Rising Incidences of Product Recall:

Abstract

There has been an increasing trend in the number of prescribed and over-the-counter drug recall over the last few years. The recall is usually due to company's discovery, customer's complaint 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. The reason for the recall can be divided into two categories: manufacturing related and safety/efficacy related. It is essential to follow all the guidelines related to drug development and manufacturing procedure so as to minimize drug recall.

Keywords: Drug product recall, guidelines, process, recall information

INTRODUCTION

The pharmaceutical industry is at an important crossroads in medical innovations, which develop cures for health conditions. Without this industry, many therapies would not be introduced to the market, and many health problems would remain unsolved. The pharmaceutical industry as a whole has traditionally been very profitable, and the global market had annual growth prediction of 5 to 8% [1, 2]. Yet amidst the massive increase in the field, factors like product returns and recalls are giving the companies new challenges, such as litigation problems, negative publicity, loss of patent protection for many major drugs and widespread efforts to contain drug spending[3]. On the other hand, increased competitiveness, fast-changing structure of competitors, complex strategic positioning, shrinking pipelines, counterfeit drugs and a fight for global market share are adding more burdens to the growth of the industry [4, 5].

A recall is a serious problem. It highlights a dangerous situation that requires fast and effective action to protect the public from harm. Product recalls are becoming extensive and have increased radically [6]. For example, the Food and Drug Administration (FDA) reported more than 1984 recalls with more than $700 million dollars manufacturers penalties, and billions more in lost revenues since 2001 [7,8]. Companies are turning to set their strategic sight on future moves. In order to operate effectively in an increasingly competitive economic and commercial landscape, they are trying to adopt more formal business processes and stricter reporting methods [9].

A drug recall is an instance to return to the maker a batch or an entire production run of a drug product, usually due to the detection of safety issues or drug product defect. When drug products are known to have potentially harmful effect on users due to their defective quality, safety or efficacy, they may be subjected to a recall and all related information's are reported to the drug office [10]. Regardless of a company's best efforts, that dangerously defective drug product may reach the customers. These products may cause disasters, leading to adverse verdicts in drug product liability litigations. The quality management of complaints and drug product recalls are necessary to ensure the safety of customer. However, there are certain other cases when all batches or lots of the drug experience recall from the market [11, 12]. The aim of present review is to focus on issues for drug recall like lack of sterility assurance, presence of particulate matter, unapproved new drugs, presence of undeclared therapeutically active moiety, microbial

contamination, container/closure problems and some other miscellaneous reasons. We shall discuss them in two parts with part-I, focusing on lack of sterility assurance, presence of particulate matter and container/closure problems.

ISSUES RELATED TO PRODUCT RECALL

I- *Lack of Sterility Assurance*

The years 2013-2016 saw eight recalls **(Table 1)** that involved a microbiological component, with a clear increase evident in 2015 and 2016. There no evident in 2013 and 2014. If we look at the data from a different perspective, we can evaluate FDA concerns for sterile vs Non-sterile products [13, 14]. Underlying causes of "Lack of Sterility Assurance" often are the result of packaging concerns (incomplete or weak seals, pinpricks in the sterile barrier, transport issues, etc). Relatively few of these "Lack of Sterility Assurance" recalls actually showed contamination. From this, it seems apparent that "Lack of Sterility Assurance" means either that there is a potential problem with the product or packages, or that the manufacturer cannot document that the product was manufactured and sterilized in a state of control. If the product is obviously contaminated, that is the cited reason for the recall in the vast majority of cases [15, 16].

Table 1: Lack of sterility assurance

S.No	Date	Product Description	Reasons/ Problems	Company
1.	17/05/2016	Unexpired sterile compounded products	Concern over lack of sterility assurance	Well Care Compounding Pharmacy
2.	19/04/2016	Sterile compounded products	Lack of sterility assurance	Pharmakon Pharmaceuticals, Inc.
3.	16/01/2016	Sterile Compounded Products that include injectable medications, sterile solutions, eye drops, and eye ointments	Lack of sterility assurance	Abbott's Compounding Pharmacy
4.	20/10/2015	All sterile compounded products	Lack of sterility assurance	Company Name Downing Labs, LLC
5.	21/09/2015	All sterile compounded products	Lack of sterility assurance	US Compounding, Inc.
6.	09/09/2015	Sterile drug products	Sterility cannot be assured	Medistat RX, LLC
7.	17/08/2015	Prolotherapy with Phenol	Non-sterility concerns	Hartley Medical
8.	07/08/2015	Human and veterinary sterile compounded drugs	Sterility Assurance	Moses Lake Professional Pharmacy

II- *Presence of Particulate Matter*

Presence of foreign visible or sub-visible particulate matter in injectable/ parenteral formulations has been one of the most commonly seen reasons for recalls. FDA reported 22 % recalls for sterile injectable drugs in period of 2013-16 caused due to presence of visible particles [17, 18]. Recent list of FDA recalls include the products as mentioned in the **(Table 2).** All injectables are mostly contaminated with some level of particulate matter. This particulate matter is a critical quality attribute, which has direct impact on product safety. Therefore, the United States Pharmacopoeia has defined the standards for particulate matter. These standards are established for all injectable preparations such as large-volume Injections, single-dose infusion and small-volume Injections, solutions for injection administered by intramuscular or subcutaneous route, except parenterals for use as irrigating solutions, radiopharmaceutical preparations and parenteral products for which the labeling specifies use of a final filter prior to administration [19,20].

The size of particulate matter is an important factor behind health risk to patients. The smallest diameter of blood capillaries is approximately 6–8 μm. Particles as small as 2 μm in diameter are

generally associated with micro-thrombi formation in patients. Particles larger than 6–8 µm can block pulmonary capillaries, with smaller particles passing through the lungs and depositing in organs such as the liver and spleen, where they are processed by phagocytic cells of the reticuloendothelial system [21, 22].

Table 2: Presence of particulate matter

S.No	Date	Product Description	Reasons/ Problems	Company
1.	05/05/2016	Sterile Preparations Compounded With Fresenius Kabi Sensorcaine-MPF (bupivacaine HCl)	Presence of glass particulate	PharMEDium Services LLC
2.	13/04/2016	50% magnesium sulfate Injection, USP	Particulate Matter	Hospira, Inc.
3.	28/03/2016	5% dextrose Injection USP	Leakage and visible particulate matter (microbial growth)	B. Braun Medical Inc.
4.	1803/2016	8.4% sodium bicarbonate Injection, USP	Presence of particulate matter	Hospira Inc.
5.	09/03/2016	amikacin sulfate Injection USP, 1 gram/4mL (250 mg/mL)	Due to the potential presence of particulate matter identified as glass in one vial	Teva Pharmaceuticals
6.	17/02/2016	0.9% sodium chloride Solution	Particulate Matter	Baxter International Inc.
8.	18/12/2015	intravenous (IV) solutions: 0.9% sodium chloride Injection, USP, 250 mL VIAFLEX Plastic Container and 70% dextrose injection (2000 mL) USP	Potential presence of particulate matter	Baxter International Inc.
9.	24/08/2015	REFRESH® Lacri-Lube®, REFRESH P.M.®, FML® (fluorometholone ophthalmic ointment) and Blephamide® (sulfacetamide sodium and prednisolone acetate ophthalmic ointment, USP)	Contains particulate matter	Allergan plc
10.	31/07/2015	0.9 % sodium chloride Injection, USP (AUTO-C)	Leaking containers, particulate matter and missing port protectors	Baxter International Inc.
11.	24/07/2015	Adrucil (fluorouracil injection, USP) 5 g/100 mL (50 mg/mL)	Potential presence of particulate matter	Teva Parenteral Medicines Inc.
12.	17/07/2015	0.9 % Sodium Chloride Injection, USP; 50mL and 100 mL	Presence of particulate matter	Baxter International Inc.
13.	08/06/2015	gemcitabine, methotrexate	Particulate Matter	Mylan
14	23/12/2013	lidocaine HCl Injection	Particulate matter	Hospira, Inc
15.	23/12/2013	5 percent dextrose Injection, USP and 0.9 percent sodium chloride Injection, USP	Particulate matter	Baxter International Inc
16.	13/12/2013	Soliris (eculizumab) 300 mg/30 mL Concentrated solution for intravenous infusion only	Found to contain visible particles	Alexion Pharmaceuticals, Inc.
17.	27/11/2013	nitroglycerin in 5% dextrose Injection	Particulates matter	Baxter International Inc.

III- *Container/Closure Problems*

Leaking containers could result in contamination of the solution. If not detected, this could lead to a bloodstream infection, worsened patient condition or other serious adverse health consequences **(Table 3)**. All medicinal products need to be protected and consequently need to be packaged in containers that conform to prescribed standards, particularly with respect to the exclusion of moisture and light and the prevention of leaching of extractable substances into the contents and of chemical interaction with the contents. However, the limits of acceptability in these various respects depend, at least in part, on climatic variables. Recommendations in the International Pharmacopoeia can only be advisory; precise quantitative standards will have to be locally determined. Labels carry the correct information and identification of the product [23, 24]. The closure is a part of the container. The container and its closure must not interact physically or chemically with the substance within in any way that would alter its quality [25, 26]. Both the

European and United States pharmacopoeias provide specifications for glass containers for injections. [27] The latter publication also gives specific guidance for the packaging, repackaging and dispensing of medicinal products. Both the European and United States pharmacopoeias also provide specifications for light-resistant containers and tightly or well-closed closures for capsules and tablets [28].

Table 3: Container/Closure problems

S.No	Date	Product Description	Reasons/ Problems	Company
1.	28/03/2016	5% dextrose Injection USP	Leakage and visible particulate matter (microbial growth)	B. Braun Medical Inc.
2.	26/01/2016	0.9% sodium chloride Injection, metronidazole Injection, and clinimix	Leaking containers and particulate matter	Baxter International Inc.
3.	31/07/2015	0.9 % sodium chloride Injection, USP (AUTO-C)	Leaking containers, particulate matter and missing port protectors	Baxter International Inc.

CONCLUSION

Product Recall is not only a blot on the company's image but also an unwanted procedure on part of manufacturers. However, in the interest of patients in particular and society in general, this is a welcome step. The manufacturers should check everything before releasing the product in market. In spite of frequent in process quality controls, QC tests past production and cGMPs in place, there has been an alarming rise in the incidences of product recall. Keeping in mind stringest FDA regulations, such an event speaks volumes about the lacunas in the existing system. Therefore, even after launch of the drug in the market, it is essential to carry out post market surveillance and investigate the drug performance in the market.

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