A review on drug recall

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A thesis submitted to the School of Pharmacy in partial

fulfillment of the requirements for the degree of

Bachelor of Pharmacy (Hons.)

School of Pharmacy

Brac University

August 2022

Declaration

It is hereby declared that

1. The thesis submitted is my original work while completing my degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled “A review on drug recall” submitted by Nazmun Nahar Nisha (17146037), of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on August, 2022.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

We are living in a time where population is increasing, as well as the demand for drugs. Drug recalls help to keep the quality system by removing defected items or drugs from the market. Drug recalls refer to pharmaceuticals that were initially approved for use but later discovered to have negative side effects, are dangerous, and cause substantial harm to the human body. Over the past years, many drugs were recalled from the market all around the world. There are some reasons that is why drugs are recalled for an assortment: safety, mislabeling, contamination, and deviations in strength or potency. The purpose of this review article is to provide an overview of recalled drugs, reasons of recall, procedures, their influence on the pharmaceutical industries, and the different actions taken to minimize pharmaceutical recalls.

Keywords

Drug recall, drug safety, drug manufacturing, pharmaceuticals, and process.

Dedication

Dedicated to my father

Acknowledgment

To begin with, I would want to express my gratitude to Allah (SWT) Almighty for His unending bounties, mercy, and kindness. All glory to God for providing me with the immense patience, strength, courage, knowledge, wisdom, and hope that I required to complete this project.

This study would not have been completed without the support of my respected supervisor Dr. Mohd. Raeed Jamiruddin (Assistant Professor, School of Pharmacy, Brac University). I have lost my father recently to Covid. I wish to acknowledge my father's dedication and belief in me and the support that he has always provided. In this situation I could not have had finished my project if my supervisor was not beside me all the time. I was able to work harder and complete the project because of his continuous effort and motivation.

I would like to also show gratitude to our honorable chairperson, Dr. Eva Rahman Kabir (Dean, School of Pharmacy, Brac University).

Finally, I would like to express my gratitude to my parents and my siblings for their unwavering support and encouragement throughout my life. They always give me the strength and courage to do anything. Their prayers and love have helped me in getting this far.

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Acronyms

NME	New Molecular Entity
NBE	New Biological Entity
PK	pharmacokinetic
FDA	Food and Drug Administration
CNS	Central Nervous System
PML	Progressive Multifocal Leukoencephalopathy
SCOUT	Sibutramine Cardiovascular Outcomes

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Chapter 1: Introduction

1.1 Background

1.1.1 Discovery of Drug

Drug research has contributed more to the improvement of medicine in the previous ten decades than any other scientific component, driven by chemistry but closely supervised by pharmacology and the clinical sciences. The emergence of molecular biology, particularly genomic sciences, has had a tremendous impact on the development of medications (J, 2000a). The majority of drugs were discovered rather than developed. As a result, many pharmacological compounds are natural products or derivatives of natural products. Recombinant proteins and monoclonal antibodies have considerably enhanced our therapeutic arsenal. Genome sciences, in combination with bioinformatics techniques, enable us to examine the genetic foundation of complicated illnesses and determine the best targets for future medications, thereby increasing the number of treatment options (J, 2000a). The biotech industry is establishing itself as the discovery arm of the pharmaceutical industry.

Natural sources provided the earliest therapeutic medicines, which came in the form of herbs, plants, roots, vines, and fungus. Until the mid-nineteenth century, nature's medicines were the only way to relieve man's pain and suffering. The first synthetic drug, chloral hydrate, was created in 1869 and sold as a sedative-hypnotic; it is still available in some countries today (Imming, 2008). The first pharmaceutical businesses sprang from the textile and synthetic dye industries, and owe much of their success to the abundant supply of organic compounds generated from coal distillation (coal-tar). Phenacetin and acetanilide, both are the earliest analgesics and antipyretics,

were simple chemical derivatives of aniline and p-nitrophenol, they were coal-tar byproducts (Jones, 2011).

Plants have played an important role in human health and well-being. Drug was derived from the French term Drogue, which means "dry herb," meaning that the first medicines were made from plants. Herbs, therefore, played an important part in the development of pharmacology and pharmaceutics. The magnificent architect of today's sophisticated Pharmacology was not constructed in a day, but it was built on an old foundation (Wadud et al., 2007). Pharmacy or pharmacology refers to the study of pharmaceuticals in general. The fate and effects of a drug in the body are the focus of a typical narrower definition of pharmacology (Imming, 2008).

1.1.2 Development Process of Drug

The innovation of a biological target (e.g., a receptor, enzyme, protein, gene, etc.) involved in a biological process that is thought to be malfunctioning in illness patients is usually the first step toward developing a new drug (Mohs & Greig, 2017). From target identification to marketing clearance, studies across all therapeutic domains demonstrate that creating a new medicine takes at least 12 years and generally much longer (J, 2000a). Developing a New Molecular Entity (NME; a small molecule drug) or a New Biological Entity (NBE; an antibody, protein, gene therapy, or other biological medication) is expected to cost more than USD 1 billion, with costs averaging USD 2.6 billion at times (DiMasi et al., 2016).

The goal of a preclinical drug discovery program is to develop one or more clinical candidate molecules with sufficient evidence of biologic action at a disease-relevant target, as well as adequate safety and drug-like properties, to be tested in people. Because most discovery programs aim to develop a large number of candidate molecules, due of concerns about safety, kinetics,

potency, intellectual property protection, and other issues, many compounds do not complete the process. Though current drug development programs universally include collaboration between chemistry, biology, toxicology, and pharmacokinetics, there is no straightforward or simple formula for developing a clinical candidate chemical that is successful (J, 2000b).

Drug developers interested in developing medicines for ailments like Alzheimer's, cancer, and other difficult-to-treat ailments are eager to learn about innovative targets that might be the focus of a new drug development project. Simultaneously, they are cautious of recent scientific studies that purport to have uncovered an NBE or a mechanism that could be of concern (Cg & Lm, 2012).

Even if there is validating evidence, a biological target will only be helpful for drug development if molecules can be developed that have a well-tolerated and therapeutically effective action on the target. Moreover, those compounds need to show that they have properties that allow them to function as a drug when given to humans. The molecules must have pharmacokinetic (PK) properties that allow for a consistent and reliable link between the drug dose provided, drug exposure at the desired site of action, and drug binding to the therapeutic target. The preclinical and subsequent clinical investigations required to evaluate a new medicine's PK characteristics are substantially challenging for CNS target resultant blood-brain barrier. Nevertheless, advances in medicinal chemistry and biological PK modeling have reduced the amount of drugs entering clinical development with suboptimal PK properties (Mohs & Greig, 2017).

1.1.3 Drug Recall

When a batch or an entire production run of a drug product is returned to the manufacturer, it is typically due to the discovery of safety concerns or a drug product flaw (Świeczkowski et al., 2020). Recall means a company's removal or modification of a marketed product that regulatory

authorities believe is in violation of the law it enforces, and for which the agency will take legal action, such as seizure. Drug goods that has been recalled has the potential to cause harm to the public due to inadequate quality, safety, or efficacy (Kim et al., 2020).

Drug recalls refer to pharmaceuticals that were initially approved for use but later discovered to have negative side effects, are dangerous, and cause substantial harm to the human body. As a result, several medications have been taken off the market. It aids in the removal of over-the-counter medications from the market. (Saleh, 2021).

When the quality of a batch of a product is doubtful, the product is intended to be recalled for further examination and decision. The objective of a drug recall is to guarantee that the drug is quickly and effectively withdrawn from the market (Sovasia et al., n.d.). Another purpose of a product recall is to protect the public's health and make the people aware of the hazardous product so that they do not consume it (Sovasia et al., 2021).

The Food and Drug Administration (FDA) issues recall orders when it detects a legal concern with a drug. These orders compel a manufacturer to remove or fix a product from the market. The company can proceed with legal action in case of failure to adhere to the directives thus issued. There is a group in charge of organizing all elements of product recalls. To protect the safety of customers, it is necessary to manage complaints and recall of drug products are required (Sovasia et al., 2021). Recalls can be unrestricted by the company or, in rare cases, enjoined by the FDA. The severity of recalls and the actions that must be taken varies. It is conceivable that a pharma manufacturer will just recall a single batch or quantity of medication. However, there are also instances where a drug's whole batch or lot is recalled from the market (Świeczkowski et al., 2020).

1.1.4 Drug Recall Classification

A recall is usually the first step in removing a medication off the market. According to the FDA, "the most effective approach to safeguard the public from a faulty or possibly dangerous product is to issue a medication recall." A recall is a voluntary action taken by a company to remove a defective drug product from the market. A company may initiate a drug recall, or the FDA can request one. In a recall, the FDA's job is to monitor a company's plan, review the recall's appropriateness, and categorize the recall (Saleh, 2021).”

Recalls are divided into three categories by the Food, Drug, and Cosmetics Act, which is regulated by the Food and Drug Administration (FDA):

A. **Class I:** There is a life-threatening danger at hand. The FDA will necessitate a consumer recall, a 100 percent effectiveness review, and appropriate public declarations. (Sovasia et al., 2021). For example: A life-saving drug's label was mixed up (Kim et al., 2020).
B. **Class II:** There is a potentially dangerous issue here, but it is not life threatening. The FDA will usually request a recall to retailers but not a complete efficacy study. Depending on the reasons for the recall, a press release may be required (Sovasia et al., 2021). For example: A low-strength medicine that isn't utilized to treat life-threatening circumstances (Kim et al., 2020).
C. **Class III:** Does not pose a major hazard. It is usually restricted to wholesale, with no effectiveness assessments or press release obligations (Sovasia et al., 2021). For example: A small flaw with the container (Kim et al., 2020).

1.1.5 Types of drug recall

Any product or batch that fails to fulfill the established quality standards, as well as safety and efficacy, must be recalled from the market (Vvss et al., 2020). Recalls are two types:

i) Voluntary recall: Any event that compromises the batch's or product's safety, effectiveness, or quality, such as:

a) If post-marketing testing reveal that the batch or lots are non-compliant with regulatory standards.
b) If the product's pharmacovigilance reports show that it poses a significant danger.
c) If the batch is discovered to be substandard as a result of a market complaint.
d) If any odd observations are discovered throughout a optical evaluation of retaining samples that specify a potential influence proceeding product quality after examination (Kim et al., 2020).

ii) Statutory recall: Drug Regulatory Authorities (Central/State) routinely issue statutory recalls in response to a directive or requirement, which follows:

a) If the quality is not up to standard, and so on, the recall of drug product or batch occurs.
b) If the drugs which are banned.
c) Violations of the law in terms of labeling and/or promotional materials (Kim et al., 2020).

1.1.6 Reasons for a Product Recall

A deployable product might be called back for a variety of reasons. Some of the probable causes are listed below:

1. If the drug cause a health risk.
2. It is possible that it is contaminated.
3. Officials from the regulatory authority finds that a sample obtained from the market and evaluated by a analyst's lab of government confirms that the product is sub-standard, as the consumer complaints about the poor qulity, and they demand that the manufacturer to recall the product.
4. The product is not exactly what it says.
5. Natural disasters, such as floods, can sometimes destroy inventories at various depots and other locations. When the maker receives this information, he either recalls the product or requests that it be returned.
6. Concerns with the product may be identified by the producer, such as poor quality detected after the product's debut, product stability issues, or a market complaint collected from a customer or medical practitioner.
7. It is mislabeled or poorly packaged. During transporting, the consignment may be damaged by accident. In this case, the product quality is unaffected, but the packaging may be destroyed, rendering it unfit for sale or distribution, forcing a recall (Kim et al., 2020).

1.1.7 Purpose for recall

The objective of a drug recall is to assure that the drug is quickly and effectively withdrawn from the marketplace (Sovasia et al., 2021). The declaration of a regulatory agency as a consequence of a violation of a government legislation, standard, and other mandatory regulations. To diminish potentially severe extra medication product liability claims or losses, this theory was proposed.

Another purpose of a product recall is to protect the public's health and make the people aware of the hazardous product so that they do not consume it (Sovasia et al., 2021).

1.1.8 Difference between recall and withdrawal:

Drug recall and drug withdrawal show significance differences such as,

Table 1: Dissimilarity amongst recall and withdrawal of drug

Drug Recall	Drug Withdrawal
A drug recall is when a corporation takes measures to remove a drug product from the market that the FDA considers is illegal or violating the law.	In a variety of situations, the FDA may have to reconsider and change a drug's approval decision. A medication may be withdrawn based on the choice.
A medication may be recalled for a variety of reasons, including packaging, manufacturing, or contamination concerns.	When the FDA determines that the drug's advantages no longer exceed the dangers, the producer will be asked to remove the product.

Chapter 2: Methodology

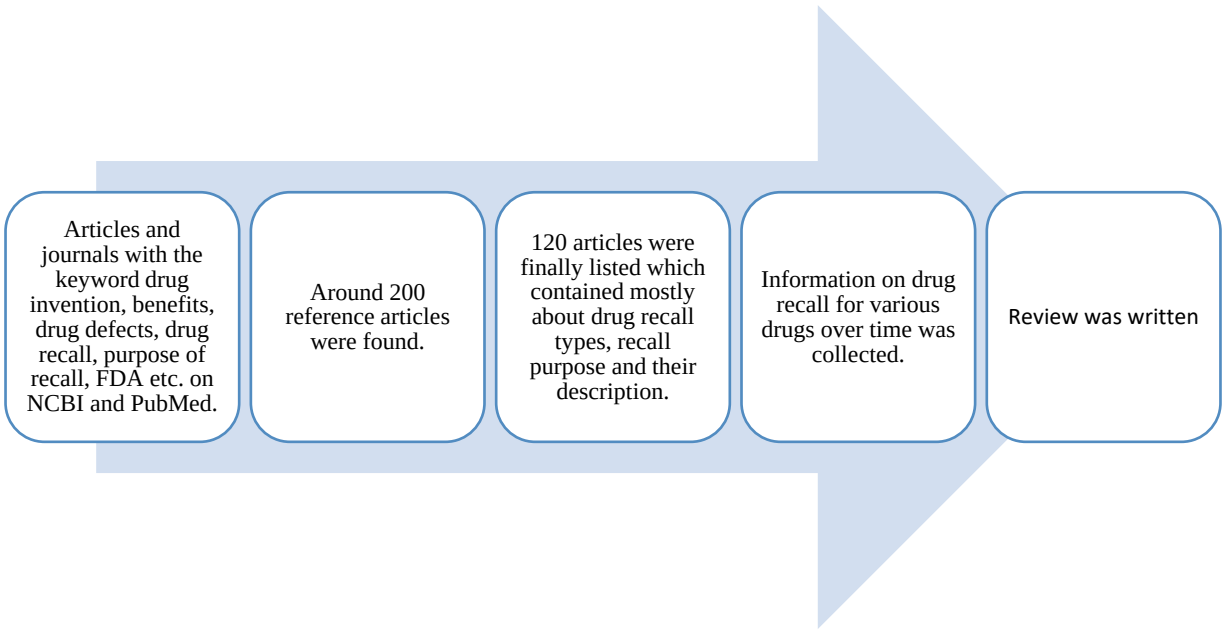

Figure 1 Methodology:

This review study involves a comprehensive overview on different aspects of drug recall around the world. The data for this review paper was collected through secondary research approaches including research articles (indexed in PubMed, NCBI, Elsevier, Science Direct, Web of Science, Scopus, etc.), news articles, academic published papers, and web sites. This study also analyzed at articles from prestigious journals. To provide the study with reliable information, a significant number of publications were analyzed, and all of the articles were properly cited. Many publications provided information and data, as well as their perspectives, which helped to write the review paper.

Chapter 3: Drugs Recall around the world

Over the last few years, there has been an upsurge in the number of pharmaceutical recalls, both prescription and OTC (over-the-counter) drugs. A company finding, a customer complaint, or an FDA inspection are the most common reasons for a recall. The recall procedure involves a well-thought-out action plan that takes into account the breadth of the recall, the need for public notice, and the recall's efficacy (Świeczkowski et al., 2020).

The US FDA recalls a huge number of drugs over the years for their defects and side effects. A list of them is given below:

i. **Efalizumab (Raptiva):** This drug was originally approved to treat psoriasis, but it was recalled after it was revealed that it caused progressive multifocal leukoencephalopathy (PML), a rare and deadly illness marked by inflammation and destruction to the white matter and central nervous system of the brain.(Saleh, 2021). Raptiva was discontinued in the United States in 2009 (*FDA*, 2015.).

ii. **Sibutramine:** Sibutramine is a weight loss drug. Those who used this appetite suppressant had a higher risk of heart disease and stroke. During a Senate hearing in 2004, FDA reviewer Dr. David Graham referred to it as "another Vioxx and later FDA recalled that drug from the market (Saleh, 2021)." After a 2009 study titled the Sibutramine Cardiovascular Outcomes Trial (SCOUT), the drug was banned in Europe. It was a part of a post-market requirement to review the cardiovascular safety of sibutramine following its European approval (Remy Melina, 2010). Because of concerns about an elevated risk of heart disease and stroke, the weight-loss medicine sibutramine has had its marketing authorization revoked in Europe and its license reduced in the United States. The European Medicines Agency advised that doctors

discontinue using the medication because the dangers exceed the benefits (Sayburn, 2010).

iii. **Isotretinoin (Accutane):** Roche's Accutane was authorized by FDA (US Food and Drug Administration) in 1982, thus it has been on the market for decades. It belongs to the retinoids class of medicines. These chemicals act by decreasing skin irritation and encouraging the sloughing off of the top layer of dead skin cells. Accutane has been shown to be helpful in the treatment of severe acne ("Accutane Recalls," 2021). The FDA received information of several suicides in the United States, hospitalizations for hopelessness or depression, suicidal feelings, attempt, and non-hospitalized depression cases, from the time isotretinoin was first marketed in 1982 through May 2000 (Wysowski et al., 2001).

This acne medicine was recalled by the company because it was linked to an increased risk of birth abnormalities, miscarriage, and early mortality in pregnant women, as well as suicidal thoughts and inflammatory bowel disease. Hoffman-La Roche, the drug's manufacturer, took Accutane off the market in the United States in 2009 (*10 Dangerous Drugs Recalled by the FDA | MDLinx*, 2021).

iv. **Levamisole (Ergamisol):** This medication was used to treat worm infestations, rheumatoid arthritis, colon cancer, and breast cancer in patients. It was recalled because it caused neutropenia, agranulocytosis, and thrombotic vasculopathy, leading to retiform purpura, a purple discoloration of the eye that required surgery (*10 Dangerous Drugs Recalled by the FDA | MDLinx*, 2021).

v. **Bromfenac (Duract):** Bromfenac is a nonsteroidal anti-inflammatory medicine that was licensed by the FDA in 1997 in the United States. Hepatotoxicity caused it to be

discontinued from clinical usage less than a year later, in 1998 (Driscoll et al., 2018). This pain reliever resulted in fatalities, liver transplants, and serious liver damage (*10 Dangerous Drugs Recalled by the FDA | MDLinx*, 2021).

vi. **Pemoline (Cylert):** Attention deficit hyperactivity disorder is known as ADHD. This disorder was treated with this central nerve stimulant. Due to the drug's potential to induce liver damage, the FDA issued a boxed warning in 1999, which was subsequently followed by a recall (*10 Dangerous Drugs Recalled by the FDA | MDLinx*, 2021).

vii. **Tylenol (Acetaminophen):** This drug was used to reduce fever as well as relief from aches and pain. This is an OTC drug. Back in 1982, the manufacturing company Johnson & Johnson recalled this drug after seven people died after the consumption of the drug. During the fall of 1982, a malevolent individual or individuals switched cyanide-laced Tylenol Extra-Strength capsules for Tylenol Extra-Strength capsules, repacked the packages, and placed them on the shelves of at least a half-dozen pharmacies and grocery stores in the Chicago area. People purchased the capsules that are poisoned, and as a result, seven people died a horrific end. Resulting the Tylenol killings, all groups were concerned about the safety of OTC medicines, although there were substantial intergroup variations (Beck & Monroe, 1982).

viii. **Terfenadine (Saldane):** In 1985, the FDA approved Terfenadine, the first non-sedating antihistamine, for the treatment of allergy disorder such as allergic rhinitis in the United States. However, it was phased out of clinical usage in the late 1990s due to concerns about arrhythmia (Kandel et al., 2014). The interactions cause irregularities in the electrical impulse that encourages and stimulates the heart to contract properly and pump blood. The Food and Drug Administration ordered Seldane, a once-daily

high-dose version of the drug terfenadine, to be withdrawn off pharmacy shelves at the end of 1997 when it was discovered to induce deadly arrhythmias when combined with other drugs (Sayburn, 2010).

ix. **Rofecoxib:** it is a selective COX-2 inhibitor and nonsteroidal anti-inflammatory drug (NSAID), which was licensed in Canada in 1999. It was approved to treat osteoarthritis, rheumatoid arthritis, acute pain, and menstrual pain, as well as their acute and chronic symptoms (Sibbald, 2004). Rofecoxib was recalled in September 2004, after The Vioxx Gastrointestinal Outcomes Research (VIGOR) study, which was published in March 2000, shown that individuals using the drug had a higher risk of cardiovascular disease than those who took a placebo. The manufacturing company Merck itself recalled the drug from the market in late 2004. (Hawker et al., 2006).

x. **Cerivastatin (Baycol):** Cerivastatin belongs to the statin class of drugs that work by inhibiting HMG-CoA reductase and cholesterol production. Inhibitors of HMG CoA (3 hydroxy, 3 methyl giutaryl coenzyme A) reductase are used to lower cholesterol levels (Wooltorton, 2001). Cerivastatin was recently taken off the market due to fatalities linked to drug-induced rhabdomyolysis, which resulted in renal failure. Patients who got the maximum dose (0.8 mg/day) and those who took gemfibrozil at the same time had a greater risk. Cerivastatin was 10 times more likely than the other five authorized statins to cause rhabdomyolysis (Furberg & Pitt, 2001). Due to an increasing number of reports of rhabdomyolysis to the US Food and Drug Administration, Bayer removed cerivastatin which was marketed as Baycol in the US and Lipobay in Europe in August 2001, and later from Japan. Rhabdomyolysis is an uncommon condition in which muscle tissue breaks down, resulting in organ failure

and death in those who take the medicine. (Marwick, 2003).

xi. **Fenflurmine:** Fenfluramine and dexfenfluramine were commonly used anti-obesity drugs until 1997, when they were taken off the market by FDA. Primary pulmonary hypertension (PPH) was a recognized adverse effect of this drug, but the health advantages of weight loss were thought to outweigh the risk of PPH. With the extensive usage of these drugs, two new diseases have been identified as possible adverse effects: valvular heart disease and neurotoxicity (Poston & Foreyt, 2000).

xii. **Troglitazone:** Troglitazone was the first thiazolidinedione to be licensed for use in the United States, in 1997, for the treatment of type 2 diabetes. However, three years later, it was withdrawn off the market due to a high prevalence of hepatic injury, including acute liver failure, associated to its use (*Troglitazone - LiverTox - NCBI Bookshelf*, 2021.). Between 1997 and 2016, these drugs were all taken off the market owing to hepatotoxicity: lumiracoxib, tolcapone, ximelagatran, troglitazone, bromfenac, trovafloxacin, nefazodone, and sitaxentan (Babai et al., 2018).

xiii. **Irbesartan:** In hypertensive individuals with type 2 diabetes, irbesartan is an angiotensin II receptor blocker used to treat hypertension, blood pressure, diabetic nephropathy, elevated serum creatinine, and proteinuria. Lupin Pharmaceuticals, Inc. has announced a voluntary countrywide recall of all irbesartan tablets and irbesartan plus hydrochlorothiazide tablets due to the probable presence of N-nitrosoirbesartan impurity. (Research, 2021b).

xiv. **Ketorolac Tromethamine Injection:** The drug is being recalled because some of the recalled batches include tiny visible gelatinous/oily particle materials that look black. Hikma voluntarily launched a recall of this product to direct customers on December

23, 2019. Hikma is extending the recall to medical facilities and retail outlets in collaboration with the US Food and Drug Administration (FDA) (Research, 2021a).

xv. **Valdecoxib (Bextra):** From 2001 until 2005, it was on the market. Valdecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that the FDA later concluded did not function any better than other NSAID pain relievers on the market. The medication was recalled due to a higher risk of severe skin responses such epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome, as well as an elevated risk of mortality, cardiac arrest, and stroke (Saleh, 2021.).

Chapter 4: Drugs Recall in Bangladesh

Some of the drugs will be recall in Bangladesh due to their toxicity. In times, there were some companies who had to recall their drugs from the market to minimize the deaths.

Metformin

Metformin combined to insulin treatment improves glycemic control and lowers the daily amount of insulin necessary in type 2 diabetes patients (DDI) (Wulffelé et al., 2002). Bayshore is withdrawing more than one batches of Metformin Hydrochloride Extended-Release due to a safety concern, according to the US Food and Drug Administration because the active compound contains a carcinogenic compound called NDMA. The incident occurred after the US Food and Drug Administration identified high levels of N-Nitrosodimethylamine (NDMA) in one batch of metformin hydrochloride extended-release tablets, USP 750 mg hence advised that the product must be withdrawn (Express, 2021.).

Ranitidine

Ranitidine is an H2 blocker that can be purchased over-the-counter (OTC) or via prescription (Dasukil et al., 2021). The US Food and Drug Administration (FDA) received a citizen petition in September 2019 indicating that particular batches of ranitidine contained substantial amounts of N-nitrosodimethylamine (NDMA), a potential human carcinogen. According to the petitioner, ranitidine might also be transformed to NDMA in vivo by emitting its dimethylamine (DMA) group, which could then be nitrosated to NDMA in the presence of nitrite. The FDA responded by issuing a public warning and initiating an inquiry (Florian et al., 2021).

The Directorate General of Drug Administration known as DGDA has placed a temporary ban on the import, production, and sale of Ranitidine in Bangladesh. According to a drug administration official, the DGDA made the decision after believing that Ranitidine, an acid reflux medication, contains a cancer-causing contaminant (Report, 2019). After finding excessive quantities of cancer-causing chemicals in the heartburn medicine Ranitidine created with raw materials from two Indian companies, the Bangladeshi government banned it. According to the DGDA, Saraca Laboratories Limited and Dr Reddy's Laboratories are the two Indian companies that offer the raw material - Ranitidine hydrochloride. Tests on these companies' raw materials and finished products indicated higher-than-normal quantities of N-nitrosodimethylamine (NDMA), according to the FDA (Food and Drug Administration) (Correspondent & bdnews24.com, 2019.)

In 20 November, 2019 Bangladesh has officially banned ranitidine, despite regulatory authorities in Europe and US investigating existence of a possible carcinogen in the popular heartburn medication (Mahase, 2019).

Valsartan

The Directorate General of Drug Administration (DGDA) of Bangladesh has issued an order requesting that some pharmaceutical companies, including Drug International, Incepta Pharmaceuticals, Renata Pharmaceuticals, ACME Laboratories Ltd, Healthcare Pharmaceuticals and Popular Pharmaceuticals to withdraw medicines containing the raw material 'Valsartan,' developed by Zhuhai Rundu Pharmaceutical Co Ltd and Zhejiang Tianyu Pharmaceutical Co Ltd of China (Research, 2019).

Several heart medicines involving Valsartan were discontinued in Europe and Asia in July 2018 after remnants of a material found in its supplies which could cause cancer were detected,

according to international sources. As a result, Chinese-made medicines containing Valsartan have been recalled from market. Valsartan, a drug manufactured by Novartis for the treatment of high blood pressure and cardiac failure, has been pulled off the market and is now only utilized in a few medications (Babai et al., 2018; Independent, 2018.).

Tranexamic acid injection

Tranexamic acid injection is an antifibrinolytic that is used in individuals with hemophilia for a short period of time (2 to 8 days) to reduce or eliminate hemorrhage and the requirement for replacement medication during and after tooth extraction. Tranexamic acid injection should be given intravenously by health care professionals. Seizures, heart arrhythmias, paraplegia, permanent brain damage, and death are all possible side effects of intrathecal tranexamic acid injection. Tranexamic acid injection as well as bupivacaine injection, also other perioperative drugs can have a similar appearance, such as the same vial cap color or packaging, which may lead to confusion. Other practice- and facility-level contributing factors, such as storing similar-looking goods in close proximity, can also play a role in these errors (*10 Dangerous Drugs Recalled by the FDA | MDLinx*, 2021.). To avoid drug mistakes that might result in serious injury or death, the Food and Drug Administration is taking steps to combat tranexamic acid injection medication errors. This involves upgrading the tranexamic acid injection package and box labels to stress the intravenous mode of administration, as well as enhancing the warnings in the tranexamic acid prescription instructions to reflect the risk of medication mistakes due to inappropriate method of administration (Research, 2020).

Chapter 5: Discussion

Over the past years, many drugs were recalled. There are the list of drugs that has been recalled-

Table 2: List of drugs that got recalled

Drug Name	Indication	Class	Recall Reason/ Remarks	Recall Year	Country
Adderall XR	ADHD, Necrolepsy	Stimulants	Stroke danger.	2005	Canada
Alatrofloxacin	Bacterial infection	Peptides	Serious liver damage that necessitates a liver transplant or death.	2006	Worldwide
Alclofenac	Mild to moderate pain relief	NSAID	Vasculitis	1979	UK
Alosetron	Diarrhoes, pain, cramps	5-HT3 receptor antagonist	Ischemic colitis; severe constipation are all serious gastrointestinal side effects. In 2002, it was reintroduced on a limited basis.	2000	US
Alpidem	Sedative hypnotive	Hypnotive	Hepatotoxicity	1995	Worldwide
Aminopyrine	Treat severe fever and pain	NSAID	agranulocytosis,blood dyscrasia,aplastic anemia,severe acne problem	1999	France, Thailand
Amobarbital	Anxiety, Epilepsy, Insomnia	Barbiturate	Risk of overdose	1980	Norway
Amoproxan	Angina	Antianginal	produce pellagroid skin changes, opthalmic toxicity	1970	France
Aprotinin	Reduce bleeding	Protein	Death incresed	2008	US
Ardeparin	Prevent deep venous thrombosis	Anticoagulant	did not reach efficacy	2001	US

Astemizole	H1 Receptor antagonist	Antihistamine	Fatal arrhythmia	1999	US, Malaysia, Multiple Nonspecified Markets
Bendazac	Prevent joint and mascular pain	NSAID	Hepatotoxicity	1993	Spain
Benoxaprofen	Pain reliever	NSAID	hepatic and renal failure; GI bleeding and ulcers	1982	Spain, UK, US, Germany
Benzarone	Coronary dilator, gout	Antihemorrhagic agent	Hepatitis	1992	Germany
Benziodarone	Gout	Vasodilator	Jaundice	1964	France, UK
Beta-ethoxy-lacetanilanide		Beta lactamase inhibitor	carcinogenicity	1986	Germany
Bezitramide	Treat severe chronic pain	Analgesic	Risk of fatal overdose	2004	Netherlands
Brotizolam	Treat insomnia	Sedative-hypnotic	Animal carcinogenicity	1989	UK
Bunamiodyl	Spleenectomy	Cinnamic acid	Nephropathy.	1963	Canada, UK, US
Cerivastatin	Treat cardiovascular disease	Statin	Risk of rhabdomyolysis	2001	US
Cisapride	GERD Treatment	Gastrointestinal agent	Risk of deadly cardiac arrhythmias	2000	US
Clobutinol	Cough suppressant	Phenylbutylamines	Ventricular arrhythmia, QT-prolongation	2007	Germany
Co-proxamol (Distalgesic)	Headache, fever	Analgesic	Overdose risk	2004	UK
Dantron	Counteract constipating effect of opioids	Organic compound	Mutagenic	1963	Canada, UK, US
Dimazole	Antifungal	Benzothiazole	Neoropsychiatric	1972	France, USA
Dofetilide	Treat arrhythmiasis	Class 3,antiarrhythmic agent	Prolonged QT	2004	Germany

Drotrecogin Alfa	Treat sepsis in adults	Serine protease	Lack of efficacy	2011	Worldwide
Flupirtine	Treat chronic pain	Nonopoid analgesic	Liver toxicity	2018	EU
Gatifloxacin	Bacterial infection	Antibiotics	Increased risk of dysglycemia	2006	US
Grepafloxacin	Bacterial infection	Antibiotics	Cardiac repolarization; QT interval prolongation	1999	UK, USA
Ingenol mebutate gel	Actinic keratosis	Cytotoxic agent	Increased risk of skin cancers	2020	Suspended in Europe
Isoxicam	Treat inflamation	NSAID	Stevens johnson syndrome	1983	France, Germany, Spain, others
Kava Kava	Anxiety Disorder	Depressant	Hepatotoxicity	2002	Germany
Lorcaserin	Weight management	Serotonin receptor agonist	Increased risk of cancer	2020	US
Lysergic acid diethylamide (L SD)	Anxiety Disorder	Psychedelics	Withdrawn because widely used recreationally. Nowadays banned in most of the world.	1950s–1960s	Worldwide
Mibefradil	Treat Heart failure	Calcium channel blocker	Fatal arrhythmia, drug interactions	1998	EU, US
Natalizumab	Immunothera py	Monoclonal antibodies	PML	2005–2006	US
Nefazodone	Depression treatment	Serotonin modulators	Branded version withdrawn for hepatotoxicity	2007	US, Canada
Ozogamicin	Treatment of acute myeloid leukemia	Antibody drug conjugate (ADC)	risk for death; veno-occlusive disease	2010	US
Tetrazepam	Acute Narrow angle glaucoma, coma	Benzodiazepi ne	Serious cutaneous reactions	2013	EU

Chapter 6: Conclusion

Over the last few years, many prescribed and OTC drugs were recalled **(**Nagaich & Sadhna**,** 2015**)**. Drug recalls, which are either voluntary or requested by regulatory organizations, are carried out primarily to enhance the quality system and to protect the general population from the repercussions of defective products (Miglani et al., 2021). The history of major drug recalls suggests that there was a lot of negligence engaged during the drug research and production process. The FDA's lengthy list of medicine recalls reveals that the pharmaceutical industry is still not adhering to the FDA's stated standards (Vvss et al., 2020).

The overall trend of drug recall rates is rising year after year, which should serve as a warning to regulatory bodies to take proactive efforts to limit and prevent excessive recalls **(**Eissa, 2020**)**.

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