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 has traditionally been very profitable, and the global market had annual growth prediction of 5 to 8%. Yet amidst the massive increase in the field, factors like product recalls 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. 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.

For a detailed introduction on this topic readers are advised to see the first part of this review. 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). Unapproved drugs are not generic medications, and neither their safety nor their efficacy can be assured. In 2013, retail pharmacies in US filled over three billion prescriptions.
Table 1: Unapproved new drug

| S. N. | Date        | Product Description                  | Reasons/Problems                                           | Company          |
|-------|-------------|--------------------------------------|------------------------------------------------------------|------------------|
| 1.    | 11/04/2016  | Super Herbs Capsules, Weight Loss    | Unapproved new drug - FDA                                  | Super Herbs      |
|       |             | Dietary Supplement                   | laboratory testing found SUPER HERBS to contain sibutramine, |                  |
|       |             |                                      | desmethylbutramine, and/or phenolphthalein.                |                  |
| 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 dicyfenac)                 | Lucy's Weight Loss System |
| 6.    | 03/12/2015  | Dietary Supplement                   | Unapproved new drug                                        | Lipo Escultura   |
| 7.    | 11/09/2015  | Miracle 30 and Miracle Rock 48      | 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. N. | 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                 | Bee Xtreme 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 desmethy carbenonafil 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   |
| 11.   | 12/06/2015  | Advanced Joint Formula capsules      | Undeclared diclofenac and chlorpheniramime                  | GandC Natural    |
| 12.   | 03/06/2015  | Smart Lipo (800, 900, 950 mg) capsules | Undeclared sibutramine, desmethylbutramine, and phenolphthalein. | SmartLipo365     |
| 13.   | 19/12/2014  | Dietary supplement capsules for weight loss | Undeclared Drug Ingredient                                  | Bethel Nutritional Consulting, Inc. |
| 14.   | 19/12/2014  | Dietary supplement capsules for weight loss | Undeclared Drug Ingredient                                  | Bethel Nutritional Consulting, Inc. |
| 15.   | 12/12/2014  | Dietary supplement capsules for weight loss | Undeclared Synthetic hormone/prohormone Ingredient          | Wyked Labs       |
| 16.   | 12/12/2014  | Dietary supplement capsules for weight loss | Undeclared Synthetic hormone/prohormone Ingredient          | Wyked Labs       |

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 negligible 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).\(^12\)

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 micro-organisms 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 Micrococcaceae and Staphylococcaceae. 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.\(^16\)

IV. Miscellaneous Reasons

The Information about counterfeit medicines is everywhere press reports, WHO fact sheets, FDA press releases, U.S. government task forces, law review articles, medical journals and international trade associations. 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).\(^17\) Yet another statistic is that in developing countries, up to 25% of the medicines used are counterfeit or substandard. Publicly discussing counterfeiting is an important tool to enforce the industry’s price discrimination structures across borders, enhancing overall industry profits.\(^26\)

| Table 3: Microbial contamination |
|-----------------------------|-----------------|-----------------|-------------------------------|
| S. N. | 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        |

| Table 4: Miscellaneous/Other |
|-----------------------------|-----------------|-----------------|-------------------------------|
| S. N. | Date         | Product Description                  | Reasons/ Problems                          | Company                      |
| 1    | 01/03/2016   | fluconazole Injection, USP, (in 0.9% sodium chloride) 200 mg per 100mL, morphine sulfate 0.5 mg/mL preservative free in 0.9% sodium chloride | Discovery of an out of specification impurity result detected | Sagent Pharmaceuticals, Inc. |
| 2    | 16/02/2016   | norepinephrine bitartrate added to sodium chloride | Super-potent | Pharmakon Pharmaceuticals       |
| 3    | 31/12/2015   | epinephrine Injection, USP (0.15 mg and 0.3 mg) over the counter acetaminophen Tablets. | Discoloration | Phar MED Diuem                   |
| 4    | 09/10/2015   | calcium chloride intravenous infusion 10% in 10 mL prefilled glass syringes | Potential Inaccurate Dosage Delivery, The acetaminophen Tablets, 500 mg is incorrectly labeled as 325 mg Tablets. Incompatibility between syringe and needleless adapters | Sanofi US                    |
| 5    | 13/07/2015   | Combination of omeprazole and misoprostol in a paste | Not approved for use as an animal drug, May produce erroneously low blood glucose results | Medline Industries, Inc.     |
| 6    | 12/12/2014   | Blood glucose test strips             |                                              | Tristar Equine Marketing, LLC |
| 7    | 27/11/2013   |                                              |                                              | 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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