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Substandard and falsified medical product recalls in Zambia from 2018 to 2021 and implications on the quality surveillance systems

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Abstract

Background: Substandard and falsified (SF) medical products are removed from circulation through a process called 'product recall' by medicines regulatory agencies. In Zambia, the Zambia Medicines Regulatory Authority (ZAMRA) is responsible for recalling SF medical products from the Zambian market through passive and active surveillance methods. This study aimed to describe the prevalence of recalls of SF medical products and to analyse the frequently recalled therapeutic categories, dosage forms, categories of defects that led to the recalls and their sources with respect to the country of the marketing authorisation holder (MAH) or manufacturer.

Methods: We conducted a descriptive cross-sectional review of the product recalls issued by ZAMRA between January 2018 and December 2021. A search for all medical product alerts and recalls issued by ZAMRA was carried out by reviewing the internal post-marketing surveillance database kept at ZAMRA headquarters. Data were extracted using a structured Excel database and analysed using Microsoft Excel.

Results: A total of 119 alerts were received during the review period, of which 83 (69.7%) were product recalls. Oral solid dosage forms were the most recalled dosage form (53%). Furthermore, the number of recalls increased in 2020 (44.6%) and 2021 (22.9%), with the majority (20.5%) of the recalled products being substandard products classified as antiseptics and disinfectants and were attributed to the high demand during the COVID-19 pandemic. Manufacturing laboratory control issues were the reason for product recall in almost half (47.4%) of the cases. Most of the products recalled originated from India (38.6%), followed by Zambia (25.3%). Only one suspected falsified product was recalled between 2018 and 2021. A total of 66 recalls of the 83 products were initiated by ZAMRA, with only 17 voluntarily by foreign MAHs. No product recall was initiated by the local representatives of foreign manufacturers or MAH.

Conclusion: The majority of the pharmaceutical product recalls in Zambia were substandard products. Manufacturing laboratory control issues lead to most recalls and require investigation of the root causes, preventive action, and strict compliance with the good manufacturing practices guidelines by manufacturers.

Keywords

Pharmacovigilance, medical products, recall, substandard, falsified, ZAMRA, Zambia

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Introduction

In May 2017, the World Health Organization (WHO) adopted the term *substandard and falsified* (SF) medical products to replace the previously used terms, spurious/falsely-labelled/falsified/counterfeit (SFFC). According to the WHO, substandard medical products, also known as 'out of specification', are 'authorised medical products that fail to meet either their quality standards or specifications, or both' and falsified medical products are products that are 'deliberately or fraudulently misrepresent their identity, composition or source'.[1] Furthermore, the WHO defines unregistered or unlicensed medicinal products as products that 'have not undergone evaluation and/or approval by the national or regional regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation'.[1]

The impact of SF medical products is devastating. They have been linked to causing thousands of deaths internationally,[2,3] contributing to antimicrobial resistance, treatment failure, poisoning, and adverse drug reactions.[4–6] Moreover, SF medical products have been linked to causing enormous economic impact globally, estimated to be between US$10 and US$200 billion annually.[6,7] In the Zambian context, SF medical products such as antimalarials have been estimated to cause an annual economic burden of US$141.5 million.[8,9] This affects access to quality-assured medical products. Medicines access in Zambia is mainly through regulated public sector, that is, government central stores supplying all government health facilities across the country through provincial hubs. For the private sector, this is mainly through regulated private hospitals, clinics, retail pharmacies and healthshops.[10,11]

The spread of SF medical products is considered a 'global pandemic',[12,13] as alarming reports have been previously published indicating that the global prevalence of SF medical products ranges from 1% to 50%.[4,14–17] However, prevalence studies are still a big obstacle even in high-income countries, and the true extent of the problem remains unknown.[18,19] A meta-analysis in low- and middle-income countries (LMICs) revealed that 19.1% of antimalarials were either substandard or falsified.[6] The WHO surveyed the quality of selected medicines from the list of 13 life-saving commodities identified by the United Nations Commission on life-saving commodities for women and children in 10 LMICs, including seven sub-Saharan African countries and excluding Zambia. The survey found that 23% of the samples (representing 40 products) were substandard.[20] Within the Zambian context, a 2010 study found that 10.3% of registered and unregistered samples were substandard.[21] In the recent past, various researchers have found and reported evidence of SF medical products in Zambia.[22,23] These known examples of SF medical products are removed from the supply chain through a process called product recall by the national medicines regulatory authorities. Product recall results from meticulous pharmacovigilance and is an essential component of drug regulation to protect public health.[24,25]

Substandard medical products can be recalled due to several factors such as inappropriate good manufacturing practices (GMP), poor storage, stability failure, defectiveness in part of a medical device, and many others.[25–28] To provide accurate information, substandard medical products can be classified in several defect categories as reported in the literature.[29,30] The European Medicines Agency (EMA) classifies substandard medical products in five high-level terms.[31] These five high-level terms include manufacturing laboratory control issues, product contamination and sterility issues, product label issue, product packaging issues, and product physical issues. Examples of manufacturing laboratory control issues include out of specification test results for any of the specifications established for the finished product. Product contamination and sterility issues include chemical (cross contamination), microbial, physical (foreign material), and lack of sterility. Product label issues can be any defect in meeting the labelling requirements, such as damaged and loose labels, missing text, wrong labelling information and illegible information on both the primary and secondary packaging. Product packaging issues include defects to the container and closure system such as damage, leaking, incorrect package type and missing a component of the container closure system. Product physical issues are defects that lead to changes in the physical presentation of the medical product, such as precipitation of the product, crystallisation and product odour.[31]

In Zambia, the Zambia Medicines Regulatory Authority (ZAMRA) has the mandate to ensure that all medicines and allied substances in the country consistently meet the established quality, safety and efficacy requirements.[32] Zambia has a robust and well-established surveillance system to monitor medical products. It is also part of the WHO Global Surveillance and Monitoring System (GSMS) member state mechanism on SF medical products and has adopted the mechanism's strategy to prevent, detect and respond to SF medical products.[33]

ZAMRA uses active and passive surveillance methods to monitor the quality of medical products on the Zambian market. Active surveillance involves post-marketing surveillance inspections of medical products, including visual inspection, labelling assessment, rapid field screening of medicines using GHPF – Minilabs® and sampling of medicines and allied substances for analysis at the National Quality Control Laboratory (NQCL).[9,11] Through the passive surveillance method, ZAMRA receives alerts about defective and suspected SF medical products from other regulatory authorities, WHO, patients and the pharmaceutical industry. Passive surveillance is important to receive alerts from poorly regulated border crossings, as eight countries surround Zambia.[34,35]

Like in most countries,[36–39] received and suspected SF medical product or possible safety issues are communicated by ZAMRA at three levels. These include the consumer or patient level meant to recall SF medical products up to patent level, and the retail/health facility level which is meant to recall products in hospitals, clinics and retail pharmacies. The third level is at the wholesale level which is meant to recall SF medical product from all public and private pharmaceutical wholesale points.[40] Communications are made in the form of emails and letters when recalls are at the health facility and wholesale level. When communicating to the public, recalls are published in print media and official social media for ZAMRA. Safety alerts are usually communicated as a precaution to users to consider before using medical products, while quality alerts include situations that can compromise the quality of the medicine, such as the detection of SF medical products.[41–43]

Well-resourced countries have introduced innovative systems such as track and trace in an effort to reduce the circulation of SF medical products and streamline the recall of SF medical products.[44,45] However, such regulations have been contested due to the lack of reliable prevalence data to support balanced debate and decision-making related to SF medical product recalls by practitioners and policymakers.[18] In the Zambian context, despite having a surveillance system to identify and withdraw SF medical products from the market, ZAMRA has not yet published any guidelines on product recall to guide the local industry. However, a draft guideline is in place, awaiting finalisation by the board once appointed by the minister of health. The available surveillance system has detected several medical products problems in recent years, leading to alerts and recalls of defective products. The authors are unaware of any published literature on the analysis of medical product recalls in Zambia. Therefore, there is a need to analyse SF medical product recalls made in Zambia to contribute to the global debate on the subject matter and provide data that stakeholders can find useful in decision-making. Information such as the prevalence of SF medical product recalls, types of defects which caused the recalls, the therapeutic category and recalled pharmaceutical dosage forms have not yet been studied in Zambia.

This study aimed to consolidate, characterise and assess information on the quality of medical products in Zambia by focusing on medical product recalls issued by ZAMRA from January 2018 to December 2021. Specifically, the study describes the prevalence of recalls of SF medical products recorded between 2018 and 2021, therapeutical categories and dosage forms, categories of defects that led to the recall, their sources with respect to the country of origin of the marketing authorisation holder (MAH) and the frequently recalled products. The findings inform relevant stakeholders about the prevalence of recalls of medical products and the implications on the quality surveillance system in Zambia.

Methods

Study design

A descriptive cross-sectional review was conducted to assess medical product alerts and recalls data from January 2018 to December 2021.

Data source

A search for all medical product alerts and recalls received and/or issued by ZAMRA was carried out by reviewing the internal post-marketing surveillance database kept at ZAMRA headquarters. Examples of two consumer/patient level recalls reviewed have been provided (see supplement data). ZAMRA actively started keeping records for medical product alerts/recall in 2017. To assess the documents, a search was done for documents recorded between 1 January 2018 and 31 December 2021.

Inclusion and exclusion criteria

In this study, a 'recall' was considered to be a circular or document issued by ZAMRA to the public, the manufacturer, distributors, and healthcare professionals as a regulatory action to control and reduce risk regarding critical quality issues, falsification or safety of a medical product for human use. All recalled medical products for human use recalled due to quality-related issues or falsification were included. Safety and quality alerts that did not lead to a recall were excluded, as were recalls made before 1 January 2018.

Data collection and analysis

To support the assessment and consolidation of the recalls, a structured Excel database was created to collect data. The following data were extracted from the alert/recall records: name of the product, dosage form, batch number(s), country of manufacture and number of manufacturers, the reason for the recall, recall initiator and year of the recall.

Data analysis

The recalled medical products were classified as substandard, falsified or unregistered according to the WHO definitions.[5] To determine the most frequent therapeutic groups affected by recalls made by ZAMRA, the Anatomical Therapeutic Chemical (ATC) second level as per WHO classification was applied.[46] The substandard medical products were further classified into the following five high-level terms using the EMA guidelines: manufacturing laboratory control issues, product contamination and sterility issues, product label issues, product packaging issues and product physical issues.[31] Medical products that were

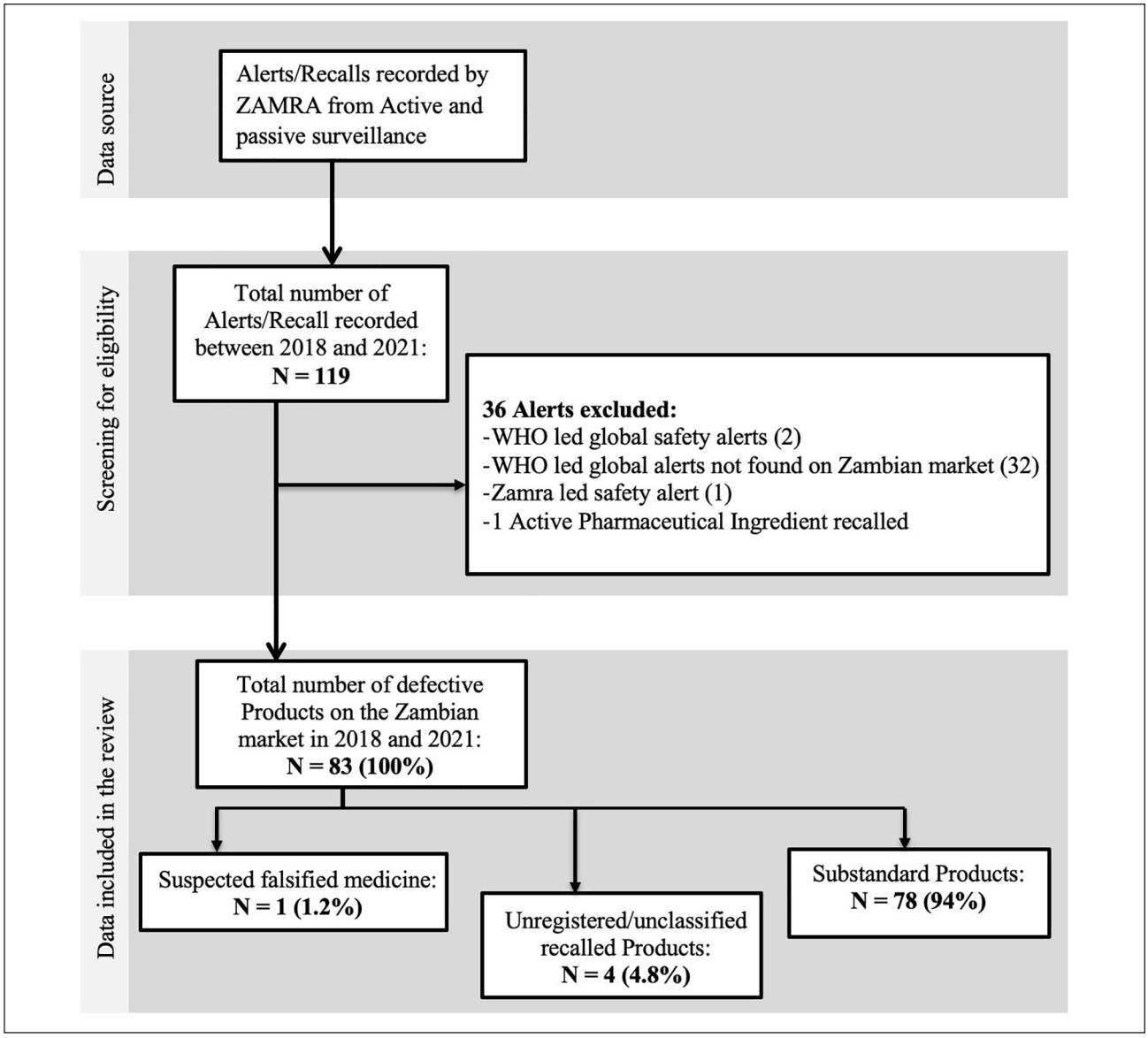

Figure 1. Flow diagram depicting the search for medical products recalled incidents.

misrepresented and met the WHO definition of a falsified medicinal product were classified as falsified medical products.[5] To determine the prevalence of SF medical product recalls over the review period, the total number of confirmed alerts recorded (denominator) was divided by the actual recalls made/issued for SF medical products (numerator) multiplied by 100%. Microsoft Excel package was used for the data analysis.

Results

Between 1 January 2018 and 31 December 2021, ZAMRA recorded 119 alerts, of which 83 alerts were SF medical product recalls (Figure 1), giving a prevalence of 69.7% during the review period. Among these 83 recalls made, 78 (94%) were for suspected substandard products, 1 (1.2%) was a suspected falsified medicine, and 4 (4.8%) were unclassified and unregistered products (i.e. could not meet the WHO definition of SF medical products).

All 83 medical products recalled between 1 January 2018 and 31 December 2021 are presented in Table 1, showing the product name, batch numbers affected, country of manufacture, year of recall and recall initiator.

The year 2020 had the highest number of recalls, 44.6% ($n=37$), followed by the year 2021, 22.9% ($n=19$), then 2018 with 19.3% ($n=16$) and 2019 with 13.3% (see Figure 2).

Considering the pharmaceutical class of the recalled medical products (Table 2), 23 classes accounted for the incidence of product recalls. According to this classification of

Table 1. List of medical products recalled between 2018 and 2021.

S/N	Name of product	Country of origin	Batches affected	Year of report	Initiator of recall/alert
1.	Chlorine solution	Zambia	2	2018	ZAMRA
2.	Chloramphenicol 5% + Beclomethasone Dipropionate 0.025% + Clotrimazole 1% + Lidocaine hydrochloride 2% ear/eye drops	India	1	2018	ZAMRA
3.	Male condoms	India	2	2018	ZAMRA
4.	Magnesium trisilicate tablets	Zambia	2	2018	ZAMRA
5.	Co-trimoxazole tablets	Zambia	1	2018	ZAMRA
6.	Vitamin B-complex injection	India.	2	2018	ZAMRA
7.	Ringers lactate solution	Zambia	3	2018	ZAMRA
8.	Dextrose 5% solution	Zambia	1	2018	ZAMRA
9.	Chinese contraceptive pill (Levonorgestrel 6 mg + Quinestrol 3 mg)	China	1	2018	ZAMRA
10.	Valsartan 320 mg tablets	Germany	All batches	2018	MAH
11.	Valsartan 160 mg tablets	Germany	All batches	2018	MAH
12.	Valsartan 80 mg tablets	Germany	All batches	2018	MAH
13.	Valsartan 40 mg tablets	Germany	All batches	2018	MAH
14.	Valsartan 320 mg + Hydrochlorothiazide 12.5 mg tablets	Germany	All batches	2018	MAH
15.	Valsartan 160 mg + Hydrochlorothiazide 12.5 mg tablets	Germany	All batches	2018	MAH
16.	Oxytocin injection	China	1	2018	ZAMRA
17.	Ringers lactate solution	Zambia	1	2019	ZAMRA
18.	Amoxicillin 125 mg + clavulanic acid 31.25 mg powder for suspension	South Africa	3	2019	MAH
19.	Amoxicillin 250 mg + clavulanic acid 62.5 mg powder for suspension	South Africa	1	2019	MAH
20.	Atazanavir 300 mg + Ritonavir 100 mg tablets	India	8	2019	MAH
21.	Isoniazid 100 mg tablets	Zambia	1	2019	ZAMRA
22.	Ciprofloxacin 250 mg tablets	Zambia	1	2019	ZAMRA
23.	Clotrimazole 1.0%w/w + Betamethasone 0.1%w/w cream	Kenya	6	2019	ZAMRA
24.	Ranitidine 150 mg tablets	Not stated	All batches	2019	ZAMRA
25.	Metronidazole 5 mg/mL intravenous infusion	India	2	2019	ZAMRA
26.	Diclofenac 75 mg/5 mL injection	China	1	2019	ZAMRA
27.	Amoxicillin 250 mg capsules	India	1	2019	ZAMRA
28.	Dexamethasone 5 mg + Neomycin 1 mg eye/ear drops	India	1	2020	ZAMRA
29.	Aspirin 453.6 mg + Caffeine 64.8 mg + Paracetamol 324 mg powder	South Africa	13	2020	ZAMRA
30.	Aspirin 226.8 mg + Caffeine 32.4 mg + Paracetamol 162 mg tablets	South Africa	13	2020	ZAMRA
31.	Aspirin 75 mg tablets	India	3	2020	ZAMRA
32.	Co-trimoxazole 240 mg Oral Suspension BP	India	6	2020	ZAMRA
33.	Amoxicillin 250 mg capsules	India	1	2020	ZAMRA
34.	Amlodipine 5 mg tablets	India	2	2020	ZAMRA
35.	Cefixime 50 mg suspension	India	1	2020	ZAMRA
36.	Paracetamol 100 mg tablets	Zambia	1	2020	ZAMRA
37.	Paracetamol 500 mg tablets	India	18	2020	ZAMRA
38.	Paracetamol 100 mg tablets	India	7	2020	ZAMRA
39.	Surgical gloves	India	1	2020	ZAMRA
40.	Wonders hand sanitiser	Zambia	All batches	2020	ZAMRA
41.	Avacare Instant hand sanitiser	Zambia	All batches	2020	ZAMRA

(Continued)

Table 1. (Continued)

S/N	Name of product	Country of origin	Batches affected	Year of report	Initiator of recall/alert
42.	Bickmac Disinfectant 20 L	Zambia	All batches	2020	ZAMRA
43.	Glitzcare hand sanitiser	Zambia	All batches	2020	ZAMRA
44.	Flost antiseptic hand gel	Zambia	1	2020	ZAMRA
45.	Classicmatch waterless hand sanitizer 100 mL	South Africa	All batches	2020	ZAMRA
46.	Classicmatch waterless hand sanitizer 50 mL	South Africa	All batches	2020	ZAMRA
47.	SoClean sanitizer germ killer	Zambia	All batches	2020	ZAMRA
48.	SoClean ant-bacterial hand sanitizer	Zambia	All batches	2020	ZAMRA
49.	3X plus liquid sanitizer	Not stated	1	2020	ZAMRA
50.	Vintage Instant hand sanitizer 50 mL	not stated	All batches	2020	ZAMRA
51.	Plus hand sanitizer 750 mL	Zambia	All batches	2020	ZAMRA
52.	Sterilix hand sanitizer	Zambia	2	2020	ZAMRA
53.	Brooks disinfectant hand sanitizer	Zambia	1	2020	ZAMRA
54.	Tasa's hand sanitizer	Zambia	All batches	2020	ZAMRA
55.	Lidocaine USP 2.0% solution	India	1	2020	ZAMRA
56.	Clotrimazole USP 500 mg pessaries	India	1	2020	ZAMRA
57.	Nystatin BP 100,000 IU/mL suspension	India	1	2020	ZAMRA
58.	Metronidazole 200 mg tablets	India	1	2020	ZAMRA
59.	Zinc sulphate USP 20 mg tablets	India	1	2020	ZAMRA
60.	Nitrofurantoin BP 50 mg tablets	India	1	2020	ZAMRA
61.	Chlorpheniramine BP 4 mg tablets	India	1	2020	ZAMRA
62.	Examination Gloves, Medium	United Kingdom	1	2020	ZAMRA
63.	Bio Claire Crème Corporelle Eclaircissante	Not stated	1	2020	ZAMRA
64.	Black Opal Even True Tone Correct Fade Cream	Not stated	1	2020	ZAMRA
65.	Folic Acid BP 5 mg tablets	India	3	2021	ZAMRA
66.	Paracetamol1 25 mg/5 mL syrup	Zambia	5	2021	ZAMRA
67.	Bupivacaine Hydrochloride USP 0.5%w/v solution	India	1	2021	ZAMRA
68.	Clotrimazole 1% w/w cream	Kenya	5	2021	ZAMRA
69.	Vitamin C 500 mg tablets	India	Various	2021	ZAMRA
70.	Latex examination gloves Large	India	1	2021	ZAMRA
71.	Male latex condoms	India	2	2021	ZAMRA
72.	Glam & Glory Hand sanitizer 100 mL	India	1	2021	ZAMRA
73.	Ascorbic acid 500 mg tablets	India	1	2021	MAH
74.	Aspirin USP 75 mg tablets	India	2	2021	ZAMRA
75.	Losartan 50 mg + hydrochlorothiazide 12.5 mg tablets	South Africa	All batches	2021	MAH
76.	Losartan 100 mg + hydrochlorothiazide 12.5 mg tablets	South Africa	All batches	2021	MAH
77.	Losartan 25 mg tablets	Germany	All batches	2021	MAH
78.	Losartan 50 mg tablets	Germany	All batches	2021	MAH
79.	Losartan 100 mg tablets	Germany	All batches	2021	MAH
80.	Losartan 50 + hydrochlorothiazide 12.5 mg tablets	Germany	All batches	2021	MAH
81.	Losartan 100 + hydrochlorothiazide 12.5 mg tablets	Germany	All batches	2021	MAH
82.	Metronidazole 200 mg tablets	India	1	2021	ZAMRA
83.	Ply Face masks	India	1	2021	ZAMRA

ZAMRA: Zambia Medicines Regulatory Authority; MAH: marketing authorisation holder; BP: British Pharmacopoeia.

the medical products, the most affected class was the antiseptic and disinfectant (20.5%), followed by antihypertensives and antibiotics (16.9%). The lowest occurrences (1.2%) were for mineral supplement, surgical glove, contraceptives, antihistamine, systemic hormone, antacid, parenteral nutrition, facemask, anti-ulcer, antituberculosis and antiviral.

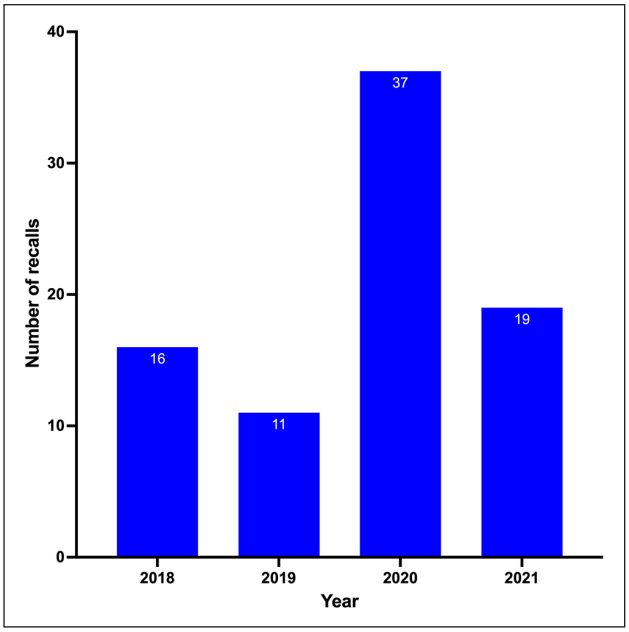

Figure 2. Number of recalled medical products in Zambia between 2018 and 2021.

Table 2. Therapeutic classification of recalled medical products (2018–2021).

S/N	Classification	Number (%) of occurrences
1.	Antiseptic and disinfectants	17 (20.5)
2.	Antihypertensive	14 (16.9)
3.	Antibiotics	14 (16.9)
4.	Analgesics	7 (8.4)
5.	Antifungals	4 (4.8)
6.	Vitamins	4 (4.8)
7.	Lightening body cream	2 (2.4)
8.	Male condoms	2 (2.4)
9.	Local anaesthetics	2 (2.4)
10.	Antithrombotic agents	2 (2.4)
11.	Examination gloves	2 (2.4)
12.	Electrolytes	2 (2.4)
13.	Mineral supplements	1 (1.2)
14.	Surgical gloves	1 (1.2)
15.	Contraceptives	1 (1.2)
16.	Antihistamines	1 (1.2)
17.	Systemic hormones	1 (1.2)
18.	Antacids	1 (1.2)
19.	Parenteral nutrition	1 (1.2)
20.	Facemask	1 (1.2)
21.	Anti-ulcer (systemic)	1 (1.2)
22.	Antituberculosis	1 (1.2)
23.	Antivirals	1 (1.2)
	Grand Total	83 (100)

Using the high-level terms classification of substandard medicine, the most common defect leading to the recall of the 78 substandard products was manufacturing laboratory controls issues, accounting for 47.4%, followed by product contamination and sterility issues (29.5%) and then product physical issues (15.4%). Less than a tenth (6.4%) of the recalls resulted from product packaging issues, while 1.3% were attributed to product label issues. The details of the reasons that led to the recall of these substandard medical products are presented in Table 3.

Of the 83 medical product recalls analysed, more than half (53%) were oral dosage forms, followed by topical applications (24.1%). Parenteral dosage forms accounted for 10.8%, other dosage forms 8.4%, while 2.4% of recalls were ocular dosage forms and 1.2% were vaginal formulations, as depicted in Figure 3.

Most of the medical products recalled ($n=32$, 38.6%) were from India, and 21 (25.3%) were locally manufactured in Zambia. The rest originated from Germany ($n=11$, 14.1%), South Africa ($n=8$, 9.6%), China ($n=3$, 3.6%), Kenya ($n=2$, 2.4%), the United Kingdom ($n=1$, 1.2%) and 5 (6%) from an unknown country. Regarding the number of manufacturers whose products were recalled, the trend was somewhat similar, with India having 20 different manufacturers, 13 from Zambian manufacturers and 3 each for China and South Africa. Germany, the United Kingdom and Kenya each had 1 manufacturer, as shown in Figure 4.

An incident of a suspected falsified product was identified and recalled from the Zambian supply chain between 2018 and 2021 during the routine post-market surveillance activities by ZAMRA. The incident involved an ear drop containing Chloramphenicol 5% + Beclomethasone Dipropionate 0.025% + Clotrimazole 1% + Lidocaine hydrochloride 2%. Several labelling inconsistencies from the packaging of the falsely labelled product as compared with the original product meant for the Zambian market were identified and summarised in Table 4.

Discussion

With the relatively high disease burden in LMICs such as Zambia, including the advent of global pandemics such as HIV and COVID-19, the demand for medical products is high, pushing the influx of SF medical products into the markets. Therefore, understanding the prevalence of SF medical products, different types of defects causing recalls, sources of SF medical products, pharmaceutical dosage forms recalled, and their therapeutic categories is important in shaping solutions aimed at curtailing the influx of SF medical products.

The results of the current study indicate a prevalence of 67.9% for recalls of SF medical products. Of the total of 83 product recalls made, 78 were substandard medical products. Similar studies have found varying numbers of recalled SF medical products. In Sri Lanka, 17 medical products were recalled between June 2018 and January 2022 due to multiple defects detected[47] whereas in the United States, a total of 21,120 products were recalled during the 30-month study period.[48]

Table 3. Recalled substandard pharmaceutical products classified using the adopted EMA defect categorisation terminology.

High-level defect term	Number of products affected	Detail of the defect leading to recall	Number of products affected
Manufacturing laboratory control issue	37 (47.4%)	Out of specification assay result	9
		Failed water leak test & Bursting pressure	4
		Out of specification impurities result after 24 months	1
		Failed uniformity of weight test	4
		Stability failures under high temperature and humidity conditions.	2
		Non-compliant to dissolution test	1
		Low alcohol content	13
		Failed pH test	1
		Failed disintegration test	1
		Failed hung and roll, bursting volume, length test	1
Product contamination and sterility issues	23 (29.5%)	Lack of sterility	1
		Visible foreign particulates	3
		Identification of nitrosamine impurities	7
		Foreign matters on capsules	1
		Foreign materials in tablets	1
		Contained Mercury and a prescription only medication, Clobetasol	1
		Excessive amounts of Hydroxyquinone	1
		Detection of 4-chloro azido methyl tetrazole	7
		Failed bioburden test	1
Product label issue	1 (1.3%)	Wrong labelling for the route of administration	1
Product packaging issues	5 (6.4%)	Defective primary packaging	5
Product physical issue	12 (15.4%)	Tablet discoloration	4
		Solution discolouration	2
		Suspension caking	1
		Failed appearance test	4
		Crystallisation of syrup	1

EMA: European Medicines Agency.

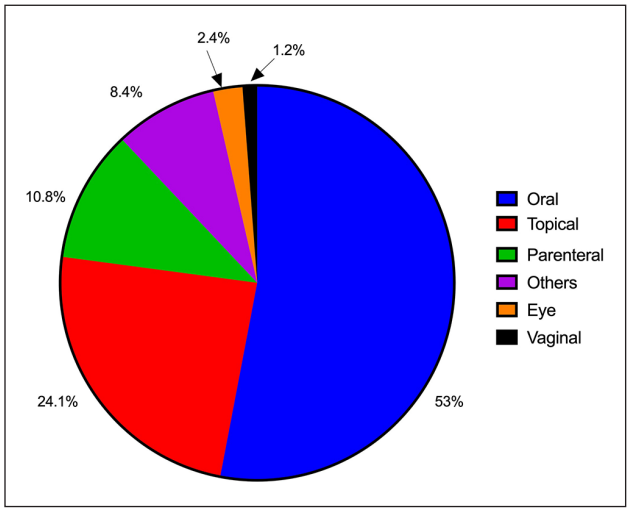

Figure 3. Affected dosage forms as a percentage of the number of recalls issued.

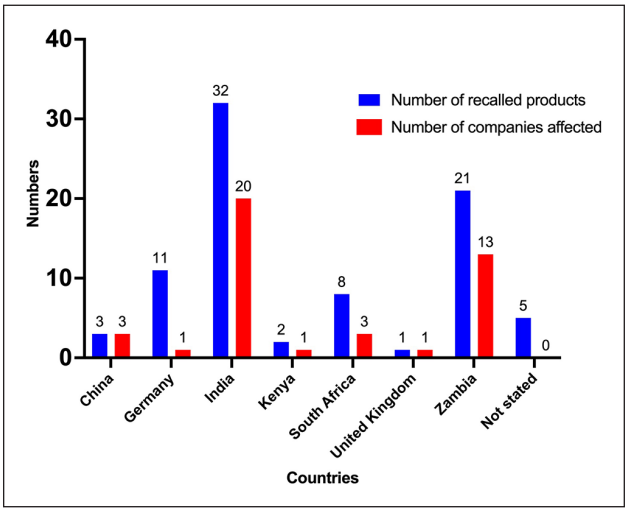

Figure 4. The number of recalled products and affected companies per country of origin.

Our findings also showed that SF medical product recalls increased in 2020 and 2021, which can be attributable to the peak period of the COVID-19 pandemic in Zambia, with 20.5% of the recalls being hand sanitizers and disinfectants. We also found that three recalled hand sanitizers could not be considered as falsified products, as

Table 4. Summary of noted labelling inconsistencies for the suspected falsified medicine.

Description	Comment/ observation as compared with genuine package
Primary label information	
Product name	• The name was the same.
Active ingredients	• The composition was the same but not in bold like on the genuine label.
Category of distribution	• Stated as prescription medicines while the genuine print had Prescription only Medicine (POM).
Zambia Marketing Authorisation Number	• The printed Marketing Authorisation number (i.e. Visa number) was not consistent with the Zambia Marketing Authorisation coding.
Storage condition	• The storage condition was different.
Expiry date	• The shelf life was different, that is, the suspected falsified product had a shelf life of 18 months compared with the 24 months on the genuine.
Name and manufacturing site address	• Name of the manufacturer was the same but with incomplete manufacturing site address.
Others	• Additional labelling, for example, instructions were provided unlike in the genuine pack. • The fill volume was less by over 1 mL compared with the original. • Orientation of text 'for external use only' and barcode was changed.
Secondary label information	
Product name	• The name was the same
Active ingredients	• The Active Pharmaceutical Ingredient (API) labelled were the same; however, they were written in a different order and smaller font size.
Expiry date	• The shelf life was different, that is, the suspected falsified product had a shelf life of 18 months compared with the 24 months on the genuine.
Storage condition	• The storage condition was different
Name and manufacturing site address	• Name of the manufacturer was the same but with incomplete manufacturing site address.
Zambia Marketing Authorisation Number	• Not printed on the pack but put on the pack using a sticker. • The printed Marketing Authorisation number (i.e. Visa number) was not consistent with the Zambia Marketing Authorisation coding.
Colour of packaging	• Slightly different packaging colours shade.
Others	• The two batches of the suspected falsified products were slightly heavier. • A combination of English and another language was used. • The font size for the 'directions for use', bar code, and other instructions were different and placed in different parts of the package compared with the genuine package. • The package had colour lining on the edge of one face, while the original package did not have.

they did not misrepresent their source, identity or composition. They were adequately labelled as containing methanol by the correct manufacturers. The recall was because they contained the wrong active ingredient, methanol. Alcohol-based hand sanitizers contaminated with harmful impurities such as methanol, benzene and acetaldehyde have been documented to pose a risk and adverse effects.[49–52] However, the impact of these recalled methanol-containing hand sanitizers on the Zambian market has not been documented or reported. The increase in the medical product recalls can also be attributed to the increased surveillance by ZAMRA, the national regulatory agency. The trend is comparable with global observations, where more than 34,000 falsified COVID-19 products were seized in 2020.[53] In a South African survey, for example, of the 94 hand sanitizer samples collected, three preparations contained no alcohol, while the rest contained either ethanol, 2-propanol or 1-propanol or a combination of two alcohols.[54] The survey further revealed that of the remaining alcohol-containing hand sanitizers, 37 (41%) contained less than 60% alcohol. Similarly, we found out that 11 of the 14 recalled hand sanitizers were recalled for containing less than 60% alcohol.

In this study, nearly half (47.45%) of defects were due to manufacturing laboratory control issues, followed by product contamination and sterility issues (29.5%). The findings are consistent with the results of a study in Canada[29] and contradict the findings of Janani et al.,[47] Almuzaini et al.,[30] Hall et al.,[48] and AlQuadeib et al.,[55] where the most frequently reported defect was product contamination and sterility issues. However, this indicates the need for continuous process improvement and corrective preventive action as errors occur even when stringent measures are implemented. In our study, product contamination and sterility issues was the second most common reason for the recall of substandard medical products. This also poses a serious threat to the end users of contaminated products. Therefore, it is of concern that ringers lactate locally manufactured by only one manufacturer, who is a major distributor of this product to government facilities, had different batches (4 in total over 2 years) affected, which could have caused a disruption in the supply chain.

Antiseptic and disinfectants 17 (20.5%) were found to be the most recalled therapeutic class of medical products, which is consistent with the results of a study conducted in Nepal.[56] This can be attributed to the increased demand for this class of products in the face of the COVID-19 pandemic, as more suppliers imported these products to meet the demand. Antihypertensive and antibiotics (16.9%, $n = 14$) are the second most recalled class of drugs. Similar findings were reported by AlQuadeib et al.[55] in Saudi Arabia. Poor quality antibiotics are particularly of concern because taking subtherapeutic doses of antibiotics can contribute to the global challenge of antimicrobial resistance.[57–59]

We also found an unregistered product that was recalled due to misrepresentation. According to the report, the product was called a Chinese contraceptive pill and was misrepresented as a herbal contraceptive but contained high levels of Levonorgestrel and Quinestrol. The availability of unregistered medicines that have not had minimal regulatory oversight or import approval poses a great risk to public health in countries with weak border controls such as Zambia. Nyika et al.[60] studied similarities and differences in the importation and distribution of unregistered medicines in the countries of the Southern African Development Community (SADC) and found that Zambia had a low relative implementation index level of 28% for minimum recommended standards for the importation of unregistered medicines. This increases the risk of exposure to SF medical products.[60]

Of the 42 manufacturers whose products were recalled, 29 (69%) were foreign-based manufacturers. The finding is similar to a study in Sri Lanka where the most recalled products involved imported products.[47] According to the Global Economic Data, Indicators, Charts and Forecasts (CEIC) website,[61] Zambia's medicinal and pharmaceutical imports were US$65,591.083 by December 2021. The high number of foreign-based manufacturers with recalled SF medical products clearly indicates an economic burden on the Zambian health sector and poses a challenge to access to quality-assured medical products.

Several factors limited this study. First, the study only assessed documented recalls over 4 years. The number of years cannot provide a conclusive trend on SF medical products in Zambia, and more data need to be collected in the next few years. However, the study provides an important insight on the quality of medicines in Zambia. Second, an in-depth analysis was not possible due to the non-availability of data on quantities recalled, the number of actual quantities of recalled products received, regional distribution of recalls and the action taken following the recall to measure the impact of the recalls. Finally, the study did not attempt to establish the classification of the recalls issued. Therefore, future studies are needed to determine the classification of the recalls and an in-depth analysis of the recalls.

Recommendation

Medical products recall is an essential process in safeguarding public health. Therefore, this must be the responsibility of the regulators and the pharmaceutical industry. This study shows that 66 of 83 recalls made were initiated by ZAMRA, and the rest by foreign-based marketing authorisation. The lack of participation of local manufacturers and distributors can be attributed to the lack of specific published guidelines on product recall. Participation by foreign-based MAH could be attributed to the condition of their marketing authorisation which requires them to implement a product-specific pharmacovigilance system and report any detected problems to the regulatory authority. There is a need for urgent publication of recall guidelines in Zambia, like other countries in the region.[62–64] This will help guide the local industry on the timelines to make medical product recalls based on the class of recall and regulatory intervention needed.

Several African national medicines regulatory authorities publish product alerts and recalls in open source databases.[39,65–67] This allows stakeholders such as researchers to produce objective evidence that can inform regulatory decisions and protect public health, as illustrated in Malawi and Rwanda, where two extremely substandard brands of misoprostol tablets were found during a quality survey and led to the issuance of recalls by the regulatory authorities in the two countries and the WHO issued an alert to other countries.[68,69] Therefore, it is recommended that all alerts be uploaded to a publicly available database (e.g. ZAMRA website and Med Safety mobile app). Information to be published on recalls should include, among others, the actual quantities recalled, quantities received, regional distribution, reason for recall and type of recall. Moreover, having evidence of documented communication with a feedback mechanism is one of the requirements for global benchmarking for the national regulatory system, which WHO has recently introduced,[70] and this would be beneficial to ZAMRA during the benchmarking process in future. Continuous surveillance of SF medical products should be increased across the country.

Conclusion

This article has shown the presence of SF medical products on the Zambian market, which were eventually recalled. The manufacturing laboratory control issues were the most frequent cause of defective medicines, while oral solid dosage formulations were the most susceptible dosage form. Recall of defective medical products affected both locally and foreign manufactured products, with the majority being imported medical products. This poses a significant economic burden on the healthcare system and impedes access to quality-assured medical products. In future, a country-wide survey covering the entire supply

chain is needed to indicate the trend of SF medical products on the Zambian market compared with other countries in the region and determine the class of recalls in Zambia.

Declarations

Ethics approval and consent to participate

Ethics approval and informed consent to participate were not applicable due to the nature of the study. Permission was, however, sort from the ZAMRA acting Director General and senior management.

Consent for publication

Permission was sort from the ZAMRA acting Director General and Senior Management

Author contribution(s)

Billy Chabalenge: Conceptualisation; Formal analysis; Methodology; Visualisation; Writing – original draft; Writing – review & editing.
Elimas Jere: Formal analysis; Validation; Writing – review & editing.
Namuchindo Nanyangwe: Formal analysis; Validation; Writing – review & editing.
Christabel Hikaambo: Data curation; Methodology; Writing – review & editing.
Steward Mudenda: Data curation; Supervision; Writing – review & editing.
Michelo Banda: Data curation; Supervision; Writing – review & editing.
Aubrey Kalungia: Conceptualisation; Data curation; Methodology; Writing – review & editing.
Scott Matafwali: Conceptualisation; Data curation; Methodology; Visualisation; Writing – review & editing.

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Competing interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The first, second and third authors are Pharmacists currently working under Zambia Medicines Regulatory Authority, Department of Medicines Control and are involved in post-marketing surveillance activities. Zambia Medicines Regulatory Authority had no role in the design of this study and collection, analysis and interpretation of data. Any views and opinions expressed are personal and belong solely to the individuals and do not represent any individual institutions, or organisations that the individuals are associated with in a personal or professional capacity. The remaining authors declare that they have no conflict of interest.

Availability of data and materials

The data set generated and/or analysed during the current study is available from the corresponding author upon reasonable request.

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