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RECALLED DRUGS: AN ANALYSIS OF SAFETY CONCERN AND RECALL ACTION

HARSHINI G, KANAKA PARVATHI K* AND DAMODHARAN N

Department of Pharmaceutical Quality Assurance, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chennai, 603203 India

***Corresponding Author: Dr. K Kanaka Parvathi: E Mail: kanakapk@srmist.edu.in**

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ABSTRACT

The provision of high-quality pharmaceutical products to consumers is the major priority of the pharmaceutical industry. The Procedure for drug recall is a strategy used by drug regulatory organisations to remove medications that pose a risk to patient safety or effectiveness. Drug recalls have a vital role in keeping the quality system because they take defective products off the market. Healthcare supply chain interruptions are significantly exacerbated by product recalls. It is very difficult to communicate recall information and to reclaim or properly dispose of the merchandise without a trustworthy product tracking system. Following the guidelines which are connected to the problems of recall and the development of drugs and manufacturing are very essential. Requiring regulatory bodies and the public health sector to concentrate on stricter regulations to prevent future drug product recalls. A drug recall procedure is a strategy used by drug regulatory organisations to remove medications that pose a risk to patient safety or effectiveness. The FDA takes action by recalling dangerous items to safeguard the public. This article will explore various reasons for the recall, recall strategy, recall procedure, steps taken to reduce drug recall and the involvement of the Food and Drug Administration (FDA) is provided.

Keywords: Recalled drugs, FDA, Reasons to recall, Reduce recall, NDMA

INTRODUCTION:

The Food and Drug Administration (FDA) regulates pharmaceutical preparations and healthcare items in general for quality and safety. Every year, there are numerous recalls of drugs and healthcare products. Among these, defects are GMP violations, insufficient manufacturing control, inaccurate measured results, software updates, stability issues, and flawed device parts. In the international market, the pharmaceutical market was expected to rise by 5 to 8% annually. Even as the industry grows, product returns and recalls contribute to the growth **[1]**. Removing a faulty or potentially hazardous product from the market is referred to as a "recall" in the industry **[2]**. To ensure a successful recall, the recall process focuses on improving consumer protection and the health system. The entire production, distribution, transportation, and dispensing processes for pharmaceutical items must be covered by the recall of pharmaceutical products **[3]**.

If any concerns are raised regarding the quality of products, this justifies jeopardising the safety of human health and the approval is revoked. In the USA, the regulatory agency FDA has defined recall in 21 CFR PART 7 sec.41.5 EMA (European Medicine Agency) decentralized agency in Europe describes recall in (Article 44 of Directive 2001/82/EC) While the Drugs and Cosmetics Act 1940 and Rules 1945 in India define products recall, complaints, and adverse reactions in Paragraphs 27 and 28 of Schedule M (Good Manufacturing Practises), the European Medicine Agency (EMA) decentralised agency in Europe describes recall in (Article 44 of Directive 2001/82/EC) **[2]**.

CLASSIFICATION OF RECALL

A numerical indication for recall classification, such as I, II, or III, is given to a specific product recall by the Food and Drug Administration to identify the relative level of health risks.

Table 1: Classification of Recall for the Drugs from the Manufacturer [4]

Category	Explanation	Exemplar
CLASS I	The product will give result in severely poor health or even death.	A life-saving medication`s label was misread.
CLASS II	Products have a remote chance of having major adverse health outcomes and may have brief or medically reversible negative health effects.	A medicine that is weaker than necessary yet is nonetheless utilised in non-life-threatening conditions.
CLASS III	It's doubtful that the product will harm your health.	A small container Flaw.

RECALL PROCEDURE FOR PHARMACEUTICAL PRODUCTS

As soon as a complaint of a regulation infringement that may result in major to slight dangers to public health is collected,

there will be a medicine recall process initiated. One of the most typical sources of complaints is FORM-483. After any site has been inspected FDA investigator of the Office of Regulatory Affairs uses it to document inspection outcomes. If the company or manufacturer fails not to respond to the observations within 15 days, the USFDA will issue a warning notice.

The recommendations which should be followed when conducting the recall are given in the below flowchart **(Figure 1)**: **[2]**

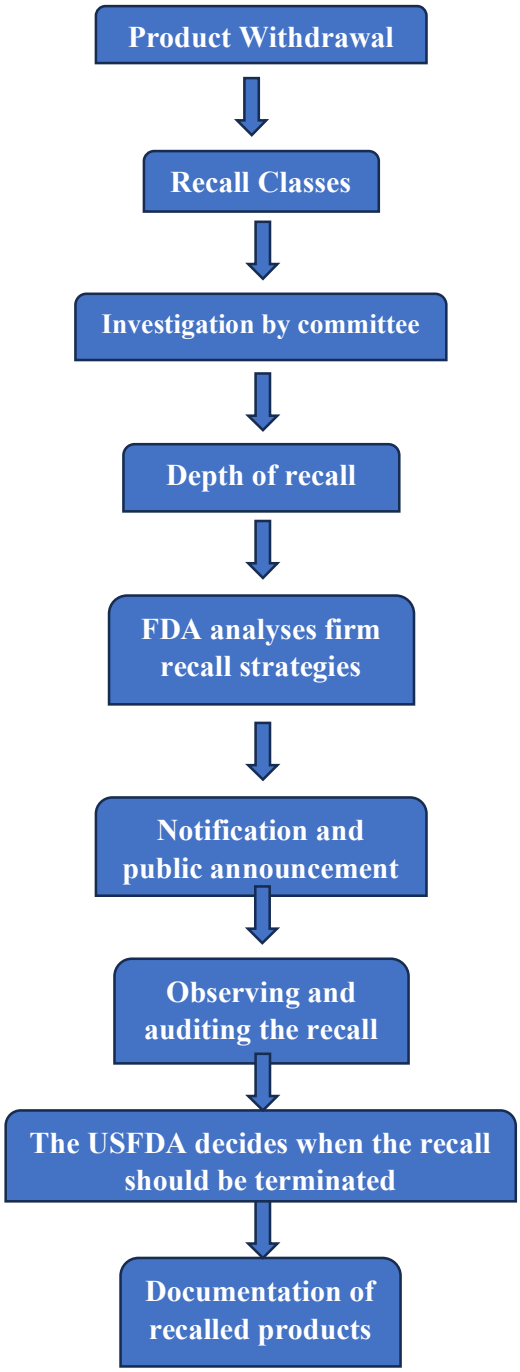

Figure 1:

The Recall's Effective Period

A recall is an efficient way for the regulatory authority to get rid of or fix consumer products that are against the law. The manufacturer should determine how long it will require to finish the relevant class of recalls. For example,

Class I- As soon as the consumption level is reached, it is time to start Class I -Recall, which needs to be finished in 12 to 14 hours.

Class II- began in less than 48 hours.

Class III- began three days ago.

Manufacturers and distributors may initiate recalls voluntarily at any time or at the Regulatory body's request. A recall typically offers greater customer protection and is more suitable than a seizure **[4]**.

RECALL STRATEGY

Considering the drug product's level of hazard and issuing, the recall plan will identify the extent of issuing to which the recall is to be made:

i) Consumer Level: This level, along with any intermediary tiers of wholesale or retail, might change depending on the product. Individual consumers, patients, patients, doctors, and hospitals can all be considered consumers or users.

ii) Retail Level: This category covers establishments like grocery stores, pharmacies, hospitals, dispensing doctors, and nursing homes, among others.

iii) Wholesale Level: every stage of distribution from manufacturer to retailer. A recall approach should consider a variety of factors, such as the following:

1. The simplicity of product identification,
2. The extent of the product's Defi- quenches or the extent to which the consumer or user is aware of the potential of extreme inefficiency
3. How long a product stays on the market? It is classified as a Class III product when exposed to a product that is
4. Unused in the market and
5. Still readily available for essential sequences. (A recall strategy typically includes an assessment of the health risks. However, the centre typically includes this element in the recall plan after reviewing the district's RR.). A public announcement is intended to inform people that a drug product poses substantial health risks. The manufacturer must furnish the regulatory body with a public warning strategy **[4]**.

REASONS FOR RECALL:

The pharmaceutical industry is among the most significant in the world. Any bad news will have an impact on the economy of other, more robust industries. Recalling pharmaceutical products is not a requirement for any corporation because it tarnishes its reputation with consumers and regulatory bodies. It costs manufacturers and regulators money, and it wastes their time. In recent years, numerous big-scale finished goods that are frequently used to treat vast populations of people for common

conditions like diabetes and hypertension have been recalled due to the inclusion of unwanted contaminants. Drug goods were frequently recalled for the following reasons: sterility issues, labelling, the existence of particles, commercialization without an NDA or ANDA, drug potency, and failure to meet dissolving parameters **[2]**.

The Most and least reasons for recall are listed below in **Figure 2**:

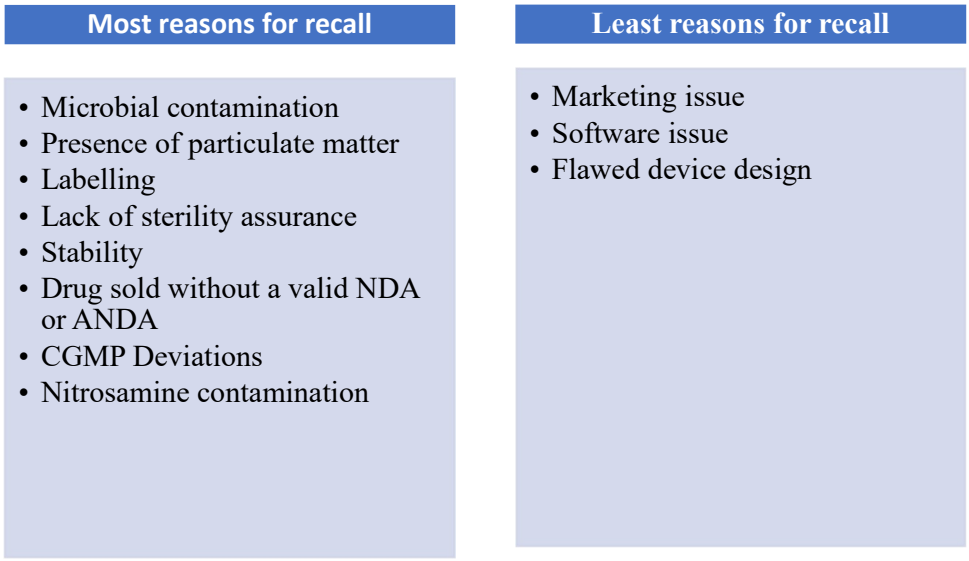

Figure 2: Most and least reasons for recall

Microbial contamination:

After a lack of sterility assurance in products, contamination with a microbiological organism in sterile pharmaceutical items ranks as the second most common cause of a recall. Among other bacteria, *Bacillus species, Candida species, Klebsiella species, Aspergillus species,* and *B. cepacia* have all been found in medicinal products **[2]**.

The pharmaceutical industry has long struggled with microbial contamination of non-sterile drug products. As a result, this problem has far-reaching effects that go beyond the obvious costs related to batch rejections or product recalls. To better understand the microbiological pattern and decide what may be done, it is crucial to understand the general microbial hazards involved in the life cycle of a medicinal product.

A QRM strategy will enable the identification, quantification, and prioritisation of risks as well as their mitigation strategies. Throughout the whole production process, QRM is a reliable method of ensuring the quality and safety of pharmaceuticals. Furthermore, 50% of the FDA's NCs were rated as moderate risk and 50% as low risk. 7% of the EMA were

deemed to be high risk, 76% to be moderate risk, and 17% to be low risk **[5]**.

Presence of particulate matter

Following Microbial contamination 2nd topmost reason for a recall is the presence of particulate matter in production. Due to the fact that parenteral preparation in pharmaceuticals is among the most commonly susceptible to the presence of particulate matter, almost all parenteral include a few trace quantities of particulate matter to circumvent the guidelines for particulate matter issued by all regulatory agencies. For this condition, appropriate authority permits up to a certain amount of presence of particle matters, but not more than the set limits **[6]**. Particulate matter limitations were set by the USFDA for large-volume & small-volume parenteral, which manufacturers may abide through order to avoid drug recalls and various issues with quality that could endanger patients by obstructing blood vessels, inflaming the lungs, or causing severe allergic reactions **[2]**.

Labelling

The goal of pharmaceutical product labelling is to give patients clarity by including all necessary information on product labels, such as dosage forms, ingredient lists with amounts, production dates, expiration dates, and use guidelines unique to the patient. Since many patients read the labels before taking products, any error in the labelling of drug items could have serious repercussions and a significant impact on system integrity **[2]**. Manufacturers must follow stringent labelling laws in order to maintain their quality control system and keep these regulatory bodies under control.

The USFDA's professional preview mandates that all processed, speed up(15-day), and even if the reported incidents are recognised safety issues and labelled AEs, direct MedWatch cases be electronically forwarded and evaluated by qualified FDA drug safety evaluators to recognize unlabelled adverse events (AEs).

The FDA has published two guidelines on the phrasing and organisation of the adverse reaction, warning and precaution, contraindication, and boxed warning portions on the packaging of pharmaceutical products to educate stakeholders. The FDA Guidance and the normal approach drug safety assessors take when conducting post-marketing pharmacovigilance activities were matched in the GSL annotation **[7]**.

Lack of sterility assurance:

Parenteral formulations are more affected by the sterility issue than other formulations. Because sterility problems are primarily brought about by poor production and the integrity of container closures during the manufacturing process, terminal sterilisation is the greatest solution to reduce microbial load. Sterile drug products for the

industry were required to be created by the application procedure, organisational structure, and testing method, as per USFDA standards published under 21 CFR Part 211 Subpart F (sp. 211.113) **[2]**. A sterile final dosage form (FDF) product filling line with liquid or solid product filling looks to be simpler to control than an API plant because fewer production stages are required. Utilising a risk-based strategy, concentrating on key phases of pharmaceutical manufacturing, and incorporating this concept into their inspection **[8]**.

Stability:

Drug stability aims to preserve a substance's chemical, biological, physical, and biopharmaceutical qualities over the duration of its protective shell. Stability is frequently impacted by elements like temperature, light, pH, oxidation, and enzymatic degradation. External factors such as light cause drugs and their metabolites to deteriorate. Affected medications include nifedipine, nisoldipine, vitamin D, flunitrazepam, lomefloxacin, and lysergic acid diethyl amide. Methods for preventing the influence of covering samples, employing sodium lights, or ultraviolet-filtered lights on stability. Drugs including Simvastatin, Aspirin, Temazepam, Benzodiazepines, and Norepinephrine all degrade when the temperature rises. During sample collection, storage, and processing, the temperature can be lowered to lessen its impact on medication stability. Another element that has an impact on the medication and its metabolites is pH. Examples include cisplatin, camptothecin, clopidogrel, and gemcitabine triphosphate. For sample handling and storage, adjust pH as necessary; buffer samples properly **[9]**.

Without an approved NDA or ANDA, marketed

If a drug that is to be marketed requires the approval of competent regulatory authorities, who can grant authorisation following a review of the applicant's application in support of safety, efficacy, and quality. Drugs that are sold without this authorization pass typical results in class 1 recalls based on risk classification. The US Food and Drug Administration (USFDA) claims that all formulations abide by regulatory requirements for The US Food and Drug Administration takes appropriate action against unapproved drugs by either issuing an injunction or seizing illegal products for 1 year (grace time) following the day the market authorisation was approved. Unapproved drugs for the pharmaceutical sector are problematic for the approval regulatory organisations, harm the confidence and reputation of the patent holder of NDA, and pose a threat to public safety **[2]**.

CGMP Deviations

The pharmaceutical industry in Brazil is required to notify Agencia Nacional de Vigilancia Sanitaria - ANVISA and consumers when it recalls unsafe medications that pose a health risk. The WHO estimates that 10.5% of medical items sold in poor nations do not adhere to acceptable manufacturing practices and quality standards. For three years (2015–2017), the Brazilian pharmaceutical industry's nonconformities to good manufacturing practices were assessed. There were 485 inspections during this period, with 61.4% of the Brazilian businesses inspected being deemed satisfactory, 23.3% being placed "on hold," and 15.3% being deemed disappointing.

Qualification and validation, documentation, and facilities were the most often mentioned aspects of disability. In Brazil, a drug recall is defined as an action intended to remove a specific batch (batches) of the drug from the market immediately and effectively, supported by appropriate data or proof of a quality variation that may represent a health risk, or upon cancellation of its registration **[3]**.

Nitrosamine contamination:

NDMA is the 3rd reason for a recall in the industry. An organic molecule called nitrosamine is created through both natural and industrial processes. The World Health Organisation (WHO) estimates that exposure levels for adults should be 0.0003-0.001 ng/kg of body. However, it was described as drug impurities. The International Agency for Research on Cancer has categorised NDMA as Carcinogen when levels are exceeded.[10]

Numerous nitroamides, including N-nitroso dimethylamine (NDMA), N-nitro-N-dimethylamine (NDEA), and N-nitro-N-methyl-4-aminobutyric acid (NMBA), were discovered over the course of the inquiry into the Nitrosamines contamination incident. For NDMA (96 ng /day), NMBA (96 ng/ day), and NDEA (26.5 ng/ day), the FDA has established an acceptable intake threshold. By way of the manufacturing process, cross-contamination, product degradation, and direct introduction, nitrosamine impurities can enter drug products. While adding nitrite- or nitric acid-treated solvents to remove any remaining azide will result in nitrosamine impurities in pharmaceutical drug products. Using certain packaging materials like printing ink or lidding foil which contain amine source.

The medication that produces nitrosamine contaminants:

- Sartan medicine
- Rifampicin drug
- Ranitidine
- Metformin
- Champix pill. **[11]**

NDMA was initially discovered in Valsartan pills in June 2018. It is a medication that

blocks angiotensin II receptors. FDA voluntarily recalled Three batches of valsartan from Zhejiang

Huahai. To discover, NDEA in an Indian-made irbesartan API, several irbesartan drugs were recalled in October 2018. Losartan was recalled in March 2019 due to the presence of NMBA. The recall has an overall impact on 1159 potentially contaminated ARB products. Ranitidine and metformin were then found to contain NDMA **[12]**.

In December 2019 three metformin formulations were recalled after being identified as having excessive amounts of NDMA in Singapore, which was the first country to test 46 metformin formulations for nitrosamine contamination. Glorious Dexa Singapore and Pharmazen Medicals Pte Ltd., both based in Singapore, promoted the three medications. Following this, inquiries were opened in Canada and Switzerland, and many batches of metformin drugs were also recalled in these nations. Following that, inquiries started in the USA and the EU. Statements detailing the testing methods were issued in December 2019, however, it wasn't until the latter week of May 2020 that the USFDA officially advised recalls.

The examination of the 38 batches of metformin products showed that 16 batches from 11 businesses had NDMA levels discovered above the 96ng daily tolerable intake limit. The largest amount of NDMA detected in tablets was 1565ng, and there was significant batch-to-batch fluctuation even within the same business **[10]**.

Animals exposed to NDEA have been proven to be effective hepatocellular cancer experimental models. Furthermore, several rat model experiments revealed that ethanol consumption would activate metabolic proteins including CYP2E1, increasing NDMA- and NDEA-mediated DNA alkylation **[13]**.

Methods for detection of Nitrosamine impurities:

Starting with quality control, nitrosamines as contaminants in pharmaceuticals can be eliminated or reduced. The following techniques for identifying NDMA contaminants in pharmaceuticals have been made public by the FDA.

- Headspace Chromatography/Mass Spectrometry Method (GC/MS).
- The Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) **[11]**.

Most drugs recalled problems in the last five years (**Figure 3**) **[14]**.

FDA has collected data on recalled products from various companies on different problems. Some of them are given below in **Table 2** for reference **[14]**.

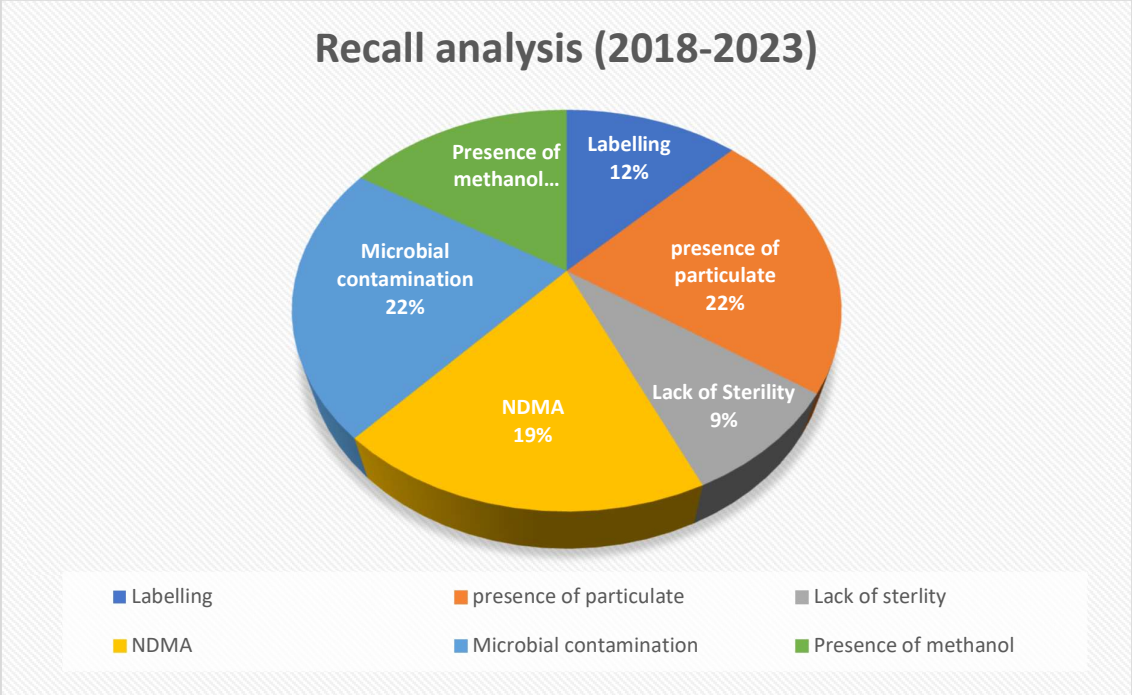

Figure 3: Most drugs recalled problems in the last five years

Table 2: FDA data on recalled products from various companies on different problems

S. No	Reason	Product	Year	Company name	Brand name	Problem
1.	Labelling error	1. Dronabinol Capsules 2.5mg and Ziprasidone Hydrochloride Capsule 20mg 2. Infusion Bags (Levetiracetam in 0.54% Sodium Chloride Injection) 3. Insulin glargine (Insulin galgineyfgn) injection	06/14/2023 02/04/2019 04/12/2022	The Harvard Drug Group, LLC d/b/a Major Pharmaceuticals and Rugby Laboratories Dr Reddy's Laboratories Ltd. Mylan Pharmaceuticals, Inc. a Viatris Company	Major Pharmaceuticals Dr Reddy`s Laboratories Ltd. Mylan	Packaging may contain incorrect product due to labelling mix-up Mislabeling Lable may be missing on some vials

2.	Microbial contamination	1. Atovaquone Oral Suspension	03/31/2023	Camber	Camber Pharmaceuticals, Inc.	Potential Bacillus cereus Contamination
		2. Wound Care Gel	01/27/2022	RevitaDerm	Blaine Labs Company	May be contamination with bacillus cereus
		3. Clobetasol Propionate	12/30/2021	Taro	Taro Pharmaceuticals, USA, inc.	Presence of Ralstonia Pickett bacteria
3.	NDMA	1. Dabigatran Etexilate Capsules, USP	03/22/2023	Ascend Laboratories	Ascend Laboratories LLC.	Detection of N-nitroso-dabigatran (NDAB) Impurity
		2. Metformin Hydrochloride Extended-Release Tablets	01/12/2022	Viona	Viona Pharmaceuticals, Inc	N-Nitrosodimethylamine (NDMA) Impurities.
4.	Lack of Sterility	1. Brimonidine Tartrate Ophthalmic Solution, 0.15%	03/02/2023	Apotex	Apotex Corp.	Potential lack of sterility
		2. 15% MSM Drops	03/03/2023	Purely Soothing	Pharmedica USA LLC	Non-sterility
5.	Stability	1. over the counter drug	05/04/2023	Advil	Family Dollar	The product was stored outside of labelled temperature requirements.
		2. Epinephrine bulk API	01/09/2023	Spectrum	Spectrum Laboratory Products Inc.	Product discolouration

IMPACT OF RECALL

Pharmaceutical items that are voluntarily or involuntarily recalled might impact on manufacturer's vulnerability to product responsibility in several different methods. Evaluations of the effects of recollection are done as a result. Pharmaceutical product recalls have the potential to affect many different aspects of the pharmaceutical industry, involving market dominance, business science, public health, supply chains, dispersion, the losing protection of patents for many drugs, and the public image of pharmaceutical companies **[2]**.

REDUCE RECALLS

Firm-Initiated Recalls

A company may at any point delete or alter a medicine that has been distributed. A company is typically not required by law to inform the FDA when recalling a faulty product, yet if the company feels the product violates the law, it is asked to inform the FDA district office **[15]**. The FDA district office is then required to pass out a "24-Hour Alert to Recall Situation" to advise the

CDFR and the DEIO. The district must send its RR (Recall recommendation) to the centre within five working days, and it must evaluate the company's capacity to carry out an efficient recall.

1. The brand of the recalled item,
2. The reason for the recall or fix, as well as the events leading up to the product's flaw's discovery,
3. The recalling company's assessment of the health risk,
4. The amount of products changed by the recall that was made within the required time frame.
5. An estimate of the total number of products in the supply chain,
6. Details on distribution, as well as direct account identification,
7. A copy of the firm's put-forward recall notification,
8. A suggested plan for carrying out the recall, and
9. the name and phone number of the company representative who must be contacted about the recall.

The business must also develop a recall plan that considers the problems mentioned in the FDA-initiated recall plan **[16]**.

FDA Controls Over Prescription Drugs

Sections 351 through 360ee of the FDCA and the accompanying regulations provide specifics on how drugs are regulated, including the guidelines for adulteration, misbranding, marketing and distribution, advertising, obtaining permission to sell and distribute, manufacturing, and performance monitoring. The FDCA moreover has several benefits that allow the FDA to fine pharmaceutical companies who violate the rules.

Contrary to popular belief, the FDA only has the authority to require the recall of newborn formula, biological products, and medical equipment that pose a substantial threat to the public's health. The FDA does not have broad recall authority on all products under its purview. The FDA can only ask a pharmaceutical company to initiate a recall when it comes to medicines **[17]**.

Auditing the Recall

The district is in charge of conducting the recall audit in both FDA-requested and firm-initiated recalls. For those with Class I and II recalls, this entails examining the company's recurring recall status reports, carrying out inspections at the recall depth, and keeping an eye on or confirming product disposition. The company must also send regular status reports to the supervising district on the recall. The FDA uses recall status reports, district-level recalls, and audits to determine the efficacy of the recall. Firm recall status reports, unless otherwise specified, should include:

1. The number of recipients who were informed of the recall as well as how they were notified.

2. The number of consignees that did not reply to the recall & the number of products that each consignee had when they received the message about the recall,

3. The proportion of consignees who did not reply to the recall notification.

4. The number of goods recalled and returned.

5. The anticipated completion date of the recall **[18]**.

Automation system:

Approximately half of the recalls were caused by labelling and packaging errors; these mistakes frequently included omitting important information, printing them incorrectly, and failing to ensure that the text, design, and barcodes were accurate. Various pharmaceutical companies recognise the importance of these errors and have automated systems in place to prevent them. Automation technologies provide a comprehensive quality system for businesses to spot faults at every level of product manufacturing, preventing brand integrity and consumer impression **[2]**.

Total quality management (TQM):

Pharmaceutical businesses utilise total quality management as a systematic strategy to ensure long-term performance and customer happiness. With this strategy, everyone works together to enhance the services and goods. Pharmaceutical businesses have built quality systems as a result of using this technique, and recalls brought on by humans, systems, or failure to handle complaints faults can be significantly decreased. In general, it might be used as a preventive tool for pharmaceutical product quality issues and drug recalls. It mostly comprises the following four steps:

- quality inspections,
- quality control,
- quality management, and
- quality assurance **[19]**

Setting corrective actions and preventive actions:

"Corrective action Preventive action (CAPA)" is a quality management strategy utilised during product development in the pharmaceutical industry. It involves identifying the root causes of issues and taking several prudent measures and safeguards to address and eliminate the issue from the system. The application of ICH Q10 can be used to address all facets of the life cycle of a product, including technological transfer, commercial manufacturing, and product discontinuations. CAPA is essential in preventing and reducing the frequency of recall incidents in the sector **[20]**.

CONCLUSION:

For better quality and safety of drug products, recalls are performed in the pharmaceutical industry. In the past 5 years, the main reasons for drug recalls are Microbial contamination, Nitrosamine

contamination, the presence of particulate, labelling, stability and lack of sterility assurance. Industries should set risk assessment limits to control mistakes and errors. Due to bad media, a company's reputation will be damaged by the public. Practising CGMP and QRM tools will help in developing solutions for recalled drugs and reduce the economic loss of the industry.

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