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A retrospective study of Warning Letters issued by US FDA over 2015-2017

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ABSTRACT

This paper provides contemporary climate of warning letters issued by US FDA over 2015 to 2017. With 1300$ Billion Revenue in 2017 United States stands as World's largest Pharmaceutical Market. Being the largest, diversified and due to globalization, US Pharma industry is the most competitive and critical sectors of the economy. So, exporting to the US is a great opportunity which is leveraged by many countries and US FDA was formed to check the quality standards of Medicines. Since the inception of US FDA, it has been giving many warning letters to Pharmaceutical Companies for violating regulatory guidelines. The back bone of this paper is to analyse warning letters and to identify what are the major violations in case of Pharmaceuticals.

Keywords: Form 483, Warning Letters, Regulatory Affairs, Regulatory Environment, Adulteration, Labelling Issues, Misbranding, Misleading Claims, FDA Warning Letters.

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1. Introduction

United States being the world's largest Market in the Pharmaceutical Industry with 1300$ Billion revenue, attracting Many organisations from all over the world to leverage the market. (1, 2) So, to maintain the quality of medicines US FDA was formed way back from 1848. With time upon addition of new laws, Federal public health protection was formed in 1906. (3) FDA is solely responsible for public health in the United States by making sure the security, efficacy, and safety of drugs, medical devices, and biological products. Even FDA looks after the veterinary drugs. FDA ensures the safety of people of US by regulating drugs, cosmetics, food supply and products that emit radiation. FDA helps in advancing public health by helping the industry in speed innovation thereby making the new products safe, efficacious and more affordable. The mission of US FDA includes the mandate to "participate through appropriate processes with representatives of other countries to harmonize regulatory requirements, reduce the burden of regulation and to achieve appropriate reciprocal arrangements.

Since the inception of US FDA, it has been issuing warning letters for efficacy claims and/or inappropriate safety by Pharmaceutical organizations, henceforth generating considerable public attention. (4) A Warning letter is considered as an official message from US FDA indicating that manufacturer has violated some sort of rule in regulatory activity. (5)

2. Objective

To know types of warning letters issued and to know the major violations in case of drugs, biologicals, and medical devices from Warning Letters.

3. Methodology

Study type: Descriptive and retrospective study. Secondary Desk Review.

Data Sources: Publicly available FDA letters sent to pharmaceutical companies from 2015 to 2017 were reviewed. A standard data collection tool was developed, including all categories violations and data is collected manually.

Study Duration:

February 2018 to April 2018, (12 weeks)

Sample Size:

A total of 1875 warning letters reviewed from 2015 January to 2017 December and out of which 694 were related to drugs and pharmaceuticals and 1181 letters were related to food and food products. (6)

Sample Inclusion and Exclusion Criteria:

Only Warning letters related to Drugs, Medical devices, Biologicals were included in Sample. Warning Letters related to Veterinary Drugs, Food, tobacco and cosmetics were excluded.

Table 1 Sample Size distribution from 2015 to 2017

Year	Drugs	Medical Devices & Biologicals	Food	Total
2015	64	146	492	702
2016	166	60	425	651
2017	213	45	264	522

For this study Warning letters issued for drugs and pharmaceuticals are considered thereby funnelled sample size is 694.

4. Results and Discussion

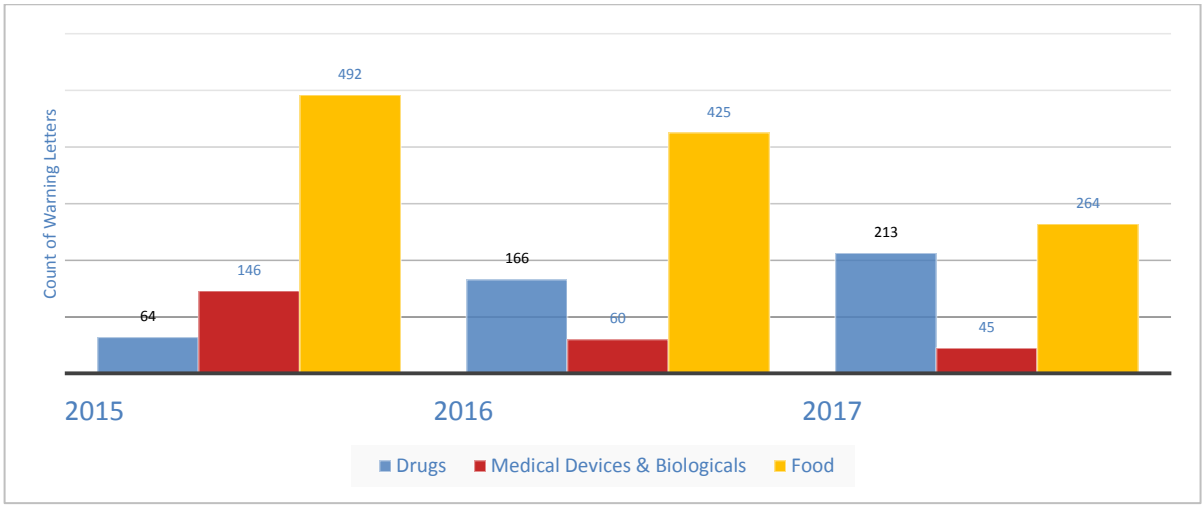

Figure 1. Distribution of Warning Letters

From the Figure 1, there is an increase in warning letters in case of drugs and pharmaceuticals and there is a decline in warning letters in case of medical devices and biologicals. Although there is decline in warning letters in case of food and food products, letters related to food are excluded in this study.

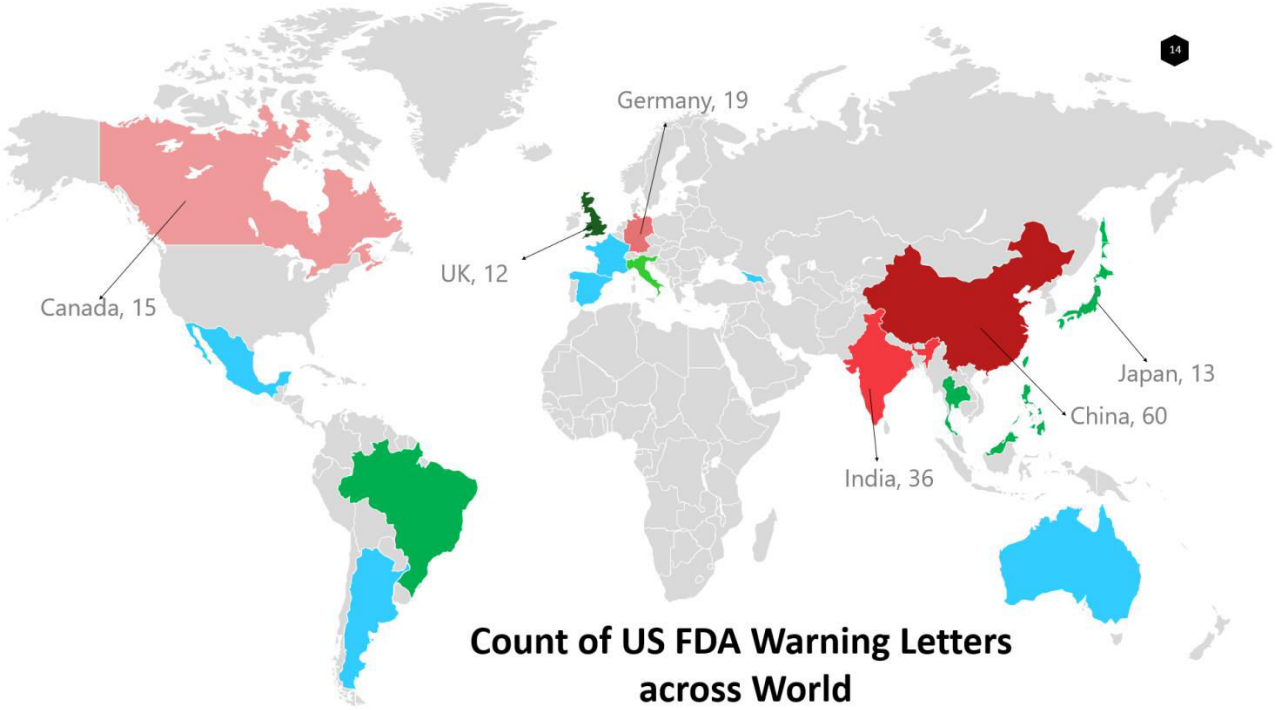

Figure 2. Count of Warning Letters from 2015-2017

From Figure 2, heat map, it is observed that China (60) & India (36) were issued most warning letters by US FDA in past 3 years. Followed by Canada (15) and Japan (13). In case of European Union Germany (19) and United Kingdom (12) were issued most followed by Italy, Spain and France. Canada also observed with more number of violations.

In case of Drugs and Pharmaceuticals a total of 1154 Violations were observed. Out of which 21 CFR Part 211, 201 and 210 were chosen for individual violation analysis. 201: Labelling of Drugs, 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General, 211: Current Good Manufacturing Practice for Finished Pharmaceuticals.

Where as in case of medical devices and biologicals total of 1316 Violations were observed. Out of which 21 CFR Part 820, 803, 807 and 806 were chosen for individual violation analysis. 803: Medical Device Reporting, 806: Medical Devices; Reports of Corrections and Removals, 807: Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices, 820: Quality System Regulation

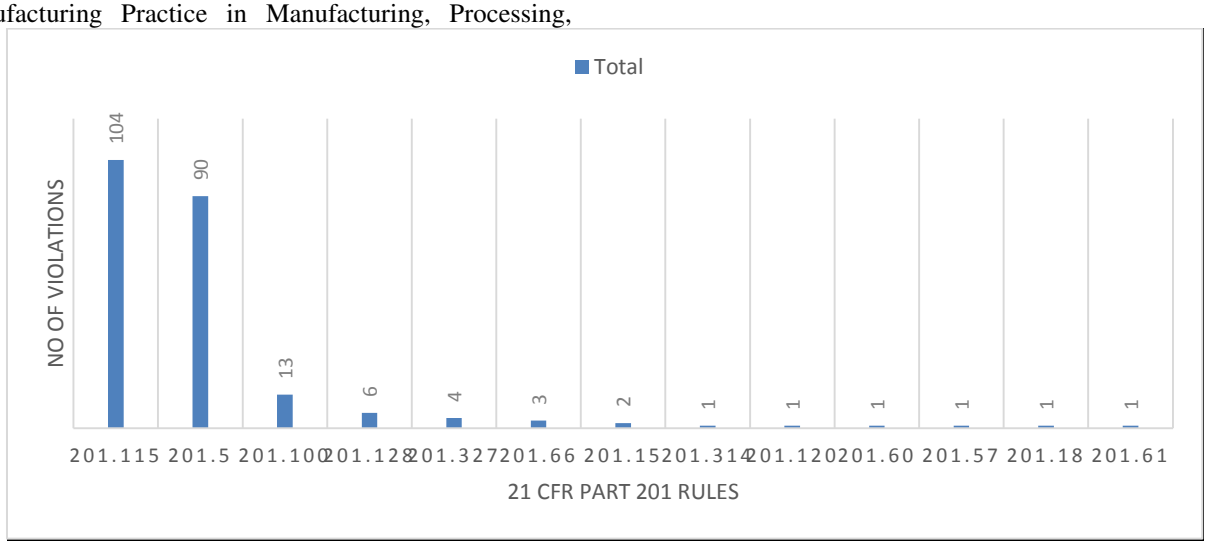

Figure 3. 21 CFR Part 201 Violations for Drugs and Formulations.

From the above Figure 3, it is observed that Section 201.115 of Title 21 CFR is most violated with 104 Violations. 201.115 deals with new drugs or new Animal drugs. If the drug is mislabelled or bore representations for its intended uses, then it is considered as a new drug.

Section 201.5 is observed for more than 90 times. It represents adequate directions for use which means a patient can use a drug safely and for the purposes for which it is intended. Statements of conditions/purposes/ recommendations must be imprinted along with dose quantity, the frequency of administration, time and route of administration.

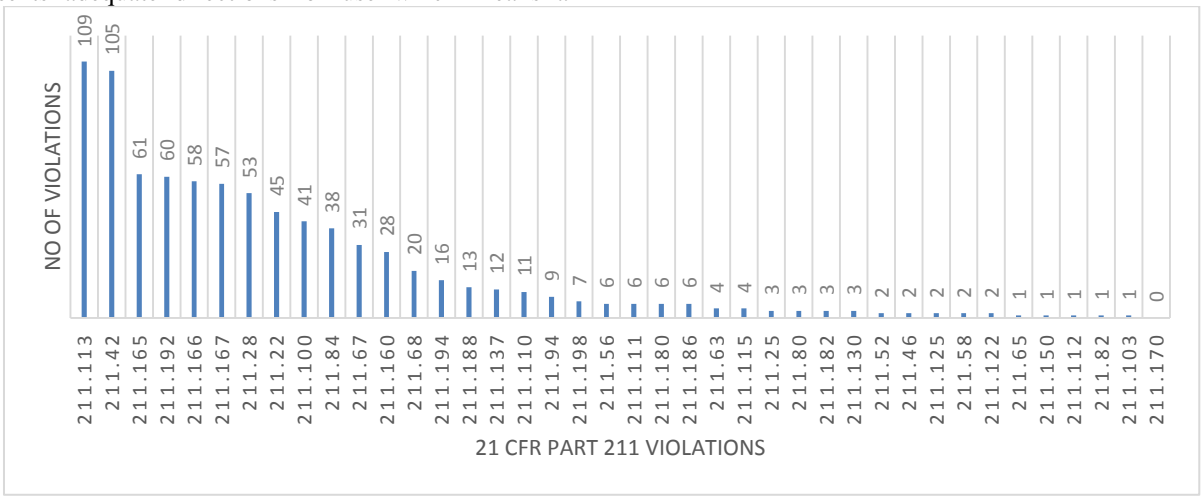

Figure 4. 21 CFR Part 211 Violations for Drugs and Formulations.

From the above Figure 4, it is observed that violation of section 211.113 is observed with 109 times. It represents Control of Microbial contamination. It says that there must be appropriate written procedures to prevent microbial contamination in the drug product. These procedures shall include validation of all aseptic and sterilization process.

Violation of section 211.42 is observed for 105 times. It represents design and construction features. It says any building for production must be a suitable size for proper operations, space for equipment and the areas must be

defined to prevent cross-contamination. Operations related to Penicillin has to be separated from other drug manufacturing to prevent cross-contamination.

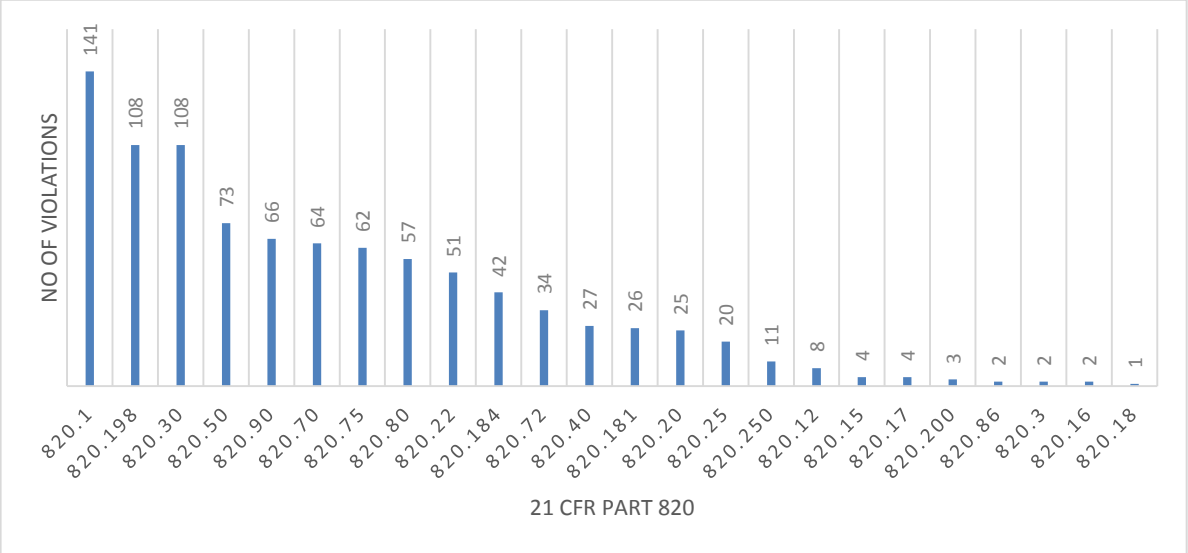

Figure 5. 21 CFR Part 820 Violations for Medical Devices.

From the above Figure 5, it is observed that Section 820.1 of Title 21 CFR is most violated with 141 Violations. It represents the CGMP requirements that are set forth in quality system regulation.

Section 820.198 Violations were observed for 108 times. It represents records storing of complaint files. This rule ensures that Manufacturer should process complaints in a uniformly and timely manner, Oral complaints are documented, even after the investigation is completed it is the responsibility of the manufacturer to maintain the records of the details of the investigation, corrective actions and replies (if any) given for complaint.

Section 820.30 Violation were observed for 108 times. It represents the Design controls of Class I, II and III devices. This rule makes sure that manufacturer establishes and maintain procedures to control the design of the device and to make ensure that requirements are met.

Section 820.50 Violation were observed for 72 times. It represents that manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements. This rule makes sure that manufacturer must evaluate the suppliers, contractors and they must be documented along with purchase data.

Section 820.90 Violation were observed for 64 times. If any product is nonconforming, there are procedures to identify, document, evaluate, segregate, and disposition. The evaluation and any investigation must be documented.

Section 820.75 and 820.70 violations were recorded more than 60 times each. These section deals with Production and process control. It includes SOP's, process parameters, compliance with specified reference standards, approval processes and process equipment. In case of process validation, it ensures that validation must be done with some qualified personnel. In case of any deviation, the entire process must have revalidated and documented.

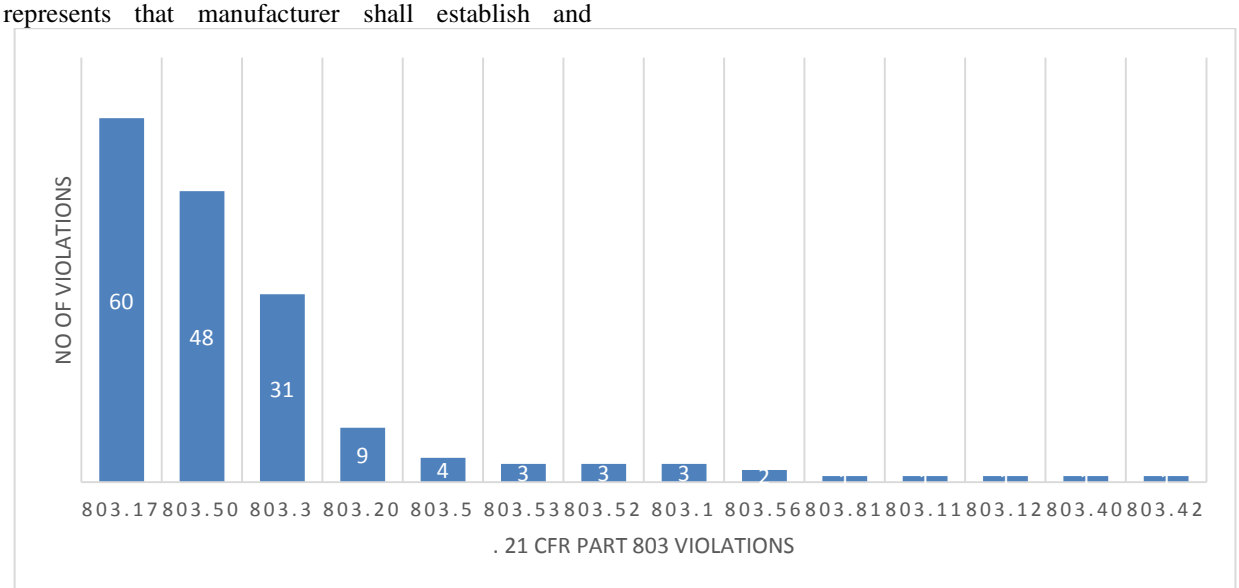

Figure 6. 21 CFR Part 803 Violations for Medical Devices.

From the above Figure 6, it is observed that Section 803.17 of Title 21 CFR is most violated with 36%. It represents the requirements for developing, maintaining, and implementing written MDR procedures. It is mainly for marketers, importers of devices

Also, 803.50 is found to second most violated. It represents reporting requirements for the manufacturer. If a patient died or hurt due to the usage of the device, it is the responsibility of the manufacturer to report to FDA with complete information. Also, Manufacturer is solely responsible for investigating of the reported case.

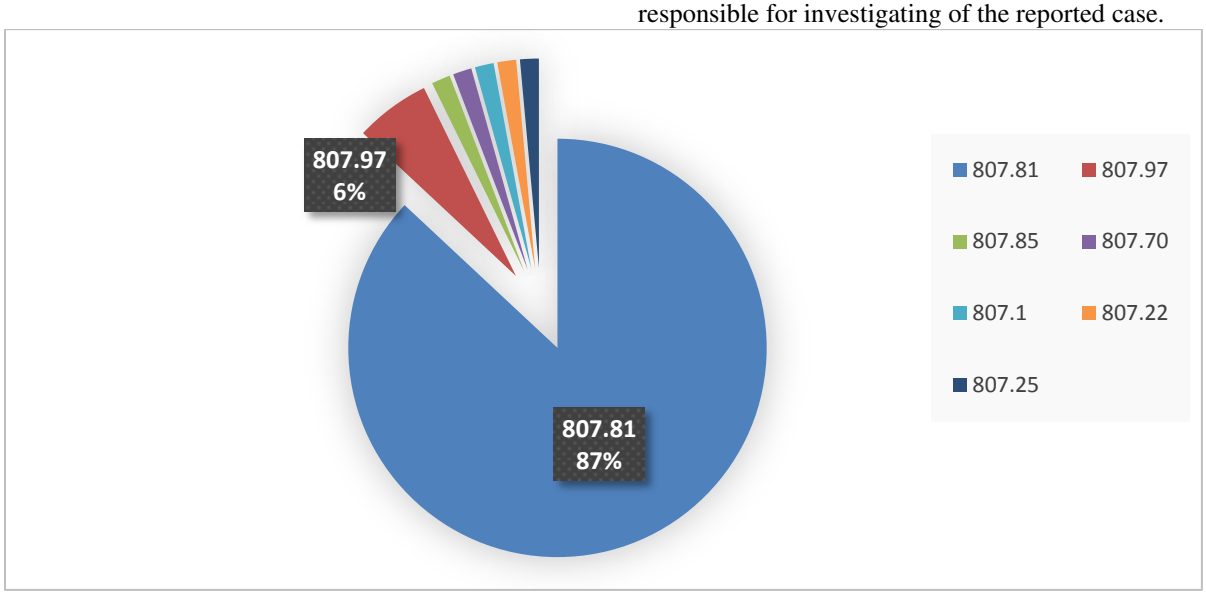

Figure 7. 21 CFR Part 807 Violations for Medical Devices.

From the above Figure 7, it is observed that Section 807.81 of Title 21 CFR is most violated with 87%. Class III (Devices having the highest risk. E.g. Heart Valve) requires Pre-Market Approval(PMA). A PMA is the most stringent type of premarket submission. Before FDA approves PMA, the sponsor must provide valid scientific evidence demonstrating reasonable assurance of safety and effectiveness for the device's intended use. The above results show that most of the manufacturers are not applying for PMA/Prior approval of PMA, before marketing their product in the US.

Second major violation of Section 807 of Title 21 CFR is 807.97 with almost 6%. Any representation that creates an impression of official approval of a device (without FDA approval) is considered as misleading and constitutes misbranding. The above result shows that firms are promoting Products/Process prior approval of FDA.

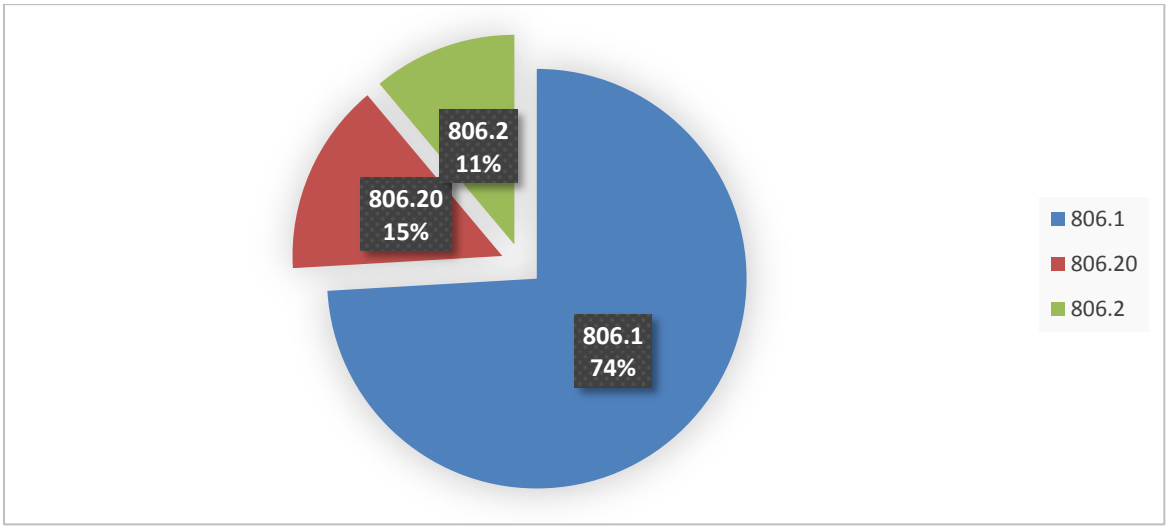

Figure 8. 21 CFR Part 806 Violations for Medical Devices.

From the above Fig. 1, it is observed that Section 806.10 of Title 21 CFR is most violated with 74%. Section 806 deals with reports of corrections and removals of device-related information. it says that it is the responsibility of Manufacturer to report or correct any device related information. Firms violating 806.10 are those which are not reporting the corrections of device-related information within 10 days of changes. Second major violation of Section 807 of Title 21 CFR is 806.20 with almost 15%. It represents the maintenance of records after corrections or changes to device-related information.

5. Conclusion

Next to China, India got most warning letters from FDA followed by Korea, Canada and Japan. China and India together account for 80% of import alerts which are

associated with warning letters. Since 2015 warning letters to drugs are increasing rapidly for drugs and formulations. Whereas they were decreasing for medical devices and biologicals. These are significance increase in warning letters for online Pharmacies. In case of medical devices its inversely relational. Total count of warning letters with time are decreasing.

Violations for online pharmacies mostly are misbranding, labelling issues, sale of not approved medicines and internet marketing with false or misleading claims. Violations for API, drugs and formulations include adulteration, misbranding. It also includes few false or misleading claims. Violations for medical devices include adulteration, QSR, pre-market approval, investigational device exemptions and misbranding.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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