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Review Article

Contingent analysis and evaluation of pharmaceutical product recall procedure of USA and India

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ABSTRACT

In this developed era with escalating health complications there are number of new drugs breaching the market. Post market clinical trials revealed that many drugs available in the market cause adverse effects. Regulatory authorities recall those defective drugs in the market based on the guidelines framed by the regulatory authorities of respective countries. In USA, guidelines for pharmaceutical product recall are described under 21 CFR Parts 7, 107 and 1270. In India, references for pharmaceutical product recalls, complaint and adverse reactions are mentioned in Para 27, 28 of Schedule M and conditions of license for defective product recall in Rule 74(j) and Rule 78(i) and banned drugs under 26A of the Drugs and Cosmetics Act, 1940 and Rules. In this paper we discussed about recall procedure of pharmaceutical products and comparative study in USA and India.

Key words: Recall, Regulatory Guidelines, Procedure.

INTRODUCTION

The pharmaceutical arena is widely spread, profitable sector and the global market is expected to grow 5 - 8% annually through 2014. To manufacture and market the pharmaceutical products first the manufacturer must follow the approval guidelines of the respective country's regulatory authority and after getting the approval the manufacturer is entitled to manufacture and market the drugs. Few a times the manufacturer or regulatory authority recall the products that is disbursed in the market when they receive complaints from any physician, consumer, pharmacovigilance person or if the manufacture observe any defects during the inspection or auditing of their product manufacturing process or in the market by the regulatory authorities. "Recall means a firm's removal or correction of a marketed product that the food and drug administration consider to be in violation of the laws it administers and against which the agency would initiate legal action" according to 21 CFR 7.3(g)[2]
Recall is a removal or correction of marketed products for the reasons related to deficiencies in quality, safety or efficacy, including labeling considered to be in violation of the laws according to Drug and Cosmetics Act 1940 & rules.

DISCUSSION

Recall Classification: Recalls classified into 3 types based on the extent of health risk on exposure of defective products.
Class I: In Class I recall there is a reasonable possibility that the use of, or exposure to, a defective product will cause serious adverse health consequences or death.
Class II: In Class II recall there is a possibility that the use of, or exposure to, a defective product may cause temporary adverse health consequences or where the probability of serious adverse health consequences is improbable.
Class III: In Class III recall the use of, or exposure to, a defective product is not likely to cause any adverse health consequences**.**

USA[3]: In USA FDA- Food and Drug Administration is the regulatory authority under Department of Health and Human Services. FDA frame regulations for Food, Pharmaceutical Drugs (Prescription and Over the Counter Drugs, Dietary supplements, Vaccines, Bio pharmaceuticals, Blood transfusions, Medical devices, Radiation emitting devices, Veterinary products, Cosmetics and tobacco products to protect public health and also monitor the recall of those products.

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LAWS AND REGULATIONS

The regulations for product recall given in different parts of 21 CFR

21CFR Part 7, Subparts A and C - Recalls - General guidelines

21CFR Part 107, Subpart E - Mandatory recall of Infant Formula

21 CFR Part 1270 - Human Tissue

PHS Act - 42 U.S.C. 262 - Mandatory recall of biological products

21 CFR Part 806 - Medical Device Corrections and Removals

FD&C Act, 518(e) - Mandatory Device Recalls

STEPWISE RECALL PROCEDURE IN USA[4]

1. Initiation of recall: Initiation of recall may be voluntary or statutory recall (FDA requested or FDA mandated).

Voluntary recall: If the firm wants to recall a product on its own (given in 21 CFR 7.46(a)). It happens when the firm detects any defect in product during inspection.

Statutory recall: If regulatory authority identifies any defect or violation of law during manufacture of product then they send a contact manufacturer to initiate recall then it is a FDA requested recall (given in 21 CFR 7.45). The Associate Commissioner for Regulatory Affairs (ACRA) approves all FDA requested recalls. If regulatory authority sends a letter to initiate recall is called FDA mandated recall. The firm should notify about recall to the district authority.

2. Recall alert: Within 24 hours after decided to recall a product the district should inform to CRU (Central Recall Unit) and OEIO (Office of Enforcement and Import Operations)/DE (Division of Enforcement). Then district submit the Recall Alert through RES (Recall Enterprise System) to CRU and OEIO/DE

Recall Alert should contain the following

- Product(s) Description
- Codes
- Recalling Firm
- Short Reason for Recall
- District Awareness Date
- Recall Initiation Date, with Type Initial Firm Notification
- Recall Status
- Voluntary or FDA Mandated Pick Lists, with Date

3. Recall Recommendation (RR): After submitting the recall alert within 5working days the district submits a complete Recall Recommendation to CRU and OEIO/DE through RES.

Recall Recommendation contain the following

- Product Description (INT), Trade Name, and Product Usage fields
- Code Information
- Recalling Firm/Manufacturer/Responsible Firm
- Reason for Recall Recommendation
- Volume of Product in Commerce
- Distribution Pattern

4. Official Samples: The district will collect samples to demonstrate the potential hazard.

5. Firm Recall Communication: Firm communicate about recall through fastest mode of communication such as press releases, telephone calls, telegrams, telefaxes, mailgrams, and first class letters. Guidelines given to Recall communication and it should contain following

- It should be brief and to the point
- To clearly identify the product(s) it should include product name, size, brand name, serial numbers(s), potency, dosage, type, model, lot number(s), UPC codes, Unique Device Identifier (UDI) etc.
- Should contain a concise statement of the reason for the recall
- It should state known or potential hazard(s), and instructions for consignees to follow in handling the recall

6. Health Hazard Evaluation and Classification of Recalling Product: CRU initiates health hazard evaluation for each recall. If the product identical to defect of previous recall product then they use precedent HHEs otherwise CRU forward information to Center Health Hazard Evaluation Committee. Center Health Hazard Evaluation Committee use work sheets to record their evaluation according to 21 CFR7.41 (a). Based on result of evaluation CRU classifies recall within 2 days.

7. Recall Number[5]: Generally after classification recall number given to that recalling product. Recall number assigned by responsible center for each recalled product. It consists of a letter which indicates the responsible center, 3 or 4 digit sequential number indicating the number of recalls initiated by that center in that year, a four digit number indicating that fiscal year. Example: F-100-2013 indicates the 100th recall by the Center for Food Safety and Applied Nutrition (CFSAN) in the year 2013

Letter		Center
F	-	CFSAN
D	-	Center for Drug Evaluation and Research (CDER)
Z	-	Center for Devices and Radiological Health (CDRH)
V	-	Center for Veterinary Medicines (CVM)
B	-	Center for Biologics Evaluation and Research (CBER)
N	-	Medical Devices (Voluntary Safety Alerts and Notifications)
A	-	Audit Numbers issued by the district performing the recall

8. Recall Strategy: Recall strategy based on the recall classification. If it's a voluntary recall then the CRU will review the recalling firm's recall strategy and give suggestions if required. CRU will develop recall strategy for FDA requested recalls. Recall strategy include type of notification, depth of recall, level of audit checks, need for public warning. If the regulatory authority approves an industry Corrective Action Program (CAP) for radiation emitting electronic product, any device then regulatory authority inform the firm that its CAP is classified as a recall.

9. Notification of other Government and Agencies: OECD/DE is responsible for maintaining contact with all other organizations like CRU, Office of Partnership (OP), Office of International Programs (OIP), and Media Relations Staff in the Office of Public Affairs etc. OEIO/DE informs the OIP of all Class I recall where product was distributed to foreign countries except Canada. OEIO/DE informs Canadian food, drug and device regulatory authorities of every recall in accordance with established communication agreement.

10. Public Warning: All recalls classified by agency will be included in FDA's weekly enforcement report. Recall press releases are posted in FDA's website 'Recalls, Marketing withdrawals, and Safety Alerts'.

11. Audit Checks: The district will issue audit check within 10days after issuance of RR. Audits are conducted to check the effectiveness of recall process. Recall effectiveness is recalling firm's responsibility. Sometimes recalling firm fail to check effectiveness where depth of recall extend to consumer level because retailers were not likely to disclose the information of their customers (patients) where the firm obtain agencies help. During FDA audit at any instant agency feel that recalling firm recall process is not effective then agency notify the firm. After notification firm show any interest to modify its recall then agency will take appropriate action such as multiple seizures and injunction.

12. Recall Termination: Recall will be terminated by FDA if the monitoring district concludes that the recalling firm has fulfilled all recall activity, recalled product disposition.

INDIA[6]: In India CDSCO (Central Drug Standard Control Organization) under Ministry Of Health and Family Welfare is a national regulatory body responsible for recalls of drug, medical devices, biological and vaccines.

LAWS AND REGULATIONS[7]: Guidelines on recall given in the Drugs & Cosmetics Act 1940 & Rules, there are references for drug product recalls, complaint and adverse reactions in Para 27 & 28 of Schedule M and also conditions of license for defective product recall in Rule 74(j) and Rule 78(i). Banned drugs under Section 26A

STEPWISE RECALL PROCEDURE IN INDIA[8]

1. Initiation of Recall: Recall initiated if they get complaints from any customer, physician etc. the complaint[9] should include

- Name, dosage form, package form, batch no
- Date and the place of occurrence of complaint
- Cause of complaint;
- Name and address of complaint in detail.

Any defects observed in the product which effect the safety and quality of product recall should be initiated without any delay (Section 25(3) and Section 25(4) of the Drugs & Cosmetics Act 1940 & Rules). Recall initiated may be voluntary recall or statutory recall.

Voluntary recall: Recall initiated by the manufacturer

Statutory recall: Recall initiated by Drug Control Authority

2. Assigning Recall Number: After taking decision to recall, the representative of recalling firm fill the **Recall log** and assign **Recall Number** to that product along with details (product name, product number, lot number, intended use, etc.,)

3. Recall Alert: The recalling firm representative should inform about recall product with seriousness of product effect on usage to all retailers, distributors, consumers using the fastest mode of communication which may include email, telephone, fax, SMS etc.

4. Notification to Regulatory Authority: If it's a voluntary recall the recalling firm should inform about recall to regulatory authority where the product in market. The DCGI member or Drug inspector of that area block that product to be recalled. The information about recalling product placed in **Safety Alerts** in CDSCO website (www.Cdsco.in).

5. Recall Classification of the Product: The state regulatory authority evaluates the degree of hazard involved with that product. Based on that evaluation they classify the product according to classification given by CDSCO in Drugs & Cosmetics Act 1940 & Rules.

6. Recovery of Stock: The distributors after receiving the recall alert they should inform to both their direct accounts and sub accounts. Immediately they should block the further distribution of that product to be recalled. The direct accounts and sub accounts return the stock available with them and also stock recovered from the customers to recalling firm storage head along with **Return Feedback**.

7. Follow-Up Action of Recalled Goods: Follow up action involves the activities to conduct audits to check the effectiveness of recall and also to investigate the reason for recall and also to rectify that mistake to prevent a recurrence of the defect. The returned goods of recalled products placed in Quarantine section and conduct inspection to know the root cause of the product defect. Based on reason for recall appropriate disposition method was employed by the licensee.

8. Recall Termination: After ensuring that the product recall completed within the stipulated time regulatory authority terminate the recall.

CONCLUSION

Pharmaceutical industry is one of the important sector to both USA and Indian economy. In this project study conducted on product recall procedure of pharmaceutical industry in USA and India. Recall of any product is not a good issue to any pharmaceutical company. Recalling a product is not an easy task because once the product entered into the market it is difficult to recover that product. The retailers were not likely to disclose the information of their customers (patients). Recall of any product is greatly affect the economy, goodwill of the manufacturing company. But if the company follows better management activities recalling it can be done smoothly. The number of recalls increasing year by year which greatly affects the public health so, need to decrease number of recall is necessary. The regulatory authorities and Pharmacovigilance should monitor the pharmaceutical firms closely to decrease the number of recall. The regulatory authorities should also monitor the disposing or waste management methods of recalled product because if they not properly dispose those potent drugs it may affect the environment and human health. Every pharmaceutical company should conduct mock recalls to ensure effectiveness of the arrangements of recall and also they should conduct internal inspections, audits to find any mistakes/ mishappenings during manufacturing process. They should maintain records of every batch

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Comparative Study of Recall Procedure in INDIA, USA

Feature under consideration	USA	INDIA
Recall definition	A Recall is a firm's removal or correction of a marketed product that FDA considers to be in violation of the laws it administers, and against which the Agency would initiate legal action	Removal or correction of marketed products for the reasons relating to deficiencies in quality, safety or efficacy, including labeling considered to be in violation of the laws.
Regulatory authorities responsible for recall	FDA-Food and Drug Administration regulates the recalls of drug, food, biologics, tobacco products, animal products.	CDSCO-Central Drugs Standard Coftrol Organization regulates recalls of drugs, medical devices, biologics, and vaccines. FSSAI-Food Safety Standards Authority of India regulates the recalls of food products.
Recall classification	3 classes	3 classes
Basis of classification	Based on relative degree of health hazard	Based on relative degree of health hazard
Types of recall	Voluntary recall, Statutory recall	Voluntary recall, Statutory recall(FDA requested/ FDA mandated)
Recall timeline	Timeline given by CRU based on product to be recalled.	• Class I - for a time line of within 24 hours up to a maximum of 72 hours. • Class II - up to a maximum of 10 days • Class III - up to a maximum of 30 days is allowed.
Rules and guidelines to recalls	The regulations for product recall given in different parts of 21 CFR 21CFR Part 7, Subparts A and C - Recalls - General guidelines 21CFR Part 107, Subpart E - Mandatory recall of Infant Formula 21 CFR Part 1270 - Human Tissue PHS Act - 42 U.S.C. 262 - Mandatory recall of biological products 21 CFR Part 806 - Medical Device Corrections and Removals FD&C Act, 518(e) - Mandatory Device Recalls	Given in Para 27, 28 of Schedule M and conditions of license for defective product recall in Rule 74(j) and Rule 78(i) and banned drugs under 26A of the Drugs and Cosmetics Act, 1940 and Rules

Flow Chart of Recall Procedure of USA

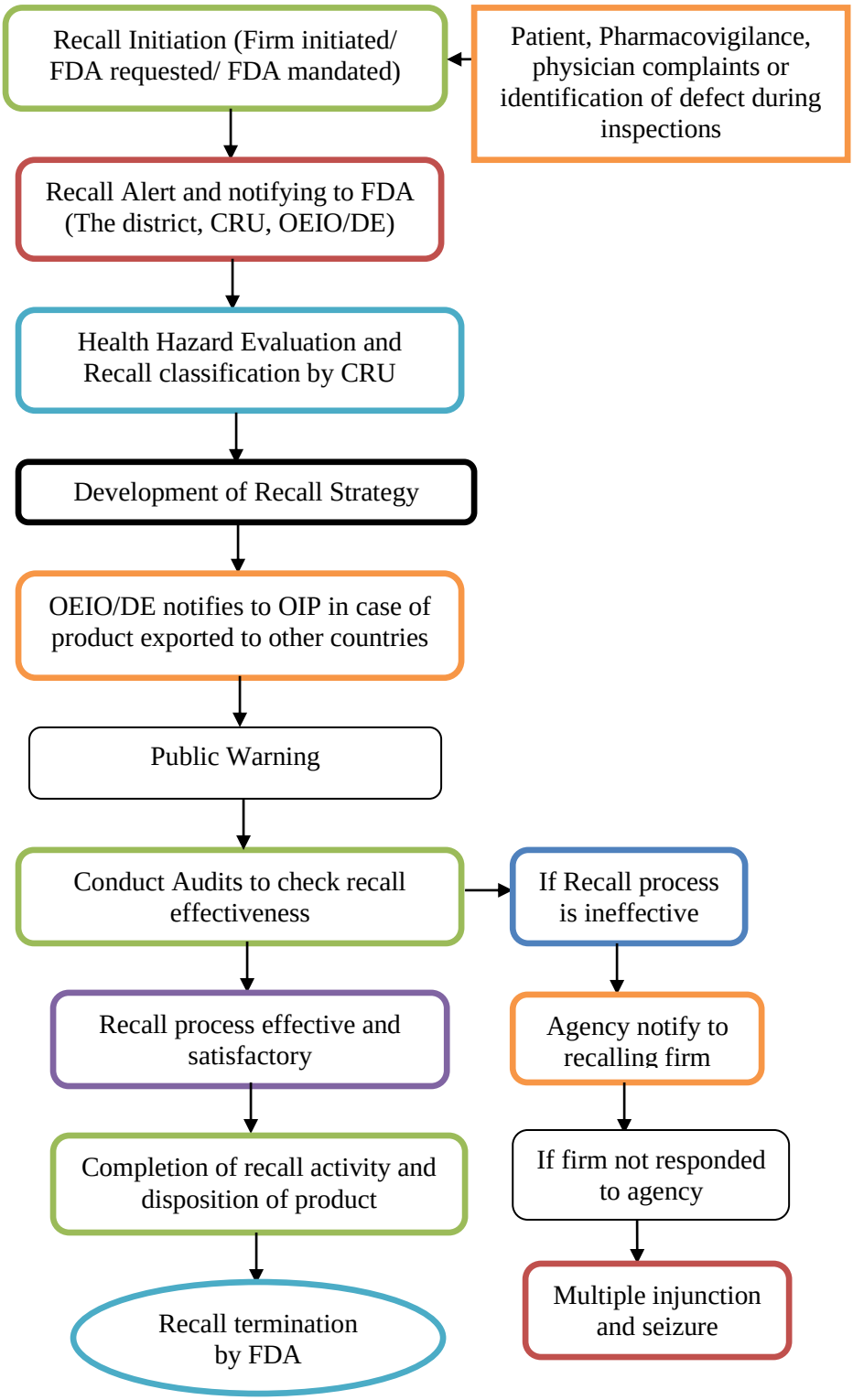

Fig 1: Flow Chart of Recall Procedure in USA

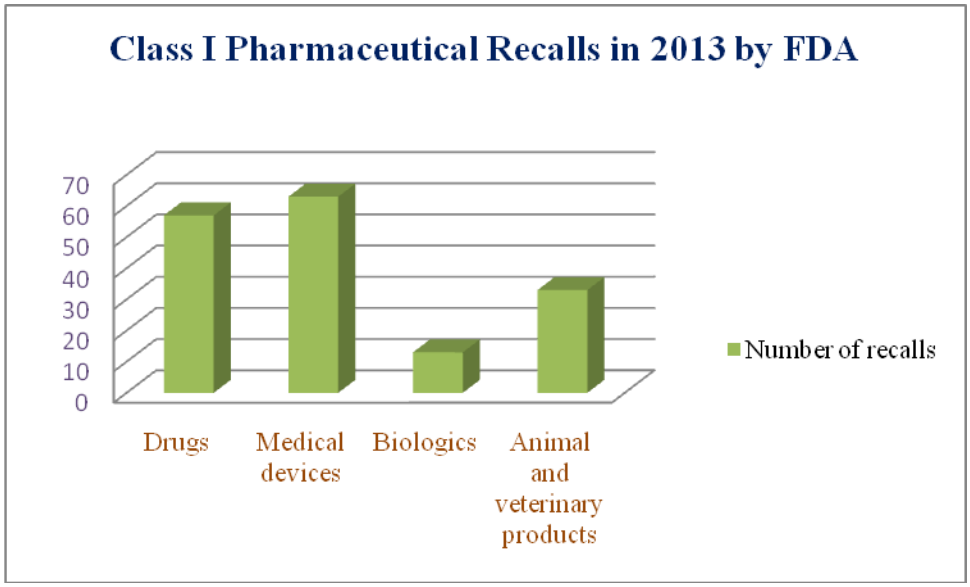

Fig 2: Class I Pharmaceutical Recalls in 2013 by FDA

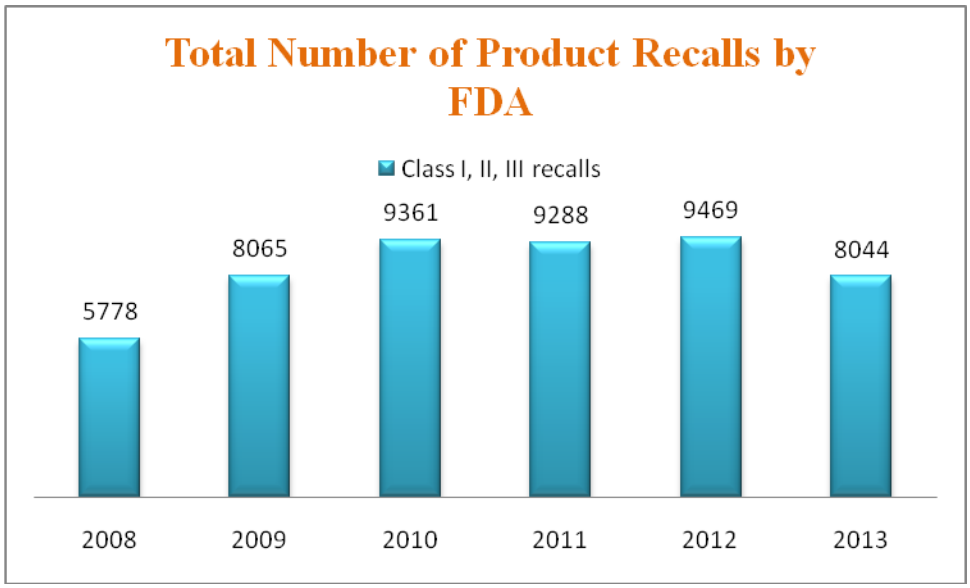

Fig 3: Total Number of Product Recalls by FDA

Flowchart of Recall Procedure in India

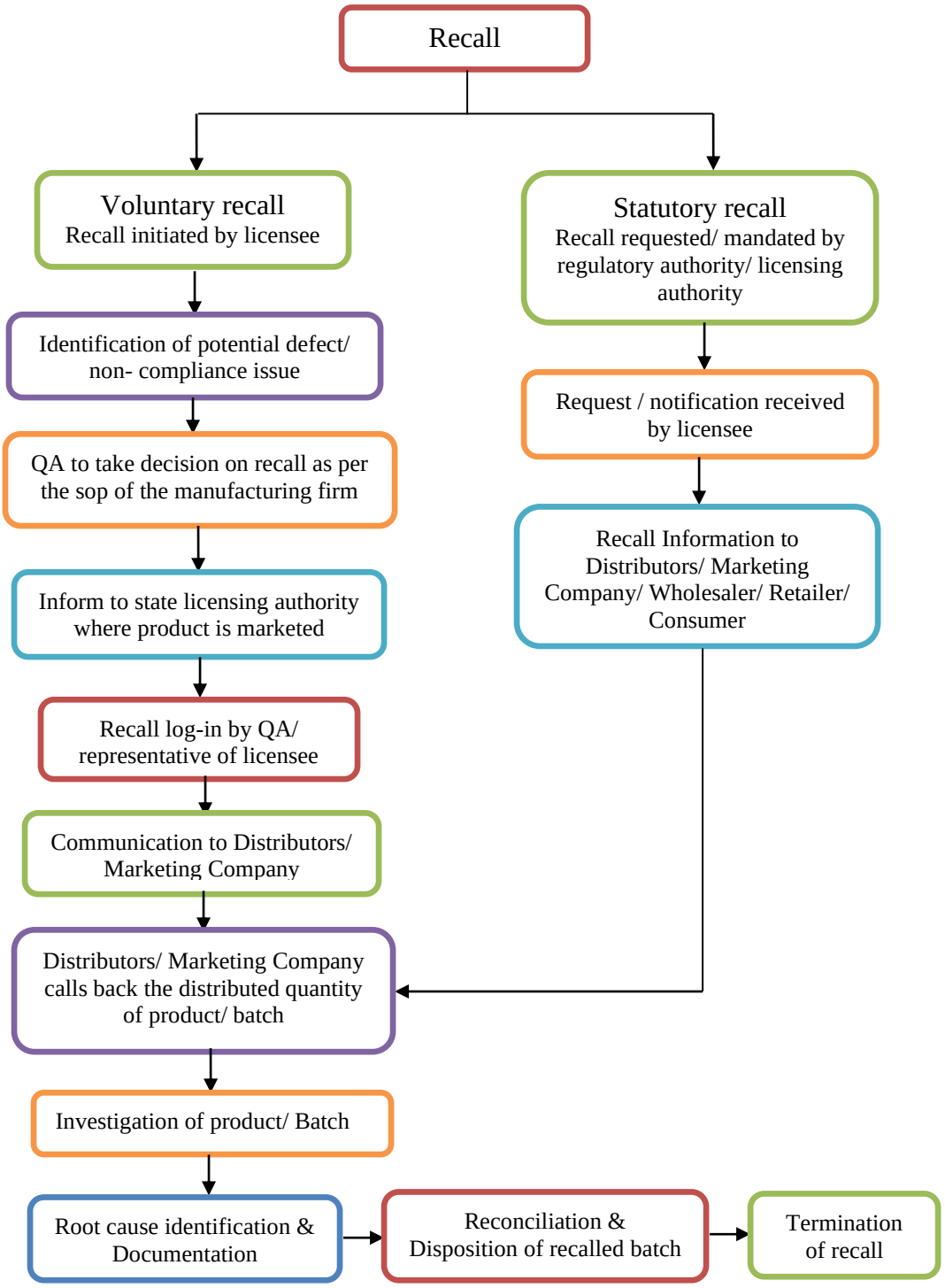

Fig 4: **Flowchart of Recall Procedure in India**