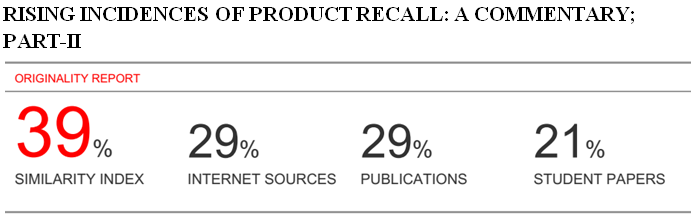
**Reviewer’s Comments**

****

**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 spending3.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 review6. 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 | SmartLipo365 |
| 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 **i**nformation 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.

**REFERENCES**

1. S Shewale, S Parekh. Reinventing patient recruitment in clinical studies, The Monitor; 2011: 10:523-535.
2. S Folland, AC Goodman, M Stano. Intercontinental Medical Statistics Health, 5th Edition; 2010.
3. NY Saddle River. Pearson Education; 2007.
4. CBR Pharma Insights. The New Pharmaceutical Sales Force, Key Trends Shaping Future Sales Strategies; Reuters online; 2009.
5. A Edwards. Manufacturing the future Integrated collaboration between CMOs and Sponsors, Contract Pharma; 2010**:** 5:124-130.
6. Chawla Viney, Singh MP and Kumar Manish; Rising Incidences of product recall, Universal Journal of pharmaceutical Research; 2016: 1(1):6-12.
7. Guidance for FDA Staff and Industry Marketed Unapproved Drugs. Compliance Policy Guide, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). September 19: 2011.
8. Brian S,Mc Gowan *et al.;* Understanding the Factors that Influence the Adoption and Meaningful Use of Social Media by Physicians to Share Medical Information, of Med. Internet Res; 2012: 656-667.
9. James M, Spears Jeffrey K, Francer, and Natalie A Turner; Embracing 21st Century Information Sharing: Defining a New Paradigm for the Food and Drug Administration’s Regulation of Biopharmaceutical Company Communications with Healthcare Professionals, Food and Drug Law Journal; 2015: 70 1: 143-159.
10. Lawrence O, Gostin and Gillian J Buckley; Committee on Understanding the Global Public Health Implications of Substandard, Falsified, and Counterfeit Medical Products; Board on Global Health; Institute of Medicine, Countering the Problem of Falsified and Substandard Drugs;2013: 10-16.
11. Berendes S P, Heywood S, Oliver P Garner; Quality of private and public ambulatory health care in low and middle income countries: Systematic review of comparative studies, PLoS Med ;2011: 8(4): 1000433.
12. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirtieth report*.* Geneva, World Health Organization; 1987 (WHO Technical Report Series, No. 748).
13. Raccasi, D *et al*.; Author Response to Sutton Letter to the Editor in Response to Friedman et al., Burkholderia cepacia: This Decision Is Overdue, PDA J. Pharm. Sci. Technol;2011: 65(5): 535–543.
14. Clarridge JE; Impact of 16S rRNA gene sequence analysis for identification of bacteria on clinical microbiology and infectious diseases, Clin Microbiol Rev;2004: 17: 840–862.
15. Álvarez Lerma F *et al*.; Moisturizing body milk as a reservoir of Burkholderia cepacia: outbreak of nosocomial infection in a multidisciplinary intensive care unit, Crit Care;2008:78-86
16. [http://msnbc.msn.com/id/5682351. (Accessed](http://msnbc.msn.com/id/5682351.(Accessed) on Aug. 12, 2016).
17. http://www.who.int/ mediacentre/factsheets/2003/fs275/ (Accessed on Aug. 12, 2016).
18. http://www.fda.gov/bbs/topics/NEWS/2005/NEW01216.html.(Accessed on Aug. 29, 2016).
19. <http://www.hhs.gov/importtaskforce/Report1220.pdf>. (Accessed on Aug. 28, 2016).
20. Anthony F. Andrisano, Jr.; To the U.S. Government: Whether or not reimportation is the answer, something must be done to help americans afford their necessary prescription drugs. Penn state Rev; 2005**:** 23.
21. See Liza Gibson; Drug Regulators Study Global Treaty to Tackle Counterfeit Drugs, Brit. Med. J; 2004.
22. <http://www.icn.ch/INR/INR52-2%20InsideView.pdf>. (Accessed on Aug. 23, 2016).
23. http://www.icn.ch/PR09\_05.htm. (Accessed on May 11, 2016).
24. <http://www.icn.ch/fr_INRsubscribe.htm>. (Accessed on Aug. 12, 2016).
25. Kevin Outterson; Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets, Health Pol’y l. & ethics; 2005: 193: 277–79.
26. http://bmj.bmjjournals.com/cgi/content/full/324/7341/800. (Accessed on April 16, 2016).