Evaluation of Class I Solid Oral Drug recalls: Can such Recalls be Preventable?

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Abstract

Marketing of defective or adulterated drugs may cause serious public health hazards. To protect the public from hazardous products, the FDA acts by recalling such products. The products which may cause the most serious health hazards, including death, are recalled under the Class I category. The objective of this research study is to analyze the retrospective data available on Class I solid oral drug recalls from June 8, 2012, to December 31, 2019, to identify the most common reasons causing the majority of recalls and to determine if they were preventable. The data on the Class I drug recalls for the past 8 years was downloaded from the FDA enforcement reports website and converted into a research database. The analysis of the final research database shows that a total of 1160 Class I drug recalls occurred during the study period. Of these, 314 (27.1%) were solid oral drug recalls. Amongst the 314 solid oral drug recalls, 274 (87.3%) were recognized as dietary supplements and 40 (12.7 %) were pharmaceutical products. On average, the recalls of dietary supplements were approximately 6.9 times higher than that of pharmaceutical products. The higher number of dietary supplements recalls might account for a lack of FDA review of the safety and efficacy of dietary supplements prior to marketing. Moreover, the most common reason, causing 96.4 % of total dietary supplement recalls, was identified to be adulteration of dietary supplements with active pharmaceutical substances and marketing them without NDA/ANDA approval. These results show that implementing stringent regulation to oversee the manufacturing and compounding of dietary supplements comparable to that of pharmaceutical products can help prevent adulteration and thus reduce Class I solid oral dietary supplements recalls. On the other hand, the major reason for pharmaceutical product recalls was identified as labelling issues, which caused 43.6 % of total recalls. Following current Good Manufacturing Practices (cGMP)

guidelines on labeling control and implementing reliable label proofreading methods will help prevent labelling errors and thus reduce the Class I solid oral pharmaceutical product recalls.

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Introduction and Background

A recall is an action taken by the Food and Drug Administration (FDA) to remove a marketed product that is in violation of FDA regulations ("Recalls Background and Definitions," 2014). The FDA recalls drugs under three different classifications (Class I, Class II, Class III) depending on the degree of risk caused by the usage of the product. See Table 1.

Table 1: Classifications of Drug Recalls	
Class I recalls	Products which cause the most serious health hazards, including death
Class II recalls	Products which cause probable health hazards with less possibility of leading to adverse health conditions
Class III recalls	Products which are not likely to cause any hazardous health condition

Definitions from "Recalls Background and Definitions," 2014

After categorizing the product recalls under any of the above three classifications, the FDA includes them in a publicly available database called Enforcement Reports ("Recalls Background and Definitions," 2014).

Enforcement Report: The Enforcement Report includes all the recalls of marketed products monitored by FDA that meet the definition of the recall ("Enforcement Report Information and Definitions," 2019).

Recall Initiation Date: The date that the firm initially starts informing the public or their agents of the recall ("Enforcement Report Information and Definitions," 2019).

Recall Termination: When the FDA confirms that all rational efforts have been made to expel or correct the violative item, as per recall policy, and legitimate disposition or rectification has

been made according to the level of hazard. (“Enforcement Report Information and Definitions,” 2019).

The FDA recalls marketed products to safeguard people from damaged or conceivably harmful products, thus reducing the morbidity and mortality triggered by defective products (Nagaich & Sadhna, 2015). For instance, in 2017 multiple lots of "Xanthium & siler combo (Bi Yan Pain) weight loss dietary supplement" were recalled by the FDA due to the presence of undeclared amounts of Ma huang, which is a potent alkaloid that can cause serious cardiovascular risks and death in patients. To protect public health the FDA recalled these dietary supplements (“Kingsway Trading Inc. Recalls ‘Xanthium & Siler Combo,” 2017). Furthermore, product recalls have substantial financial impacts on the pharmaceutical industry (Bala et al., 2017). For example, in 2012, the recall of 1 million packages of Lo-ovral tablets (norgestrel–ethinyl estradiol) and its generics due to a packaging error which resulted in a $60 million loss to the company (Carone, 2015).

Furthermore, a study published by Hall et al. (2016), states that from June 8, 2012 to December 31,2019 there were a total of 21,120 drug product (including prescription and over the counter drugs and dietary supplements) recalls that occurred under Class I , II and III recall classifications. The major reasons for these recalls were identified as labelling issues, safety issues, incorrect potency, contamination, and defects in the products. Additionally, a study published by Wang et al. (2012), shows that about 40 % of all Class I recalls are due to adulteration of drug products. Moreover, according to Harel et al. (2013), more than half of the total Class I recalls that occurred from 2004 to 2012 in the USA were that of dietary supplements.

Dietary supplements are regulated as food by the FDA and are regulated under the Dietary Supplements Health Education Act (DSHEA) that was passed in October 1994. Current regulation doesn't require manufacturers to submit proof of safety or efficacy prior to marketing (Denham, 2011). However, the FDA monitors dietary supplements for safety after the product has entered the marketplace. Moreover, the FDA does require the makers of dietary products to strictly follow current good manufacturing practices to guarantee quality through the manufacturing, compounding and packaging processes. Despite these regulations, dietary supplements have been found to be adulterated with prohibited pharmaceutical products, exposure to which could cause hazardous adverse health effects, including death (Harel et al., 2013)

The FDA has taken some actions to control adulterated supplements. The actions include the formation of global enforcement groups to target the manufacturers of the dietary supplements and conducting campaigns to enhance public and health workers knowledge about adulteration happening among dietary supplements (Cohen et al., 2012). Despite these measures and the Dietary Supplement Health and Education Act (DSHEA), marketing the contaminated dietary products with active pharmaceutical ingredients has continued, leading to potential adverse effects on the purchasers and causing increased numbers of recalls (Nagaich & Sadhna, 2015).

The huge number of recalls happening recently raises concerns about the possible clinical impacts of substandard and otherwise defective drug products that are available in the marketplace. Lack of stringent supervision allowed for the marketing of many supplement products adulterated with unapproved pharmaceutical compounds, causing potential harm to consumers (Cohen et al., 2012). Therefore, the goal of this project is to analyze the reasons,

recurrences, and qualities of Class I solid oral drug recalls and assess if such recalls might be preventable.

Purpose and Objective

Marketed drugs, dietary supplements, and medical devices with a reasonable probability of causing potential health hazards to the consumers are subject to Class I recall by the FDA. In this paper, the Class I recalls of solid oral dosage forms under the "Drugs" category from the FDA Enforcement reports are analyzed to assess the most common cause of recalls and if such recalls are preventable. Currently, little to no data are available about the extent to which Class I recalls of solid oral dosage forms are occurring in the USA. Therefore, the objective of this paper is to describe the frequency, characteristics, and reasons for Class I recalls of solid oral dosage forms of dietary supplements in comparison with pharmaceutical products.

Objectives

The study objective is to evaluate and categorize the reasons for the recalls of Class I solid oral drugs from June 8, 2012 to December 31, 2019. This study will quantitatively and qualitatively compare Class I solid oral pharmaceutical product recalls with that of dietary supplements. Furthermore, this study will quantify and categorize the most common reasons causing the majority of Class I pharmaceutical product and dietary supplements recalls and assess if the most common reason for recalls might be avoidable so that these recalls may be prevented.

Methodology

The Class I drug recall enforcement reports from June 8, 2012 through December 31, 2019 was obtained from the FDA website. The June 8th, 2012 was selected as the starting date for analysis because recall enforcement reports were only available as downloadable files since then .The search term "enforcement reports" was used to search the FDA website which resulted in an "Enforcement reports | FDA" hyperlink (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/enforcement-reports). The webpage "Enforcement reports | FDA" has two search options. They are "view weekly Enforcement reports" and "search enforcement reports." The "search enforcement reports" was selected, which led into a new webpage with advanced search options. Advanced search options enable users to apply filters to the data fields like product type as "Drugs," recall class as "Class I," classified from dates as June 8, 2012, classified to date as December 31, 2019 and searched, which resulted in 1160 recalls. The search results were downloaded as .CSV files using the export icon located above search results. ("Enforcement Report," n.d.).

The downloaded .CSV file was exported into Excel and used to create a research database with only variables that were necessary for this research project. The research database was constructed with variables, such as recall number (unique identifier), classification, product type, reason for recall, product description, recall initiation date, center classification date, and termination date. The research database had the list of all the Class I recalls of the over the counter and prescription drugs as well as other products included under the Drugs category, such as toothpastes, antiperspirants, dandruff shampoos and sunscreens, which was saved and analyzed for year by year analysis of all Class I recalls. The year information in the "recall

initiation date" column was used to calculate the number of recalls per year. The database copy was further reconstructed to fit the actual criteria of research.

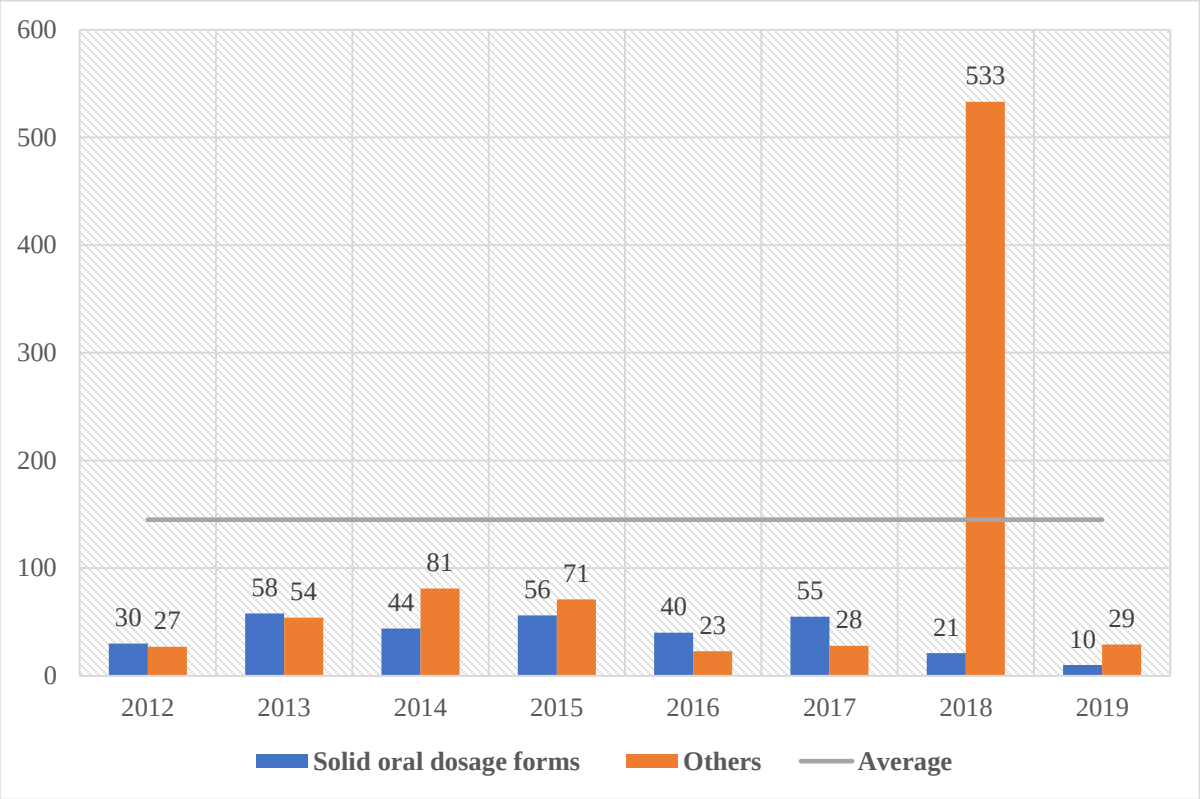
The "product description" column information was used to differentiate solid oral dosage forms and non-solid oral dosage forms. Identified non-solid oral dosage forms were removed from the database copy. Product names in the "product description" column were searched using www.google.com to find the product type and were classified into pharmaceutical products and dietary supplements in the product type column. The "reason for recall" column contains both main reasons and sub-reasons of recalls which were separated by a delimiter. The "reason for recall" column was divided into two columns named "reason for recall" and "sub-reason for recall" to facilitate the analysis. This database copy was used for the remaining research analysis. Excel was used to analyze the data and to generate reports, charts and figures. All the searches were made before March 1, 2020.

Results

The FDA recalls enforcement report indicates a total of 11,305 Class I, Class II, and Class III recalls under the "Drugs" category from June 8, 2012 to December 31, 2019. As per the enforcement report, the "Drugs" category includes prescription and nonprescription drugs, dietary supplements and other products such as antiperspirants, dandruff shampoos, toothpastes, and sunscreens. Of the 11,305 total drug recalls that occurred in the past eight years, there were 1160 recalls under the Class I category. Among the 1160 total Class I drug recalls, 314 (27.1 %) were solid oral dosage forms (tablets and capsules), which includes prescription and over the counter pharmaceutical drugs and dietary supplements. The remaining 846 (72.9%) of 1160 were classified as others, that includes over the counter and prescription pharmaceutical drugs and dietary supplements in formulations other than tablets or capsule forms, and other products such as antiperspirants, dandruff shampoos, toothpastes and sunscreens.

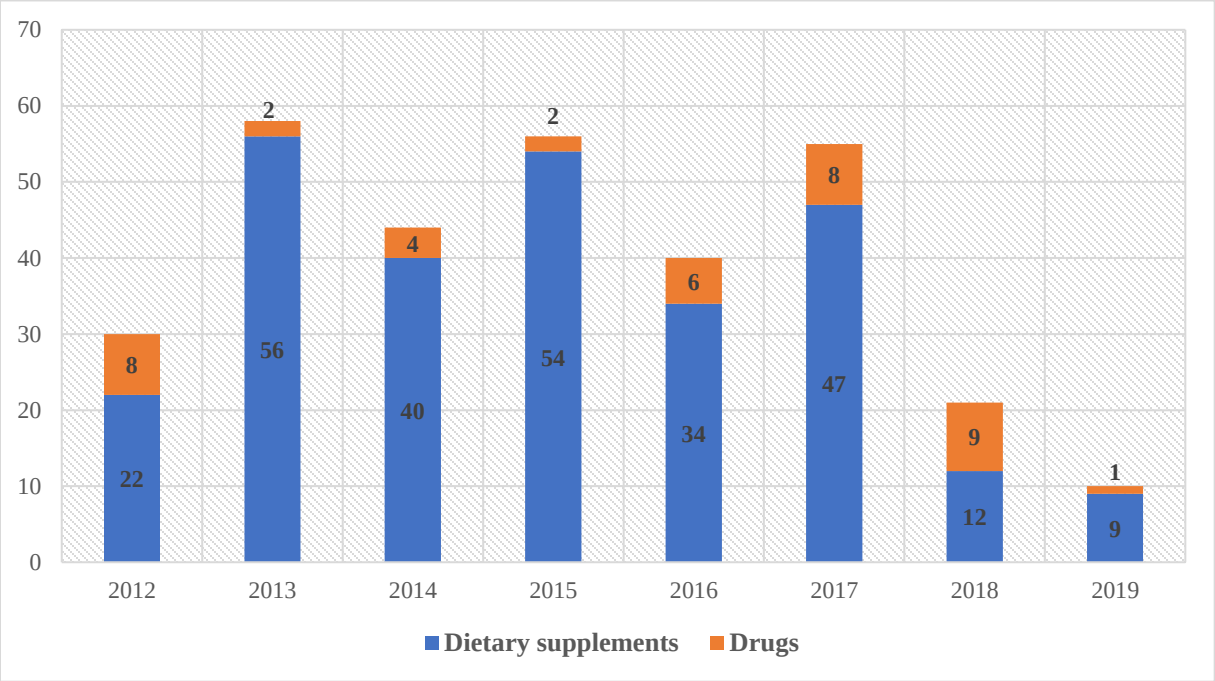
The total 1160 Class I recalls, when viewed by year, indicates an average of 145 recalls noted per year with a standard deviation (*SD*) of 168.5, a high of 554 recalls noted in 2018, and a low of 39 recalls noted in 2019. See Figure 1.

Figure 1: Total Class I Drug Recalls by Year



The total Class I solid oral dosage recalls were further separated into dietary supplements and pharmaceutical products. Of the 314 solid oral dosage forms recalled, 274 (87.3%) were of dietary supplements and 40 (12.7%) were of pharmaceutical products. Further analysis of dietary supplement indicates an average of 34.3 dietary supplement recalls per year with a SD of 18.3 and a high of 56 recalls in 2013 with a low of 9 recalls in 2019. Analysis of pharmaceutical products indicates an average of 5 recalls per year with a SD of 3.2 and a high of 9 recalls in 2018 with a low of 1 recall in 2019. See Figure 2.

Figure 2: Solid Oral Dosage Form Class I Drug Recalls by Year



Reasons for recalls of Dietary supplements:

The reasons for the recalls of 274 Class I solid oral dietary supplements were examined. It was found that 264 (96.4%) dietary supplements were recalled due to marketing without an approved NDA/ANDA, 5 (1.8%) dietary supplements were recalled due to microbial contamination of non-sterile products, 3 (1.1 %) dietary supplements were recalled due to presence of superpotent drug, and 2 (0.7 %) dietary supplements were recalled due to labeling issues.

The main reason for the recall of Class I solid oral dosage form dietary supplements was noted to be “marketed without an approved NDA/ANDA”, which accounts for 264 (96.4%) of all dietary supplements recalls. Further, the major reason for dietary supplements recalls was classified into sub-reasons. See Table 2.

Table 2: Further Classifications of Marketed Without an Approved NDA/ANDA

Classification of Marketed Without an Approved NDA/ANDA	**Count (%)**
Presence of Undeclared Phosphodiesterase (PDE 5) Inhibitors in Dietary Supplements	98 (37.1)
Presence of Undeclared Sibutramine or its Analogs	43 (16.3)
Presence of Undeclared Sibutramine or its Analogs and Phenolphthalein	33 (12.5)
Other *	24 (9.1)
Presence of Undeclared Steroids or Steroid-like Substances or Anabolic Steroids	16 (6.1)
Presence of Undeclared Phosphodiesterase (PDE 5) Inhibitors and Flibanserin in Dietary Supplements	11 (4.2)
Presence of Salicylic Acid	11 (4.2)
Presence of Undeclared Phenolphthalein	5 (1.9)
Presence of Undeclared Active Pharmaceutical Ingredients	4 (1.5)
Labeling Claims Shows Presence of Unapproved Drugs	4 (1.5)
Presence of Undeclared Phenolphthalein and Fluoxetine (Antidepressant)	3 (1.1)
Presence of Undeclared NSAIDs	3 (1.1)
Presence of Undeclared Sibutramine, Phenolphthalein and NSAIDs	2 (0.8)
Contains Methylstenbolone or Dymethazine	2 (0.8)
Presence of Undeclared Sibutramine and NSAIDs	1 (0.4)
Presence of Undeclared NSAIDs, Dexamethasone, and Methocarbamol.	1 (0.4)
Presence of Undeclared NSAIDS and Methocarbamol	1 (0.4)
Presence of Undeclared Diuretic called Triamterene	1 (0.4)
Presence of Undeclared Fluoxetine	1 (0.4)

**no specific sub reason available on FDA recalls enforcement report*

Moreover, of the 264 dietary supplements recalled due to being marketed without an approved NDA/ ANDA reason, 109 (41.3 %) were found to be marketed as natural sexual

enhancement agents, 100 (37.9 %) were found to be marketed as natural weight loss agents, 18 (6.8 %) were found to be marketed as muscle mass building agents, 5 (1.89 %) were found to be marked as natural muscle pain relievers, and 32 (12.12 %) were marked for other non-specified reasons.

Reasons for recalls of Pharmaceutical Products

A total of forty pharmaceutical products were recalled under the Class I category from June 8, 2012 to December 31, 2019, of which 17 (42.5%) pharmaceutical products were recalled due to labelling issues. See Table 3.

Table 3: Reasons for Class I pharmaceutical Product Recalls	
Reason for Recall	**Pharmaceutical products (%)**
Labelling issues	17 (42.5)
Failed Content Uniformity Specifications	8 (20)
Superpotent Drug	5 (12.5)
Presence of Foreign Tablets/Capsules	3 (7.5)
Failed Dissolution Specifications	2 (5)
Marketed Without an Approved NDA/ANDA	1 (2.5)
Failed Tablet/Capsule Specifications	1 (2.5)
Defective Container	1 (2.5)
Product mix-up	1 (2.5)
Contraceptive Tablets Out of Sequence	1 (2.5)

Further analysis of labelling issues, which contributed the most pharmaceutical product recalls, indicates 13 (76.5 %) recalls were due to label mix up, 3 (17.6 %) recalls were due to labeling error on declared strength of the product, and 1 (5.9 %) recall was due to a labeling error.

Other reasons, such as microbial contamination of non-sterile products attributed to 5 (1.6%) of dietary supplement recalls, where as other reasons like presence of foreign tablets/capsules, failed dissolution specifications, failed content uniformity specifications, failed content uniformity specifications, defective container, product mix-up, and contraceptive tablets out of sequence attributed to 16 (41.0%) of total pharmaceutical products recalls.

Discussion

Recalling marked products is the method employed by the FDA to safeguard people from damaged or conceivably harmful products. Drug recalls might affect the health of patients who were using these drugs on a daily basis. As well, product manufacturing companies and governments will suffer from huge losses of resources. To prevent such adverse health effects and economic losses, there is a need to understand the reasons for recalls and find out methods to prevent them.

The year by year analysis of total Class I drug recalls from June 8, 2012 to December 31, 2019, shows an upward trend until 2018, with the highest number of recalls in 2018 and a sharp decline in 2019. The highest number of recalls in 2018 accounts to the 465 homeopathic products (liquid orals, nasal gels, oral sprays, lotions and creams) recalls initiated by FDA on 7/20/2018 due to concerns of microbial contamination. The 465 products were manufactured by a single company called King Bio which has not followed quality control measures in regards to water purity during the manufacturing process ("FDA alerts consumers, pet owners not to use products manufactured by King Bio," 2018). In addition, an average of 145 drug recalls per year was noted to have occurred under Class I category during the study period. Further analysis of only the Class I solid oral drug recalls showed an upward trend until 2017, and a decline since then. The Class I solid oral drug recalls were further classified into dietary supplement recalls and pharmaceutical products recalls. The analysis of dietary supplement recalls showed an upward trend until 2017 and then there was a sharp decline in the years 2018 and 2019. The year wise analysis of pharmaceutical product recalls showed variable trends until 2018 and a sudden drop in 2019.

Further quantitative data analysis showed that, on an average Class I dietary supplement recalls were 6.9 times higher than that of pharmaceutical products. The high number of dietary supplement recalls might account to lack of FDA supervision on safety and efficacy of dietary supplements prior to marketing.

Additionally, analyzing the reasons for dietary supplement recalls showed that 96.4% of recalls were due to adulteration of dietary supplements with active pharmaceutical products and marketing them without NDA/ANDA approval. However, for the same reason there were only 2.6 % of pharmaceutical product recalls.

Further analysis of dietary supplement recalls caused under marketing without NDA/ANDA approval category disclosed that the presence of undeclared phosphodiesterase (PDE 5) inhibitors caused 41.2 % of dietary supplement recalls, the presence of undeclared sibutramine and its analogs caused 16.3 % of dietary supplement recalls, the presence of undeclared carcinogenic chemicals like phenolphthalein along with other medications like sibutramine and/or NSAIDS, fluoxetine caused 14.8 %, and the presence of phenolphthalein alone caused 1.9 % of dietary supplement recalls. Furthermore, the presence of other active pharmaceutical substances like steroids, NSAIDS, dexamethasone, methocarbamol, triamterene, or fluoxetine caused 14.4 % of all dietary supplement recalls, the presence of unapproved drugs as per labeling claims caused 1.5 % of dietary supplement recalls, and non-specified reasons caused 9.1% of dietary supplement recalls.

Presence of undeclared active pharmaceutical substance like PDE 5 inhibitors, previously withdrawn products like sibutramine and carcinogenic chemicals like phenolphthalein in the

dietary supplements causes serious health hazards like potentially unsafe drop in blood pressure, serious cardiovascular side effects, and cancers in the patients innocently using them.

The lack of FDA oversight prior to marketing dietary supplements might have led to tainting of dietary supplements with active pharmaceutical ingredients jeopardizing consumers' health (Marcus, 2012). Implementing stringent regulation to oversee the manufacturing and compounding of dietary supplements comparable to that of pharmaceutical products can help reduce marketing of such adulterated and hazardous products and thus preventing recalls (Zakaryan & Martin, 2012). In addition, Zakaryan & Martin (2012) mentioned, enforcing mandatory FDA premarket approval for all the dietary supplements under nontraditional herbal products category can potentially prevent adulterated and defective dietary supplements from entering the market thus protecting public health and preventing recalls. Furthermore, as per current regulations, to recalls a dietary supplement from market, FDA must prove that the dietary supplement, is adulterated, mislabeled or hazardous to consumers (Denham, 2011). Such "reactive approach" regulations should be reformed so that FDA can act quickly to remove defective products from market before substantial number of consumers are adversely affected (Zakaryan & Martin, 2012).

Other reasons such as microbial contamination of non-sterile products have caused 1.8 % recalls, and presence of super potent drugs has caused 1.1% of dietary supplement recalls. The contamination of dietary substances with microbial products causes unwarranted infections in the consumers and presence of super potent drugs can cause adverse effects leading to serious complications. Conducting frequent inspections of dietary supplement manufacturing firms by regulatory bodies to monitor cGMP practices can help minimize the marketing of contaminated dietary supplements, thus minimizing recalls and protecting public health.

On the other hand, analyzing reasons for pharmaceutical product recalls showed that 43.6% of total recalls were caused due to labelling issues whereas only 0.7% of dietary supplements were recalled due to the labelling issues. Further analysis of pharmaceutical product recalls caused under labelling issues category revealed that, revealed that about 76.5% of recalls were due to label mix up reasons, 17.6% of recalls were due to labeling error on declared strength of the product and 5.9% recalls were due to labeling error reasons.

Even with stringent regulation of pharmaceutical product labelling, it is shocking to know that nearly 44% of all Class I solid oral pharmaceutical product recalls occurred due to labelling issues. Labeling errors and pharmaceutical product recalls can be minimized by implementing newer technical tools for reliable quality control methods that check and proofread product labels. Errors and recalls can also be minimized by stringently following cGMP guidelines on packaging and labeling control (21 CFR 211). Newer proofreading technical tools, like "Artwork Proofing Tools," are available which can be used to reduce labeling errors.

Additionally, other reasons like presence of foreign tablets/capsules, failed dissolution specifications, failed content uniformity specifications, defective container, product mix-up, and contraceptive tablets out of sequence have caused 41% of pharmaceutical products recalls, and the presence of superpotent drugs has caused 12.5% of pharmaceutical products recalls. The above reasons can be minimized by stringently following cGMP regulations by the pharmaceutical manufacturing firms and by frequent inspections of the firms by the FDA.

Limitations of the study

The current study has only focused on Class I recalls of solid oral drugs that might have caused to underestimate the magnitude of recalls.

Conclusion

Analysis of Class I solid oral drug recalls for the past eight years showed that on an average the recalls of dietary supplements were approximately 6.9 times higher than that of pharmaceutical products. Furthermore, the most common recall reason for dietary supplements was identified as adulteration of dietary supplements with active pharmaceutical substances and marketing them without NAD/ANDA approval. Regardless of presence of the DESHA act, the increase in the number of dietary supplements recalls in comparison with pharmaceutical products indicates a lack of FDA supervision on safety and efficacy of dietary supplements prior to marketing. The lack of FDA supervision is contributing to the tainting of dietary supplements with active pharmaceutical ingredients jeopardizing consumers' health. Implementing stringent regulation to oversee the manufacturing and compounding of dietary supplements comparable to that of pharmaceutical products can help prevent adulteration and thus reduce overall Class I solid oral dietary supplement recalls.

On the other hand, the most common reason for pharmaceutical product recalls was identified as labelling issues. Manufacturing and packaging units of pharmaceutical products should strictly follow cGMP guidelines on labeling control and can implement reliable quality control methods to check and proofread product labels to help prevent labelling errors and thus reduce Class I solid oral pharmaceutical product recalls.

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