Review of Warning Letters Issued by US FDA Over Past 3 Years

By

Lakshmi Sai Ananth

Dissertation submitted for the partial fulfillment of the

MBA Pharmaceutical Management

Academic year, 2016-2018

The IIHMR University, Jaipur

1, Prabhu Dayal Marg, Sanganer, Airport
Jaipur 302029, Rajasthan
Ph: 0141 3924700, Fax: 3924738
Website: **www.iihmr.edu.in**

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Jaipur 302029, Rajasthan
Ph: 0141 3924700, Fax: 3924738
Website: **www.iihmr.edu.in**

INSTITUTE OF HEALTH
MANAGEMENT RESEARCH
(WHO Collaborating Centre for District Health System Based on Primary Health Care)

IIHMR UNIVERSITY

TO WHOMSOEVER MAY CONCERN

This is to certify that **Lakshmi Sai Ananth** student of MBA ~~Hospital~~ and ~~Health~~ ~~Management/~~ Pharmaceutical / ~~Rural~~ Managementfrom The IIHMR University, Jaipur has undergone internship training at **Greatfour Systems Private Limited** from **February 8th to May 5th 2018.**

The Candidate has successfully carried out the study designated to him during internship training and his approach to the study has been sincere, scientific and analytical.
The Internship is in fulfillment of the course requirements.

Iwish him all success in all his future endeavors.

Dean, Academics and Student Affairs
The IIHMR University, Jaipur

Dr Saradha Kumar
Associate Professor
The IIHMR University, Jaipur

1, Prabhu Dayal Marg, Near Sanganer Airport, Jaipur- 302029, Rajasthan, India.
Ph.: 0141- 3924700, 2791431- 32, Fax: 0141 3924738, E-mail: iihmr@iihmr.edu.in, Web.: www.iihmr.edu.in

May 5, 2018

To Whomsoever It May Concern

This is to certify that **Lakshmi Sai Ananth** from IIHMR, Jaipur was hired as an Intern for the period 8th February, 2018 to 5th May, 2018.

During his internship, he worked on assignment pertaining to regulatory and labelling research and analysis of FDA warning letters.

We value his contribution to GreatFour Systems.

We wish him all the very best in his future endeavors.

With best wishes,

for **GreatFour Systems Pvt. Ltd.,**

Bharat Gujavarti
Vice President - Products

GREATFOUR SYSTEMS PVT. LTD. HYDERABAD

THE IIHMR UNIVERSITY, JAIPUR

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled **REVIEW OF WARNING LETTERS ISSUED BY US FDA OVER PAST 3 YEARS** and submitted by **Lakshmi Sai Ananth** Enrollment No **0070** under the supervision of **Dr. Saurabh Banarjee** for award of MBA in Hospital and Health/ Pharmaceutical / Rural Management in Health and Hospitals of the University carried out during the period from 8th Feb 2018 to 5th May 2018 embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.

Signature

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List of Tables and Figures

Acronyms/Abbreviations

QSR	Quality System Regulation
CGMP	Current Good Manufacturing Practices
CDER	Centre for Drug Evaluation and Research
CBER	Centre for Biologics Evaluation and Research
HACCP	Hazard Analysis and Critical Control Points
DMR	Device Master Record
CAPA	Corrective and Preventive Actions
CBD	Cannabidiol
PADE	Postmarketing Adverse Drug Experience
BLA	Biological Licence Application
PMA	Pre-Market Approval
IDE	Investigational Device Exemptions
MedDRA	Medical Dictionary for Regulatory Activities
FDA	Food and Drug Administration
CFR	Code of Federal Regulations
U.S.C	United States Code
CTD	Common Technical Document
IPRF	International Pharmaceutical Regulation Forum
ICH	International Conference on Harmonization
PANDRH	Pan American Network for Drug Regulatory Harmonization
PIC/S	Pharmaceutical Inspection Cooperation Scheme
RHSC	Regulatory Harmonization Steering Committee

Executive Summary

Origin of FDA

With 1100$ Billion Revenue in 2016 United Stands stands as Worlds largest Pharmaceutical Market. Being the largest, diversified and due to globalization, US Pharma industry is the most competitive and critical sectors of the economy (ITA, 2016). 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.

Origin of FDA was dated back to 1848, during the creation of Agricultural Division in Patent Office. It begins as consumer protection agency and begun in 1906 as Pure Food and Drugs Act law, which is formed by the culmination of over 100 bills in 25 years to prevent serious abuses and long-standing of consumer product marketplace. (Services, FDA Basics: When and Why FDA was formed ?, 2018)

FDA was predecessed by Bureau of Chemistry of US Department of Agriculture. During 1906 Harvey Washington Wiley is a chief chemist who is responsible for Federal public health protection. Also, in response to public outrage regarding the unhygienic conditions in Stockyards of Chicago described in Sinclair's book The Jungle paved the strong way for the FDA formation. In time Job description of Chief chemist was renamed to Commissioner of food and drugs (Services, How did the Federal Food, Drug, and Cosmetic Act come about?, 2018).

Mission of FDA

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. It also helps public to get accurate scientific information of food and drugs to maintain and improve public health. (Services, What We Do, 2017)

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." (Sources, Food and Drug Administration, 2018)

FDA Collaborations & Forums:

FDA along with other regulatory agencies across the world have been working in collaboration for years to harmonize regulatory standards. Examples include:

International Conference on Harmonization(ICH): International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). All information regarding technical aspects of pharmaceutical product registrations and scientific aspects were discussed among regulatory authorities of United States, European Union, and Japan. ICH includes Quality, Safety, Efficacy and Multidisciplinary guidelines (ICH, n.d.).

Regulatory Harmonization Steering Committee(RHSC): Asia-Pacific Economic Cooperation (APEC) Life Sciences Innovation Forum (LSIF) Regulatory Harmonization Steering Committee (RHSC). The FDA participates in the RHSC and its working groups, such as Cell and Tissue-based Therapeutic Products, Pharmacovigilance, Good Review Practices, Good Clinical Practice Inspection, Supply Chain Integrity and Product Quality, Biotherapeutic Products, Multi-regional Clinical Trials, etc (APEC, 2017).

International Pharmaceutical Regulators Forum (IPRF): The IPRF facilitates the implementation of ICH and other internationally harmonized technical guidelines for pharmaceuticals. The main purpose of IPRF is to create an environment for Pharma regulators so that they can exchange information regarding regulatory news and issues with mutual concern (FDA U. , Enhance collaboration with other foreign regulatory agencies and international partners to strengthen regulatory capacity and enhance global public health protection, 2017).

Pan American Network for Drug Regulatory Harmonization (PANDRH): formed in 1999 with main objective to strengthen the regulatory systems in America. To develop, approve and implement common proposals taking consideration of local laws and international guidelines (Charles Preston, 2014).

Pharmaceutical Inspection Cooperation Scheme (PIC/S): PIC/S are two instruments in between countries and inspection authorities. It strives to improve among CGMP between regulatory bodies and Pharmaceutical Industry (Ltd, 2012).

World Health Organization (WHO): FDA in collaboration with WHO established PAHO/WHO Collaboration Center for Biological Standardization, which provides expertise in research according to WHO written standards and guidelines (FDA W. , 2014).

US FDA Warning Letter

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. A Warning letter is considered as an official message from US-FDA indicating that manufacturer has violated some sort of rule in regulatory activity (FDA U. , Warning Letters and Notice of Violation Letters to Pharmaceutical Companies, 2017).

Determination of violations is generally done by inspecting the manufacturing plant by FDA itself or can also be issued with evidence from state personnel. Generally, warning letter by FDA is considered as informal and advisory. So, here agency position is to communicate on the issue of interest (violation is the case in here) rather than enforcement action. So, a warning letter is not a final letter issued by FDA to sue.

FDA defines an FDA warning letter as.,

"...a correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations. Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. A Warning Letter is one of the Agency's principal means of achieving prompt voluntary compliance with the Act.

Ideally, FDA expects firms, government agencies, and individual manufacturers to comply with law voluntarily rather than being enforced. Even though if FDA observes any deviation from the law, it gives an opportunity to take actions and corrective measures by issuing a warning letter. Then only FDA proceeds with enforcement action. So, warning letter in this process is just a prior notice for nature of the violation (Sources, FDA Warning Letter, 2017).

Actions by the Food and Drug Administration (FDA) for inappropriate safety and/or efficacy claims by drug companies have recently generated considerable public attention.

US FDA issues warning letters for

a. Drugs and pharmaceuticals which include
    a. **Drugs for human use**,
    b. Drugs for veterinary use,
    c. **Vaccines, Blood, and Biologicals**,
    d. Medical devices and
    e. **Radiation-emitting devices**.
b. Food products which include food supplements, packed foods and seafood and poultries.
c. Tobacco products
d. Cosmetics

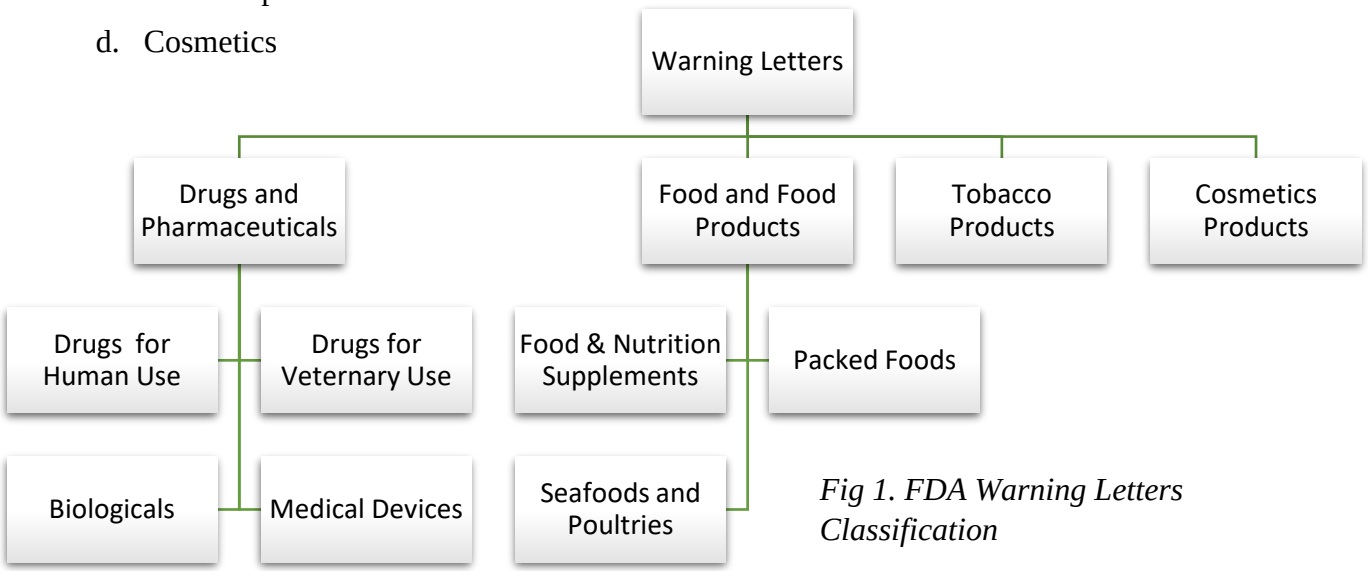

Fig 1. FDA Warning Letters Classification

Anatomy of Warning Letter

A structured warning letter consists of the following elements

Title

The title "WARNING LETTER" is written on top of every letter.

Delivery

Mode of delivery is stated on the cover of the warning letter. Generally, warning letters were sent by overnight delivery and return receipt is requested. Every return receipt is documented for future purpose.

Addressee

A warning letter is addressed to the highest member of organization/firm that FDA inspected. A copy of the letter is also sent to the highest known head of the inspected facility. There are instances where FDA expects written replies from other officials of the firm and in this case, they may be included in addresses.

Inspection details

Generally, date of inspection and description of violated conditions violated practices and products in brief. But, enough information is written so that respondent can dive into the issue and correct the matter. Warning letters also include laws that are violated. They were cited where ever applicable. The main difference between warning letter and Form FDA 483 is that warning letter cites regulatory references where ever applicable.

Promised corrections

During the inspection, there is a chance that facility head may promise the corrections later. Those will be included in the warning letter. It may also include those corrections that organization provides in a written response.

Response request

After the issue of a warning letter, US FDA requests correction letter response within a specific period, in general, 15 days. In meantime authorities from the organization can discuss with district officials or center officials.

Warning statement

A warning letter contains a statement that warns that FDA can enforce if the issue is not corrected. It includes some examples of enforced actions. But, there are no commitments from FDA that they will take those actions.

Additional impact for device manufacturers

Warning letters for medical devices and radiation-emitting devices contain the following statement, “Federal agencies are advised of all Warning Letters about devices so that they may take this information into account when considering the award of contracts.” Warning letters for medical devices and radiation-emitting devices which violate the CGMP guidelines contain the following statement "Additionally, PMA for Class III devices to which deviations related to QSR will not be approved until the violations have been corrected. Also, Requests for Certificates to Foreign Governments will not be issued until the deviations were corrected.”.

Issuer

At the end of the warning letter, the main head of the issuing office, the district director, division director, or higher agency official is also mentioned.

Standardized closing text

“The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist. You are responsible for complete investigating and determining the causes of the violations identified above and for preventing their recurrence of other violations. It is your responsibility to assure your firm complies with all requirements of federal law and FDA regulations.”

"You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts."

"Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the time within which you will complete the correction."

Rationale of Study

Generally, in pharma companies it is responsibility of Regulatory Affairs staff to look after Labelling follows regulatory authorities. But, with increase in number of Brands and basket of products time complexity is increasing in managing these regulatory guidelines. With the help of present technology it is possible to automate things. This study helps to prioritize burning issues to develop applications for pharma industry.

Research Objectives

The objectives of this study are

a. To understand the types warning letters issued by US FDA across different Countries.
b. To understand what the major violations in case of drugs, biologicals, and medical devices.

Research Methodology

- **Study Type**:
  - Secondary Desk Review. Publicly available FDA letters sent to pharmaceutical companies from 2015 to 2017 were reviewed. A standard data collection tool was developed using MS Excel, including all categories violations. Other information collected included the type of regulatory letter and media in which violations were found (FDA U. , Warning Letters, 2015-2018).
- **Study Duration**: Three Months (Feb 2018 to April 2018)
- **Sample Size**: 694
- 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 1159 letters were related to food and food products.

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

Table 1. Sample Size Distribution from 2015-2017

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

Results and Findings

Distribution of US FDA Warning Letters 2014-2017 across different Nations

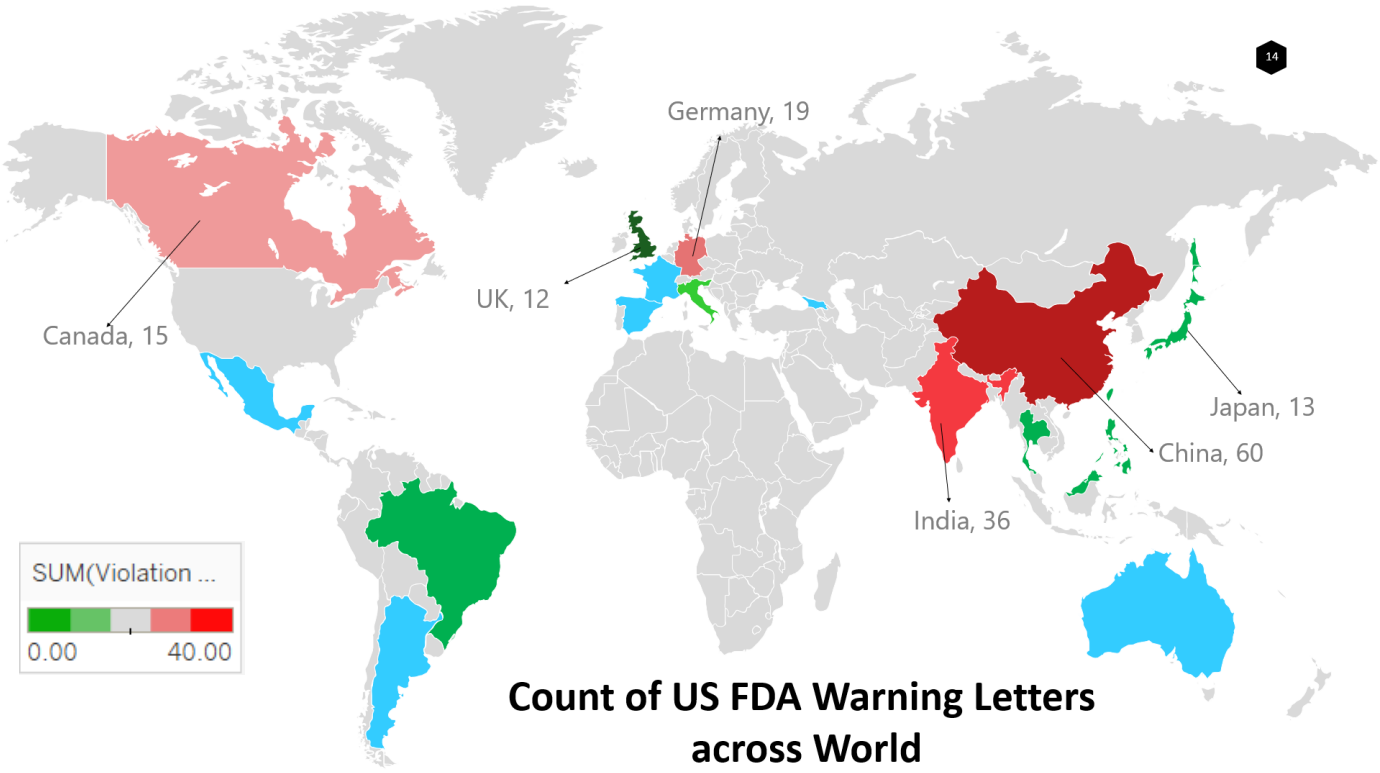

Fig 2: Heat Map of Count of Letters issued to different countries

From the above heat map, it is observed that China & India were issued most warning letters by US FDA in past 3 years. Followed by Canada and Japan. In case of European Union Germany and United Kingdom were issued most followed by Italy, Spain and France. Canada also observed with more number of violations.

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Total Count of 21 CFR Violations (Drugs and Formulations)

21 CFR Violations	Drugs
21 CFR Part 211	845
21 CFR Part 201	228
21 CFR Part 210	45
21 CFR Part 207	12
21 CFR Part 312	7
21 CFR Part 341	4
21 CFR Part 352	4
21 CFR Part 310	3
21 CFR Part 343	1
21 CFR Part 347	1
21 CFR Part 349	1
21 CFR Part 355	1
21 CFR Part 530	1
21 CFR Part 556	1

A total of 1154 Violations were observed. Out of which 21 CFR Part 211, 201 and 210 were chosen for individual violation analysis

Major Violations:

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.

Table 2: Total count of 21CFR Violations (Drugs & Formulations)

Total Count of 21 CFR Violations (Medical Devices)

A total of 1316 Violations were observed. Out of which 21 CFR Part 820, 803, 807 and 806 were chosen for individual violation analysis.

Major Violations:

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

Table 3: Total count of 21CFR Violations (Medical Devices)

21 CFR Violations	Medical Devices
21 CFR Part 820	941
21 CFR Part 803	168
21 CFR Part 807	69
21 CFR Part 806	27
21 CFR Part 812	26
21 CFR Part 878	14
21 CFR Part 890	13
21 CFR Part 211	9
21 CFR Part 822	9
21 CFR Part 50	6
21 CFR Part 1040	5
21 CFR Part 1270	5
21 CFR Part 882	4
21 CFR Part 876	3
21 CFR Part 884	3
21 CFR Part 1002	3
21 CFR Part 1010	3
21 CFR Part 1020	2
21 CFR Part 201	1
21 CFR Part 56	1

21 CFR Part 201 Violations (Drugs and Formulations)

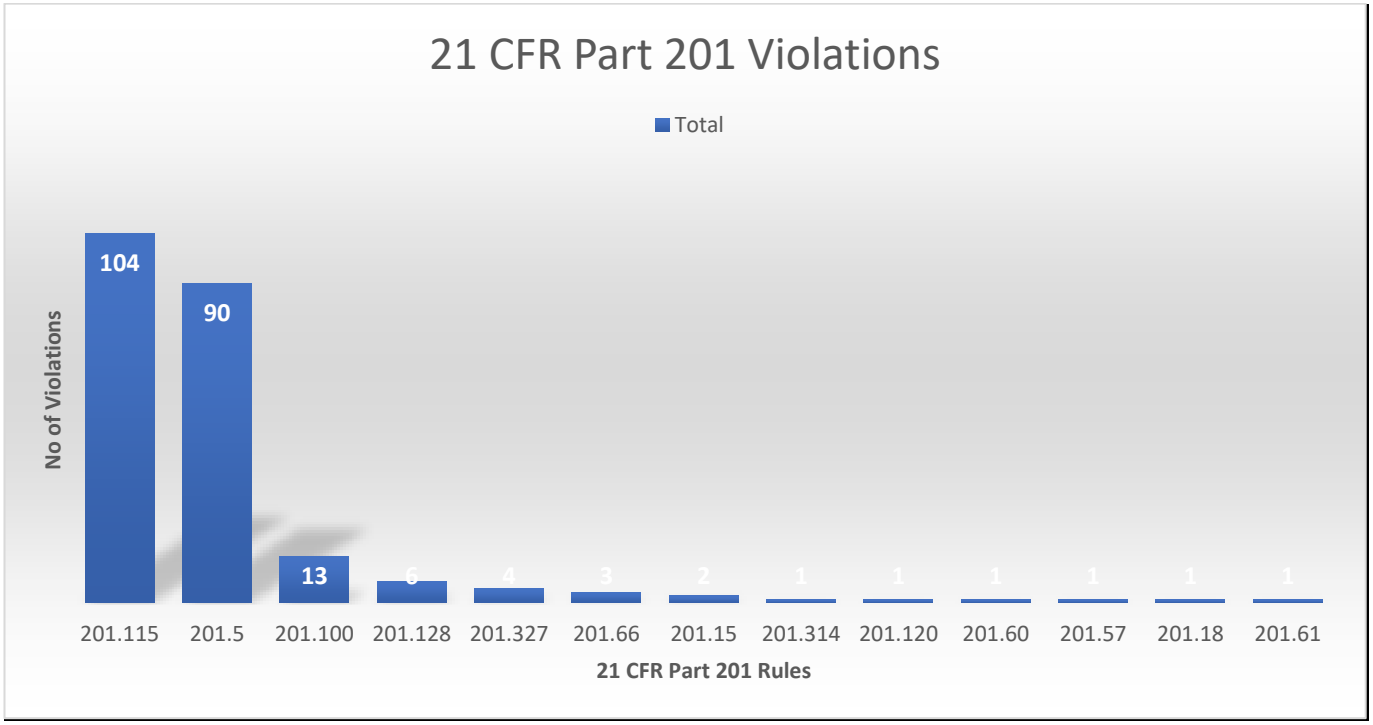


Figure 2: 21 CFR Part 201 Violations for Drugs and Formulations.

From the above Fig. 1, it is observed that Section 201.115 of Title 21 CFR is most violated with 104 Violations. 201.115 (Electronic Code of Federal Regulations, 2018) 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 (Electronic Code of Federal Regulations, 2018) 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.

21 CFR Part 211 Violations (Drugs and Formulations)

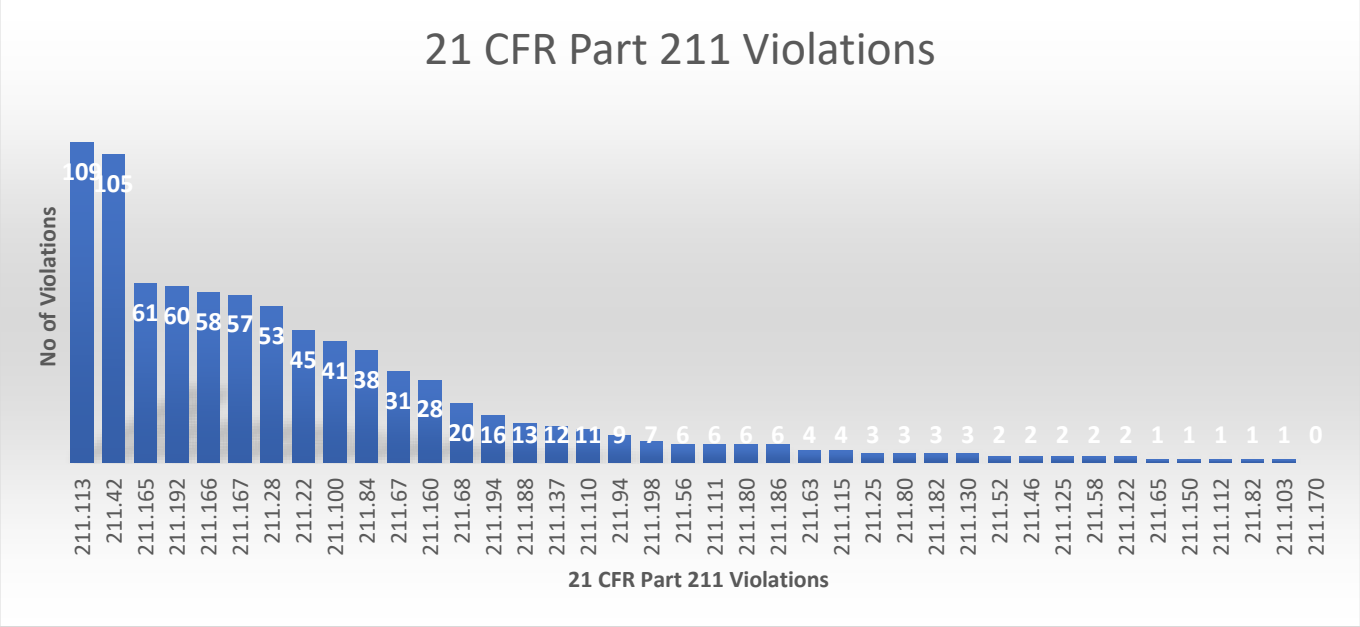


Figure 3: 21 CFR Part 211 Violations for Drugs and Formulations.

From the above Fig. 1, it is observed that violation of section 211.113 (Electronic Code of Federal Regulations, 2018) 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 (Electronic Code of Federal Regulations, 2018) 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.

21 CFR Part 820 Violations (Medical Devices)

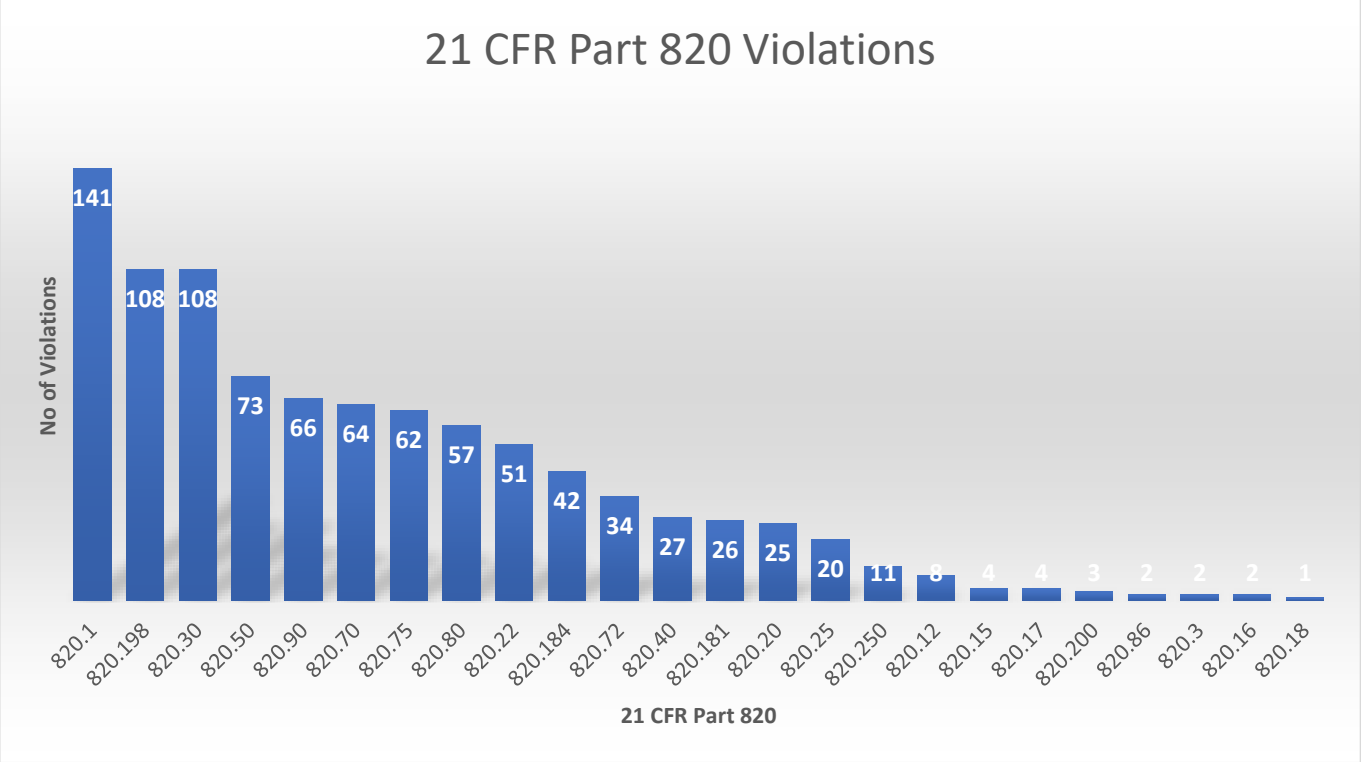


Figure 4: 21 CFR Part 820 Violations for Medical Devices.

From the above Fig. 1, it is observed that Section 820.1 (Electronic Code of Federal Regulations, 2018) 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 (Electronic Code of Federal Regulations, n.d.) 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 (Electronic Code of Federal Regulations, 2018) 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 (Electronic Code of Federal Regulations, 2018) 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 (Electronic Code of Federal Regulations, 2018) 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 (Electronic Code of Federal Regulations, 2018) and 820.70 (Electronic Code of Federal Regulations, 2018) 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.

21 CFR Part 803 Violations (Medical Devices)

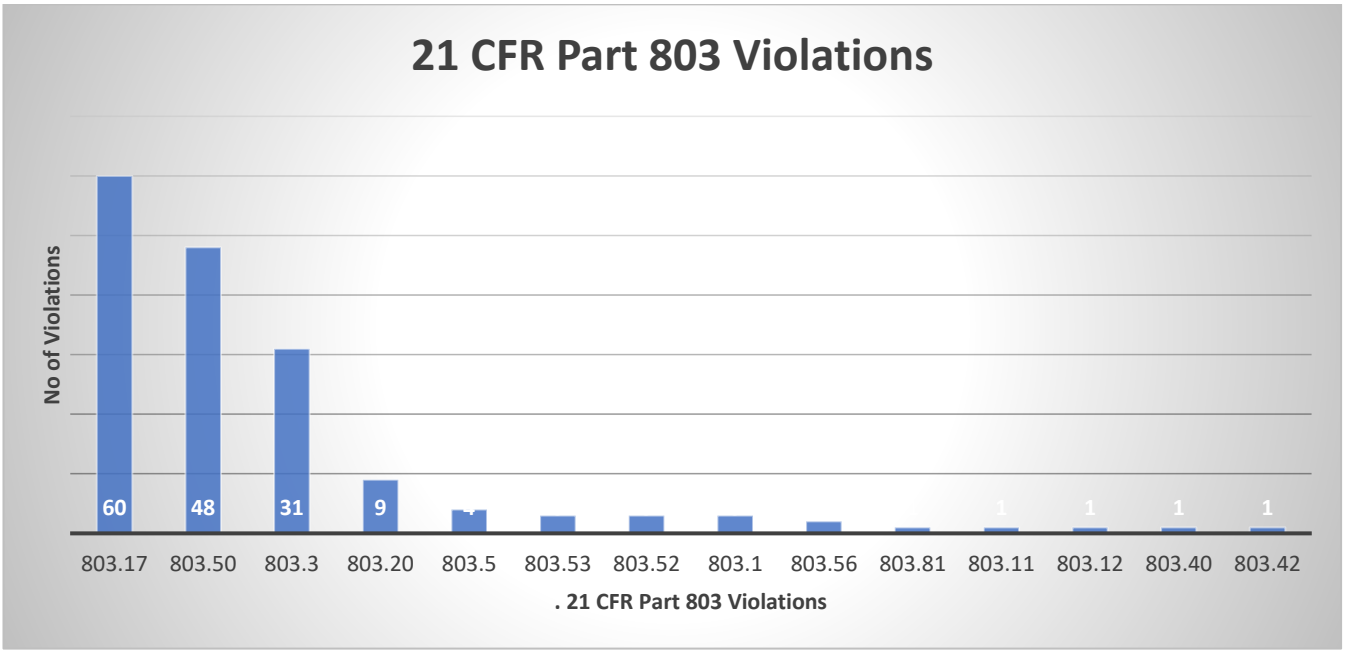


Figure 5: 21 CFR Part 803 Violations for Medical Devices.

From the above Fig. 1, it is observed that Section 803.17 (Electronic Code of Federal Regulations, 2018) 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

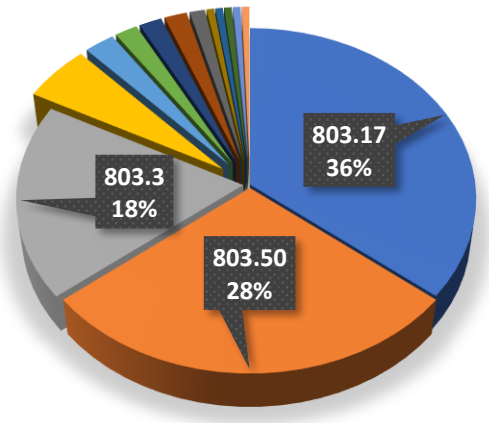


Figure 6: 21 CFR Part 803

Also, 803.50 (Electronic Code of Federal Regulations, 2018) 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.

21 CFR Part 807 Violations (Medical Devices)

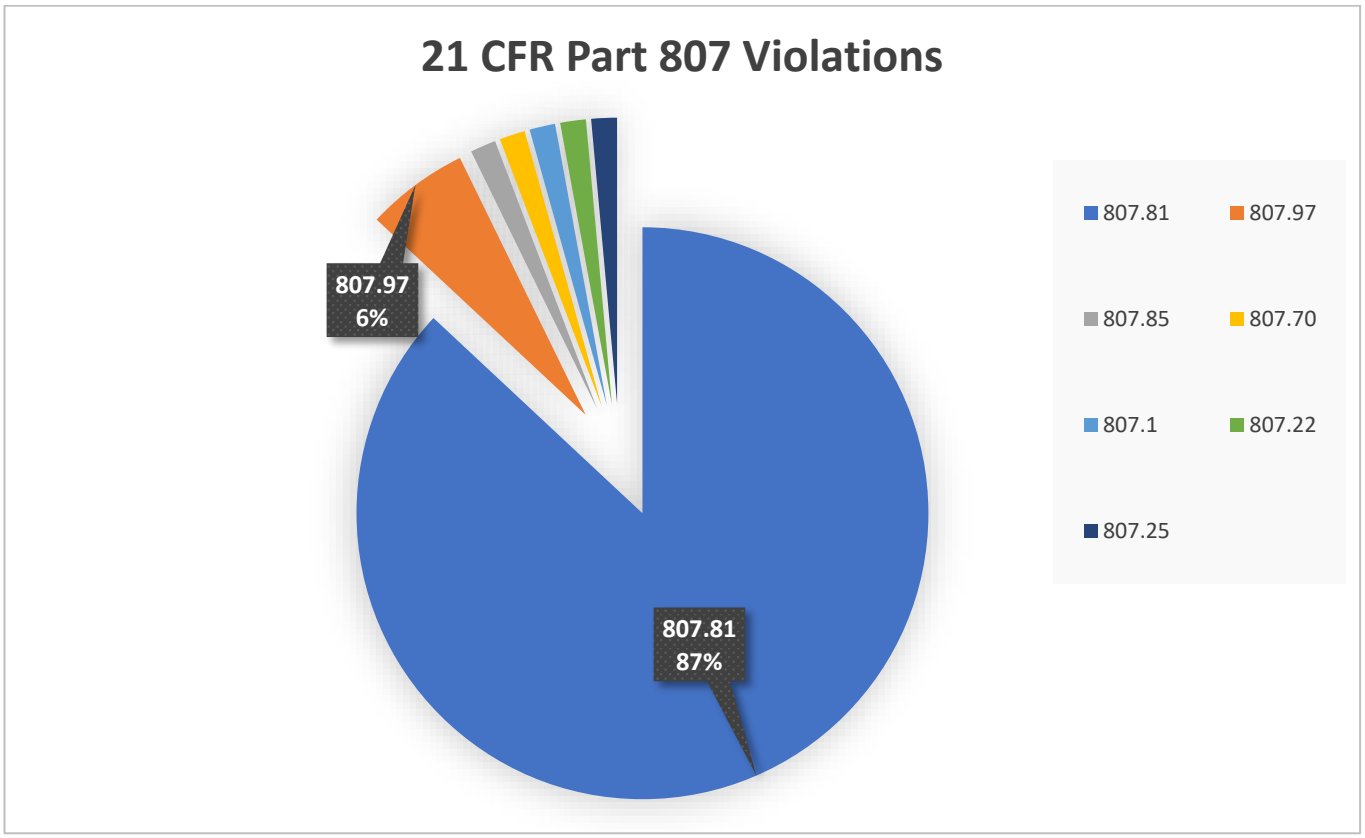


Figure 7: 21 CFR Part 807 Violations for Medical Devices.

From the above Fig. 1, it is observed that Section 807.81 (Electronic Code of Federal Regulations, 2018) 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 (Electronic Code of Federal Regulations, 2018) 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.

21 CFR Part 806 Violations (Medical Devices)

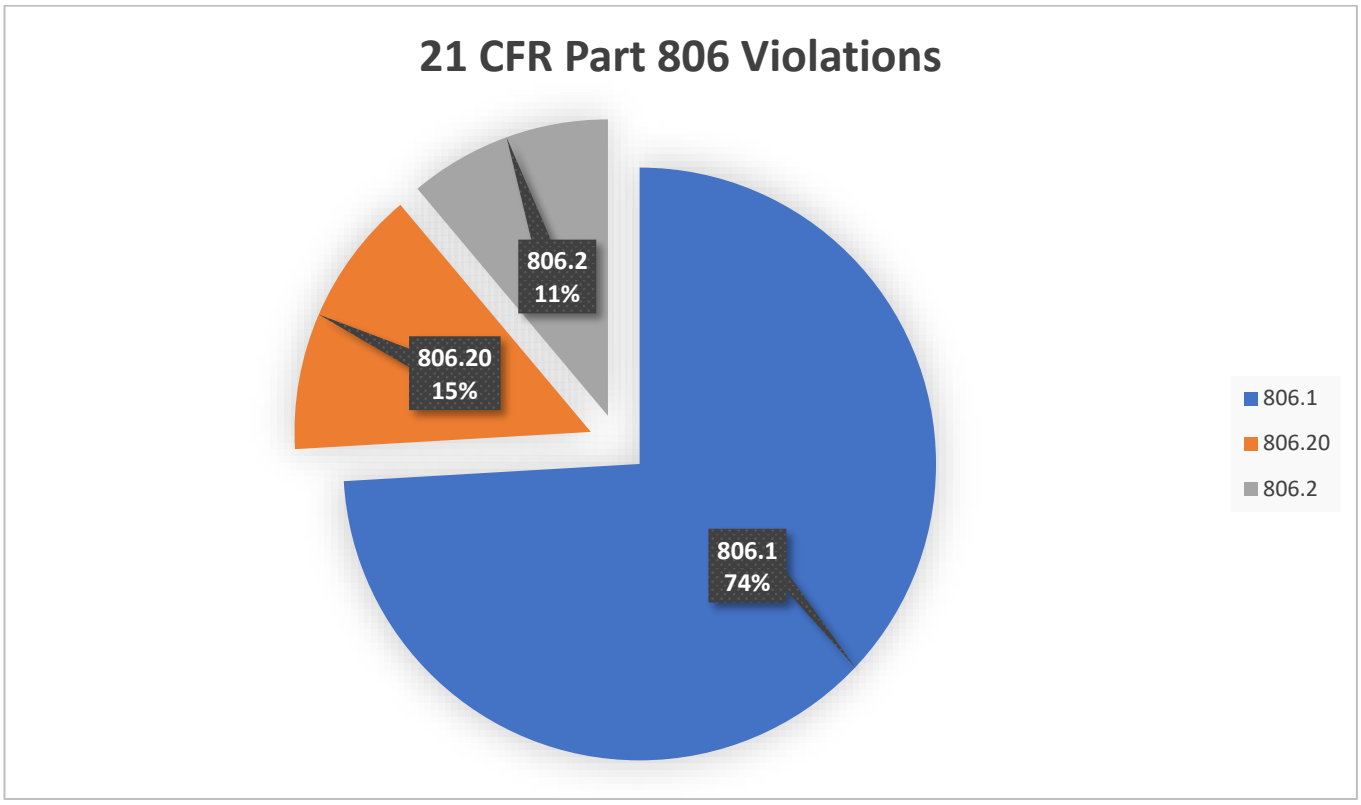


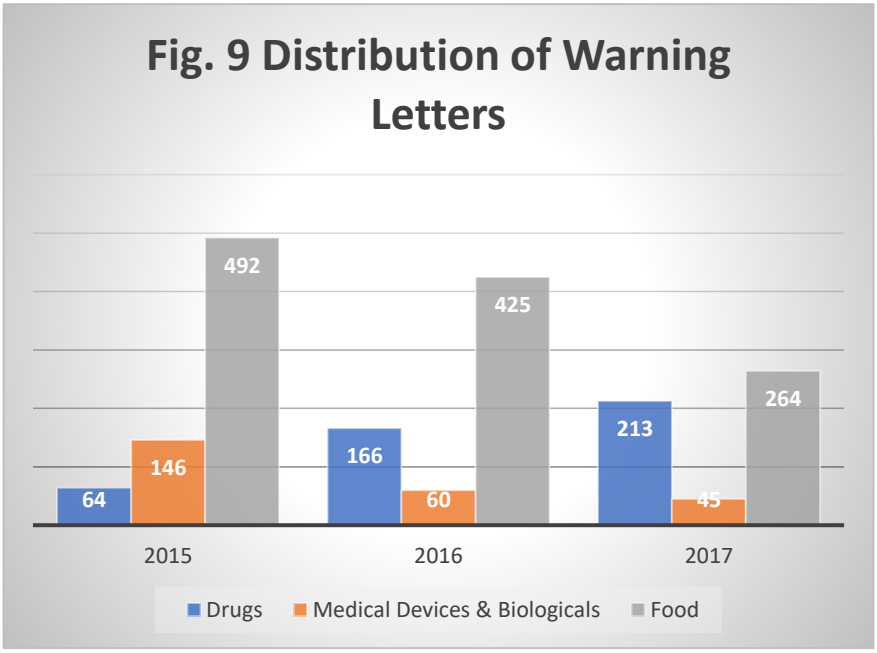
Figure 8: 21 CFR Part 806 Violations for Medical Devices.

From the above Fig. 1, it is observed that Section 806.10 (Electronic Code of Federal Regulations, 2018) 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.

Conclusion and Discussion

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.



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

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Appendix

Finished Products, API, Formulations & Compounding Pharmacies																	
S No	Year	Month	Organisation	Country	Issuing Authority	Issues in Warning Letters			21 CFR Violations			FD & C Act Violations					
						Remark1	Remark2	Type of Product	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	

Table 4: Check List for Data Collection

Medical Devices and Biological Products																	
S No	Year	Month	Organisation	Country	Issuing Authority	Issues in Warning Letters			21 CFR Violations			FD & C Act Violations					
						Remark1	Remark2	Type of Product	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	

Table 5: Check List for Data Collectio