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Original Article

Handling of Recall in Pharmaceutical Industries

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ABSTRACT

D*rug recalls occur almost every year, and there are certain measures to certify the recalls. The recalls may be due to the discovery of the company, customer's complaints or Food and Drug Administration (FDA) observation. The process of recall involves a planned specific course of action, which addresses the depth of recall, need for public warning, and the extent of effectiveness checks for the recall. The FDA review and/or recommend changes to the firm's recall strategy, as appropriate. 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. Product recalls clashes thousands of companies every year affecting: sales, testing customer relationships and disrupting supply chains. Drug recall is incubus for pharmaceutical companies. It effects the reputation of the company.[1]*

Keywords: *Drug product recall, Food and Drug administration, process, critical recall information.*

INTRODUCTION:

Recall is a process for withdrawing a pharmaceutical product from the market or distribution chain due to the defects in the product or any complaints or adverse reactions by the product.

The board of pharmacy and poisons will control the effectiveness of recall activities and provide technological, organizational and scientific advice during recall. If the company's recall efforts are inadequate then the board will take necessary measures to remove the drug from the market. [2] Regulation 28(8) & 33(5) of the Pharmacy and Poisons rules need a holder of a wholesale dealer licence and a manufacturer to line up and maintain a system of management that may alter the rapid and, to this point as practicable, complete recall of any lot or batch of a pharmaceutical substance or product from sale to the general public within the event of the pharmaceutical substance or product being found to be dangerous or injurious to health. It is obligatory that each one licensees comply with Pharmacy and Poisons Ordinance and associated Regulations. Any person who is guilty of an offence under the above provisions of regulation is liable on conviction to a fine of $100,000 and to imprisonment for 2 years.

The role of the Drug Office of the Department of Health in an exceedingly recall is to assess the adequacy of the Licensee's decision on the recall of the product and to monitor the progress and effectiveness of the recall. The Drug Office could alert the general public of the product problem and instruct the Licensee to recall and eliminate the product according to the circumstances. [2]

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1.1. OBJECTIVES

- Sale and distribution of affected product must be stopped.
- Regulatory authority, management and customers must be notified regarding recall of product.
- Affected product must be removed from the warehouse, market place efficiently.
- Effectiveness and outcome of recall must be reported by conducting root cause analysis.
- Corrective action plan must be implemented to prevent another recall.[3]

2. CAUSES:

The following are the reasons for recall:

- Serious adverse reactions reports not included in the package.
- Labelling of the product is incorrect.
- Formulation of the product is incorrect.
- If any unexpected adverse reactions occur then product is recalled.
- Ongoing stability studies report is improper. [1,4]

3. CLASSIFICATION[5]

Recalls are divided as follows:

3.1. Class I:

This form of recalls occurs when goods are potentially life-threatening or may pose a significant health danger.

E.g. include:

- Wrong Product (Contents of the products and labels are different)
- Product is correct but wrong strength.
- Contamination due to microbes in sterile injections and ophthalmic.
- Chemical contamination
- Mix ups
- Wrong API

3.2. Class II:

This type of recall takes place when the defects of the product might cause illness.

Examples:

- Mislabelled product
- Missing or wrong information.
- Contamination due to microbes in non- injectable and non- ophthalmic sterile products.
- Specification non- compliance
- No proper closures

3.3. Class III:

This type of recall may take place when the defect of the product doesn't cause a significant hazard on health of patient, but recall must be initiated.

Examples:

- Faults in packaging i.e. expiry date or missing of batch number or wrong batch number.
- Faults in closure.
- Contamination

Class I and II must be considered as immediate health recalls. This must be reported for review and investigation to the Department of Health.

Class III is linked to non-safety recalls.

4. LEVELS OF RECALL

Department of health must assign the level of recall along with its classification. Significance of hazard, level to which distribution took place and the channels by which products are distributed must be considered as important factors to determine the level of recall.[6]

Three levels of recall:

Wholesale level: It covers all wholesale distribution parties, and can include wholesalers and retail pharmacies.

Retail level includes:

- Retail pharmacies
- Public & Private pharmacy
- Nursing homes
- Dental and medical practitioners.
- Clinical investigators
- Other outlets for retail

Consumer level: It includes:

- Consumers and patients
- Wholesale and retail levels.

5. TYPES OF RECALL [7]

Type A : This type of recall is designed to reach all the medicine suppliers i.e. all the wholesalers throughout the country, retail outlets, doctors, directors of hospitals, pharmacists, nurses, etc.

Type B: This form of recall is intended to include wholesalers around the country, hospital services administrators, retail stores, doctors, nurses, pharmacists, licensed prescribers and dispensers.

Action: Letter of recall to all distribution points.

Type C: This sort of recall is intended to hit wholesale and other points of distribution (e.g., stores, physicians, hospitals). This can be done by members who call wholesalers and/or retail outlets. If it is known where the product in question was distributed to, it may be possible to make specific phone calls or letters of recall to arrange the return of the product.

Action: Precise telephone calls, if known where the drugs were delivered, letters to / representatives calling at the distribution points.

6. GENERAL PROCEDURE TO HANDLE RECALLS:

Quality assurance will investigate if there is any complaint from a consumer or from the Drug Control Authority.

- After investigating and evaluating the complaints then QA manager must initiate the Recall.
- Class of Recall will be decide based on the evaluation.
- Quality Head shall be notified by the following information:
  - ✓ Explanation for taking of action and the complete identity of the product must be provided.
  - ✓ Date of action
  - ✓ Evaluation of risks
  - ✓ Quantity of the product to be recalled must be specified.
  - ✓ Recall level
  - ✓ Drug control involvement extent.
  - ✓ Specify if there is any complexities or any special problems
  - ✓ Preventive action must be recommended
- If the recall level is of type I or II / if the recall is initiated, Drug Control Authorities will notify it to the QA head of the site.
- Head of Distribution and Marketing must be informed about the recall and necessary product information. Further distribution will be stopped and gives clear directions regarding recall.
- Recall communication must obtain stock information of product which must be recalled and must get confirmation that further sale or distribution is stopped. These type of products must be quarantined. Depending upon the level of recall, person will be sent to all the depots, chemists and hospitals to check whether recalled products are quarantined.
- If the product defect is Class I, then the drug must be recalled by sending announcement to customer level and making public announcement by using media to all chemists, customers and distributors.
- Head of Distribution / Marketing must check whether the information has reached everyone by making calls or personnel visits to their locations.
- If the product defect is Class II, announcement must be sent to field staff and distributors. Distributors must discontinue the sale of the product batch.
- If the product defect is Class III, then the recall of product from distribution outlets.

- Entire stocks which must be recalled, should be collected to Warehouse and must be held under strict security.
- Quality Head of the site must instruct the manager of warehouse about where the material should be transferred for disposal.
- Destruction must be accomplished under the supervision of representatives of QA department Production department.
- Destruction records must be maintained for six months after the date of expiry. [8,9,10]

7. RECALL NOTIFICATION

It is statutory that the company notifies the Registrar, Pharmacy and Poisons Board or, in his absence, his nominee immediately after becoming aware of the issue, before or after implementing a recall. If the warning fails, the drug must be recalled as a matter of urgency, the company can proceed according to its preference and follow up the pharmacy contact and Poisons Board to be pursued in the process. [11]

8. BASIC INFORMATION REQUIRED FOR RECALL

- Name of the product, strength of the product, size of package, assigned batch number and any identification of the recalled product.
- Total quantity of the recalled product.
- The date of distribution of the product.
- Area where the product is distributed and if exported, to which country is it exported.
- Customers list for whom the products were issued
- Nature of defect and the reason for initiating the recall.
- Suggested action to be taken and its urgency [12]

9. HEALTH HAZARD ASSESSMENT

Before conducting a recall, the organization must monitor, compile and analyze all existing information on the magnitude and nature of the risk to safety. An assessment of the health threat posed by a drug to be recalled or recommended for recall shall be carried out by the Board of Pharmacy and Poisons and shall take into account, but not be limited to, the assessment of the factors following:

If any illness has arisen due to drug Danger to different parts of the population, such as babies, surgical patients, etc., would be at greater risk as they are exposed to the products.

The degree of severity of the health threat to which the public will be exposed at highest danger.

The chance of danger incidence [13]

10. INITIATION OF RECALL

If the Licensee wants to conduct a recall of a prescription product, it has to inform with the Recall Notification Form the recall situations. The Licensee must not wait until all relevant information is processed and collected until the Department of Health is informed of this information.

This "early" notification is required to enable the Health Department to comment and review on the written notice, and to provide guidance and assistance in the recall process. [14]

Necessary information includes:

10.1 Problem details:

- Name, contact number & Fax number of the individual who reports the problem
- Date of Report
- Problem location
- Nature of problem
- Number of reports received which are similar
- Test results

10.2 Product **Description**

- Product name and definition including dosage from, active ingredients, registration no, power, size of pack or form.

- Batch number, and date of expiry.

- Manufacturer / distributors and contact details, fax and e-mail numbers.

- Mfg Date and the release date

- Quantity of the batch,

- Local distribution list

11. RECALL POLICY

The following must be considered while a policy is being formulated for recall

Health hazard evaluation result

Ease of product identification

To what extent is the deficiency of the product is clear to the customer

Essential product's availability [15

12. ELEMENTS OF A RECALL STRATEGY

- The extent of the recall depends on the degree of the product's hazard and the extent of its distribution; the recall strategy must specify the extent to which the recall extends within the distribution chain as follows:
- Consumer or user level as well as any intermediate wholesale or distributor or retail level
- Retail level as well as any intermediate wholesale or distributor level
- Wholesale level.
- • Recall the company's contact with any or all involved parties. [16]

13. COMMUNICATION OF THE RECALL

- It is the responsibility of the recalling company to promptly notify the parties involved, regarding recall & the same must be communicated to the board. The material, structure, and scope of the recall communication will correlate with the product's danger and the plan developed for that recall.

Recall communication must convey:

- That the product involved is subject to recall
- Any further sale or use of the remaining product must be immediately discontinued.
- The instructions on what to do with the items. [17]

14. RECALL COMMUNICATION IMPLEMENTATION

Recall communication can be done in following ways:

- ✓ Phone
- ✓ Telegram
- ✓ Public media
- ✓ Special delivery

- In serious cases, MEDICAL RECALL and URGENT must be written in bold red letters.
- Public warning is necessary for dangerous products. [18]

15. RECALL COMMUNICATION CONTENTS

It should:

- Be short
- Name & strength of the product, pack size & other description of product.
- Defect nature is indicated
- Action urgency must be specified
- Reason for action must be indicated
- Health risk must be specified
- Specific instructions must be provided regarding what should be done with the recalled product. [19]

16. POST RECALL PROCEDURES

The Pharmacy and Poisons Board (PPB) must be provided with a report within 2 weeks of the recall. The report must contain the following information:

- Product name
- Product strength
- Size of the pack
- Batch number
- Nature of defect
- Action taken
- Urgency of the action
- Reason for action
- Indication of health risk
- Preventive action

Full reconciliation must be submitted within 90 days from closure of recall. [20,21]

Example for drug recall:

- Recently many of the Sartan drugs such as irbesartan, valsartan, etc.. were known to contain nitrosamine impurities which were harmful to the patients. Hence, the drugs were tested for Nitroso dimethylamine (NDMA) content and the drugs found with these contents were recalled immediately and necessary

modifications were to be made in the manufacturing process.

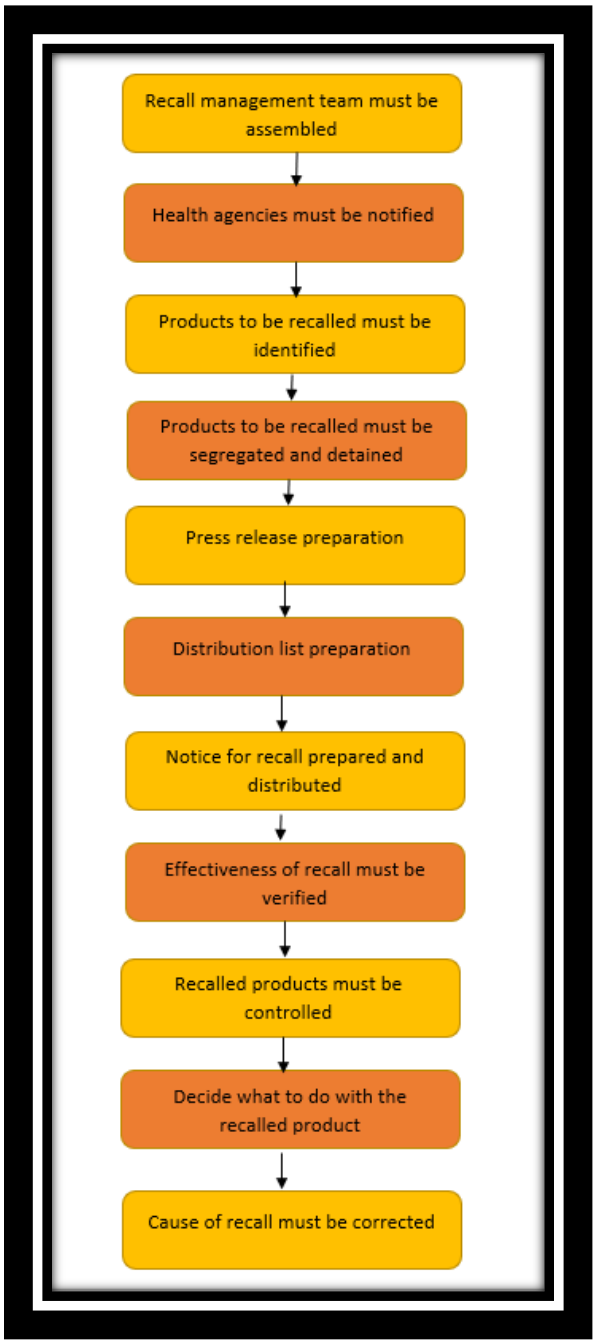

Fig: 1: Product Recall Flow Chart

17. **Drugs recalled in the year 2019 due to presence of NDMA impurity:** [22]

Table 1: Drugs recalled in the year 2019

Product description	Reason for recall
Ranitidine Tablets 150mg and 300mg	NDMA (Nitroso dimethylamine) impurity
Ranitidine Tablets, 150 mg and 300 mg, and Ranitidine Syrup (Ranitidine Oral Solution, USP), 15 mg/mL	Due to potential N-Nitroso dimethylamine (NDMA) amounts above levels established by the FDA
Ranitidine Oral Solution, USP 150 mg/10 mL	Potential presence of N-Nitroso dimethylamine (NDMA) above levels established by the FDA
Ranitidine HCl 150mg and 300mg Capsules	Potential presence of N-Nitroso dimethylamine (NDMA) above levels established by the FDA
Ranitidine Liquid Unit Dose Cups	NDMA (Nitroso dimethylamine) impurity
Ranitidine	NDMA (Nitroso dimethylamine)
Ranitidine Syrup (Ranitidine Oral Solution, USP), 15mg/mL	Due to above levels of N-Nitroso dimethylamine (NDMA)
Ranitidine Hydrochloride Capsules 150 mg and 300 mg	May contain N-Nitroso dimethylamine (NDMA)
Ranitidine Tablets & Capsules	Contains N-Nitroso dimethylamine (NDMA)
Zantac 150, Zantac 150 Cool Mint, Zantac 75 (OTC Products)	May Contain N-Nitroso dimethylamine (NDMA)
Ranitidine (all pack sizes)	Presence of N-Nitroso dimethylamine (NDMA)
Ranitidine Tablets 75mg and 150mg	Contain a nitrosamine impurity called N-nitroso dimethylamine (NDMA)
Ranitidine Hydrochloride Capsules	Due to an Elevated Amount of

	Unexpected Impurity, N-Nitroso dimethylamine (NDMA)
Losartan Potassium Tablets, USP and Losartan Potassium/Hydrochlorothiazide Tablets, USP	Due to the Detection of N-Methyl nitroso butyric acid (NMBA)
Losartan Potassium USP	Due to The Detection of N-Nitroso N-Methyl 4-Amino Butyric Acid (NMBA)
Losartan potassium tablets	Detection of an impurity – N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)
Irbesartan Tablets, USP 75 mg, 150 mg, and 300 mg dosage forms	Due to detection of NDEA (N-Nitroso diethylamine) Impurity
Losartan Potassium 25 mg and 100 mg Tablets USP	Due to The Detection of N-Nitroso N-Methyl 4-Amino Butyric Acid (NMBA)
Losartan potassium tablets, USP; Losartan potassium and Hydrochlorothiazide tablets, USP	Due to The Detection of N-Nitroso N-Methyl 4-Amino Butyric Acid (NMBA)
Losartan Potassium USP	Due to The Detection of N-Nitroso N-Methyl 4-Amino Butyric Acid (NMBA)
Losartan Potassium USP	Due to The Detection of N-Nitroso N-Methyl 4-Amino Butyric Acid (NMBA)
Losartan Potassium USP	Due to the Detection of Trace Amounts of N-Nitroso N-Methyl 4-amino butyric acid (NMBA)
Valsartan Tablets USP	Due to detection of N-Nitroso diethylamine (NDEA)
Valsartan and Amlodipine and Valsartan tablets	Due to the detection of NDEA (N-Nitroso diethylamine) Impurity
Losartan Tablets USP 25 mg, 50 mg, and 100 mg	Due to The Detection of N-Nitroso N-Methyl 4-Amino Butyric Acid (NMBA)
Losartan Potassium/Hydrochlorothiazide Combination Tablets	Due to detection of NDEA (N-Nitroso diethylamine) Impurity
Irbesartan and Irbesartan HCTZ Tablets	Due to the detection of NDEA (N-Nitroso diethylamine) Impurity
Losartan potassium tablets, USP	Due to the detection of trace amounts of N-nitroso diethylamine (NDEA)

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