A RETROSPECTIVE STUDY OF RAPID ALERTS AND PRODUCT RECALLS CONDUCTED BY THE PHARMACY AND POISONS BOARD, KENYA BETWEEN 2016 AND 2021.

By:

OTIENO GRACE ACHIENG

U53/37658/2020

A dissertation submitted in partial fulfillment of the requirements for the award of the degree of Master of Pharmacy in Industrial Pharmacy of the University of Nairobi.

Department of Pharmaceutical Chemistry, Pharmaceutics and Pharmacognosy

Faculty of Health Sciences

UNIVERSITY OF NAIROBI

2022

DECLARATION

This dissertation is my original work and has not been submitted anywhere for examination, degree or award

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OTIENO GRACE ACHIENG

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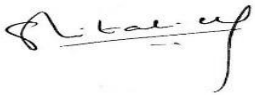
This dissertation has been submitted for examination with our approval as University supervisors.

Sign:  **Date: 17/11/2022**

PROF. SHITAL MAHINDRA MARU

Department of Pharmaceutical Chemistry, Pharmaceutics and Pharmacognosy,

Faculty of Health Sciences, University of Nairobi.

Sign:  **Date:17/11/22**

DR. LUCY TIROP

Department of Pharmaceutical Chemistry, Pharmaceutics and Pharmacognosy,

Faculty of Health Sciences, University of Nairobi.

Sign:  **Date: 17/11/2022**

DR. DENNIS SURE BAGWASI ONGARORA-Department of Pharmaceutical Chemistry, Pharmaceutics and Pharmacognosy, Faculty of Health Sciences, University of Nairobi.

DECLARATION OF ORIGINALITY

Name of Student:	Otieno Grace Achieng
Registration number:	U53/37658/2020
Faculty:	Health Sciences
Department:	Pharmacy
Course Name:	Masters of Pharmacy in Industrial Pharmacy

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DEDICATION

This work is dedicated to my daughter Margret Amor Nanteza Kogoma. May this work inspire you to pursue greater heights.

ACKNOWLEDGEMENT

I would like to acknowledge my supervisors Prof. Shital Mahindra Maru, Dr. Dennis Sure Bagwassi Ongarora and Dr. Lucy Tirop for the constructive guidance that enabled me to do this work.

I would like to acknowledge the financial and moral support accorded to me by my family; my husband Dr. Collins Owuor, my parents Dr. Samwel Boaz Otieno and Mrs Ruth Otieno, my siblings Suzzane Adhiambo and Caren Anyango and my dear daughter Amor Nanteza.

Above all, I would like to acknowledge God Almighty for giving me the health and the wisdom I needed to pursue this work .

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ACRONYMNS AND ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
EAC-MRH	East Africa Community Medicine Regulatory Harmonization Program
EMA	European Medicines Agency
EP	European Pharmacopoeia
GMP	Good Manufacturing Practice
FDA	Food and Drug Administration
HCG	Human Chorionic Gonadotrophin
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
PPB	Pharmacy and Poisons Board
MAH	Market Authorization Holder
MHRA	Medicines and Healthcare Products Regulatory Agency
NDA	National Drug Authority
NDEA	N-nitrosodiethylamine

NMBA	N-methyl-4-aminobutyric acid
NMDA	N-nitrosodimethylamine
R-(ECG)	Reduced European Crisis Group
TMDA	Tanzania Medicines and Medical Devices Authority
UK	United Kingdom
USA	United States of America
USP	United States Pharmacopoeia
WHO	World Health Organization

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DEFINITION OF TERMS

Authorized Person-In a manufacturing establishment, a person responsible for release of batches of finished products for sale (WHO, 1997)

Branded Drug-Drug produced by the innovator company (EAC, 2014)

Defect- A flaw in a product that affects quality (Professionals, 2021).

Falsified Medicine- Medical products that fraudulently or deliberately misrepresent their identity, composition or source (Pisani et al., 2021).

Generic Drug-Drug produced by any other manufacturer other than the innovator after the API patent has expired (EAC, 2014).

Market Authorization Holder- A company, non-profit organization or firm that has been granted authority to market a specific medicinal product (Shukla, 2017).

Product Recalls-The process of retrieving product with defects or safety concerns from customers by the manufacturer or a regulatory authority (Vvss et al., 2020).

Periodic Safety Update Reports- A report prepared by market authorization holder at regular intervals post-authorization describing worldwide safety experience with a specific medicinal product (Dharmesh et al., 2018).

Sterility Assurance Level- When products have been sterilized, the probability that one unit remains nonsterile (Kolluru, 2020).

Substandard Medicines- Authorized medical products that fail to meet their quality standards and specifications (Liu & Lundin, 2016).

ABSTRACT

Product recalls refer to removal from market of specified batches of a product due to presence of quality defects, reported serious or fatal adverse reactions or due to falsification. There is need to review quality defects that lead to product recalls in Kenya due to potential consequences to public health and the economy. The study aimed to identify the proportion, causes, and profile of substandard and falsified medicines in Kenya and to compare product recall procedures and requirements followed in Kenya with those followed in Uganda and Tanzania.

The methodology involved reviewing rapid alerts and product recalls communicated through the PPB website between 2016 and 2021. Information collected included product description details, recall information and details on the defect. A predesigned data collection instrument was used. Data was stored in a password protected Microsoft Access database and exported to SPSS 23 for analysis. Descriptive statistics was also used to analyze other variables.Guidelines on product recalls was accessed from regulatory authority websites of Kenya, Uganda and Tanzania and comparatively analyzed.

Substandard products accounted for 93% of product recalls while falsified products were 7%. Tablets and injectables were the most recalled dosage forms. Antibacterial agents accounted for 20% of substandard products followed by analgesics at 12.9% while antimalarials were the most falsified accounting for 40% of falsified medicines..Of the recalled products, 38% of substandard products and 80% of falsified products were not found in the retention register of 2022 while majority had only one batch recalled. The main causes of substandard products were found to be tableting defects, dissolution defects and variations in content from specifications. Product recall procedures followed by PPB, TMDA and NDA had similarities in classification of recalls, content of communication to regulator, depth of recall and contents of final report. There were variations in timelines for communication, mode of communication, methods of recall, public warning mechanisms, progress reports and considerations for termination of recall.

The study concludes that there is a higher proportion of substandard product compared to falsified products with antibacterial agents and tablets being most affected. It also identifies major causes of substandard pharmaceutical products as tableting defects, dissolution defects and variations in content from specification. Manufacturers and market authorization holders should identify causes of product recalls and their burden to public health and economy and gaps in product recall procedures. Pharmacy and Poisons Board should strengthen post-marketing surveillance programs to identify more substandard and falsified products in the market.Stakeholders can come up with measures to minimize product recalls. EAC-MRH program should develop guidelines for medicine recall that will guide product recall procedures within the East-African Community

CHAPTER 1: INTRODUCTION

1.1 Background Information

1.1.1 Overview of Product Recalls

Product recalls refer to removal from the market of specified batches of a product. They are initiated by competent drug authorities upon receiving information on defective product batches from product manufacturer or distributor(Vvss et al., 2020). Recalls of pharmaceutical products are initiated due to customer complaints about quality or adverse reactions of a product. It can be initiated due to detection of failure of GMP processes after the product has been released or if results of ongoing stability studies or an inspection process denotes stability issues. Other reasons for initiating recalls include known counterfeiting or tampering with product, reports of adverse reactions and at request of the competent drug regulatory authority(Wolyniak, n.d.).

Drug regulatory authorities require that manufacturers and distributors have established procedures for product recalls and withdrawals. The recall should be initiated upon detection of a defect(Shukla, 2017). Defects are classified as critical, major and minor. Critical defects are those that are regarded as life-threatening. They require immediate action. Examples include incorrect labelling, counterfeiting, products that have been tampered with or detection of contaminants in sterile products. Major defects are those that pose potential risk to the patient but are not life-threatening. Recalls for major defects are initiated within a few days of establishing the defect. Examples of major defects are failure of assay to correspond with set limits, misinformation or lack of information on labels and microbial contamination of non-sterile products. Defects classified as minor are those that pose minor risk to patient. Recalls for these types of defects are also initiated within a few days. Examples of minor defects include minimal risk contamination and defaults in packaging(Hemanth et al., 2020).

In most cases, a client complaint precedes product recalls(Vvss et al., 2020). Each pharmaceutical manufacturing and distributor agency should have a designated person to deal with complaints. This is usually the authorized person or the person in-charge of quality control. In the event of a complaint, the designated person will acknowledge receipt of the complaint.They then appoint a team to review the complaint. The quality control department will institute an investigation. A report is then issued by the department. Should the report indicate a defect in product related to quality, the competent authority which is the national drug regulatory authority is informed. The authority then mandates a recall of the

affected batch(Shukla, 2017). It is the manufacturers and distributors responsibility to make follow-ups and keep associated records of the recall. All the company's decisions and mitigating measures need to be recorded and these should be matched with batch manufacturing records of the specific batch. A review of these records should be done regularly to identify common problems(Health & Authority, 2015).

1.1.2 Classification of drug recalls

Two main reasons exist for drugs recalls. First, recalls are done due to adverse effects. The second reason is a lapse in safety and efficacy that result into serious adverse drug reactions and death(Duan & Gao, 2021).

US FDA defines class I recalls as those that are instituted when use/exposure of a defective/violative product will cause serious adverse health consequences or death. Examples of class I recalls include microbial contamination of sterile product and different Active Pharmaceutical Ingredient(API) in the product than is indicated on the label. Class I recalls are instituted immediately a defect is detected and rapid alerts are issued communicating the same to stakeholders.

Class II recalls are defined as those that are instituted when use/exposure to defective product causes temporary or medically reversible adverse health consequences or where probability of serious adverse health consequences are remote. Examples of class II recalls are missing information on package insert or contamination of non-sterile product. These recalls are instituted within a few days of identifying the defect (FDA,2017)

Class III recalls are instituted when it is determined that use/exposure to a defective product is unlikely to cause adverse health consequences. Examples of class III recall include faulty closures without medical implications or faulty package such as that which lacks batch number, has wrong batch number or wrong expiry date. Like class II recalls, class III recalls are instituted within a few days of identifying the defect/violation (FDA, 2017).

1.1.3 Recall policy for pharmaceuticals in various jurisdictions

Drug regulatory authorities dictate when and how recalls should be carried out. They also dictate the parties responsible and the procedure to be followed as well as the mandatory actions required of the responsible parties.

In Canada, drug recalls are overseen by Health Canada; the regulatory body that regulates health products and technologies . The agency denotes the responsible party during the recall as the manufacturers, distributors and sellers of medicine. Responsible parties are required to take full responsibility of product recalls. They are required to determine the health risk, classify the recall as type I, type II or type III and take appropriate actions to alleviate the risk(Health Canada, 2019). They also need to inform Health Canada of preliminary report of their investigation, maintain appropriate distribution records to enable rapid tracing of defective products, document their procedures and undertake recalls when ordered by Health Canada. It is the responsibility of responsible persons to provide information on recall within 24 hours of commencing, written reports about the health risk assessment within 72 hours, progress reports of the recall and conduct checks to establish effectiveness of the recall. Responsible parties are required to have recall procedures in writing that can be utilized if need be(Health Canada, 2019).

The Food and Drug Administration oversees all pharmaceutical recalls in the USA(Wolyniak, n.d.). The agency identifies the responsible party as manufacturer or distributor of the defective product. They are required to initiate voluntary recall in case of a product defect or violation. FDA can also request a firm to conduct a recall as a matter of urgency. Firms risk facing seizures or court action should they not initiate a recall(Becerra & Roth, 2022). Unlike Health Canada which requires responsible parties to conduct health risk assessment, the FDA conducts evaluation of the health hazard and classifies recalls(Eissa, 2019). The affected firm is required to develop a recall strategy for all firm-initiated recalls. The strategy is reviewed by FDA to determine its adequacy. For FDA-initiated recalls, the agency will develop its own recall strategy. When initiating a recall, the firm must relay the following information to FDA; product identity, reason for the recall, quantity of the batch produced and which is in circulation, risk assessment report, distributor details and any recall strategy and name and contacts of person tasked with the recall at the firm. Additionally, the firm needs to submit periodic status reports with details such as number of consignees notified, number of consignees who have responded and quantity of affected products retrieved by the time of writing the report(*Guidelines on Recall and Rapid Alert System Version : 2017*, 2017).

Manufacturers and distributors are further required to have a contingency plan that can be used to initiate and effect a recall when needed and code products for easier identification. They are also required to maintain distribution records to enable easy tracing of defective products. Food and Drug Administration(FDA) terminates a recall when it has been determined that all efforts have been made to remove or correct the affected product as pertains to the recall strategy(Becerra & Roth, 2022).

The European Medicines Agency (EMA) categorizes responsible persons as the manufacturer and market authorization holder. They are required to report to EMA any quality defect detected. They are also to report on any restriction to supply the affected medicines in other jurisdictions by other competent authorities(Professionals, 2021). EMA has a supervisory authority that assesses the report and makes recommendation on the required action. The assessment is carried out together with the rapporteur responsible for the product. Information that must be provided to EMA by the responsible parties include history of the incident, distributors of the batch, proposed corrective action by MAH and effectiveness of recall communication if this had been communicated(Dharmesh et al., 2018). The R(ECG) decides on risk management strategies after reviewing the risk. The strategies may involve recalling batches. A rapid alert is issued in this case. The committee agrees on depth of recall. EMA generally recommends that class I recalls should be to patient level, while class II and class III should be to distributors and pharmacies. Records should be stored electronically in product folder upon termination of recall(European Commission, 2014).

In Kenya product recalls are overseen by Pharmacy and Poisons Board (PPB). The agency denotes responsible parties during a recall as the holder of certificate of registration of a product or the parallel importer of the product. PPB provides oversight to ascertain effectiveness of the recall and to provide technical/scientific guidance. PPB identifies reasons for product recalls as occurrence of serious ADR that was not stated in the insert, increased frequency of certain ADR, incorrect labelling, incorrect formulation or unfavorable result of stability test (PPB,2022). Product recalls in Tanzania are overseen by Tanzania Medicine and Drug Agency(TMDA) while in Uganda the National Drug Authority oversees product recalls. PPB classifies recalls as class I, II and III similar to TMDA while NDA classifies recalls as class A, B and C. All three agencies specify communication content, risk assessment and procedures for termination of recall.

1.1.4 Recall Strategy

The FDA requires that recall strategies should have three important elements; depth of recall, a public warning and effectiveness checks. Depth of recall specifies the extent of recall in the distribution chain. It determines whether the recall will extend to wholesalers, retailers or individual consumers. A public warning known as safety alert is usually issued by FDA but a firm can issue its own warning that is approved by FDA. The warning can be a general one which utilizes media or a specialized one which

communicates to a subset of the population like professionals. The effectiveness check confirms that all consignees in the distribution chain have received communication concerning the recall and have traced and returned the affected batch(U.S Food and Drug Administration, 2015).Other regulatory bodies like EMA, PPB, TMDA and NDA also specify depth of recall, public warning mechanisms and effectiveness checks for various classes of product recall(Vvss et al., 2020).

1.2 Statement Of The Research Problem And Study Justification

Defective medicines pose a serious public health problem. They are classified as either substandard or falsified medicines(Hemanth et al., 2020). Substandard medicines are those that do not meet the regulator's quality requirements due to Good Manufacturing Practices(GMP) deficiencies and manufacturing incompetencies(Sammons & Choonara, 2017). Falsified medicines are those that have been intentionally tampered with(Almuzaini, Choonara, et al., 2013). Reporting of quality defects continues to increase across many jurisdictions resulting in product recalls. A survey of quality defects in recalled medicines in the UK found a ten-fold increase in number of quality defects reported over a ten-year period(Almuzaini, Sammons, et al., 2013). The problem is more prevalent in low and middle income countries. WHO estimates that one in ten medical products in low and middle income countries is substandard or falsified (WHO,2020) Another study reports a incidence of 13.6% of both substandard and falsified medicines(Borse et al., 2021).(McManus et.al 2020) found an decrease in incidence of substandard and falsified medicines from 28.5% in 2013 to 25% in 2018(McManus et al 2020). There has been a reported failure rate of 10.5% of all medical products in low and middle income countries due to substandard and falsified medicines with antimalarial and antibiotics accounting for pharmaceuticals with most quality defects. This impacts negatively on public health(*WHO* 2020).

Further, identification of defective medicines almost always results into product recalls. This poses astronomical losses to pharmaceutical companies(Ozawa et al., 2018). A survey of substandard medicines in the UK noted that 222 products were recalled out of 280 substandard products(Almuzaini, Sammons, et al., 2013). A study of economic impacts of product recalls identified major effects as supply chain interruptions and financial losses that often exceed the cost of recall as well as loss of the company's stock. It is estimated that defective medicines cost low and middle income countries between 10 and 200 billion yearly(Ozawa et al., 2018).

The consequences of defective medicine to public health and economy cannot be ignored. There is need to review quality defects that result in product recalls so that manufacturers can avoid them. This study aims to identify the most common quality defects that resulted to product recalls in Kenya. It also aims to identify incidence and impact of falsified medicines and compare procedures and requirements of product recalls followed by drug regulatory authorities in East African region. The study will help stakeholders quantify the incidence of defective medicines in Kenya, identify the nature of defects and the formulations that are most affected. It is expected to ease the burden of defective medicines to both the economy and public health of Kenya.

1.3 Research Questions

1. What are the proportion of substandard and falsified medicines among product recalls conducted by Pharmacy and Poisons Board between 2016 and 2021?
2. What is the profile of products recalled by Pharmacy and Poisons Board between 2016 and 2021?
3. What are the causes of product recalls conducted by Pharmacy and Poisons Board in Kenya between 2016 and 2021?
4. Are the pharmaceutical product recall procedures and requirements followed by Pharmacy and Poisons Board Kenya comparable with those of NDA and TMDA.

1.4 Objectives

1.4.1 General Objective

To identify the proportion, causes, and profile of substandard and falsified medicines in Kenya and to compare product recall procedures and requirements followed in Kenya with those followed in Uganda and Tanzania

1.4.2 Specific Objective

1. To determine the proportion of substandard and falsified medicines among product recalls conducted by Pharmacy and Poisons Board between 2016 and 2021.
2. To assess the profile of products recalled by Pharmacy and Poisons Board between 2016 and 2021.
3. To identify the causes of product recalls conducted by Pharmacy and Poisons Board in Kenya between 2016 and 2021.
4. To compare pharmaceutical product recall procedures and requirements followed by Pharmacy and Poisons Board Kenya with those of NDA and TMDA

CHAPTER 2: LITERATURE REVIEW

2.1 Incidence of defective medicines

Defective medicines can be broadly classified as substandard or falsified(Hemanth et al., 2020). Substandard medicines are those that do not meet quality standards or specifications of competent authorities. Substandard products often result from inefficient quality control, poor packaging or poor storage conditions (Borse et al., 2021). Falsified medicines on the other hand are those that have been made to misrepresent their identity. Usually, falsified medicines are manufactured deliberately with criminal intent. Falsifications of medicinal product may involve errors in packaging, labelling and composition of product when compared with the genuine product(Liu & Lundin, 2016).

Both substandard and falsified pharmaceutical products are detrimental to public health because they may fail to treat the diseases they claim to treat. This leads to increased morbidity and mortality in addition to loss of confidence in healthcare systems. Both branded and generic products can be substandard or falsified(Johnston & Holt, 2014).

It is particularly difficult to estimate the worldwide incidence of defective medicines since there are few published studies regarding the subject. Most studies conducted on the subject focus on low and middle income countries particularly in Africa and South East Asia. This focus is due to lack of stringent regulatory oversight in these jurisdictions compared to high income countries(Ozawa et al., 2018). Several studies indicate a high incidence of substandard/ falsified antimicrobial and anti-parasitic drugs in low and middle income countries. WHO and FDA puts the figure at between 10% and 30% although other studies have disputed these figures(Hauk et al., 2021).

In high income countries, WHO estimates that 1% of all medicines circulating are falsified. However, few studies exist to back this claim(Nayyar et al., 2015). A retrospective review of MHRA database of drug recalls in UK revealed that 10% of drug alerts issued resulted from critical defects and necessitated a class I drug recall. The study scope was recalls conducted between 2007 and 2012(Almuzaini, Sammons, et al., 2013). Another study of the same nature conducted in Canada detected 653 defective medicines that resulted in drug recalls and alerts between 2005 and 2013. The study noted a gradual increase in reports of defective medicines from 42 in 2005 to 143 in 2013. Researchers could neither attribute the increase to increased production of defective medicines or increased reporting(Almuzaini et

al., 2014). A systematic review of quality of medicines conducted worldwide between 2013 and 2018 however noted a decrease of substandard medicines of 3.5% from 28.5% to 25%(McManus & Naughton, 2020).

A study of FDA recalls conducted between 2016 and 2018 showed yearly increase in recall rates with peaks between May and August of each year(Eissa, 2019).

The studies on recalled products have also reported adverse consequences of defective medicines. The most common consequence is decreased/lack of therapeutic response. This was noted among patients taking antimalarial, antibiotics, imatinib and tacrolimus. The defect that led to this consequence was insufficient active pharmaceutical ingredient(Johnston & Holt, 2014). Sub-therapeutic doses have also led to emergence of resistant strains of bacteria, viruses and parasites(Mac Leod et al., 2015). This had negative outcomes for infectious diseases like tuberculosis and malaria. Few studies have examined the incidence of defective medicines among drugs used for non-communicable diseases although Schaferman et.al noted that drugs for non-communicable diseases were more likely to have high failure rate compared to antibiotics. The study also noted that drugs produced in Africa were more likely to be substandard or falsified at 22.2% than Asia at 17.7% and Europe at 5.1%(Schäfermann et al., 2020).

Fatalities and increased morbidity have been reported as a consequence of defective medicines(Cohn et al., 2013). The presence of oversulphated chroinditin sulphate as an impurity in heparin for example resulted in hypersensitivity and fatalities(Guerrini et al., 2008).

2.2 Nature of Defects

Analysis of various published articles suggest that three defects are commonly responsible for defective drugs. These include variations in content of the formulation both quality and quantity, presence of contaminants and ineffective packaging(Professionals, 2021). Other notable causes are lack of sterility assurance, stability defects and GMP inefficiencies(European Commission, 2014).

2.2.1 Variations in content.

Pharmaceuticals are formulated based on standards found in pharmacopoeias(Uddin et al., 2016). Pharmacopoeias commonly used are the United States Pharmacopoeia(USP) and the British Pharmacopoeia(BP). A formulation is considered substandard if the active pharmaceutical ingredient does not fall within the limits specified in the pharmacopoeia(Mamun et al., 2017).

Several studies conducted on antimalarial have found formulations with API that is below the required limits. In some cases, formulations didn't have the stated API at all. 53% of Artesunnate samples in

Burma, Laos, Vietnam, Cambodia and Thailand were found to have no artesunnate (Johnston & Holt, 2014). Studies in Colombia, Estonia, India, Latvia, Russia, Vietnam found that 10% of the anti-Tb drugs, Rifampicin and Isoniazid have API with quantity outside the limits. Among these 21% of fixed dose combinations and 13% of single dose formulations were found to be substandard(Johnston & Holt, 2014).

Commonly used antibiotics like penicillins, macrolides, fluoroquinolones and tetracycline have been found to be substandard. A study of amoxicillin, ampicillin, ketoconazole and metronidazole in Nigeria found that 25% of capsule formulations and 40% of dry syrup formulation fell outside the British pharmacopoeial limits. For cream formulations, as much as 80% of products fell outside pharmacopoeial limits(Kingdom, 2015). The same was noted in Lebanon, Jordan, Egypt and Saudi Arabia where 56% of capsules and 8% of dry suspensions had API below the required limits(Torumkuney et al., 2020).

Formulations used for non-communicable diseases have also been found to be substandard. Researchers in Mexico found content deviations of tacrolimus in various generic brands. The standard deviation was noted to be up to 30(Petan et al., 2008).

The cardiovascular agents, streptokinase, carvedilol and various anti-hypertensive have been found to have content variation as well. A study in Rwanda found 20% of sampled anti-hypertensive to be substandard at the time of testing. The figure increased to 70% after storage in accelerated conditions for 6 months. The defect noted was variations in API outside recommended limits(Johnston & Holt, 2014). A similar study on antihypertensive in 10 countries in sub-Saharan African countries put the figure of poor quality drugs with insufficient API at 24.3%(Bernard et al., 2017). Generic samples of carvedilol tested in 19 countries had a failure rate of 48.6%(Smith et al., 2006). In Italy, 24% of generic Ramipril had API amount that was outside the required limits. Storage of the sample in accelerated conditions caused a substantial loss in API in 47% of sample to below limits(Angeli & Trezza, 2009). The oncology drug docetaxel was assayed in 14 countries in Asia, Middle East, Africa and Latin America. The study found that 21 of 31 generic brands had variations in API content(Vial et al., 2008). Generic isotretinoin was assayed using Roche criteria for content, European pharmacopoeia and United States Pharmacopoeia. Up to four samples out of 14 had API content outside limits while 2 and 3 failed using EP and USP respectively(Taylor & Keenan, 2006).

Cases where stated API is different from what is stated on the label have also been rampant. This can be attributed to mislabeling. Finasteride formulations were labelled as citalopram in USA. Zolpiclone

labelled formulations were found to contain furosemide instead. In Canada, a batch of rifampicin had clonazepam instead while another batch of minocycline had amlodipine instead. Such mislabeling and mix-ups constitute critical defects that necessitate class I recalls(Johnston & Holt, 2014).

2.2.2. Impurities and Contaminants

Contaminants can get into pharmaceutical product during manufacturing, distribution or during use. Contamination affects quality, safety and efficacy of product. For this reason, pharmaceutical products that are contaminated are likely to be recalled(Mahfuz & Alam, 2020). A study conducted in Canada examined nature of defects that led to product recalls. The study attributed 21% of recalls to contamination from impurities, micro-organisms and lack of sterility assurance. Contaminants ranged from visible particles, micro-organisms, cross-contamination and contamination with drug-like substances(Almuzaini et al., 2014). A similar study conducted in UK attributed 27% of drug recalls to contamination. Impurities accounted for the bulk of these recalls followed by lack of sterility assurance and then microbial contamination(Almuzaini, Sammons, et al., 2013). In Croatia, 30.2% of recalls of blood products was attributed to bacterial contamination(Vuk et al., 2013). Thus, contamination is a major reason for pharmaceutical product recalls.

Contaminants may be of mechanical, chemical or microbial nature(Bohrer, 2012). Mechanical contamination refers to presence of foreign extraneous substances in pharmaceutical products. They often arise from the environment or from containers used for packaging such as glass, metal or plastic(Langille, 2013). Presence of particulate matter in parenteral products is a major cause of recalls. Between 2008 and 2012, 22% of recalls of injectable pharmaceuticals by FDA was attributed to presence of particulate matter. The contaminants were cellulosic fibers, glass particles, stainless steel, garment fibers, human hair, iron oxide and barium sulfate(Tawde, 2015). Packaging material like glass and metal often gets into formulation and has led to recall. Glass delamination led to recall of 10 injectable pharmaceutical products by FDA between 2018 and 2019 and 4 injectable products between 2020 and 2021(Kabirdas B & Sharda M, 2022).

The second major class of contaminants are those of chemical nature also known as impurities(Bohrer, 2012).

FDA classifies impurities as organic, inorganic and residual solvents(Nithyanandan et al., 2016). ICH guidelines broadly classifies impurities as those associated with the active pharmaceutical ingredient and those created during formulation or due to aging. Impurities arising from active pharmaceutical ingredient can be organic, inorganic or residual solvents(ICH Q3A, 2006).

Organic impurities include; starting material or intermediates that remain unreacted during the manufacturing process. An example is p-aminophenol in paracetamol. Various pharmacopoeia state acceptable limits for these impurities. By-products are end-products of the processes that are not required. Degradation products resulting from breakdown of API usually occur during storage or during formulation of various dosage forms. Catalysts, ligands and reagents may also occur as organic impurities. Unintended enantiomeric form of chiral drugs may also occur as impurities. They are regarded as impurities since they may have different pharmacological activity(Nithyanandan et al., 2016).

The sources of inorganic impurities include reagents, ligand, catalysts, heavy metals from water, reactors and filter aids. Residual solvents remain as volatile impurities in the product(Nithyanandan et al., 2016).
In recent times, several drug products have been recalled due to detection of nitrosamine impurities like N-nitrosodimethylamine(NMDA), N-nitrosodiethylamine (NDEA) and N-methyl-4-aminobutyric acid (NMBA). Nitrosamine impurities may arise from the manufacturing process or due to degradation during storage and may have genotoxic and carcinogenic properties(Tuesuwan & Vongsutilers, 2021). A review of FDA product recall database reveals that more than 1400 products have been recalled due to presence of nitrosamine impurities. These include valsartan, metformin, ranitidine, losartan, ibesartan and nizatidine(Farrukh et al., 2019). Similar recalls have been conducted by the European Union (Medicines Agency, 2019).
The last major class of contaminants is microbial contamination. Micro-organisms commonly found in pharmaceuticals include bacteria, fungi and viruses. Some micro-organisms produce endotoxins and exotoxins that have potential for infections and mortality(Sandle, 2017).21 product recalls conducted by FDA between 1995 and 2002 were attributed to fungal contaminants like yeast and mold(Vijayakumar & Sandle, 2012). *Burkholderia cepacia* complex, a gram negative bacteria has led to recalls of albuterol solution, nasal sprays and docusate sodium in Saudi Arabia(Alquadeib et al., 2020) and USA. Several product recalls have also been attributed to presence of *Pseudomonas aeruginosa*(Sandle, 2020).

2.2.3 Packaging Defects

Packaging plays a critical role in ensuring safety, efficacy and easy identification of pharmaceutical products. In addition, an effective package provides information on product, improves presentation, eases dosing and provides convenience to the patient(Ahmad & Hamid, 2021).
Various pharmacopoeia provides specifications for containers and closures of solid oral dosage forms and also for sterile product glass containers. Deviation from these specifications leads to an ineffective

package(Ahmad & Hamid, 2021). Packaging inefficiencies often lead to critical defect of product and forces market authorization holders to initiate class I drug recalls(MHRA,2021).
Defects in packaging range from mis-labeling, misinformation, incorrect markings, poorly updated leaflet instructions, damaged primary packaging materials, missing batch numbers, missing expiry date, leakages, mixing of dosage forms and even out of order packaging(Hemanth et al., 2020).

Mislabeling and misinformation account for a large number of pharmaceutical product recalls. In a study of class I recall of solid oral dosage forms conducted by FDA between 2012 and 2019, 43.6% of all recalls were attributed to labelling issues(Syarifudin, 2020). In 2010, four over the counter products containing guaifenesin were voluntarily recalled due to mislabeling(Hemanth et.al.,2020).). Leakages and inadequate sealing is also a common cause of drug recalls. B. Braun medical and Baxter International recalled 5 products due to leaky containers that allowed passage of light and moisture in 2015 and 2016. The products recalled included metronidazole injection, dextrose injection and sodium chloride injection(Gollamudi, 2020).

A study of drug recalls conducted by MHRA in UK between 2001 and 2011, identified major packaging defects, minor packaging defects and delivery defects as cause of recalls. Major packaging defects included mix-ups and mis-labelling. Quetiapine was found in package labelled as ibuprofen while ephedrine was labelled erroneously as atropine. Warfarin 3mg tablets were also mislabeled as bendroflumethiazide 2.5mg. These accounted for 10% of all product recalls. Minor packaging defects included missing patient information leaflets, misinformation in regards to strength or dose, un-updated patient leaflets. They accounted for 25% of recalls. Delivery defects included broken seals, faulty salbutamol inhaler valves, broken and leaking capsules of temozolomide and fentanyl transdermal patched that self-activated(Almuzaini, Sammons, et al., 2013).

A similar study done in Canada of recalls conducted between 2005 and 2013 also identified major packaging defects involving mislabeling and mix-ups. Mislabeling and mix-ups affected trazodone, amlodipine, minocycline, rifampicin, morphine sulfate, fluvoxamine, octreotide acetate omega and prednisolone. These accounted for 10% of recalls. Minor packaging errors included missing or incorrect batch numbers, expiry dates or manufacturer name. This accounted for 11% of recalls. Delivery defects included loose seals, cracked vials and faulty delivery devices. It accounted for 5% of all recalls(Almuzaini et al., 2014).

2.2.4 Lack of Sterility Assurance

Parenteral products rapidly get into circulation allowing them to by-pass the body's defense mechanisms. For this reason, regulatory authorities require that they be sterile(Kabirdas B & Sharda M, 2022) CGMP requires that facility design, processes, procedures, personnel, systems and materials for sterile drug processing should be designed to ensure aseptic manufacture(Shukla, 2017). Lack of sterility assurance leads to microbial contamination that could introduce endotoxins and pyrogens into the blood stream. These may cause severe illness and even death(Kolluru, 2017).

Lack of sterility assurance is a major cause of recall of parenteral products(Kolluru, 2020). A retrospective review of risk communication documents in Canada identified 35 instances of lack of sterility assurance(Almuzaini et al., 2014). A similar study in the UK identified 18 instances of lack of sterility assurance in parenterals over a ten-year period. Another study reviewing safety alerts and product recalls by FDA in 2016, identified 12 cases of lack of sterility assurance. The products affected included 5% dextrose injection, eye-wash, lyophilized HCG and sermorelin and various compounded products(Almuzaini, Sammons, et al., 2013).

2.2.5 Stability Defects

ICH guidelines require pharmaceutical products to retain pharmacopoeial specifications throughout the duration of storage and use(ICH, 2003). Instabilities at any point during the drug use cycle may result into toxic products or products with decreased therapeutic effect(Rehman et al., 2020).

Environmental factors like light, oxygen, temperature and moisture are often the reason for instabilities. Other causes are chemical interactions between drug and excipients and microbial effect on product(Rehman et al., 2020). Stability studies are conducted to examine the effect of various environmental factors on stability of pharmaceutical products. These studies could be real-time, accelerated or long-term(Jose et al., 2014). Often pharmaceutical products will be marketed before results of long-term stability studies are obtained. Unfavorable results could lead to product recall and safety alerts(Jasim & Alsaab, 2020)

A study conducted in Canada identified stability defects as the reason for 32% of product recalls and safety alerts. They ranged from impurities exceeding specifications at different time-points, failure to

disintegrate, dissolve or release drug according to specifications before expiry date and instability of active pharmaceutical ingredient(Almuzaini et al., 2014).

In a UK study, stability defects accounted for 8% of recalls and safety alerts by MHRA. Stability defects identified were dissolution failure before expiry and instability of active pharmaceutical ingredient. Some stability failures were unspecified(Almuzaini, Sammons, et al., 2013).

2.2.6 Others

Other quality defects that have led to product recalls and safety alerts include GMP failures like poor analytical procedures, unavailable records, unsanitary production facilities and unapproved drug(MHRA, 2021).

2.3 Formulations affected by Recalls

Pharmaceutical products are prepared as dosage forms containing the active ingredient and excipients. Several formulations exist that facilitate drug administration through various routes. They include oral solids like tablets and capsules, oral liquids like syrups, parenterals, transdermal patches, otic, ophthalmic and topical products like creams, ointments and topical solutions. Several studies show some formulations were recalled more often than others. Parenterals, due to their ability to by-pass body's defense mechanisms, are more likely to be recalled than other formulations(Langille, 2013).

A study of FDA drug recalls conducted between 2009 and 2019 found 48.5% of pharmaceuticals recalled were injectables. Oral solid formulations accounted for 26% of recalls while liquid oral formulations accounted for 5.8%. All other formulations accounted for between 0.2 and 4.7% of recalls(Gollamudi, 2020).

Syarifudin et.al examined class I recalls affecting solid oral dosage forms between 2012 and 2019 in USA. They found that 27.1% of class I recalls could be attributed to solid oral formulations. These included prescription, over the counter pharmaceutical drugs and dietary supplements(Syarifudin, 2020).
A review of risk communication documents distributed between 2005 and 2013 in Canada. attributed injectables for most of the type I recalls followed by oral solid dosage forms then oral liquid dosage forms(Almuzaini et al., 2014).

CHAPTER 3: METHODOLOGY

3.1 Study Design

The study was a retrospective descriptive study of product recalls and rapid alerts communicated by Pharmacy and Poisons Board over a 5-year period (2016-2021) through their website. Information collected included formulation, API, dosage form, dosage and indication of recalled product as well as registration status.

Information on nature of defect, number of affected batches, mode of recall, year of recall, type of defect and current retention status of the product was also collected. Information was collected from the online product recall database of Pharmacy and Poisons Board between May and October 2022 using a predesigned data collection sheet. (Appendix 1). Product recall guidelines and requirements were accessed from the Pharmacy and Poisons Board Kenya, National Drug Authority Uganda, Tanzania Medicine and Medical Devices Authority and comparatively analyzed.

3.2 Study Area Description

The study was conducted on the Pharmacy and Poisons Board website using the publicly available online product recall and rapid alerts databases (https://web.pharmacyboardkenya.org/product recalls) , (https://web.pharmacyboardkenya.org/rapid alerts). For each recall conducted the database details the date of recall, product name, INN name, batches recalled, name of manufacturer and reason for recall. More information pertaining to the recalled product was obtained from Pharmacy and Poisons Board retention register 2022PPB - eCTD (pharmacyboardkenya.org) which is also publicly available. This information included strength of the recalled product, name of market authorization holder, dosage form, route of administration, pharmacotherapeutic group, retention year, manufacturing site, country of origin and manufacturing site address It was also conducted on Tanzania Medicines and Medical Devices Authority en1626772826-en1623839245-GUIDELINE FOR RECALL,HANDLING-final most (1).pdf (tmda.go.tz) and National Drug Authority Uganda websites INS-GDL-37-Guideline-for-recall-of-a-medical-product.pdf (nda.or.ug) where product recall guidelines were accessed.

The Pharmacy and Poisons Board is a body established under Pharmacy and Poisons Act cap 244 of the laws of Kenya. Its mandate is to regulate manufacture, sale and distribution of drugs, poisons and medical devices. It also regulates the practice of pharmacy. The board ensures quality of drug products sold in the Kenyan market is good by conducting inspections of local and foreign manufacturing sites to ascertain compliance with good manufacturing practices (GMP). The board also conducts inspections and

audits of wholesalers and retailers to ensure compliance with good distribution practices(GDP). When necessary, PPB initiates a product recall upon receiving sufficient evidence of critical or major defects of a product or critical adverse reactions resulting from use of a product. Further, the board also oversees company-initiated product recalls usually initiated by market authorization holders. All product recall information is kept in a product recall database.

Tanzania Medicines and Medical Devices Authority is a body corporate established under cap 219 laws of Tanzania. It is mandated with regulating the quality, safety and efficacy of medicines manufactured in Tanzania or imported to the country for use by general public. The authority is tasked with recalling defective medicines such as falsified, substandard or expired. The procedures followed are detailed in TMDA recall, handling and disposal of unfit medicines and cosmetics regulations 2015en1626772826-en1623839245-GUIDELINE FOR RECALL,HANDLING-final most (1).pdf (tmda.go.tz) .

National Drug Authority is a government body in Uganda mandated to regulate the manufacture, importation, distribution and licensing of drugs in Uganda. The body is also charged with recall of medicines deemed defective in Uganda and procedures are detailed in Guidelines for the recall and withdrawal of Medical ProductINS-GDL-37-Guideline-for-recall-of-a-medical-product.pdf (nda.or.ug).

3.3 Study Population

The study population was limited to product recalls mandated or overseen by Pharmacy and Poisons Board between 2016 and 2021.

3.3.1 Inclusion Criteria

Product recalls conducted between 2016 and 2021 of pharmaceutical products.

3.3.2 Exclusion Criteria

Product recalls conducted between 2016 and 2021 that were not in the Pharmacy and Poisons Board product recall database were excluded.

3.4 Sample Size Determination

Preliminary studies reveal a total of 71 product recalls and 18 rapid alerts communicated through the pharmacy and poisons board website between 2016 and 2021. From 89, 13 entries were excluded because they belonged to medical device/borderline category. 1 was excluded for being a double entry. This left a sample size of 75.

3.5 Training Procedures and Pilot Study

Two research assistants were trained on the data collection procedure. Data collection was done using the predesigned data collection tool (appendix 1). Suitability of the data collection form was assessed by collecting data and entering in the form as a pilot test. Inconsistencies were noted and necessary changes incorporated before the main study began.

3.6 Data Collection

The two trained research assistants together with the principal researcher extracted data from entries in the product recall and rapid alert database. A predesigned data collection tool (appendix 1) was used to collect all the necessary information required for this research.

3.7 Data Collection Instrument

Data collected from the database included formulation, indication, dosage, legal category of product, marketing authorization status of product, nature of defect, extent of defect, affected batches, cause of defect, and affected patient populations. The instrument had three sections. Part 1 entailed product description, part II entailed recall information and part III had information on defects (Appendix 1).

3.8 Variables

Independent variables were formulation, dosage, indication and legal category of product. Dependent variables were nature of defect, cause of defect and current retention status of product.

3.9 Quality Assurance Procedures

The data collection form was pretested before use. Inconsistencies were noted from the pilot study. Necessary modifications were done to the data collection form. Data cleaning was done after data collection before data analysis.

3.10 Data Management and Analysis

Data was collected using the predesigned data collection tool (Appendix 1). The data was entered into a Microsoft access database that is password-protected. Descriptive statistics were used to summarize the following data: batch affected, dosage form of the recalled product, pharmacological/legal category of the product, active pharmaceutical ingredient, class of the product, route of administration, product origin, registration status, year of recall, type of defect, affected population and retention status 2022.

Proportions or cross-tabulation of frequency data were also conducted. Analyses were performed using SPSS, version 23(IBM, Armonk, NY).

3.11 Ethical or Institutional Approval

Ethical and instituitional approval were not needed for this study.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Introduction

In this chapter, the results of the study are presented in accordance with the objectives of the study. First the data on proportion of substandard and falsified products are presented. The profile of the substandard and falsified products is presented in the next data set with details like active pharmaceutical ingredient, pharmacological class and dosage form presented. The next section examines causes of recall of substandard products. The third section details recall information with details like mode of recall, type of defect, affected patient populations, year of recall and current retention status of both substandard and falsified products.

Lastly, a comparative analysis of product recall guidelines of PPB Kenya, NDA Uganda and TMDA Tanzania is presented.

4.2 Proportion of Substandard and Falsified Pharmaceutical Products

Table 1 shows proportion of substandard and falsified products that were recalled over the 5 year period. Of the total recalled products 93.3% were substandard and 7% were falsified. There was a yearly increase in number of recalled sub-standard products with exception of 2021. This was comparable to a similar study of FDA recalls(Eissa, 2019). Falsified products were recalled in only three of the five years with 2021 having the highest number of falsified pharmaceutical products.

Table 1: Proportion of Pharmaceutical Product Recalls between 2016-2021

Time	Class	Frequency (N=75)	Percentage (%)
Study Period (2016-2021)	Sub-Standard	70	93.3
	Falsified	5	6.7
2016	Sub-Standard	3	100.0
	Falsified	0	0.0
2017	Sub-Standard	11	100.0
	Falsified	0	0.0
2018	Sub-Standard	16	88.9
	Falsified	2	11.1
2019	Sub-Standard	15	100.0
	Falsified	0	0.0
2020	Sub-Standard	15	93.8
	Falsified	1	6.3
2021	Sub-Standard	10	83.3
	Falsified	2	16.7

4.3 Profile of Recalled Products

4.3.1. Pharmacological Category of Product

Table 2 shows the pharmacological category of recalled products. Antiinfectives accounted for most of the recalled products. Antibacterials accounted for 20% of substandard products, antihelminthics for 8.6% while antimalarials and antiretrovirals accounted for 1.4% each. This is comparable to WHO estimates that postulates that 10 to 30% of antimicrobial and antiparasitic drugs circulating in low and middle income countries are defective(Ozawa et al., 2018). Analgesic and antipyretics accounted for 14.3% of substandard products. Antimalarials accounted for 40% of falsified products while vaccines, monoclonal antibodies and contraceptive each accounted for 20% of recalled falsified products.Infectious

diseases were the most affected with substandard products followed by pain and fever. Malaria claimed the largest burden of falsified medicine while vaccination, autoimmune conditions and contraception had similar chance of getting falsified medicines

Table 2: Pharmacological/Legal category of product

Pharmacological/Legal category of product	Overall (N=75; %.)	Sub-Standard (n=70, %.)	Falsified (n=5, %.)
Analgesic and antipyretic	10(13.3.	10(14.3.)	0(0.0.)
Antacid	2(2.7.)	2(2.9.)	0(0.0.)
Antibacterial	15(20.0.)	15(21.4.)	0(0.0.)
Anticoagulant	1(1.3.)	1(1.4.)	0(0.0.)
Antiflatulent	1(1.3.)	1(1.4.)	0(0.0.)
Antifungal	2(2.7.)	2(2.9.)	0(0.0.)
Antihelminthic	6(8.0.)	6(8.6.)	0(0.0.)
Anthelminthic, antinematodal	1(1.3.)	1(1.4.)	0(0.0.)
Antihistamine	3(4.0.)	3(4.3.)	0(0.0.)
Antihypertensive	6(8.0.)	6(8.6.)	0(0.0.)
Antihypertensive, diuretic	1(1.3.)	1(1.4.)	0(0.0.)
Antileprotic	1(1.3.)	1(1.4.)	0(0.0.)
Antimalarial	3(4.0.)	1(1.4.)	2(40.0.)
Antiprotozoal	2(2.7.)	2(2.9.)	0(0.0.)
Antipsychotic	1(1.3.)	1(1.4.)	0(0.0.)
Antiretroviral	1(1.3.)	1(1.4.)	0(0.0.)
Antithrombotic agents	1(1.3.)	1(1.4.)	0(0.0.)
Antitussive	2(2.7.)	2(2.9.)	0(0.0.)
Betalactam antibacterial	1(1.3.)	1(1.4.)	0(0.0.)
Contraceptive	2(2.7.)	1(1.4.)	1(20.0.)
Glucose	1(1.3.)	1(1.4.)	0(0.0.)
Histamine 2 blockers	1(1.3.)	1(1.4.)	0(0.0.)
Inactivated polio vaccine	1(1.3.)	1(1.4.)	0(0.0.)
Iron products	1(1.3.)	1(1.4.)	0(0.0.)
Laxative	1(1.3.)	1(1.4.)	0(0.0.)
Monoclonal antibody	2(2.7.)	1(1.4.)	1(20.0.)
Neuromuscular blocker	1(1.3.)	1(1.4.)	0(0.0.)
Phosphodiesterase inhibitor	1(1.3.)	1(1.4.)	0(0.0.)
Proton pump inhibitor	1(1.3.)	1(1.4.)	0(0.0.)
Short acting adrenergic Beta 2 agonist	1(1.3.)	1(1.4.)	0(0.0.)
Vaccine	1(1.3.)	0(0.0.)	1(20.0.)
Vitamins	1(1.3.)	1(1.4.)	0(0.0.)

4.3.2. Active pharmaceutical ingredient of recalled products

Table 3 presents the summary of the active pharmaceutical ingredients of the recalled products disaggregated by sub-standard and falsified classifications. Among the sub-standard products Albendazole 7(10.0%) constituted the majority followed by paracetamol 6(8.6%), and Gentamicin 4(5.7%). Among the falsified products the active pharmaceutical ingredients were as follows; Chloroquine (1 (20.0%); Corona virus vaccine (1 (20.0%); Levornogesterol (1(20.0%); Primaquine sulphate (1(20.0%); and Eculizumab (1(20.0%).

Table 3: Active Pharmaceutical Ingredients of the Recalled Products

Active Pharmaceutical Ingredient	**Overall (N=75)**	**Sub-Standard (n=70)**	**Falsified (n=5)**
1. Albendazole	7(9.3%)	7(10.0%)	0(0.0%)
2. Aluminium hydroxide, magnesium hydroxide,	1(1.3%)	1(1.4%)	0(0.0%)
3. Aminosidine	1(1.3%)	1(1.4%)	0(0.0%)
4. Amoxicillin	2(2.7%)	2(2.9%)	0(0.0%)
5. Amoxicillin and Clavulanic acid	2(2.7%)	2(2.9%)	0(0.0%)

6. Anti Rho-D Immunoglobulin	1(1.3%)	1(1.4%)	0(0.0%)
7. Aspirin	1(1.3%)	1(1.4%)	0(0.0%)
8. Atazanavir/Ritonavir	1(1.3%)	1(1.4%)	0(0.0%)
9. Atracurium	1(1.3%)	1(1.4%)	0(0.0%)
10. Bisacodyl	1(1.3%)	1(1.4%)	0(0.0%)
11. Carbocystein and promethazine	1(1.3%)	1(1.4%)	0(0.0%)
12. Cefuroxime	1(1.3%)	1(1.4%)	0(0.0%)
13. Cetrizine	1(1.3%)	1(1.4%)	0(0.0%)
14. Chlorhexidine, silver sulphadiazine	1(1.3%)	1(1.4%)	0(0.0%)
15. Chloroquine	1(1.3%)	0(0.0%)	1(20.0%)
16. Chlorpheniramine	1(1.3%)	1(1.4%)	0(0.0%)
17. Chlorpheniramine, Diphenhydramine, Ephedrine, Ammonium chloride, Sodium citrate, menthol	1(1.3%)	1(1.4%)	0(0.0%)

18. Ciprofloxacin	2(2.7%)	2(2.9%)	0(0.0%)
19. Clofazimine	1(1.3%)	1(1.4%)	0(0.0%)
20. Clotrimazole	1(1.3%)	1(1.4%)	0(0.0%)
21. Corona virus vaccine	1(1.3%)	0(0.0%)	1(20.0%)
22. Dextrose	1(1.3%)	1(1.4%)	0(0.0%)
23. Diclofenac	1(1.3%)	1(1.4%)	0(0.0%)
24. Diphenhydramine and Promethazine	1(1.3%)	1(1.4%)	0(0.0%)
25. Eculizumab	1(1.3%)	0(0.0%)	1(20.0%)
26. Enalapril	1(1.3%)	1(1.4%)	0(0.0%)
27. Erythromycin	1(1.3%)	1(1.4%)	0(0.0%)
28. Ferrous sulphate	1(1.3%)	1(1.4%)	0(0.0%)
29. Fluphenazine	1(1.3%)	1(1.4%)	0(0.0%)

30. Furosemide	1(1.3%)	1(1.4%)	0(0.0%)
31. Gentamicin	4(5.3%)	4(5.7%)	0(0.0%)
32. Gripe water	1(1.3%)	1(1.4%)	0(0.0%)
33. Irbesatan	1(1.3%)	1(1.4%)	0(0.0%)
34. Ketoconazole	1(1.3%)	1(1.4%)	0(0.0%)
35. Ketorolac	1(1.3%)	1(1.4%)	0(0.0%)
36. Levornogesterol	2(2.7%)	1(1.4%)	1(20.0%)
37. Lopidogrel with aspirin	1(1.3%)	1(1.4%)	0(0.0%)
38. Losartan	1(1.3%)	1(1.4%)	0(0.0%)
39. Losartan and Hydrochlorthiazide	1(1.3%)	1(1.4%)	0(0.0%)
40. Magnesium carbonate, sodium carbonate	1(1.3%)	1(1.4%)	0(0.0%)
41. Mentholatum	1(1.3%)	1(1.4%)	0(0.0%)

42. Metronidazole	2(2.7%)	2(2.9%)	0(0.0%)
43. Omeprazole	1(1.3%)	1(1.4%)	0(0.0%)
44. Oral polio vaccine	1(1.3%)	1(1.4%)	0(0.0%)
45. Paracetamol	6(8.0%)	6(8.6%)	0(0.0%)
46. Primaquine sulphate	1(1.3%)	0(0.0%)	1(20.0%)
47. Ranitidine	1(1.3%)	1(1.4%)	0(0.0%)
48. Salbutamol	1(1.3%)	1(1.4%)	0(0.0%)
49. Sildenafil	1(1.3%)	1(1.4%)	0(0.0%)
50. Silver sulphadiazine	1(1.3%)	1(1.4%)	0(0.0%)
51. Sulfadoxine and Pyrimethamine	1(1.3%)	1(1.4%)	0(0.0%)
52. Trimethoprim, sulphamethoxazole	1(1.3%)	1(1.4%)	0(0.0%)
53. Valsartan	2(2.7%)	2(2.9%)	0(0.0%)

54. Vitamin C	1(1.3%)	1(1.4%)	0(0.0%)
55. Warfarin	1(1.3%)	1(1.4%)	0(0.0%)

4.3.3. Dosage form of the recalled product

The dosage forms of recalled products are detailed in table 4. Tablets were the most recalled dosage form accounting for 48% of total recalls, 48.6% of sub-standard products and 40% of falsified products.This percentage is higher than that found by a study of FDA recalls which attributed 27.1% of recalls to solid oral formulations(Syarifudin, 2020). Injectables were the second most recalled accounting for 14.7% of total recalls, 12.9% of sub-standard recalls and 40% of falsified products. This figure is lower than was established by a study of FDA recalls over a ten year time-period that attributed 48.5% of product recalls to injectables, 26% to oral solids and 8% to oral liquids(Gollamudi, 2020). Similarly a Canada study attributed injectables as the most recalled dosage form followed by oral solid dosage forms then oral liquids(Almuzaini et al., 2014).

Table 4: Dosage form of the recalled products

Dosage form	Overall (N=75, %)	Sub-Standard (n=70, %)	Falsified (n=5,%)
Capsule	2(2.7.)	2(2.9.)	0(0.0.)
Cream	4(5.3.)	4(5.7.)	0(0.0.)
Dispersible tablet	1(1.3.)	1(1.4.)	0(0.0.)
Gel	1(1.3.)	1(1.4.)	0(0.0.)
Injection	11(14.7.)	9(12.9.)	2(40.0.)
Oral suspension	4(5.3.)	4(5.7.)	0(0.0.)
Powder for oral constitution	2(2.7.)	2(2.9.)	0(0.0.)
Powder for oral suspension	1(1.3.)	1(1.4.)	0(0.0.)
Powder for syrup	1(1.3.)	1(1.4.)	0(0.0.)
Suspension	3(4.0.)	3(4.3.)	0(0.0.)
Syrup	6(8.0.)	6(8.6.)	0(0.0.)

Tablets	36(48.0.)	34(48.6.)	2(40.0.)
Tablets, syrup	1(1.3.)	0(0.0.)	1(20.0.)
Transdermal patch	1(1.3.)	1(1.4.)	0(0.0.)
Varied	1(1.3.)	1(1.4.)	0(0.0.)

4.3.4 Other Product Characteristics

Table 5 details parameters like legal class of product, route of administration, product origin and registration status. Prescription drugs accounted for 76% of product recalls while 24% could be attributed to non-prescription drugs.In the substandard category, 75.7% were prescription drugs and 24.3% were non-presription drugs while 80% of falsified products were prescription and 20% non-prescription. Oral administration accounted for 76% of the total recalled products, 8% of the products were topically administered while intravenous and intramuscular accounted for 5% each. For both substandard and falsified, oral route accounted for the highest number of recalls.

The study attributed 46.7% of recalls to locally manufactured products and 53.3% to imported products. All falsified products were imported while 50% of substandard were imported and 50% locally manufactured.Majority of the recalled products were registered with only 5.3% being unregistered and 8% being of unknown registration. For falsified products, 60% were unregistered, 20% had emergency use registration while 20% were registered.

Table 5: Other product characteristics

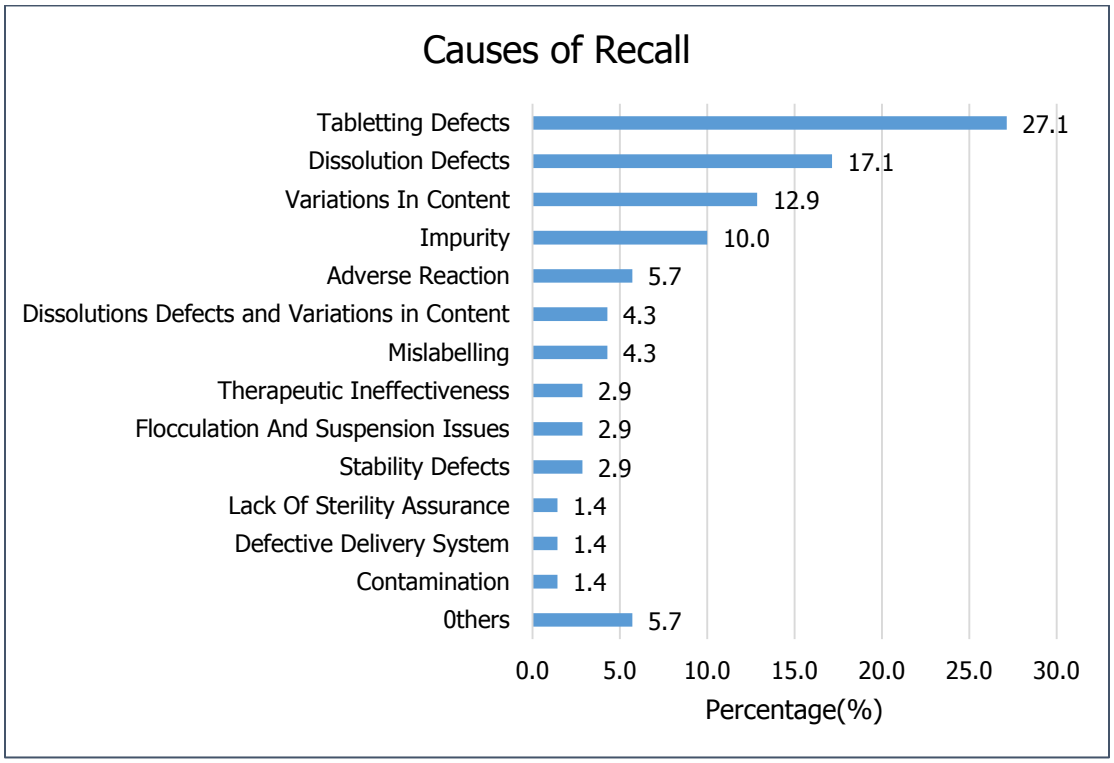
Parameter	Category	Overall (N=75, %)	Sub-Standard (n=70, %)	Falsified (n=5, %)
Legal class	Prescription	57(76.0.)	53(75.7.)	4(80.0.)
	Non-Prescription	18(24.0.)	17(24.3.)	1(20.0.)
Route of administration	Intramuscular	4(5.3.)	3(4.3.)	1(20.0.)
	Intravenous	4(5.3.)	3(4.3.)	1(20.0.)
	Intravenous & intramuscular	3(4.0.)	3(4.3.)	0(0.0.)
	Oral	57(76.0.)	54(77.1.)	3(60.0.)
	Topical	6(8.0.)	6(8.6.)	0(0.0.)
	Varied	1(1.3.)	1(1.4.)	0(0.0.)
Product Origin	Domestic	35(46.7.)	35(50.0.)	0(0.0.)
	Imported	40(53.3.)	35(50.0.)	5(100.0.)
Registration status	Emergency Use	1(1.3.)	0(0.0.)	1(20.0.)
	Not Registered	4(5.3.)	1(1.4.)	3(60.0.)
	Registered	64(85.3.)	63(90.0.)	1(20.0.)
	Unknown	6(8.0.)	6(8.6.)	0(0.0.)

4.4 Causes of Recall

Figure 1 details causes of product recalls of substandard products.Tabletting defects accounted for the highest proportion of product recalls at 27.1%. These defects were tablet erosion or breakage, color changes, molding, mottling, sticking ,picking lamination and capping. These were followed by dissolution defects at 17.1% and variations in content at 12.9%. Mislabelling and adverse reaction accounted for between 4 and 6%. In contrast, studies conducted in UK and Canada noted the main cause of recall of substandard products to be contamination and impurities at 27% (Almuzaini, Sammons, et al., 2013)and 21%(Almuzaini et al., 2014) respectively. Mislabelling accounted for 43.6% of recalls of oral solid dosage forms conducted by FDA(Syarifudin, 2020) and 10% of recalls in Canada(Almuzaini et al., 2014). Flocculation and suspension defects such as caking and creaming accounted for 2.9% of defects.

Delivery defects accounted for 1.4% of recalls. This was lower than the figure reported by a Canadian study at 5%(Almuzaini et al., 2014). Lack of sterility assurance accounted for 1.4% of recalls which was comparable to12 cases noted by FDA in 2016(Kolluru, 2020), 18 instances in UK over a ten year period(Johnston & Holt, 2014) and 35 cases in Canada(Almuzaini et al., 2014). Stability defects accounted for 2.9% of recalls and rapid alerts against 32% in Canada(Almuzaini et al., 2014) and 8% in UK(Johnston & Holt, 2014). Some defects were classified as others and they accounted for 5.7% of recalls. They included incomplete packs, missing patient leaflets and unapproved drugs.

Figure 1:*Causes of recall*



4.5 Recall Parameters

Table 6 reviews various parameters pertaining to the recall of pharmaceutical products between 2016 and 2021. The parameters include mode of recall, type of defect, affected patient population, year of recall and retention status in 2022. Voluntary recalls inititaited by the manufacturer/MAH accounted for 13.3% of recalls while statutory recalls mandated by PPB accounted for 86.7% of recalls. All falsified products underwent statutory recalls while 14.3% of substandard products underwent voluntary recalls and 85.7% underwent statutory recalls. Major defects accounted for 53.3% of recalls followed by critical defects at 26.7% and minor defects at 17.3%. Hence class II recalls were the majority followed by class I and class III. It is important to note that all falsified products were classified as critical defects and instituted class I recalls. There was a yearly increase in number of recalled products between 2016 and 2020 with a drop in 2021. Most substandard products were recalled in 2018 while 40% of falsified products were recalled in 2018 and 2021. Populations most affected by substandard products were adult at 40% while paediatrics accounted for 24.3% and pregnant women at 2.9%. Majority of recalled products were still retained in 2022 at 62% while 38% were not in the retention register. Falsified products had the highest likelihood of not being retained at 80% against 34.8% of substandard products that were not retained.

Table 6:Recall Parameters

Parameter	Category	Overall (N=75, %)	Sub-Standard (n=70, %)	Falsified (n=5, %)
Mode of Recall	Voluntary	10(13.3.)	10(14.3.)	0(0.0.)
	Statutory	65(86.7.)	60(85.7.)	5(100.0.)
Type of defect	Critical	20(26.7.)	15(21.4.)	5(100.0.)
	Major	40(53.3.)	40(57.1.)	0(0.0.)
	Minor	13(17.3.)	13(18.6.)	0(0.0.)
	None	2(2.7.)	2(2.9.)	0(0.0.)
Affected patient populations	Adults	29(38.7.)	28(40.0.)	1(20.0.)
	Adults & Children	25(33.3.)	22(31.4.)	3(60.0.)
	Children	17(22.7.)	17(24.3.)	0(0.0.)
	Female Adults	2(2.7.)	1(1.4.)	1(20.0.)
	Pregnant	2(2.7.)	2(2.9.)	0(0.0.)
Retained 2022	No	27(38.0.)	23(34.8.)	4(80.0.)
	Yes	44(62.0.)	43(65.2.)	1(20.0.)
Year of Recall	2016	3(4.0.)	3(4.3.)	0(0.0.)
	2017	11(14.7.)	11(15.7.)	0(0.0.)
	2018	18(24.0.)	16(22.9.)	2(40.0.)
	2019	15(20.0.)	15(21.4.)	0(0.0.)
	2020	16(21.3.)	15(21.4.)	1(20.0.)
	2021	12(16.0.)	10(14.3.)	2(40.0.)

4.5.1 Number of batches affected

Table 7 shows number of batches affected by recall. In 49.3% of all recalls, only one batch was affected while two batches were affected in 21.3% of recalls. All batches were recalled in 10.7% of all recalls. For sub-standard products one batch was recalled in 50% of the cases while two bactches were recalled in 21.4% of the cases. For falsified products, one batch was recalled in 40% of the cases.

Table 7: Batch Affected of the recalled products

Batch Affected	Overall (N=75, %)	Sub-Standard (n=70, %)	Falsified (n=5, %)
One	37(49.3.)	35(50.0.)	2(40.0.)
Two	16(21.3.)	15(21.4.)	1(20.0.)
Three	3(4.0.)	3(4.3.)	0(0.0.)
Four	3(4.0.)	3(4.3.)	0(0.0.)
Five	1(1.3.)	1(1.4.)	0(0.0.)
Six	1(1.3.)	1(1.4.)	0(0.0.)
Seven	1(1.3.)	1(1.4.)	0(0.0.)
All Batches	8(10.7.)	7(10.0.)	1(20.0.)
Varied	3(4.0.)	2(2.9.)	1(20.0.)
Not Specified	2(2.7.)	2(2.9.)	0(0.0.)

4.6 Comparison of Recall Procedures of PPB, TMDA and NDA

Table 8 shows comparison of recall procedures and requirements of PPB, TMDA and NDA.

Parameters that were assessed included classification, communication content and timelines to regulator and public, health risk assessment and termination of recall. World Health Organization(WHO) classifies TMDA as one of the regulatory agencies at maturity level 3(ML3) meaning 'stable well functioning and intergreted regulatory systems'(WHO,2018). Pharmacy and Poisons Board and National Drug Authority Uganda have not attained this maturity level. A comparative analysis of the recall procedures was carried out between the three bodies as a way of benchmaking Kenya with countries in the region.

PPB and TMDA classify product recalls as class I, II and III with class I involving products with critical defects that could cause life-threatening effects or serious injury. Class II recalls involve products with major defects that pose serious health risks while class III recalls involve products that pose minor health risks. NDA however classifies recalls as class A, B and C with class A involving products with critical defects while class C involves products with minor defects and minor health risks.

Upon detection of defect, PPB requires initial communication to have the following information; description of defect, brand name, INN name, API, product strength, doage form, description of the package, batch number, manufacturing and expiry date,finished product manufacturer's name and address, name and address of MAH holder and contact details, total quantity in circulation, list of customers and areas of distribution of the product. TMDA requires the same information in addition to reasons of recall, nature of defect and date and circumstance of discovery of defect.NDA initial communication requirements are name of product, strength, pack size, nature of defect, urgency of recall, reason for recall, indication of health risk and clear instructions on what to do with the recalled product.
The timelines for initial communication to the regulator depends on the class of recall. For class I, PPB requires communication within 24hours, class II PPB requires communication within 72 hours while class III PPB requires communication within 5 days. TMDA and NDA do not specify timelines for initial communication between the manufacturer/MAH and regulator upon detection of defect.

The depth of recall was similar for all the three regulators. For PPB and TMDA, the depth of recall for class I was consumer/user level, class II was retail level, while class III was wholesale/distributor level. For NDA class A recalls extended to consumer/user level, class B extended to retail level while class C extended to wholesale/distributor level.

There were minimal differences in the mode of communication regulators required manufacturers/MAH to use to communicate to stakeholders. PPB requires class I recalls to be communicated via phone,email,radio,tv followed by letter while class II and III recalls are to be communicated via letters,emails and phone. TMDA requires class I recalls to be communicated via media release, letters to facilities and individuals, class II recalls to be communicated via letters to private and public drug outlets and wholesale and retailers while class III recalls only need to be communicated via telephone calls and letters. NDA requires class A,B and C recalls to be communicated via telephone, fax, email,telegram and public media as well as letters marked as URGENT and MEDICINAL RECALL in bold red.

PPB specifies method of recall for class I as direct uplift of stocks, class II and III via wholesaler. TMDA and NDA do not specify method of recall. PPB and TMDA puts duration of class I recalls at 14 days, class II at 21 days and class III at 28 and 30 days respectively.NDA does not specify duration of class A, B and C recalls.

PPB and NDA require public warnings for certain classes of recalls. PPB requires public warning in form of rapid alerts for class I recalls and none for class II and III. NDA requires press release for class A and B recalls while TMDA guidelines do not specify need for public warnings.

PPB and NDA require conduction of health risk assessment by MAH/Manufacturer. Considerations for health risk assessment for both regulatory bodies are diseases/injuries that have occurred due to product use, health risk to particular population segments, degree of seriousness of health hazard to population at greatest risk, likelihood of risk occurring and immediate and long-term consequences. PPB also requires listing of available alternative products as part of the health risk assessment. TMDA guidelines do not require health risk assessments to be conducted.

PPB and TMDA guidelines require submission of progress reports. PPB requires submission of initial report at 1 week, a followup report at 2 weeks and final report at 4 weeks. TMDA requires weekly progress reports while NDA only requires a final report after 30 days. Contents of the final reports are similar for PPB and TMDA with product particulars,quantity distributed, root cause analysis, corrective and preventive action being key components. PPB further requires detailed timeline of corrective action and steps for disposal. NDA requires product particulars in the final report , details of the defect, actions taken, copies of recall correspondence and steps taken to prevent recurrence of the problem.

Termination of the recall by PPB and NDA occurs after all stocks have been removed from circulation and reconciliation done and appropriate corrective and preventive actions have been instituted. TMDA recall guidelines do not specify termination of recall requirements.

Table 8: Comparison of recall procedures and requirements of PPB, TMDA and NDA

Classification of recalls	**PPB**	**TMDA**	**NDA**
	CLASS I	CLASS I	CLASS A
	CLASS II	CLASS II	CLASS B
	CLASS III	CLASS III	CLASS C
Content of initial communication	Description of quality defect Brand name INN name API Product strength Dosage form Description of package, batch number, manufacturing date, expiry date Finished product manufacturers name and address Name and address of MAH holder and contact details Total quantity of medical product in circulation List of customers Area of distribution of product	Proprietary name/generic name Dosage form Strength Batch number Pack size Name and address of manufacturer Manufacturing date and expiry date Reasons for recall Nature of defectiveness/possible defectiveness Date and circumstances of discovery of defect Total quantity of product to be recalled/has been distributed Area of distribution of the product List of customers to whom the product was distributed	Name of product Strength Pack size Nature of defect Urgency of recall Reason for recall Indication of health risk Specific clear instructions on what to do with the product recalled

Initial report timeline	1 week	Weekly	Not specified
Follow-up report timeline	2 weeks	Weekly	Not specified
Final report timeline	4 weeks	Not specified	30days
Contents of final report	Mechanism of recall notification and communication Extent of recall Distributed quantity of affected batches Root cause analysis/investigative report Corrective and preventive action Timelines for corrective action Steps for disposal of recalled product	Re conciliation between distributed and recovered quantities Investigative report on causes Corrective and Preventive actions taken	Product particulars Nature of defect Action taken Urgency of action taken Reason for action taken Indication for degree of health risk and reported health problems Copies of recall correspondence Steps taken to prevent recurrence of problem
Considerations for assessment of health risk	Diseases /injuries that have occurred due to product use Health risk to particular population segments Degree of seriousness of health hazard to which population at greatest risk is exposed	Not specified	If disease/injury has already occurred Risk to various population groups Seriousness of risk to the population at risk Likelihood of risk occurring Immediate/long-term consequences of exposure to the risk

<table>
<tr><td></td><td>Likelihood of occurrence of risk
Immediate and long-term consequences
Available alternative products</td><td></td><td></td></tr>
<tr><td>Considerations for termination of recall</td><td>Reconciliation report for all stocks under recall
Detailed investigative report leading to recall
Corrective action preventive action plan and report
Destruction certificate issued by PPB</td><td>Not specified</td><td>All stocks removed from circulation
Appropriate corrective measures instituted</td></tr>
<tr><td>Timelines for initial communication to regulato</td><td><table><tr><th>CLASS I</th><th>CLASS II</th><th>CLASS III</th></tr><tr><td>24 HOURS</td><td>72 HOURS</td><td>5 DAYS</td></tr></table></td><td><table><tr><th>CLASS I</th><th>CLASS II</th><th>CLASS III</th></tr><tr><td>NOT SPECIFIED</td><td>NOT SPECIFIED</td><td>NOT SPECIFIED</td></tr></table></td><td><table><tr><th>CLASS A</th><th>CLASS B</th><th>CLASS C</th></tr><tr><td>Not specified</td><td>Not specified</td><td>Not specified</td></tr></table></td></tr>
<tr><td>Depth of recall</td><td><table><tr><td>Consumer level</td><td>Retail level</td><td>Wholesale level</td></tr></table></td><td><table><tr><td>Health facilities Individual</td><td>Public and private drug</td><td>Wholesale retail</td></tr></table></td><td><table><tr><td>Consumer/ user level</td><td>Retail level</td><td>Wholesale/distributor level</td></tr></table></td></tr>
</table>

				suppliers customers	outlet Health facilities					
Mode of communication	Phone Email Radio TV Press announcement, Followed by letter	Letter, email, phone	Letter, Email, phone	Media release, letters to facilities and individual customers	Letters to private and public drug outlets, wholesalers and retailers	Telephone calls Letters	Telephone Fax Email Telegram Public media Letters marked URGENT and MEDICINAL RECALL in bold	Telephone Fax Email Telegram Public media Letters marked URGENT and MEDICINAL RECALL in bold	Telephone Fax Email Telegram Public media Letters marked MEDICINAL RECALL in bold red	

							red	red		
Method of recall	Direct uplift of stocks	Via whole saler	Via whol esale r	NOT SPECIF IED	NOT SPECIFI ED	NOT SPECIF IED	NOT SPECIFI ED	NOT SPECIFI ED	NOT SPECIFI ED	
Duration of recall	14 DAYS	21 DAYS	28DA YS	14 DAYS	21 DAYS	30 DAYS	NOT SPECIFI ED	NOT SPECIFI ED	NOT SPECIFI ED	
Public warning	Rapid alerts	none	none	Not specifie d	Not specified	Not specifie d	Press release	Press release	Not specified	

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

Substandard products accounted for the largest proportion of recalled products. Antiinfectives products had the highest likelihood of being substandard followed by analgesics and antipyretics. This corresponds to the high proportion of infectious diseases in the country. Antimalarials were the most falsified class of drugs while vaccines, emergency contraceptives and monoclonal antibodies have similar chances of being falsified. Dosage forms most likely to be substandard were tablets and injectables and this was the same for falsified products. Majority of substandard and falsified products are imported in line with the high proportion of imported pharmaceuticals versus locally manufactured in Kenya. Majority of substandard and falsified pharmaceutical products are prescription drugs and orally administered.Most substandard drugs in Kenya are due to tableting defects, dissolution defects and variations in content.

Most recalls of substandard products and all recalls of falsified products are initiated by Pharmacy and Poisons Board. Most substandard products had major defects while all falsified products had critical defects.

Substandard products impacted the treatment and management of bacterial infections to a high degree followed by pain and fever. The non-communicable disease most affected by substandard products was hypertension. Falsfied products impacted the treatment and management of malaria, emergency contraception, autoimmune conditions and Covid 19 vaccination.

Only one batch was affected in most of the recalls of substandard products and most of the products were retained in 2022. A majority of falsified products were not retained in 2022.

The product recall procedures followed by PPB are comparable to those of TMDA and NDA. There are similarities in classification of recalls, content of the initial communication to regulators,depth of recall and contents of the final report. There were notable differences in timelines for communication, mode of communication, methods of recalls, public warning mechanisms, progress reports and considerations for termination of recall.

5.2 Recommendations

East African Community Medicine Regulation Harmonization (EAC-MRH) programme should develop guidelines for recall of pharmaceutical products just like they have developed guidelines for medicine registration, pharmacovigilance, GMP among others. These guidelines will harmonize product recall procedures within the East African region.

Pharmacy and Poisons Board should have more stringent post-marketing surveillance programs to enable identification of substandard and falsified programs.

Manufacturers and Importers of tablets, injectables of antiinfectives should have more robust in-process and quality control systems to enable detection of substandard products before releasing to the market.

5.3 Study Limitations

The study relied on information available on product recall and rapid alert database on the Pharmacy and Poisons Board website. There was no access to product recall communication and reports sent by MAH to PPB. It was difficult to accesss recall information like extent and classes of recall and therefore hard to determine if recall procedures were adhered to.

Further research work should focus on whether guidelines on product recall procedures from the three regulators; Pharmacy and Poisons Board, National Drug Authority and Tanzania Medicine and Medical Devices Agency are followed during recall process by market authorization holders. This will ascertain effectiveness of recalls.

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APPENDIX 1

For the study "A retrospective review of rapid alerts and drug recalls conducted by Pharmacy and Poisons Board between 2016 and 2021".

PART 1: PRODUCT DESCRIPTION

1.Serial Number

……

2.Brand Name of Product

…….

3.Active Pharmaceutical Ingredient

…….

4.Legal category of product

……

5. Pharmacological class of API

…….

6. Dosage form

……

7.Indication

……

8. Strength

…….

9.Batch number

…….

10.Distributor/Market Authorization Holder

…….

11.Manufacturer

……..

12. Country of origin

…….

13. Registration Status

……..

PART 2: PRODUCT RECALL INFORMATION

1.Date of initiation of recall

……..

2.Classification of recall

……

3.Depth of recall

……

4. Cause of recall

……

PART 3: NATURE OF DEFECT

1.Type of defect

…….

2. Number of affected batches

……

3.Affected patient populations.

……..

4.Current registration status
