

district levels and healthcare facilities during sample collection. This is a common problem during sample collection, especially in peripheral areas where medicine supply is low. The low resources allocated to the PMS plan also contributed to the low percentage of collected samples.

Samples were collected from CHCs, a Military Hospital and a Wholesaler in descending order of quantity collected. Samples of medicines were more readily available as the cities are highly populated with high business volumes.

The majority of the medicines collected (73%) and discussed herein were imported, which could be attributed to the dependence of the country on imported medicines from abroad.

Collected medicine samples were subjected to a screening evaluation involving labelling information review, laboratory ID testing by TLC, IR, UV, HPLC, UV-DAD and other tests, as well as the disintegration test, whereby all samples complied with tested parameters. This rate of compliance shows that there were effective controls on the importation of medicinal products at South Africa's ports of entry.

Results of the labelling information review depicted that there were some deficiencies in the labelling of the products on primary and secondary packaging (35%), PIs (69%) and PILs (81%).

Deficiencies relating to the label include the absence of the registration number, the absence of SAHPRA-approved scheduling status, sugar status, sugar name and quantity, sweetener name and quantity, information available in English and a foreign language, as well as the omission of the category and class of the medicines.

Deficiencies relating to the PI include that no PI was provided with some samples, information available in English and a foreign language, sugar and sweetener statement not included in PI, SAHPRA scheduling status and registration number not included in PI, absence of excipients in formulation, sugar and sweetener statement, name and quantity of sugar omitted, the omission of the category and class of the medicines and numerous translation errors found on the PIs.

Deficiencies relating to the PIL included that no PIL was included with some samples, sugar and sweetener statement, sugar and sweetener names and quantities omitted, incorrect translation of indications, instructions before taking and side effects incorrectly translated, the registration number contained commas instead of full stops, the "access to the corresponding Professional Information" was included under this heading instead of "Name of the holder of the certificate of registration", the date of most recent amendment for one sample was incorrectly translated and the date of registration was omitted from the PIL, the sugar statement, name and quantity of sugar was not included on some

of the PILs, mannitol is listed as part of the formulation of some samples but was not included under the sugar contents or sweetener of the PIL.

Adherence of market authorisation holders to the requirements on product labelling, requirements, and package insert information and law enforcement by SAHPRA, could lead to the improvement of the observed trend.

All sampled medicines conformed to screening test requirements. The results further underscore the suitability and usability of sample survey techniques for the quality assurance of medicines.

In confirmatory testing by pharmacopoeia monograph or manufacturer's specifications, all samples tested met the specifications except one (1) sample, Enalapril 10 mg tablets, which initially failed the assay test. The sample, which failed the assay specifications, had an enalapril content of 90,3%, which was below the release acceptance range of between 93%-105%. The content results, however, fell within the stability acceptance range of between 90%-110%.

6. REGULATORY ACTION TAKEN

The following regulatory actions have been taken by SAHPRA:

6.1 All manufacturers whose medicines failed labelling information review have been directed to rectify the anomalies which were found during the evaluation.

6.2 Investigation of the batch of Enalapril 10 mg tablets was found to be transported from India to South Africa without data loggers to monitor the temperature and humidity conditions during transportation.

6.3 All investigation outcomes were shared with the relevant SAHPRA unit.

7. CONCLUSION

The survey has revealed a significant failure rate of label information review for human medicine samples, 42% (11/26). This indicates inadequate compliance and enforcement post-registration phase of the medicinal product life cycle. Thus, more effort is required for the failed samples in labelling information review, to enforce HCRs/MAHs to ensure that their products meet product information requirements before being imported or manufactured domestically and allowed onto the South African market. Strengthening surveillance activities, which are of paramount importance to identify

medicines which are not labelled in a manner that conforms to the labelling requirements, is necessary.

Moreover, this survey calls for continuous monitoring of the quality of medicines circulating on the market and reminding distributors and sellers of medicines of the importance of adhering to good distribution practices in relation to storage, labelling and proper handling of medicines.

8. RECOMMENDATIONS

The following are recommendations from the experience gained in this survey:

8.1 Marketing authorisation holders should be reminded to comply with labelling requirements.

8.2 Before embarking on sample collection, sample collectors should be trained on how to conduct sampling as well as the pros and cons of adhering to and not adhering to the sampling SOPs.

8.3 Reviewers of labelling information should be trained to improve the recording of deficiencies observed during labelling information review.

8.4 Considerations to move to a Risk-Based PMS approach to utilise resources adequately.

8.5 Adequate human resources will ensure that a greater number of samples are collected and tested to ensure the statistical significance of the results obtained.

8.6 Ensure cooperation of sampling facilities to provide the required samples by requesting assistance from the Director-General of the National Department of Health and Provincial Heads of Pharmaceutical Services before the collection of samples.

8.7 Simplify the Supply Chain Management/Procurement process to streamline the approval process for the testing laboratory as an approved supplier. Extend the validity period of the Technical Quality Agreement, as well as the approval of the laboratory testing facility, to reduce administrative workload.

8.8 Make use of pre-determined Pharmacopoeia monograph methods for analysis for cost-saving purposes, in that the same column and reference standards can be used for different samples of a medicine.

8.9 Ensure sufficient samples are collected for the laboratory to perform campaign testing for additional cost savings.

9. LIMITATIONS

Limitations encountered during planning, implementation, analysis and writing of the report include:

9.1 Limited capacity of a SAHPRA-contracted Quality Control Laboratory with regard to workload against human resources, which led to a delay of analytical results following the Transnet strike.

9.2 Lack of a method for analysis of some medicine samples, for example, Dolutegravir tablets, which required method development and validation, hence the extended time taken for analysis.

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