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Medicine recalls in Saudi Arabia: a retrospective review of drug alerts (January 2010–January 2019)

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Abstract

Background: A new incidence of a substandard medicinal product is discovered weekly as stated by the World Health Organization (WHO) around the world. After discovering an incidence of a substandard medicinal product, a drug recall announced to remove the affected medicinal product from the market. Drug recalls in Saudi Arabia (SA) are made by the Saudi Food and Drug Authority (SFDA) or the distributors of the drug when certain criteria are met. A retrospective study of drug recalls in SA was carried out. Data were collected through a website search of the SFDA for drug recalls since January 2010–January 2019.

Results: SFDA recalled 84 substandard medicinal products which related to 47 alert letters and 52 drugs. The number of drug recall reported by SFDA increased six-folds in 2018 than in 2010. The major frequent therapeutic class of drug recall was the antihypertensive drugs followed by the antibiotic drugs (27.7% and 10.8%, respectively). The majority of the recalls were tablets followed by parenteral dosage forms (58% and 25%, respectively). The major reasons for the drug recalls were due to contamination (32.14%) followed by non-compliance with manufacturer's specifications (20.48%). Two manufacturers were accounted for 34.52% of all recalled drugs.

Conclusion: Substandard medicinal products are considered as a serious problem in SA. Contamination was the main cause of drug recalls, which requires root investigation of causes and for strict protective tools to be applied by drug manufacturers.

Keywords: Drug recall, Substandard, Falsified, Saudi FDA, Review

Background

Recently, an increase in records of medicinal recalls (prescribed and/or over the counter drugs) was reported worldwide. When a medicinal product is removed from the market, it is called drug recall. It may be occurred due to contaminations with other ingredients or the presence of adverse effects associated with medicine administration [1–12]. A drug recall is a significant tool that can decrease the morbidity and mortality due to problems in medicinal product manufacturing and distribution. This was evident in 2005 in the outbreak of bloodstream infections (total no. cases, 80 with no

deaths) caused by *P. fluorescens* contaminated heparinized saline intravenous flush syringes [13].

In 2017, the World Health Organization (WHO) agreed on definitions proposed to specify what may be classified as defective medicinal products. WHO indicates that medicinal products are to be denoted as substandard medical products “these are authorized medical products that fail to meet either their quality standards or specifications, or both,” whereas *falsified* medical products are “medicinal products that deliberately/fraudulently misrepresent their identity, composition or source” [14].

Although all these definitions may not incarcerate the wide range of substandard medicinal products including those that were expired, inactive, or improperly stored/

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transported [2]. These arguments in definitions further obscure global management and local regulation of counterfeits and point to the need for an internationally accepted definition of what constitutes a “counterfeit” medicine [2, 15–17].

In Saudi Arabia, the Saudi Food and Drug Authority (SFDA) is the responsible firm of protecting the public health from the danger of medicinal product defects. The drug sector at SFDA is the department responsible for receiving and evaluating complaints about medicinal products. The SFDA was founded under the Council of Ministers in 2003 and launched in 2009, as an independent body corporate. The main objective for the SFDA is to ensure the safety of food and drug for humans and animals, as well as electronic medical instruments [18, 19].

The SFDA defines a drug with a quality defect “any drug with faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorization or product specification file, or any other serious quality problem” [20].

Drug alerts are released by the SFDA to the manufacturer, distributor, healthcare professional, and public, when a defective medicine is reported to threaten patients’ safety. SFDA has several tools for delivering drug alerts to the public and to healthcare providers. All recalls are made available to the public via Saudi Drug Bulletin on SFDA’s website or posted on drug alerts and news page on SFDA website. Since 2017, there is an integrated site for drug recall, which opened an important communication tool with the public, healthcare providers, pharmacies, drug manufacturers, and distributors [19, 21–24]. When drug recalls are announced, public notification occurred to stop using this product and discard any unused amount and additionally, counseling the public what to do and the best alternative choice to maintain patient safety with an efficient safe drug.

In February 2019, SFDA inaugurated the electronic tracking system for pharmaceutical monitoring. Through this system, the authority aims to track pharmaceutical products electronically at all stages of production and consumption ensuring the availability of medicines and their safety, in cooperation with government and private hospitals, clinics and health centers, government and commercial warehouses dedicated to the import and storage of medicines, community pharmacies, and the final consumer of the drug. This monitoring system contributes to the reduction of the circulation of products with quality defect, the provision of medicines, and their location, in addition to achieving drug safety by stopping the circulation of withdrawn or suspended drugs [24].

This is the first review to study the drug recall in SA and initiate a collection of recall medication letters from the SFDA website. The aims of this study were to analyze and characterize drug alerts reported by the

SFDA from Jan 2010 to Jan 2019, excluding herbal and/or cosmetic drugs. It also discusses the number of the drug recall per year, the major therapeutic drug recall class, the most pharmaceutical dosage form recalls, and the reasons for recalls.

Methods

Drug alerts about recalled drugs were collected from the official SFDA website through the section assigned for drug news and alerts, and the section assigned for drug recall which was launched in 2017. The search includes all drug alerts reported between Jan 2010 and Jan 2019 excluding herbal and cosmetics recalls.

The following information was extracted from drug alerts: the name of the medicinal product, the name of the active ingredient(s), dosage form, strength, manufacturer; batch number affected; the date and recall reason; and the subsequent action taken by SFDA.

The drug recalls collected were categorized into one of the following groups: defective medicinal products, falsified medicinal products, or adverse reactions. Defective medicinal products were then reclassified depending on the type of the defect into the following: contamination, non-compliance with manufacturer’s specification, packaging defect, failure to demonstrate bioequivalence, and problems related to the active ingredients. The medicinal products were classified as falsified only when it was stated in the drug alert that the product was considered by the SFDA as falsified medicinal products. The authors were unable to determine if the defect was non-intentional or intentional because no data was available to support their statement.

Moreover, recalled medicinal products were classified by the WHO Anatomical Therapeutic Chemical (ATC) Classification System. In this classification, the first category classifies medicinal products according to the main therapeutic class. This was carried out to underline the most frequent therapeutic groups affected by these recalls [25]. Also, the most common manufacturers of recalled medicinal products were identified.

Results

Recall letters were collected from SFDA website, and from it, the identification of the recall drug, name, and reason for the recall was listed in Table 1. SFDA issued a total of 84 drug recalls during the period of the study January 2010–January 2019, consisting of 47 letters of drug recalls which include 52 drug generic names, and five of these drug recalls (6%) were not registered in SFDA (Table 1). Most of these recalls were reported for one product, although some were reported for up to six drug products.

Unfortunately, during the period of the study, drug recalls increased from nine drug recalls in 2010 (10.71%)

Table 1 Drug recalls data (January 2010 – January 2019)

No. of recall letters	No. of recall drugs	Trade name	Reference of recall (web link)	Reason of recall
1	1	Sibutral®	https://www.sfda.gov.sa/ar/drug/news/pages/699-ar-7-3.aspx	Lead to serious side effects such as cardiovascular disease
	2	Reductil®	https://www.sfda.gov.sa/ar/drug/news/pages/699-ar-7-3.aspx	Lead to serious side effects such as cardiovascular disease
	3	Avandaryl®	https://www.sfda.gov.sa/ar/drug/news/Pages/703-ar-15-3.aspx	Lead to serious side effects such as cardiovascular disease
	4	Avandamet®	https://www.sfda.gov.sa/ar/drug/news/Pages/703-ar-15-3.aspx	Lead to serious side effects such as cardiovascular disease
2	5	Avandia®	https://www.sfda.gov.sa/ar/drug/news/Pages/703-ar-15-3.aspx	Lead to serious side effects such as cardiovascular disease
	6	Serevent®	https://www.sfda.gov.sa/ar/drug/news/Pages/911-ar-6-11.aspx	Increased risk of asthma complications requiring hospitalization in children and adults
	7	Sere vent®	https://www.sfda.gov.sa/ar/drug/news/Pages/911-ar-6-11.aspx	Increased risk of asthma complications requiring hospitalization in children and adults
3	8	Oxis®	https://www.sfda.gov.sa/ar/drug/news/Pages/911-ar-6-11.aspx	Increased risk of asthma complications requiring hospitalization in children and adults
	9	Foradil®	https://www.sfda.gov.sa/ar/drug/news/Pages/911-ar-6-11.aspx	Increased risk of asthma complications requiring hospitalization in children and adults.
4	10	Augmentin®	https://www.sfda.gov.sa/ar/drug/news/Pages/777-31-10.aspx	Free from active substances
5	11	Methylprednisolone acetate®	https://www.sfda.gov.sa/ar/drug/news/Pages/drugnews1-12-1433-2.aspx	contamination with an accidental fungal lead to meningitis
6	12	Yutopar®	https://www.sfda.gov.sa/ar/drug/news/Pages/drugnews19-05-13a1.aspx	Lead to serious side effects such as cardiovascular disease
7	13	Protelos®	https://www.sfda.gov.sa/ar/drug/news/Pages/drognews20-07-2014a1.aspx	Lead to serious side effects such as cardiovascular disease
8	14	Omafen®	https://www.sfda.gov.sa/ar/drug/news/pages/drug03-03-2016a1.aspx	Contamination of small aluminum foil in the strips
9	15	Loric®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib2/LORIC-300MG-TABLET.pdf	Non-compliance with manufacturer's specifications-does not pass the solubility test
10	16	Peptac®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/PEPTAC-150MG-TABLET.pdf	Non-compliance with manufacturer's specifications
11	17	Triaxone®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/(sterile_water).pdf	Similar trade name of another product
12	18	Enoxirt®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Lidocaine-HCL.pdf	An error in packaging stage
13	19	Human albumin ®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Human-Albumin.pdf	Contaminated with ethyleneglycol
	20	Human albumin®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Human-Albumin.pdf	Contaminated with ethyleneglycol
	21	Human albumin®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Human-Albumin.pdf	Contaminated with ethyleneglycol
	22	Human albumin®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Human-Albumin.pdf	Contaminated with ethyleneglycol
14	23	Dextrose®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/dextrose.pdf	Non-compliance with manufacturer's specifications—do pass physical test
15	24	Metronidazole®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/METRONIDAZOLE-INJECTION.pdf	Non-compliance with manufacturer's specifications—do pass physical test
16	25	Peptac®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/peptac.pdf	Non-compliance with manufacturer's specifications

Table 1 Drug recalls data (January 2010 – January 2019) (Continued)

No. of recall letters	No. of recall drugs	Trade name	Reference of recall (web link)	Reason of recall
17	26	Paracetol®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/paracetol.pdf	Non-compliance with manufacturer's specifications—contaminated with black impurities
18	27	Gentacin®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/GENTACIN.pdf	Non-compliance with manufacturer's specifications—broken container upon storages
19	28	Olfen®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/olfen1.pdf	Non-compliance with manufacturer's specifications—do not pass solubility test
22	29	Vaxigrip single dose®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/VAXIGRIP.pdf	Non-compliance with manufacturer's specifications
20	30	Omacid®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/OMACID.pdf	Non-compliance with manufacturer's specifications—do not pass assay test
21	31	Jusprin®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/JUSPRIN-81MG.pdf	Non-compliance with manufacturer's specifications—do not pass dissolution test
23	32	Pedovex®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Clopidogrel.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence test
	33	Cardlet®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Clopidogrel.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence test
	34	Vidapart®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Clopidogrel.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence test
	35	Clopex®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Clopidogrel.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence test
24	36	Clogrel®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/clogrel.pdf	Non-compliance with manufacturer's specifications
25	37	Lynparza®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/LYNPARZA%2050mg.pdf	Non-compliance with manufacturer's specifications—do not pass stability test
26	38	Thiamine®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Thiamine100Mg.pdf	Do not pass the (friability test) test, which may affect the safety, efficacy of the preparation
27	39	Metaphage®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/MetaphageTablet.PDF	Non-compliance with manufacturer's specifications—do not pass bioequivalence test
28	40	Apo-Primidone®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Apo-Primidone250mgTablets.pdf	Non-compliance with manufacturer's specifications- higher lead content in the formulation
29	41	Leukeran®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Leukeran2MG.TAB.pdf	Non-compliance with manufacturer's specifications—wrong write for the Arabic name on the container
30	42	Claradone®	https://www.sfda.gov.sa/ar/drug/circulations/Documents/CLARADONE-OINTMENT.pdf	Non-compliance with manufacturer's specifications
31	43	Valista®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	44	Valista®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	45	Valista®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	46	Co-valista®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	47	Co-valista®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	48	Co-valista®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	49	Co-valista®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -Nitrosodimethylamine (NDMA), carcinogen

Table 1 Drug recalls data (January 2010 – January 2019) (Continued)

No. of recall letters	No. of recall drugs	Trade name	Reference of recall (web link)	Reason of recall
	50	Co-valista®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	51	Diostar®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	52	Diostar®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	53	Diostar plus®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	54	Diostar plus®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
	55	Diostar plus®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/2948_001.pdf	Contamination with <i>N</i> -nitrosodimethylamine (NDMA), carcinogen
32	56	Glymide®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/GlymideDiatab.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay
	57	Diatab®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/GlymideDiatab.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay
33	58	Parazole®	https://www.sfda.gov.sa/ar/drug/circulations/Documents/PARAZOLE100.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay
34	59	Taxotere®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Taxotere20mg.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay higher drug concentration than stated
	60	Enoxirt®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/3361_001.pdf	Change the source of active ingredient without SFDA approval
	61	Narapril®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/3361_001.pdf	Add different source of the active ingredient without SFDA approval
35	62	Narapril®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/3361_001.pdf	Add different source of the active ingredient without SFDA approval
	63	Narapril®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/3361_001.pdf	Add different source of the active ingredient without SFDA approval
	64	Julmentin®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/3361_001.pdf	Non-compliance with manufacturer's specifications—do not change the expiration date from 3 to 2 years
	65	Julmentin®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/3361_001.pdf	Non-compliance with manufacturer's specifications—do not change the expiration date from 3 to 2 years
	66	Angiotec®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Drug-circ97.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay
	67	Angiotec®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Drug-circ97.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay
	68	Angiotec®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Drug-circ97.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay
36	69	Lipomax®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Drug-circ97.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay
	70	Lipomax®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Drug-circ97.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay
	71	Lipomax®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Drug-circ97.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay
	72	Dialon®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Drug-circ97.pdf	Non-compliance with manufacturer's specifications—do not pass bioequivalence assay
37	73	Smooderm®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/SmoodermCream.pdf	Non-compliance with manufacturer's specifications—do not write batch number, manufacturing, and expiration date
38	74	Lobet®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/lobet.pdf	Non-compliance with manufacturer's specifications—presence of impurity in the formulation

Table 1 Drug recalls data (January 2010 – January 2019) (Continued)

No. of recall letters	No. of recall drugs	Trade name	Reference of recall (web link)	Reason of recall
40	75	Ozurdex®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/OZURDEX.pdf	Non-compliance with manufacturer’s specifications—presence of impurity in the formulation
39	76	BCG-medac®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/BCG-medac.pdf	Non-compliance with manufacturer’s specifications—errors in quality control of the catheter tubes
41	77	Azimac®	https://www.sfda.gov.sa/ar/drug/circulations/Documents/AZIMAC_Film_coated.pdf	Non-compliance with manufacturer’s specifications—presence of impurity in the formulation
42	78	Paracetol®	https://www.sfda.gov.sa/ar/drug/circulations/Documents/PARACETOL_10_mg.pdf	Non-compliance with manufacturer’s specifications—presence of impurity in the formulation
43	79	Cefuzime®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Cefuzime.pdf	Non-compliance with manufacturer’s specifications—do not pass dissolution test
44	80	Riazole®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Riazole125mg.pdf	Non-compliance with manufacturer’s specifications
45	81	Losanet®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/LOSANET50mg-100mg.pdf	Contaminated with toxic carcinogenic material <i>N</i> -nitrosodiethylamine (NDEA)
	82	Losanet®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/LOSANET50mg-100mg.pdf	Contaminated with toxic carcinogenic material <i>N</i> -nitrosodiethylamine (NDEA)
46	83	Jusprin®	https://www.sfda.gov.sa/ar/drug/circulations/DocLib1/Jusprin81mg.pdf	Non-compliance with manufacturer’s specifications
47	84	Zordyl®	https://www.sfda.gov.sa/ar/drug/news/Pages/d23-1-2019a1.aspx	Non-compliance with manufacturer’s specifications—do not pass drug stability test

to 52 drug recalls in 2018 (61.9%), increased six-folds by 2018 (Fig. 1).

Considering the therapeutic class of the drugs recalled (Table 2), nineteenth classes accounted for the incidence of the drug recalls. According to classification of medicinal products, the most affected class was the antihypertensive

drugs (23 cases, 27.4% occurrence) followed by the antibiotic drugs (9 cases, 10.71% occurrence). While the lowest incidence of occurrence (1 case, 1.2% occurrence) occurred with the drugs classified under anthelmintic, anticonvulsant, antiosteoporotic, and local anesthetic drugs during the period of the study.

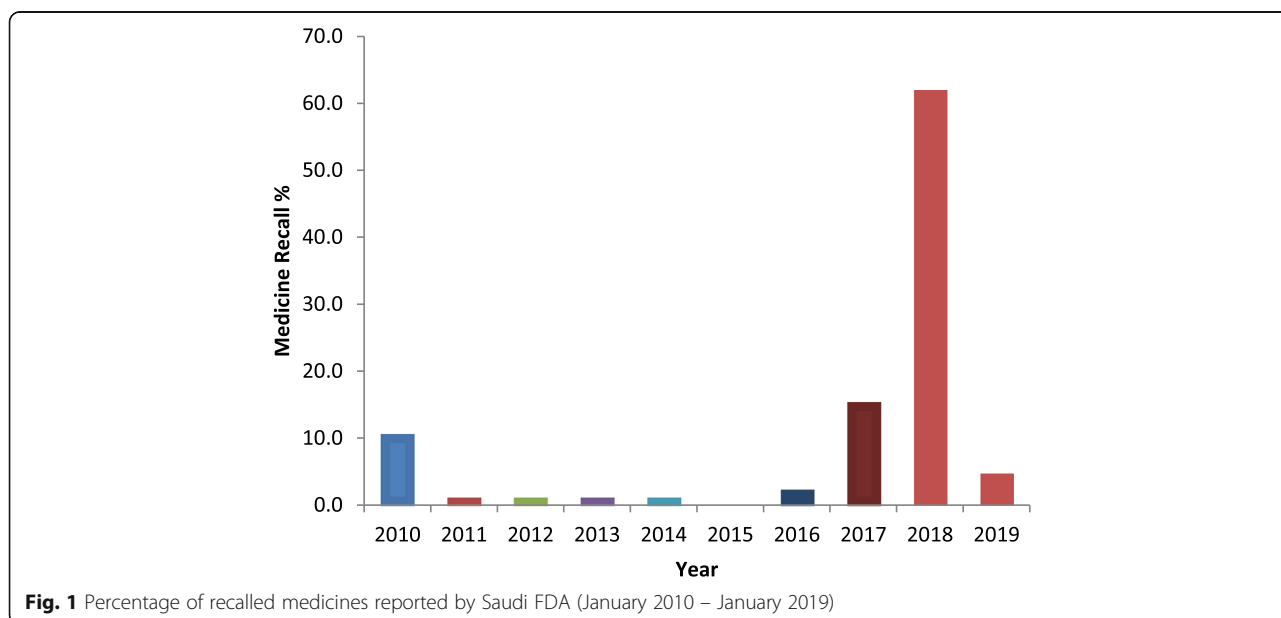


Fig. 1 Percentage of recalled medicines reported by Saudi FDA (January 2010 – January 2019)

Table 2 Therapeutic class for the drug recall data (2010 – January 2019)

No.	No. of occurrence	Class	Occurrence %
1	23	Antihypertensive	27.7
2	9	Antibiotics	10.8
3	7	Antidiabetic	8.4
4	6	Non-steroidal anti-inflammatory-analgesic	7.2
5	5	Antiplatelet	6.1
6	5	Bronchodilator-long acting beta agonists	6.1
7	4	Plasma volume expander	4.8
8	3	Statins—anticholesterol	3.5
9	3	Anticancer	3.5
10	3	Antacid	3.5
11	3	Corticosteroids	3.5
12	3	Vitamin	3.5
13	2	Antimicrobial and antiseptic oral rinse	2.4
14	2	Vaccine	2.4
15	2	Antiobesity	2.4
16	1	Anthelmintic	1.2
17	1	Anticonvulsant	1.2
18	1	Antiosteoporotic	1.2
19	1	Local anesthetic	1.2
total	84	19-therapeutic class	100

Moreover, with respect to the pharmaceutical dosage forms, the majority of the 84 recall pharmaceutical dosage forms were for tablet formulations (58%) followed by parenteral dosage forms (25%) as shown in Fig. 2.

Drug recalls were mainly due to one of the following reasons (Table 3): defective medicinal products 78.06%, adverse reaction 12.05%, or falsified medicinal products 1.2%. The most important cause was a defective medicinal product which was due to one of the following reasons: contamination 32.5%, non-compliance with manufacturer's specification 21.43%, failure to demonstrate bioequivalence 19.28%, packaging defect 9.64%, and problems related to the active ingredients 4.81%.

The most important problem, with defective medicinal products, in which 27 drugs affected out of 84 (32.14 %) was due to contamination represented by *N*-nitrosodimethylamine (NDMA, carcinogen), ethylglycol, non-specified impurities, *N*-nitrosodiethylamine (NDEA, carcinogen), aluminum foil, fungal contamination, black impurities, or high lead content accomplished by 15.66%, 4.82%, 4.82%, 2.41%, 1.2%, 1.2%, 1.2%, and 1.2%, respectively. The second important reason was the non-compliance with manufacturer's specifications (20.48%) followed by failure to demonstrate bioequivalence (19.28%).

The study recognized 33 manufacturers for 84 medicinal products which were recalled by the SFDA. Manufacturers for recalled medicinal products are listed in

Fig. 3. Two manufacturers were found the most commonly denoted for drug recalls. Together, they produced 29 drugs, accounting for 34.52% of all recalled drugs.

The most frequent dosage forms reported for recall were the tablet formulations accounting for 58% of incidents.

Discussion

In general, the SFDA performance has developed since it was started in 2009 [16, 18–21]. The launch and improvement of the SFDA's website as well as the inclusion of an incorporated site for pharmacovigilance created an important communication tool with health care professionals and the public. The pharmacovigilance electronic system is an online automatic reporting service for adverse reactions and defective medicinal products to enhance the reporting for health care professionals and the public [16, 18–21]. It is now possible to report medicinal products that could be defective online or over the phone if the healthcare professional or public considers that the defect in a medicinal product may produce serious adverse reactions to public health [16, 18–21].

The SFDA has launched guidelines to healthcare professionals describing methods for reporting medicinal products that could be defective. These guidelines illustrate the part that healthcare professionals perform in the initial evaluation of the medicinal products that

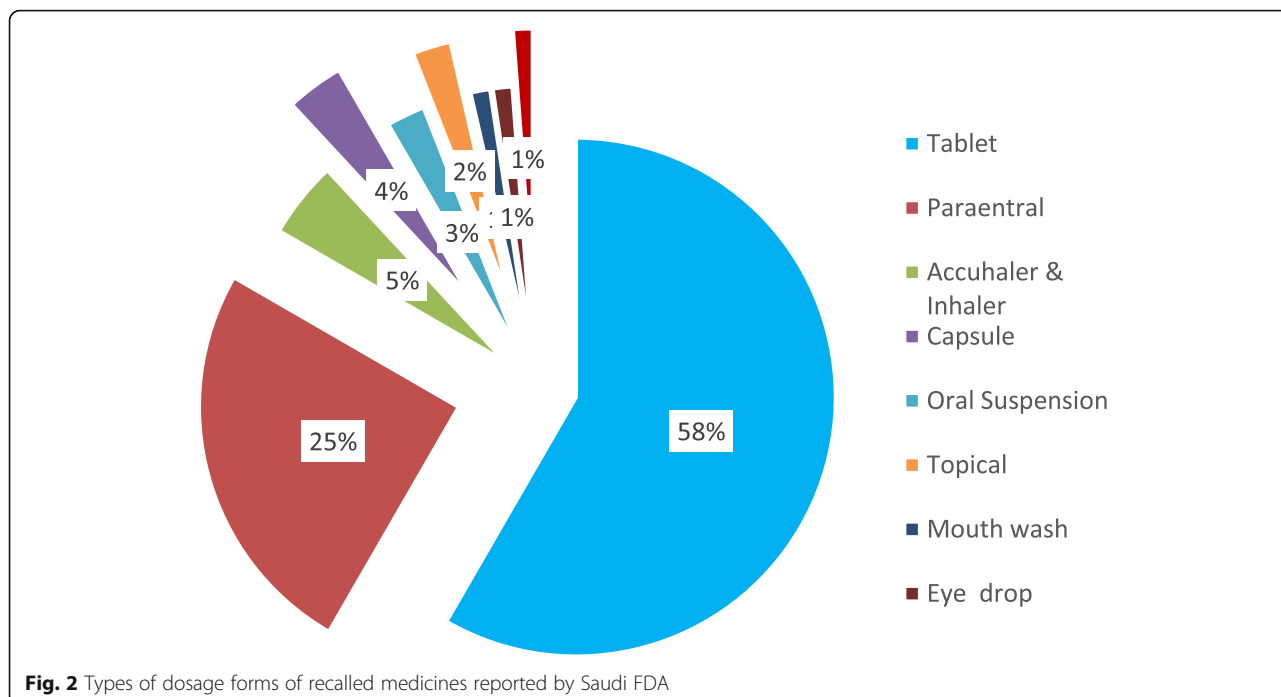


Fig. 2 Types of dosage forms of recalled medicines reported by Saudi FDA

could be defective. They also demonstrate consequent evaluations that can be performed by the SFDA before it reports a drug alert. Moreover, the ease of access through the SFDA’s website to these guidelines may enhance healthcare professionals’ understanding about how to manage the medicinal products that could be defective [24].

This is the first review that studies the problem of medicinal product recalls in Saudi Arabia by assessing the drug alerts posted on SFDA website.

There were few publications about drug recalled in different countries and categories, such as the retrospective analysis by Freeman et al. [10] that results in a total of 21,120 products which were recalled during the 30-month study period and recalls of cosmetic and personal care products from 2002 to 2016 [10]. Almuzaini et al. [26] demonstrate a total of 653 defective medicines in Canada during their study from 2005 to 2013.

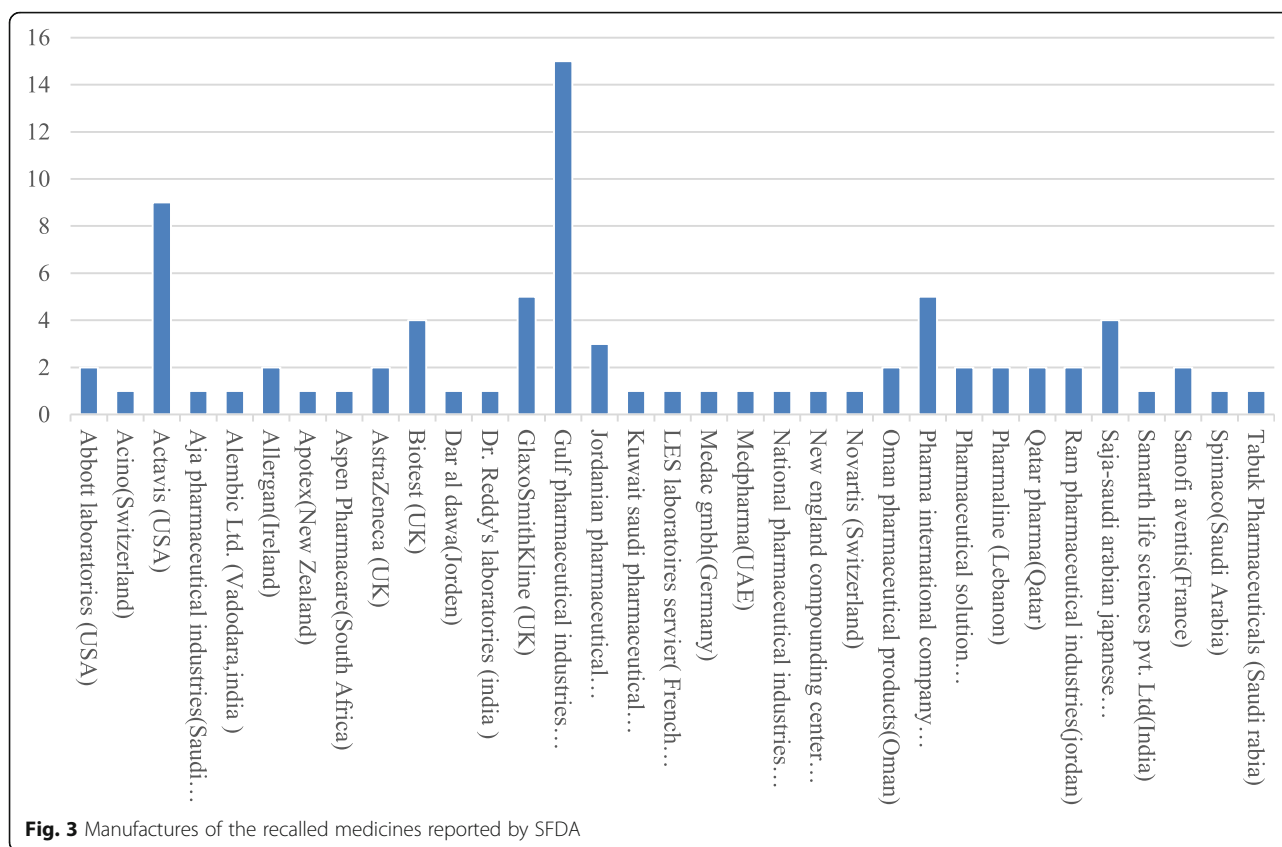
Between 2002 and 2016, 806 million medical devices were recalled [16].

Our investigations of medicinal product recalls from Jan 2010 to Jan 2019 have shown that the rate of recalled medicinal products increased; however, there is inadequate information to prove this. Also, the main cause behind the increased rate of recalled medicinal products is unknown. It could be due to new regulations and guidelines by the SFDA that have been contributed to easier detection of medicinal product defects, or it could be due to an increased rate of manufacture of defective medicinal products.

This is the first review that discusses the number of substandard and falsified medicines in Saudi Arabia by evaluating the reasons for drug recalls, trade names, and therapeutic classes posted on Saudi FDA website which are not arranged; they posted according to the SFDA recall letter days.

Table 3 Reasons for the drug recall data (2010 – January 2019)

	Reason for recall	Number of medicinal product	Percent %
1	Quality defects	73	78.06
	1. Contamination	27	32.53
	2. Non-compliance with manufacturer's specifications	18	21.43
	3. Failure to demonstrate bioequivalence	16	19.28
	4. Problems related to packaging	8	9.64
	5. Problems related to the active ingredients	4	4.81
2	Adverse reaction	10	12.05
3	Falsified medicine	1	1.20



During the period of the study (2009–2019), the study over ten consecutive years has shown the recall for substandard medicines is an increasing trend, and the drug recalls increased six-folds by 2018. The most affected therapeutic class was the antihypertensive and antibiotic drugs (27.4% and 10.71%, respectively).

Not surprisingly, over half numbers of recalls (58%) for tablet formulations (58%) followed by parenteral dosage forms (25%). Similarly, Almuzaini et al. found that the most frequent type of formulations reported to be defective were tablets [26, 27]. The sterility precaution during the manufacturing process of tablet formulations is less than that required during parenteral formulations. However, serious adverse reactions can result as reported in January 2012 in Pakistan. Isosorbide mononitrate tablets were contaminated with large doses of pyrimethamine (an antimalarial drug) which led to the death of 151 patients and 664 cases of pyrimethamine toxicity [11].

Medicinal product contamination is considered as a major problem. The Food and Drug Administration (FDA) recalled all unused corticosteroid medication vials for injection in October 2012. The reason was vial contamination with various bacterial/fungal strains. The use of contaminated vials leads to 64 deaths and 751 incidents [26]. Contamination was the first significant reason for drug recalls followed by non-compliance with

manufacturer's specification, then failure to demonstrate bioequivalence (32.5, 21.43, 19.28%), respectively. Similarly, Hall et al. carried out a retrospective study evaluating the relationship between recall companies and medicines recalled by FDA from June 20, 2012, to December 31, 2014. They found that the most common reasons for drug recall were contamination (50.1%) [10]. Also, Almuzaini et al. evaluated drug alerts in the UK (2001–2011), they found that contaminations are the most common reasons for drug recall (27%) [25].

Thirty-three manufacturers were recorded for the 84 medicinal products which were recalled by the SFDA. Two manufacturers were found the most commonly denoted for drug recalls 34.52%.

Conclusion

Saudi Arabia is one of the countries which is affected by the problem of substandard medicinal products. An investigation of SFDA drug recalls (Jan 2010 and Jan 2019) revealed that contaminations of the drug products were the most cause of drug recalls, and tablet formulations considered the most affecting dosage forms. The most affected therapeutic class was the antihypertensive drugs followed by the antibiotics drugs. Both healthcare professionals and consumers should be stayed informed actively about drug safety and drug recalls.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s43094-020-00112-3>.

Additional file 1. Tha Excell collection data from January 2010 – January 2019 taken from the SFDA website.

Abbreviations

ATC: Anatomical Therapeutic Chemical Classification System; NDMA: *N*-Nitrosodimethylamine; NDEA: Ethylglycol, non-specified impurities; SA: Saudi Arabia; SFDA: Saudi Food and Drug Administration

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Authors’ contributions

BA conceptualized the whole idea, worked as the project administration, supervised the whole other members, analyzed the data, wrote the original draft, and reviewed and edited the manuscript. IA contributed to the analysis of the data, writing of the original draft, and review and editing of the manuscript. AA, SA, and RA are bachelor students, who collected the data from the web site, arranged it in Excel sheet, and double-checked the data. All authors have read and approved the manuscript and ensure that this is the case.

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The authors declare that they have no competing interests.

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