Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2018; 10(4): 102-106

ISSN- 0975 1556

Research Article

Pharmaceutical Product Recall in USA and EU: Comparative analysis

Bigoniya Dharmesh[1], M P Venkatesh[2*], T M Pramod Kumar[2]

[1]*Pharmaceutical Regulatory Affairs, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, Mysuru-570015*

[2]*Department of Pharmaceutics, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, Mysuru-570015*

Received: 24th May, 17; Revised: 17th Dec, 17; Accepted: 13th Feb, 18; Available Online:25th Mar, 18

ABSTRACT

Counterfeit/ falsified medicines contain low quality ingredients, wrong dose, may be deliberately mislabelled or have fake packaging or ingredients. According to the WHO, the prevalence of spurious, falsely-labelled, falsified or counterfeit medicines is a growing trend worldwide. Drug recalls are conducted for critically defective products that pose health risks to patients; either voluntarily by manufacturers or by mandate of regulatory authorities. US-FDA and EU-EMA control and implement the process of drug product recalls with their legal provisions in CFR and directives respectively. The regulatory provisions adopted for drug recall was investigated i.e., recall notification, type, classification, health hazard assessment, strategy, rapid alert system, evaluation system and termination. Recall guidelines are well developed in both countries, with a well-defined peer recall classification, health hazard assessment system and public warning methods. In both the countries, recall is classified as Class I, II and III but strategy in US-FDA is well defined with detailed procedure unlike in EU. USA follows timeline based product recall and termination by proper notification of proper implementation of corrective and preventive action; however, the recall timeline and termination process is not defined in EU. Comparative assessment of drug recall data for USA and EU showed that numbers of recalls are much higher in USA compared to EU.

Keywords: Guideline, Pharmaceutical product, Recall, USA, EU.

INTRODUCTION

Counterfeit/falsified medicines pose a growing threat to public health all over the world. Counterfeit/falsified medicines may contain low quality ingredients, wrong doses, may be deliberately mislabeled or have fake packaging or ingredients. Government authorities and pharmaceutical industry itself focus on and devote a lot of their resources to the quality, safety and efficacy of medicines. Drug products are subjected to recall when reported to have caused potentially harmful effect on users due to defective quality, safety or efficacy issues. The regulatory agencies have the power to withdraw a defective product from the market, recall or suspend production whenever any issue encountered with the safety of a medication.

US Food and Drug Administration (US-FDA)

The US Food and Drug Administration (US-FDA) is a federal agency under the United States Department of Health and Human Services, one of the United States federal executive departments. The US-FDA is responsible for protecting and promoting public health through the control and supervision food and drug products in pursuant to the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301) and other laws are responsible for the quality drugs available to be public. Since1906, drug products are required to be accurately labeled; though before 1962 there was no mechanism of drug approval. In 1961, thalidomide caused horrifying birth defects affecting approximately 10,000 to 20,000 people making it the worst medical disasters in history. Thalidomide prompted the formation of Kefauver-Harris Drug Amendments in 1962, granting oversight of drugs by the FDA and compelling manufacturers to prove that the drugs are safe for public consumption. Now the primary focus of the regulatory bodies of the countries is to ensure that medicines are safe[1].

European Medicines Agency (EMA)

The European Medicines Agency (EMA) formerly known as European Agency for the Evaluation of Medicinal Products (EMEA) is a European Union agency for the evaluation of medicinal products. The EMA operates as a Decentralized scientific agency of the European Union towards protection and promotion of public and animal health through the evaluation and supervision of medicines. Article 47 of Directive 2001/83/EC and Article 51 of Directive 2001/82/EC on the Community code relates to medicinal products for human and veterinary use respectively. The European Directorate for the Quality of Medicines & HealthCare (EDQM) is the Directorate of the Council of Europe that traces its origins and statutes to the Convention on the Elaboration of a European Pharmacopoeia. The EDQM's committee of experts has developed scientific indicators for measuring the quality of pharmaceutical care in Europe. The

**Author for Correspondence: venkateshmpv@jssuni.edu.in*

EDQM's standards are published in the European Pharmacopoeia, which is recognized as a scientific benchmark worldwide and is legally binding in the EU member states. Published and regularly updated by the EDQM/Council of Europe in English and French, the European Pharmacopoeia is uniform reference that works for official European quality standards. The European Commission and the Council of Europe on co-funded basis established a European network of Official Medicines Control Laboratories (OMCLs). The OMCL network and observers of the European Pharmacopoeia Convention ensures that patients receive the same quality of pharmaceutical products throughout Europe. EMA ensures safety of medicinal products and impose Recall or return of a dangerous product that has already been supplied or made available to consumers by the producer or distributor and in some cases market withdrawal preventing the distribution, display and offer of a product dangerous to the consumer[2,3].

Recallprocedure in USA

USFDA provides guidance for manufacturers and distributors to follow with respect to voluntary removal or correction of marketed violative products.

Recall policy

USFDA recognize the voluntary nature of recall by providing guidance for firms to effectively discharge recall responsibilities. Alternatively FDA can initiate court action for removing or correcting violative, distributed products by setting forth specific recall procedures. Recall may be undertaken voluntarily and at any time by manufacturers and distributors, or at the request of the FDA.

Recall classification based on health hazard evaluation

Evaluation of the health hazard is conducted for a product to be recalled or considered for recall by an *ad hoc* committee of FDA Considerations were given to the factors i.e., adverse event already occurred due to use of product, assessment of the degree of seriousness of the health hazard, likelihood of occurrence of the hazard, consequences of occurrence of hazard. Based on these determinations, the FDA assign the recall a classification, i.e., Class I, Class II or Class III to indicate the relative degree of health hazard of the product being recalled or considered for recall.

Recall strategy

For a FDA requested and also for a firm initiated recall a recall strategy takes into account the following factors to suit the individual circumstances of the particular recall, i.e., results of health hazard evaluation, product identification, product's deficiency, continued availability of essential products etc. The FDA review the adequacy of a proposed recall strategy developed by a recalling firm and recommend changes as appropriate. A recalling firm should conduct the recall in accordance with an approved recall strategy.

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

Public warning

Public warning is issued to alert the public about the serious hazard to health presented by the product being recalled. It is reserved for urgent situations where other means for preventing use of the recalled product appear inadequate. The FDA in consultation with the recalling firm ordinarily issues such publicity. Public warning is issued as, general public warning in the national or local media news or through specialized media news, e.g., professional or trade press, or to specific segments of the population such as physicians, hospitals, etc.

Effectiveness checks

Guide entitled "Methods for Conducting Recall Effectiveness Checks" describes different methods approved by FDA. The recalling firm is responsible for conducting effectiveness checks and FDA also assist where necessary and appropriate. The recall strategy specify the level of effectiveness checks to be followed as

Level A: 100 percent of consignees to be contacted;

Level B: depends on a case-by-case basis, < 10 percent to > 100 percent of consignees

Level C: 10 percent of consignees to be contacted;

Level D: 2 percent of consignees to be contacted; or

Level E: No effectiveness checks.

Recall communications

The format, content and extent of a recall communications commensurate with the hazard of the product being recalled and the strategy of recall. In general terms, the purpose of a recall communication is to convey details of product, cease further distribution or use of any remaining product and instructions regarding what to do with the product. Recall communication is done by telegrams, mail or first class letters conspicuously marked in bold red on the letter with the envelopes marked "urgent" for class I and class II recalls, telephone calls or other personal contacts.

Public notification of recall

The weekly FDA Enforcement Report provide descriptive list of new recalls according to classification, whether FDA requested or firm initiated along with specific action being taken by the recalling firm.

Recall status reports

Recalling firm submit periodic recall status reports to the FDA to assess the progress of the recall. The frequency of reports is determined by the relative urgency of the recall. Generally, the reporting interval is between 2 and 4 weeks. The report contains information about number of consignees notified and date and method of notification. Number of consignees responded and did not responded, quantity of products returned, results of effectiveness checks and estimated time frames for completion of the recall are also reported.

Termination of a recall

Table 1: Comparative account of drug recall guidelines implemented in USA &Europe.

Recall Procedure	USA	Europe
Recall definition	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	Recall mean any measure aimed at achieving the return of a dangerous product that has already been supplied or made available to consumers by the producer or distributor
Regulatory body	United States Food and Drugs Administration (USFDA)	European Medicines Agency (EMA)
Legal requirement	21CFR Part 7, Subparts A and C; 21CFR Part 107, Subpart E; 21 CFR Part 1270 - Human Tissue PHS Act - 42 U.S.C. 262.	Article 40 of Directive 2001/83/EC and Article 44 of Directive 2001/82/EC is required under Article 13(1) of Directive 2003/94 and Article 13 of Directive 91/412/EC
Initiation of Recall	Voluntary, FDA requested or FDA mandated recall	Voluntary or at the request of the competent authorities in accordance with Article 8(1)(f)
Recall Classification	Class I, II and III	Class I, II and III
Health hazard evaluation	By the Health Hazard Evaluation Committee	Relative health hazard associated with the use or exposure to the recalled product
Termination of a Recall	Written notification of termination to the recalling firm	NA
Recall strategy	A recalling firm should conduct the recall in accordance with an approved recall strategy	NA
Notification and Public Warning	Notifies the firm, press release, FDA's web site, when required to other federal and state government agencies and to foreign governments	Notification by the European Commission
Recall timeline	Timeline given by CRU based on product to be recalled.	Not defined
Monitoring and Auditing the Recall	Implements a recall audit program	The effectiveness recalls periodically evaluated and documented

Recall is terminated when FDA satisfied that all reasonable efforts have been made to remove or correct the product in accordance with the recall strategy. It is determined that the product has been removed and proper disposition or correction has been made. FDA issues written notification of recall termination to the recalling firm. On the other hand, a recalling firm may request termination of recall by submitting a written request to FDA and provides prove of effective recall in accordance with the criteria set forth[4].

Recall procedure in Eu

Procedures for handling complaints regarding quality defects in drugs

EMA has written procedures describing action taken, course upon receipt of complaint. All complaints are documented and assessed for potential quality defect or other issues. Quality defect investigation address the issues i.e., description of quality defect, extent of the quality defect, testing of reference samples, sample of defective product, assessment of the risk(s), assessment of the impact of recall, identification of the potential root cause(s) of the quality defect and need for appropriate Corrective and Preventative Actions (CAPAs).

Investigation and decision-making

The validity and extent of all reported quality defects are documented and assessed in accordance with Quality Risk Management principles. Following quality defect investigations decisions are made reflecting the level of risk presented by the quality defect and any non-compliance with respect to the requirements of marketing authorization. The decision making processes should ensure that appropriate risk-reducing actions and documented. Quality defects are to be reported by the manufacturer in a timely manner to the marketing authorization holder/sponsor and all concerned Competent Authorities.

Defect classification

Recalls are classified with regard to the relative health hazard associated with the use of or exposure to the recalled product. There are three possible classifications:

Class I: defects are potentially life threatening.

Class II: defects could cause illnesses or mistreatment, but are not Class I.

Class III: defects may not pose a significant hazard to health, but withdrawal may be initiated for other reasons.

Product recalls and other potential risk-reducing actions

Recall activity undertaken following established written procedures. The batch/product distribution records are made readily available to the persons responsible for recalls containing sufficient information of wholesalers and directly supplied customers. All concerned Competent Authorities are informed in advance but in

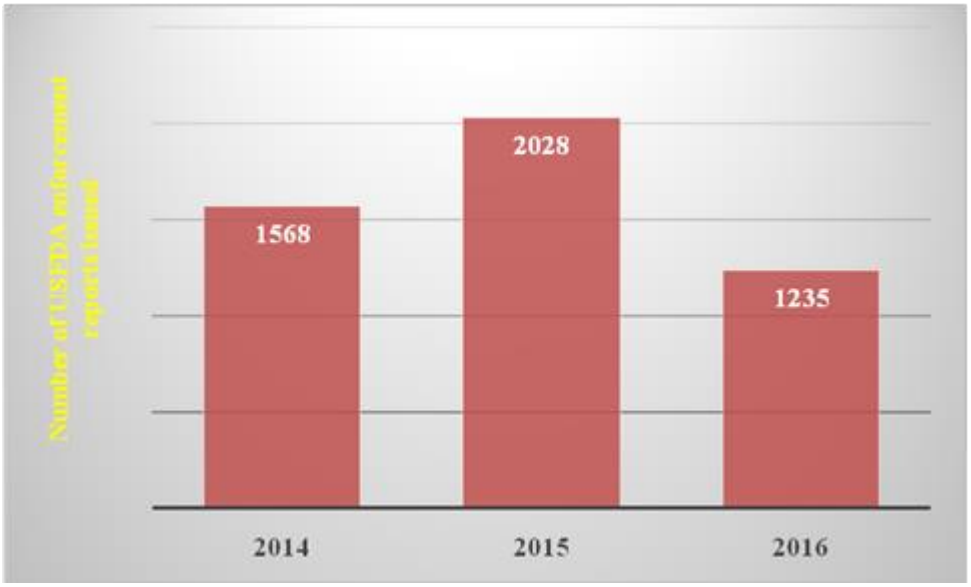

Figure 1: Drug product recall data of USFDA for year 2014 to 2016.

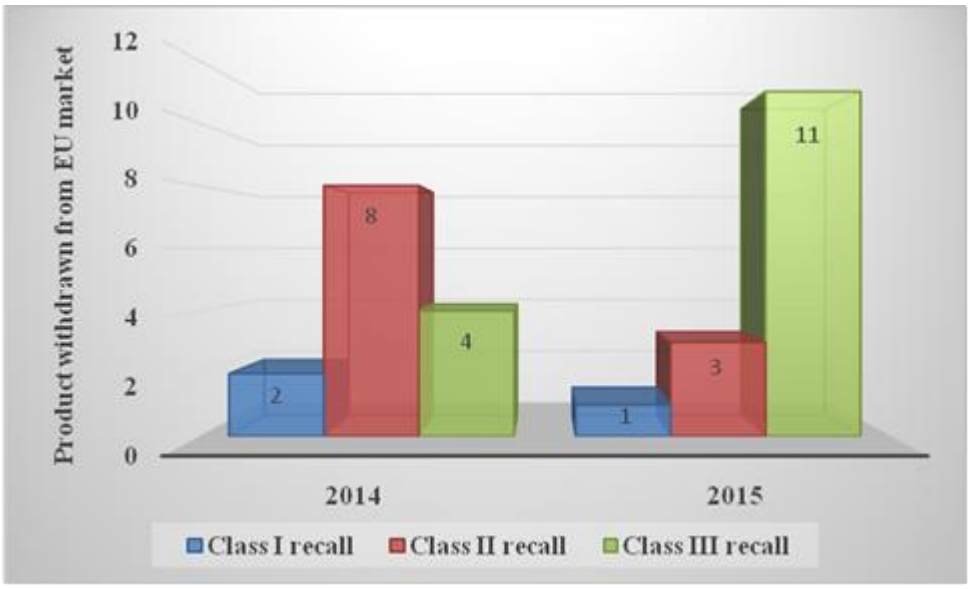

Figure 2: Drug product recall data of EMA for year 2014 and 2015.

cases where products are intended to have potential to seriously impact patient or animal health rapid risk-reducing actions may be taken in advance. The progress of the recall process is recorded until closure and a final report is issued, including reconciliation between the delivered and recovered quantities of the concerned products/batches.

Exchanges of information and rapid intervention situations

The Commission forward notification to the other Member States. If the notifying Member State considers that the effects of the risk do not or cannot go beyond its territory, it shall notify the measures concerned and in particular if they are in response to a new risk which hasnot yet been reported in other notifications.

Final provisions

Information available to the authorities of the Member States or the Commission relating to risks to consumer health and safety posed by products shall in general be available to the public, in accordance with the requirements of transparency. Member States and the Commission take steps necessary to ensure not to disclose information covered by professional secrecy in duly justified cases, except for information relating to product safety[5].

DISCUSSION

The regulatory bodies controlling drug regulation USFDA and EMA for USA and European Union. The legal provisions 21 CFR and European Commission (EC) directive respectively for USA and EU. In both the countries recall is classified as Class I, II and III with slight difference in terminologies. Recall strategy in US-FDA is well defined with detailed procedure though in EU the process is not clear. In USA recall must be conducted in accordance with the approved recall

strategy. Recall notification and public warning are provided in newspapers, television, radio, press release and in FDA's web site mostly for Class I recall. In USA, timeline is based on product to be recalled and in EU the recall timeline is not defined. Recall investigation report is required to be submitted and assessment of effectiveness of recalls are done and documented. USFDA issues written notification of termination to the recalling firm ensuring proper implementation of corrective and preventive action. The recall termination process is not well defined in EU. Comparative assessment of drug recall data for USFDA and EU showed that number of recalls are much higher in USA for year 2014, 2015 and 2016 compared EU[6,7]. This may in turn implicate that USFDA is having much larger number of manufacturing units approved and drugs marketed throughout the globe and thus may resulted in more number of drugs recalled due to quality related issues (Figure 1 and 2).

CONCLUSION

Drug product recall is not a desirable event for any pharmaceutical company also recalling a product is not an easy task once released into the market as recovery from different levels are difficult and tedious job. Recall of any product adversely affects the financial status and commercial goodwill of the manufacturing company[8]. The regulatory bodies ensure proper fulfilment of recalling by implementing strict guideline defining procedure from notification to termination. Recalling can be done smoothly when company management follows guideline, and do all the recalling activities as defined.

REFERENCES

1. US Food and Drugs Administration (USFDA). As amended through P.L. 114-255, Enacted December 13, 2016 [Internet]. Federal Food, Drug, and Cosmetic Act (FD&C Act). United States Code, Title 21. 2016; [Assessed on: 3rd Mar, 2017]. Available at: https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/federalfooddrugandcosmeticactfdcact/default.htm
2. Convention on the Elaboration of a European Pharmacopoeia (CETS) No: 050. 1964. Treaty Office, Council of Europe. Council of Europe, Strasbourg, 22.
3. Convention on the Elaboration of a European Pharmacopoeia (CETS) No: 134. Protocol to the Convention on the Elaboration of a European Pharmacopoeia. Treaty Office, Council of Europe. Council of Europe, Strasbourg, 1992; 22.
4. US Food and Drugs Administration (USFDA). Regulatory Procedures Manual [Internet]. Recall Procedures Chapter 7. 2013; [Assessed on: 3rd Mar, 2017].Available at: https://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074312.pd.
5. European Commission (EU), Health and Consumers Directorate-General. Public Health and Risk Assessment. Medicinal products – quality, safety and efficacy. EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Part 1; Chapter 8: Complaints [Internet]. Quality Defects and Product Recalls. 2014; [Assessed on: 3rd Mar, 2017].Available at: http://ec.europa.eu/health/files/eudralex/vol-4/2014-08_gmp_chap8.pdf.
6. Anonymous. 2016. Total number of all drug product recall enforcement reports issued by the FDA from 2012 to 2016 [Internet]. 2016;[Assessed on: 12th Feb, 2017]. Available at: https://www.statista.com/statistics/618383/total-fda-drug-enforcement-reports/.
7. European Medical Agency. [Internet] Annual Report 2015;[Assessed on: 12th Feb, 2017]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2016/05/WC500206482.pdf.
8. Pasumarthy NVG, Pichukala A, Lakshmi T, Nagabhushanam MV, Reddy DN. Contingent analysis and evaluation of pharmaceutical product recall procedure of USA and India. World Journal of Pharmaceutical Sciences 2014; 2(12): 1728-1735.