Rising Incidences of Product Recall: A Commentary; Part-II

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 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].

For a detailed introduction on this topic readers are advised to see the first part of this review[6]. In this previous part published in this journal we have discussed issues like Lack of sterility assurance, Presence of particulate matter and Container/Closure problems. In this second part, the focus will be on Unapproved new drugs, Presence of undeclared therapeutically active moiety, Microbial contamination and some other miscellaneous reasons.

ISSUES RELATED TO PRODUCT RECALL

I- 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 expected 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. The lack of evidence demonstrating that these

unapproved drugs are safe and effective is a significant public health concern (**Table 1**) [7]. Unapproved drugs are *not* generic medications, and neither their safety nor their efficacy can be assured [8]. In 2013, retail pharmacies in US filled over three billion prescriptions. These prescriptions, as well as those prescriptions administered directly by healthcare professionals, were intended to treat or prevent myriad conditions and diseases, because physicians can lawfully prescribe FDA-approved products for any purpose, including uses unapproved by FDA, if the physician believes such use would benefit the patient. Because almost all prescription medicines have side effects and contraindications, including some serious and fatal side effects, it is essential that healthcare professionals have access to timely, accurate and comprehensive information about the medicines they prescribe [9,10].

II- Presence of Undeclared Therapeutically Active Moiety

Falsified and substandard drugs may contain toxic ingredients; some of the most compelling stories of pharmaceutical crime are of frank poisoning. By far the more common problem however, is medicine that simply does not work. Medications for chronic and infectious diseases alike have been found falsified and substandard. Data from the FDA office of criminal investigation indicate that pills and tablets are the most commonly compromised products they investigate, mostly produced by individual criminals, not negligent businesses [11]. The WHO is developing a system for the global surveillance and monitoring of falsified and substandard drugs. Different regulatory authorities have different, often widely divergent, requirements. To complicate the problem, many small regulatory authorities lack the technical depth to evaluate the bioequivalence data generics manufacturers submit (**Table 2**) [12].

Table 1: Unapproved new drug

S.No	Date	Product Description	Reasons/ Problems	Company
1.	11/04/2016	Super Herbs Capsules, Weight Loss Dietary Supplement	Unapproved new drug- FDA laboratory testing found SUPER HERBS to contain sibutramine, desmethylsibutramine, and/or phenolphthalein.	Super Herbs
2.	09/01/2016	Dietary Supplement	Unapproved new drug	R Thomas Marketing LLC
3.	18/12/2015	Dietary Supplement	Unapproved new drug	SmartLipo 365
4.	11/12/2015	Dietary Supplement	Unapproved new drug (undeclared hydroxythiohomosildenafil, an analogue of sildenafil)	Reesna Inc.,
5.	09//12/2015	Dietary Supplement	Unapproved new drug (Undeclared diclofenac)	Lucy's Weight Loss System
6.	03/12/2015	Dietary Supplement	Unapproved new drug	Lipo Escultura
7.	11/09/2015	Miracle 30 & Miracle Rock 48 dietary supplements	Unapproved new drug	The One Minute Miracle Inc.

8.	24/08/2015	Dietary Supplements	These products contain the undeclared drug ingredient salicylic acid making these unapproved new drugs	Novacare, LLC
9.	23/12/2013	Dietary Supplement	Unapproved new drug	Deseo Rebajar Inc.
10.	29/11/2013	Dietary Supplement	Unapproved new drug	IQ Formulations

Table 2: Presence of Undeclared Therapeutically Active Moiety

S.No	Date	Product Description	Reasons/ Problems	Company
1.	10/05/2016	Marketed as a dietary supplement	Products contain sildenafil, and analogs of sildenafil	SOS Telecom, Inc.
2.	05/04/2016	Marketed as a dietary supplement	Contains ligandrol	Invisiblu International LLC
3.	28/01/2016	Pink Bikini and Shorts on The Beach	Undeclared sibutramine, phenolphthalein	Lucy's Weight Loss System
4.	20/01/2016	licorice Coughing Liquid	Contains undeclared morphine	Master Herbs, Inc.
5.	23/12/2015	Dietary Supplement	Undeclared sibutramine and phenolphthalein	BeeXtreme LLC
6.	25/11/2015	Compounded Multivitamins	Contains high amounts of Vitamin D3	Glades Drugs
7.	28/10/2015	Dietary Supplement	Undeclared Active Pharmaceutical Ingredients	Premiere Sales Group
8.	25/09/2015	Capsules intended for male sexual enhancement	Undeclared desmethyl carbondenafil and dapoxetine	TF Supplements
9.	23/09/2015	Pink Bikini and Shorts on The Beach	Undeclared Sibutramine and Phenolphthalein	Lucy's Weight Loss System
10.	24/08/2015	Dietary Supplements	These products contain the undeclared drug ingredient salicylic acid making these unapproved new drugs	Novacare, LLC
12.	12/06/2015	Advanced Joint Formula capsules	Undeclared diclofenac and chlorpheniramine	G&C Natural
13.	03/06/2015	Smart Lipo (800, 900, 950 mg) capsules	Undeclared sibutramine, desmethylsibutramine, and phenolphthalein.	SmartLipo365
14.	19/12/2014	Dietary supplement capsules used for weight loss	Undeclared Drug Ingredient	Bethel Nutritional Consulting, Inc.
15.	19/12/2014	Dietary supplement capsules used for weight loss	Undeclared Drug Ingredient	Bethel Nutritional Consulting, Inc.
16.	12/12/2014	Dietary supplement capsules used for body building and weight loss	Undeclared Synthetic hormone/prohormone Ingredient	Wyked Labs

III-Microbial Contamination

One of the most important areas in pharmaceutical process control is the development of systems to control the number, survival, and proliferation of microorganisms during manufacturing of non-sterile and sterile pharmaceutical products (**Table 3**). In relation to this general profile,

commonly considered four main sources of microbial contaminations are clean room air, personnel, surfaces and water. An earlier study, pointed out that maintaining the integrity of a pharmaceutical production environment of clean room is a constant battle [13, 14]. Most common microorganisms in clean rooms are gram-positive bacteria. These microorganisms often have a close phylogenetic affiliation as indicated by comparative analysis of partial 16S rDNA studies, such as between the *Micrococci* and *Staphylococci* [15]. In addition, there are, in fewer numbers, certain fungi associated with clean rooms. Clean room microflora is predominantly of gram-positive bacteria. With the genera *Staphylococcus* and *Micrococcus*, many of the species are indigenous to humans. Although Gram-positive microorganisms are ubiquitous in clean rooms and make up the overwhelming majority of isolates [16].

Table 3: Microbial contamination

S.No	Date	Product Description	Reasons/ Problems	Company
1.	31/12/2014	Ribavirin powder for solution	Microbial Contamination	Valeant Pharmaceuticals North America LLC
2.	18/12/2013	Sterile injectable medications	Potential for microbial contamination	Abrams Royal Pharmacy

IV-Miscellaneous Reasons

The information about counterfeit medicines is everywhere press reports [17], WHO fact sheets [18], FDA press releases [19], U.S. government task forces [20], law review articles [21], medical journals [22] and international trade associations [23]. One widely–cited "fact" attributed to the WHO is the claim that counterfeit medicines make up more than 10% of today's global medicines available in the market (**Table 4**) [24]. Yet another statistic is that in developing countries, up to 25% of the medicines used are counterfeit or substandard [25]. Publicly discussing counterfeiting is an important tool to enforce the industry's price discrimination structures across borders, enhancing overall industry profits [26].

Table 4: Miscellaneous/ Other

S.No	Date	Product Description	Reasons/ Problems	Company
1.	01/03/2016	fluconazole Injection, USP, (in 0.9% sodium chloride) 200 mg per 100mL	Discovery of an out of specification impurity result detected	Sagent Pharmaceuticals, Inc.
2.	16/02/2016	morphine sulfate 0.5 mg/mL preservative free in 0.9% sodium chloride	Super-potent	Pharmakon Pharmaceuticals
3.	31/12/2015	norepinephrine bitartrate added to sodium chloride	Discoloration	Phar MED Diuem
4.	30/10/2015	epinephrine Injection, USP (0.15 mg and 0.3 mg)	Potential Inaccurate Dosage Delivery	Sanofi US
5.	09/10/2015	Over the counter acetaminophen Tablets.	The acetaminophen Tablets, 500 mg is incorrectly labeled as 325 mg Tablets.	Medline Industries, Inc.

6.	13/07/2015	calcium chloride Intravenous Infusion 10% in 10 mL prefilled glass syringes	Incompatibility between syringe and needleless adapters	Mylan Institutional LLC
7.	12/12/2014	Combination of omeprazole and misoprostol in a paste	Not approved for use as an animal drug	Tristar Equine Marketing, LLC.
8.	27/11/2013	Blood glucose test strips	May produce erroneously low blood glucose results	Abbott

CONCLUSION

The authors have tried to exhaustively review the reasons behind drug product recall in two parts of this article. Drug Product Recall as a whole brings bad name to the company but is essential in the larger interest of society. However, through careful handling, manufacturing, packaging and transportation, such incidences may be kept to a minimum. An aptitude for no mistakes at every level of organization may help achieve this goal easily.

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