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A Multidimensional Study: Drug Recall Monitoring

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ABSTRACT
Drug prescribing is the most important part of the document. The safety of drug products approved by US Food and Drug Administration is conducted in little number of individuals before it comes to the market. A drug recall process is an approach of the drug regulatory bodies to withdraw the medicine that can cause potential harm or its safety or efficacy. Number of drugs are known to cause hazardous effects in humans, but are still used. Some are been withdrawn voluntarily by some manufacturers and Regulatory Authorities due to their deficiency in the quality, safety or efficacy. When companies recognize or get information that their products are defective or dangerous, then they issue recollects on their own. The explanation for the recall will be divided into several classes. It is essential to follow all the guidelines that are related to drug development and manufacturing procedure to minimize drug recall. This article will provide an overview regarding of recall procedures, their impact and analysis on the pharmaceutical business, and therefore the various steps taken to scale back pharmaceutical recalls.
Keywords: Drug recall, drug safety, drug manufacturing, pharmaceuticals, research

I. INTRODUCTION:

Safety and quality of healthcare products and pharmaceutical preparations specifically are of nice concern to regulate by regulatory agencies such as the United States Food and Drug Administration (FDA). Every year, there are many recalls of drugs and healthcare products from the market due to varied reasons of defects, which can embrace violation of Good Manufacturing Practice (GMP), lack of adequate manufacturing control, inaccuracy of the measured results, software updates, stability failure, defective device parts, and lots of others.Thepharmaceutical industry as a whole has traditionally been terribly profitable, and also the internationalmarket had annual growth prediction of 5 to 8% [1-2].Nevertheless, amidst thelarge increase in the field, factors like product returns and recalls are giving the companies new challenges, such as litigation problems, negativepublicity, loss of patent protection for several major medication and widespread efforts to contain drug spending. On the opposite hand, increased competitiveness, quick dynamic structure of competitors, complicated strategic positioning, shrinking pipelines, counterfeit medication and a fight for international market share are adding more burdens to the expansion of the industry. A recall is a major problem. It highlights a dangerous state of affairs that need quick and effective action to protect the public from damage. Product recalls have become intensive and have exaggerated radically.A drugrecall is an instance to return to the maker a batch or an entireproduction run of a drug product, usually due to the detection of issues of safety or drug product defect. When drug products are known tohave potentially harmful effect on users due to their defective quality, safety or efficacy, they will be subjected to a recall and all related information's are reported to the drug workplace [3-5].

Regardless of a company's best efforts, that dangerouslydefective drug product might reach the purchasers. These products might cause disasters, resulting in adverse verdicts in drug product liability litigations. The quality management ofcomplaints and drug product recalls arenecessary toconfirm the safety of customer.However, there arecertain other cases when all batches or lots of the drugexperience recall from the market. Theaim ofpresent review is

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to target problem for drug recall like lack of sterility assurance, presence of particulate matter, unapproved new drugs,and presenceofundeclared therapeutically active moiety, microbial contamination, container/closure issues and a few alternative miscellaneous reasons.

Category of Drug Recall:

A drug recall happenswhen the Food and Drug Administration receives various adverse reaction reports from physicians with regard to a selected drug, or when the manufacturer realizes that there was a deficiency in their manufacturing process to put it simply, a drug recall removes the affected prescription or over-the-counter medicine from the market. Generally, a recall must be warranted by the high likelihood that the drug will cause very serious injury or death. While all drug recalls are not to be taken lightly, the FDA classifies them as Class I, II or III [6-8].

- Class I recall: Includes a health hazard situation where there is reasonable possibility that the use of the product will lead to serious, adverse health problem or death.
- Class II recall: Includes a potential health hazard situation where there is a remote possibility of adverse health consequences from the use of the drug product.
- Class III recall: Includes a state of affairs wherever the utilization of the drug product is not probably to cause adverse health outcome.
- Market withdrawal: Once a product encompasses a minor violation that may not be subject to FDA legal proceeding "market withdrawal" happens. The drug product is removed by the firm from the market or corrects the violation.
- Medical device safety alert: Released in circumstances where a medical device may present an unreasonable risk of substantial harm. These things are thought of remembers in bound cases.

Recall Level:

Aswith the classification, the extent of recall is to be assigned by Department of Health. In crucial the recall level, the principal factors to be considered are the importance of the hazard, the channels by that the pharmaceutical products are distributed, and also the level to that distribution has taken place.

There are threelevels of recall - Wholesale, Retail and Consumer.

Wholesale level: During whichall parties concerned in wholesale distribution and should embrace wholesalers and retail pharmacies.

Retail level: In this all public and private pharmacies, Clinical investigators, the institutions in which clinical investigations are performed, Medical, dental, alternative health care practitioners and other retail outlets e.g., medical shops, supermarkets and health food stores.

Consumer level: This might vary with product, as well as any intermediate wholesale or retail level, patients and other consumers.

Reasons for Recall of the Product [9-10]

A dispensed product can be called back for various reasons. Some of the motivesmay be as follows:

1. Product complaintswith the aid of using customers revel that the product is sub-standard, and as a result the manufacturer decides to recall the product from market.
2. Regulatory or governing body officials find that a sample drawn by them from the market and analyzed by the government analyst's lab shows that the product is not as per label quality.
3. Sometimes stocks at various depots, etc. are affected by natural calamities like floods, etc. and get damaged. When this fact involves manufacturer, he recollects the product or asks to return the product.
4. The manufacturer himself may also locate the troubles with the product, together with substandard quality, which has been detected after the dischargeof the product, problems associated with the stability of the product.
5. Accidental harm to consignment might also takes place during transportation. In such a cases package might get broken and cannot be sold or dispensed as such in market and hence to be recalled.

Recall procedure

A recall is probably initiated if the involved parties can provide the Department of Health with a list of complaints or reports about the quality, safety, or efficacy of the pharmaceutical product sold by that company. Certain facts are critical to allow the evaluation of the validity of the report of quality defects, safety or efficacy problem with pharmaceutical products, the potential danger to consumers and the action appropriate to situation. Serious issues which can also additionally cause to recall of class1 or Class 2 must be reported to the Department of health

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within 24 hrs. after receipt of the grievance or report for investigation. For much less severe issues would result in class 3 recall, the pharmaceutical product issue report form should be sent to department of health and it should not later than 72 hrs. after receipt of compliant or report of a problem. It should be noted that the licensee has send the pharmaceutical product problem report form to department of health prior to their decision on recall.

When the licensee decides to initiate a recall of a pharmaceutical product, it is required to notify the recall situations with the recall notification form. The licensee shall not wait to submit this information until all applicable information is prepared and assembled prior to notification to the department of health. The information requires details of the problem with including Name, telephone number of the person, date of report, location of the problem and severity of that problem. Another information required is to details of the product and health hazard evaluation and proposed action. After that assessment and evaluation of product recall is carry out. The procedure is divided into following stages [11-12].

1. Receipt of Pharmaceutical Product Problem Report Notification to Department of Health.
2. Initiation of Recall
3. Assessment of Recall
4. Recall
5. Progress of recall and Report
6. Evaluation of the recall

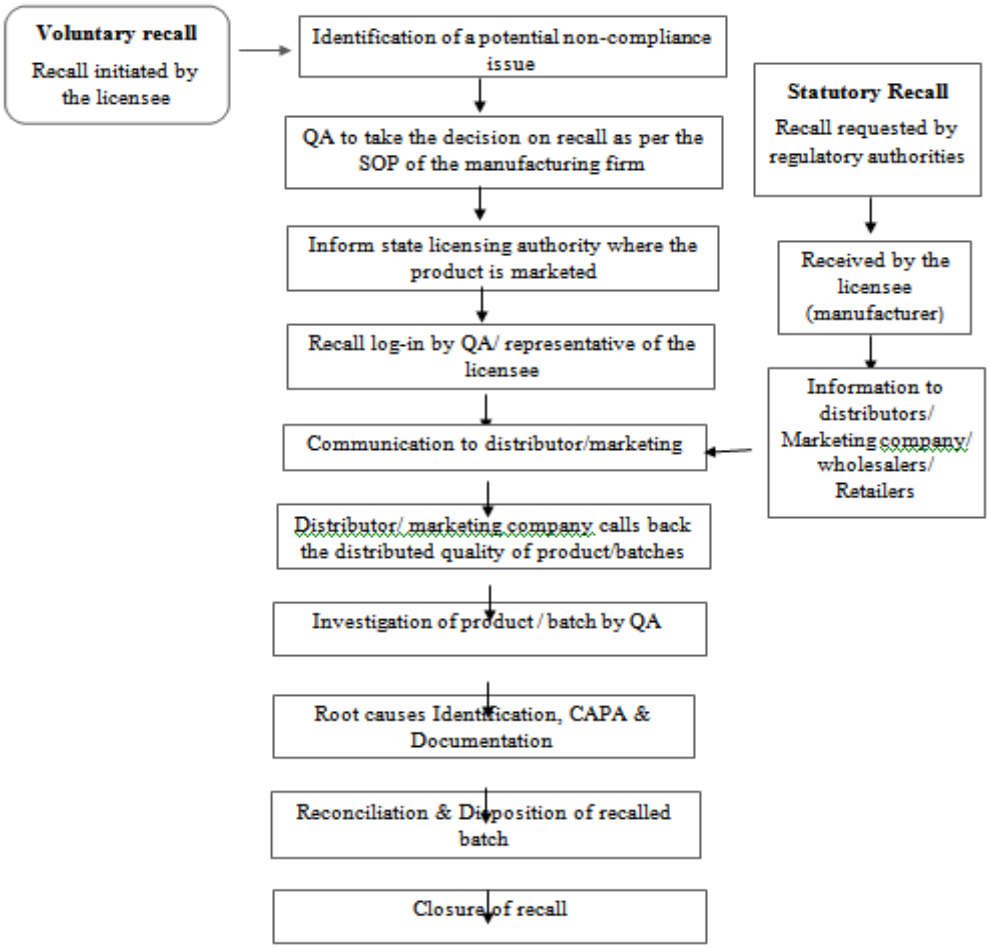

Fig: 1 Recall Procedure

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Minimization ofproduct recalls

The drugs recall makes the pharmaceutical company's financial situation in bad condition. The reputation of the company decreases due to recalls. Minimization of recall can be done by following way.

- By ensuring compliance with regulations and standards.
- By providing legal protection as well as a drug product and corporate brand protection through better response times.
- By decreasing cycle time and production costs by speeding up quality and process efficiency.
- By reducing the risk of missing or incomplete data through closed-loop product recall decision-making process.
- By providing flexible yet monitored environments through fully configurable process workflows.
- By improving the quality of the product via operating processes by integrating with the best quality control systems.
- By increasing operational transparency.
- By increasing responsibility through automated audit trials.

Analysis of pharmaceutical product recall

The pharmaceutical industry is one of the most important industries in the world, with total global revenue of $1.3 trillion, nearly $20.1 billion of which comes from the Indian Pharmaceutical industry and any negative news will affect the economy of healthy industries.Recalling drug products is not an obligatory action for any company because it creates an unfavorable image in the eyes of the consumers and regulatory authorities. It results in financial loss, waste of valuable time for manufacturers and regulators [13]. Various major finished products that are commonly used for treating large populations for common diseases like diabetes, hypertension have been recalled in recent years due to presence of undesirable impurities. The common reasons for the recall of drug products were due to sterility issue, labeling, presence of particulate matter, marketed without an approved NDA/ANDA, potency of drugs, failed in dissolution specifications [14].

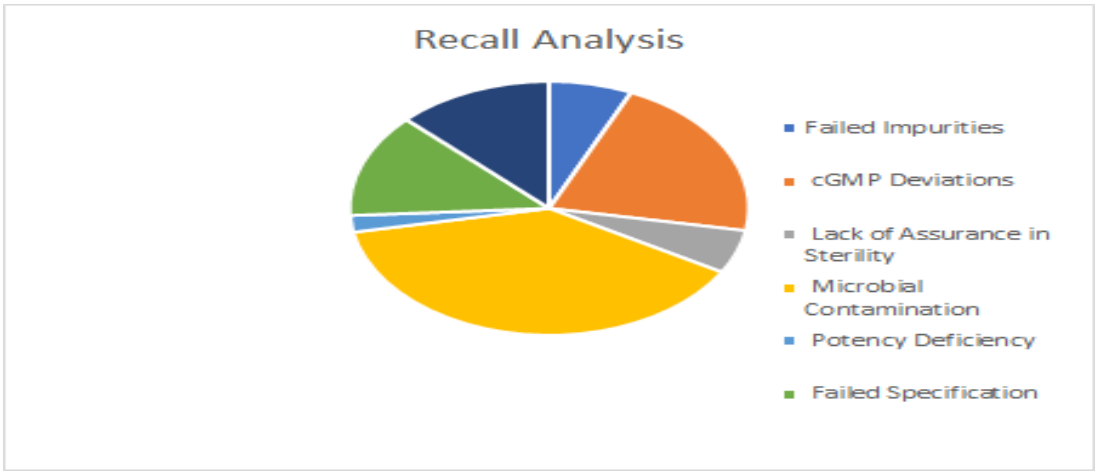

Fig: 2 Recall Procedure

Issue related to product recall:

1. Unapproved New Drug

The FDA's evidence-based system of drug approval and the OTC monograph system play essential roles in ensuring that drugs are both safe and effective. For instance, during the drug approval process the applicant must demonstrate that its manufacturing processes can reliably produce drug products of excepted identity, strength, quality and purity. The manufacturers of unapproved drug products have not received FDA approval and do not conform to a monograph for making Over-the-Counter (OTC) drugs. Unapproved drugs are not generic medications, and neither their safety nor efficacy can be assured [13].

2. Presence of undeclared Therapeutically Active Moiety:

Falsified and substandard drugs may contain toxic ingredients. Medications for chronic and infectious diseases alike have been found falsified and substandard. Data from the FDA

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office of criminal investigation indicate that pills and tablets are the most commonly compromised products they investigate, mostly produced by individual criminals. The WHO is developing a system for the global surveillance and monitoring of falsified and substandard drugs.

3. Microbial Contamination:

One of the most important areas in pharmaceutical process control is the development of the systems to control the number, survival and proliferation of microorganisms manufacturing of non-sterile and sterile pharmaceutical products.

4. Presence of particulate matter:

Parenteral formulations are one of the most susceptible to presence of particulate matter, to nullify these all-regulatory agencies issued guidelines for particulate matter. Authorities allow the presence certain amount of particulate matter but not exceeding the set limits. (19) USFDA set limits of particulate matter for both Large Volume Parenteral (LVPs) and Small Volume parenteral (SVPs) which can be followed by manufacturer to prevents recalls and any other quality defects problem which cause harm to consumers [14].

5. Lack of Assurance of sterility:

Major reason for recalls, in the last 5 years recall due to sterility issue. Mainly sterility issue occurs in the manufacturing process due to poor manufacturing and integrity of container closure. To reduce recall due to lack of sterility terminal sterilization is best choice to minimize microbial load.

6. Marketed without an Approved NDA/ANDA.

To market any drug whether its NDA or ANDA company needed approval from regulatory authorities which can give authorization to an applicant. After reviewing of data for safety, quality, and efficacy, marketed without approval will be a reason of mostly class I recalls according to risk.

FDA take appropriate action against either it is order or seizure of unapproved products in 1year from the date of approval of market authorization.

7. Labeling

Labeling of pharmaceutical products provides clarity to the patient and tries to make the quality system transparent for the ease to consumer by providing all the essentials details on the label of the products including dosage form, ingredients with their quantity, manufacturing date, expiry date, use of direction for patients.

Any mistake in labeling of drug products may lead to serious complication and affect the system integrity to large extent in many patients.

Impact of recall

Recalls of pharmaceutical products, whether voluntary or requested, can affect the manufacturer's product responsibility exposure in a various way. Recalls of drug impacts the market shares, compare shares, corporate science, public health, supply chain and company's reputation.

Steps to reduce the recall

Recalling drug products is serious event that poses a numerous risk to the general public and public health, if it is not handled properly, it can result in harm and increase the health incident.

The recall is curse for pharmaceutical companies, as to maintain the good reputation to public(market) and relationships with authorities. As the numberof recallshas increased rapidly in recent years, the majority of them were due to lack of quality, and other errors and issues. Preventive the cause is one of the best methods to reduce recalls.

Compliance with regulatory agencies – To reduce recall or quality defects company must adhere to laws, guidelines, regulations to meet requirement.

Follow cGMP (Current Good manufacturing Practice) – recall due to lack of good manufacturing practices hold a large number and raise serious concern. WHO cGMP and 21 CFR part 210 & 211 to control the defects and their consequences [15].

Automation system- Around half of the recall was due to labeling and packaging error, printing error, accuracy text, design, barcodes were the common reasons. The various pharmaceutical industry company's accepts the automation system to prevent these. Automation technologies help to detect human errors, prevents brand honor, automation provides an all-in-one quality system for companies to identify errors at every stage of production of products [16].

Total quality management- is a systemic approach adopted by the pharmaceutical company for customer satisfaction. In this all the members are work together for the improvement of the services and their products. It mainly comprises four main steps that are quality inspections, quality control, quality management and quality assurance which can generally implement as preventive,

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measure for the drug recall and quality defects in products [17].

A risk management program can reduce the occurrence of recalls.

The following strategies for managing recalls:

1. **Reducing risk:** Strict quality control measures have to follow from product development onwards to prevent the recall.
2. **Assuring risk:** find out the difficult possibilities due to which recall happens is another strategy to predict and revolve the recall issue.
3. **Transferring risk:** the third-party, who is also involved in making the product, who is capable of share risk and to pay for the costs of a drug recall, could help to overcome recall loss. [3]

Root Cause Analysisand Corrective and Preventive Actions:

An appropriate level of root cause analysis work should be applied during the investigation of quality defects. In cases where the true root cause of the quality defect cannot be determined, consideration should be given to identifying the most likely root causes and to addressing those.Where human error is suspected or identified as the cause of quality defect, this should be formally justified and care should be exercised so as to ensure that process, or system-based error if present.Appropriate CAPAs should be identified and taken in response to quality defect. The effectiveness of such actions should be monitored and assessed.Quality defect records should be reviewed and trend analyses should be performed regularly for any indication of specific or recurring problems requiring attention. [14]

II. CONCLUSION

There has been increasing trend in the number of prescribed and OTC drug recalls over the last few years. The recall is usually due to company's discovery, customer's complaint or FDA observation. The critical recall information list includes the identity of the product, summary of the failure, amount of product produced in the distribution chain and direct account. Drug recall is incubus for pharmaceutical companies as it effects the reputation of the company. To alleviate this global issue, regulatory agencies such as CDSCO, USFDA and the European Medicines Agency have given their continuous effort. However, it is a challenging task for researchers and industrialists to explore innovative techniques and methods for precise estimation of impurities from various pharmaceutical products.As a result, researchers must accept recall events and begin working on preventive measures to minimize their effects and develop a system to control them by improving work culture and providing training to their employees. For industry, recalls can be a disaster, it affecting everything from the company's reputation in the market to its bottom line. However, by properly executing recalls and taking various preventive measures, recalls can be controlled or the risk of an unavoidable recall reduced.

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