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USFDA is one the most regulated agency. The USFDA quality production office (OMQ) office at the Center for Drug Evaluation and Research (CDER) assesses compliance with drug cGMP based on test reports and evidence collected by USFDA investigators. The material described in the FDA warning letters may be the result of a subsequent communication between the FDA and the recipient of the book which may alter the regulatory nature of the discussions discussed in the publication. An FDA Form 483 is issued to strict supervisors upon completion of an examination once the investigator (investigators) has identified any circumstances in their judgment which may be a violation of the Food Drug and Cosmetic (FD & C) Act and related legislation. This study is about analysis on FDA warning letters in the year 2018, 2019, 2020 related to Manufacturing Quality and to comparison between India and other nations. This is to analyze that the issuance of warning letters related to manufacturing quality in India or among other nations is increasing or decreasing.

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USFDA is one the most regulated agency. The USFDA quality production office (OMQ) office at the Center for Drug Evaluation and Research (CDER) assesses compliance with drug cGMP based on test reports and evidence collected by USFDA investigators. The material described in the FDA warning letters may be the result of a subsequent communication between the FDA and the recipient of the book which may alter the regulatory nature of the discussions discussed in the publication. An FDA Form 483 is issued to strict supervisors upon completion of an examination once the investigator (investigators) has identified any circumstances in their judgment which may be a violation of the Food Drug and Cosmetic (FD & C) Act and related legislation. This study is about analysis on FDA warning letters in the year 2018, 2019, 2020 related to Manufacturing Quality and to comparison between India and other nations. This is to analyze that the issuance of warning letters related to manufacturing quality in India or among other nations is increasing or decreasing.

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Author: Department of Regulatory Affairs.

I. INTRODUCTION¹⁻²

The United States Food and Drug Administration (FDA or USFDA) is a joint organization of the Department of Health and Human Services. The FDA is responsible for protecting and promoting public health through the safety and management of food, tobacco products, food additives, drugs and medicines (vaccines), vaccines, biopharmaceuticals, blood transfusions, medical equipment, radiation devices (ERED), cosmetics, animal feed & feed and animal products.

The FDA's primary focus is enforcement of the Federal Food, Drug, and Cosmetic Act (FD&C) Act, but the agency also imposes other laws, in particular Section 361 of the Public Health Service Act, and related legislation. Much of this enforcement activity is not directly related to food or drugs, but includes things like lasers, cell phones, condoms, and disease control in a variety of situations from domestic pets to human sperm that are used to aid reproduction.

FDA organization

FDA is an agency within the Department of Health and Human services and consists of nine center level organization and thirteen Headquarter (HQ) offices. The FDA overview chart including the office of commissioner and FDA HQ offices is shown in A.a.

II. FDA WARNING LETTER ^{2,4}

The FDA warning letter is an official notice from the FDA that indicates serious violations. The warning letter was issued by senior FDA officials after they reviewed the inspector's report. The warning letter is considered to be an increase from 483 awareness.

The most common causes of FDA warning letters are:

Written procedures that do not comply with the rules

Failure to follow written procedures

Failure to prove that regulations have been followed with adequate documentation

Alerts are sent in person to ensure they are viewed and treated quickly. According to FDA 483, the FDA warning letter requires a written response within 15 days.

If the cause of the FDA warning letter is serious, the FDA may increase the deadline. You are responsible for correcting violations described in the FDA warning letter.

Warning letters are made public. Anyone can find out that the company has been given a letter. We have even heard of competitors using a company warning letter as a bad example of why a potential customer should choose his own company over a competitor.

Like the 483 looks, warning books can be very expensive to deal with. Obtaining a warning letter can greatly delay the marketing time and cost money in the process.

III. METHODOLOGY

The number of warning letters issuance to the pharmaceutical companies has gradually increased from the past 3 years i.e., 2018,2019,2020. Of all the violations the major cause for issuing warning letters is due to deviations in cGMP. Many of the deviations in cGMP was observed in finished pharmaceuticals. This discussion deals with the analysis of FDA warning letters in the Fy 2018, Fy 2019, Fy 2020 related to manufacturing quality and to know that which country is getting more warning letters compared to other countries.

Part – 1¹⁷

In the Fy 2018, Total of 91 warning letters are issued to different companies by FDA throughout the world. Out of 91 warning letters, 7 warning letters are issued by Office of Prescription drug promotion, 3 warning letters are issued by Office of compliance, 63 warning letters are issued by Office of Manufacturing Quality, 4 warning letters are issued by Office of Scientific Investigations, 14 warning letters are issued by Office of unapproved drugs & labeling compliance. Many of the warning letters are issued by Office of Manufacturing quality due to deviations in cGMP. As deviations in cGMP is the major issue the warning letters has gradually increased.

Frequency distribution of warning letters related to manufacturing quality in 2018 was shown in table.1.1 and plot was shown in figure1.1. a

Part- 2¹⁸

In the FY 2019, total of 88 warning letters are issued by FDA to different companies in different countries. Out of 88 warning letters, 10 warning letters are issued by Office of Prescription drug promotion, 4 warning letters are issued by Office of compliance, 47 warning letters are issued by Office of Manufacturing quality, 3 warning letters issued by Office of Scientific Investigations, 22 warning letters issued by Office of Unapproved drugs & Labeling compliance, 2 warning letters issued by Office

of Drug security, integrity and recalls. Many of the warning letters are issued by Office of Manufacturing quality due to the increased deviations in cGMP. As the cGMP violations is the major issue the no of warning letters are gradually increasing. Compared to FY 2018 the no of warning letters related to manufacturing quality was decreased.

Frequency distribution of warning letters related to manufacturing quality in 2019 was shown in table 2.1 and plot was shown in figure.2.1. a.

Part-3¹⁹

In the FY 2020, total of 159 warning letters are issued by FDA to different companies in different countries. Out of 159 warning letters, 6 warning letters are issued by Office of Prescription drug promotion, 2 warning letters are issued by Office of compliance, 23 warning letters are issued by Office of Manufacturing quality, 1 warning letter is issued by Office of Scientific Investigations, 127 warning letters issued by Office of Unapproved drugs & Labeling compliance. Many of the warning letters are issued by Office of Unapproved drugs & labeling compliance. Compared to FY 2018, FY 2019 the no of warning letters related to manufacturing quality was decreased.

Frequency distribution of warning letters related to manufacturing quality in the year 2020 was shown in table 3.1 and plot was shown in 3.1.a.

Part-4

In this part, analysis of warning letters issued by FDA related to manufacturing quality in the FY2018, FY2019, FY2020 based upon geographical area. comparison of warning letters in FY 2018, 2019, 2020 based upon geographical area was shown in table 4.1 and the plot was shown in 4.1.a From the plot 4.1.a, it is assumed that.

In the FY 2018 the highest number of warning letters are issued to India when compared with other geographical areas.

In the FY 2019 the highest number of warning letters are issued to China when compared with other geographical areas.

In the FY 2020 the highest number of warning letters are issued to India when compared with the other geographical areas.

In India, the number of warning letters issued by FDA is increased in FY 2019 when compared with FY 2018, the number of warning letters issuance is decreased in FY 2020 when compared with FY 2018 & FY 2019.

In China, the number of warning letters issued by FDA was gradually decreased from FY 2018 – 2020.

In United states, the number of warning letters issued by FDA was gradually decreased from FY 2018 – 2020.

Part-5

In this part the frequency of warning letters issued by FDA in the year 2018, 2019, 2020 was compared and the plot was shown in 5.a.

From the plot 5.a, it is observed that issuance of warning letters by FDA related to manufacturing quality has gradually decreased from FY 2018 – FY 2020.

In FY 2018, 63 warning letters are issued by FDA related to manufacturing quality in different organizations.

In FY 2019, 47 warning letters are issued by FDA related to manufacturing quality in different organizations.

In FY 2020, total of 23 warning letters are issued by FDA related to manufacturing quality in different organizations.

It is concluded that the number of warning letters issuance is gradually decreasing.

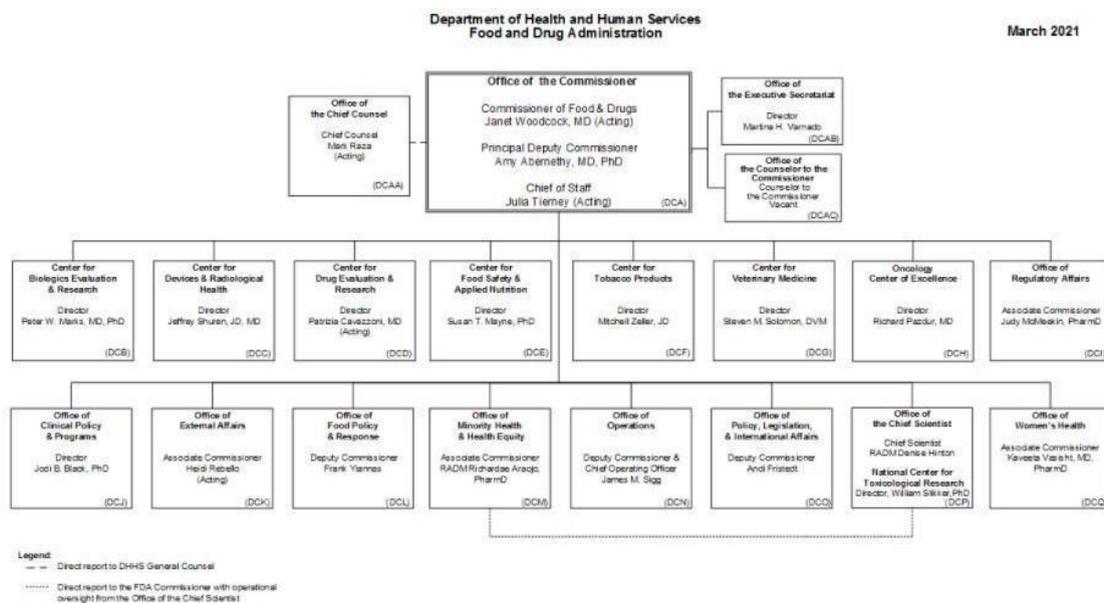


Fig A.a: Flow chart of FDA organization along with Head quarters^{1,2}

Table 1.1: Frequency distribution of warning letters in FY 2018

S.NO	Country	API	Finished Pharmaceuticals
01	India	4	6
02	United states	3	3
03	China	9	13
04	South Korea	-	6
05	North Korea	-	2
06	Mexico	-	2
07	Canada	-	3
08	Japan	3	-
09	France	-	2
10	Taiwan	-	2
11	Australia	1	1
12	Ireland	-	1
13	Spain	-	1

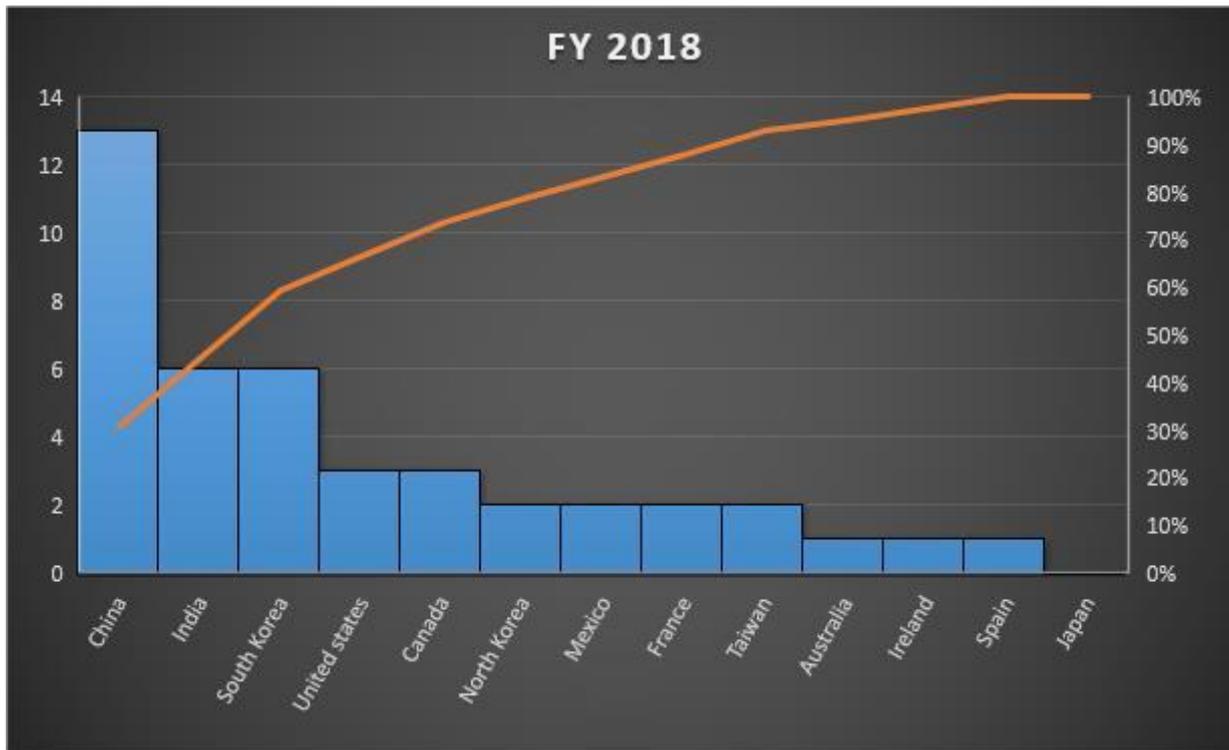


Fig 1.1.a: Frequency plot for FY 2018

Table 2.1: Frequency distribution of warning letters in FY 2019

S.No.	Country	Api	Finished Pharmaceuticals
01	India	5	14
02	United states	3	2
03	China	1	6
04	South Korea	-	2
05	Australia	1	-
06	Bahamas	-	1
07	Costa Rica	-	1
08	Singapore	-	2
09	Taiwan	-	1
10	Canada	-	1
11	France	-	1
12	Proandre SL	-	1

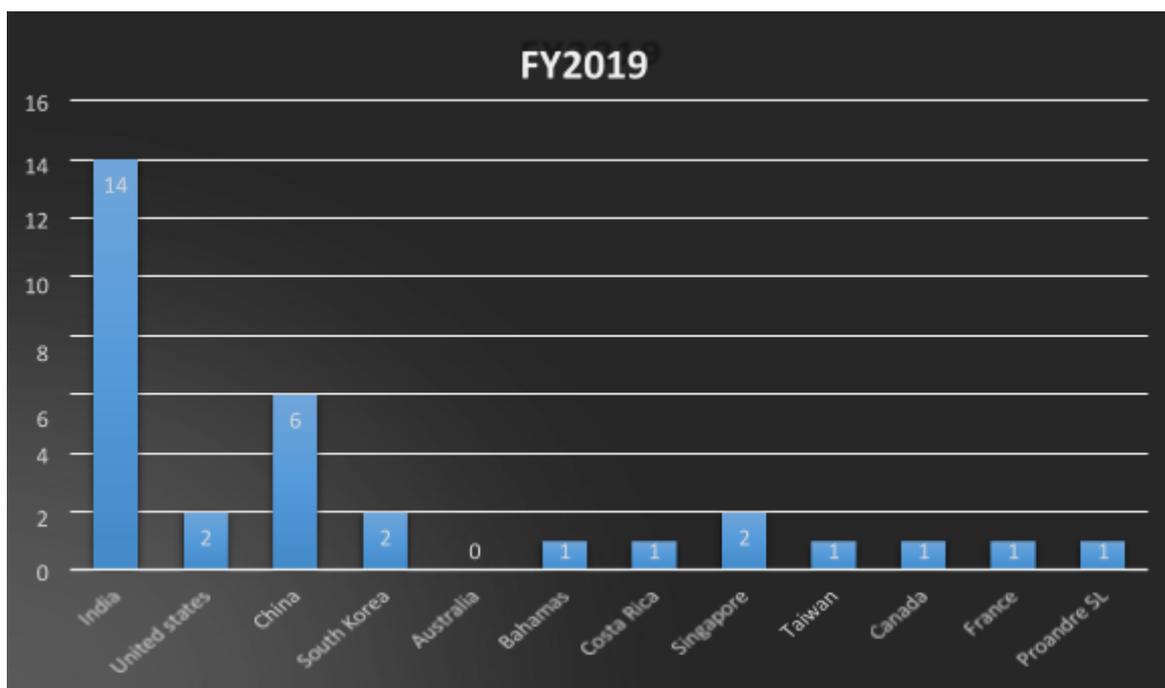


Fig 2.1.a: Frequency plot for FY 2019

Table 3.1: Frequency distribution of warning letters in the FY 2020

S. No	Country	Api	Finished Pharmaceuticals
01	India	-	6
02	United states	-	1
03	China	-	5
04	South Korea	-	3
05	Canada	-	2
06	Japan	-	1
07	Bulgaria	-	1
08	Denmark	-	1
09	Germany	-	1
10	Trinidad & Tobago	-	1
11	Australia	-	1

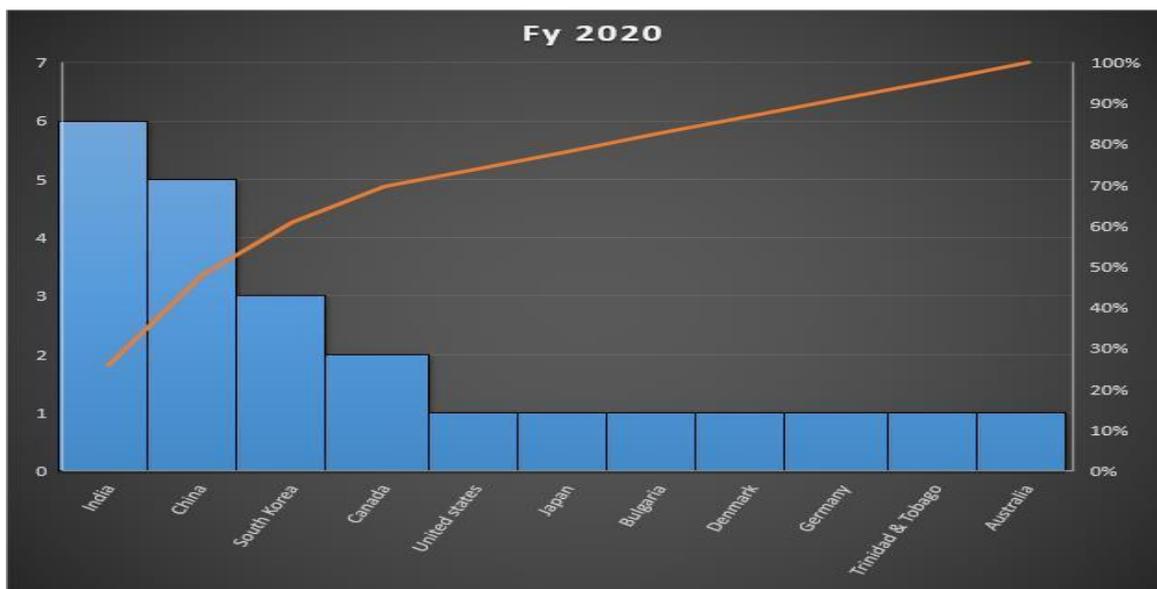


Fig 3.1.a: Frequency plot for FY 2020

Table 4.1: Comparison of warning letters in FY 2018, 2019, 2020 based upon geographical area

S.NO	COUNTRY	FY 2018	FY 2019	FY 2020
01	India	10	19	6
02	China	22	7	5
03	United states	6	5	1
04	South Korea	6	2	3
05	Japan	3	0	1
06	Canada	3	1	2
07	Australia	2	1	1
08	France	2	1	0
09	Taiwan	2	1	0

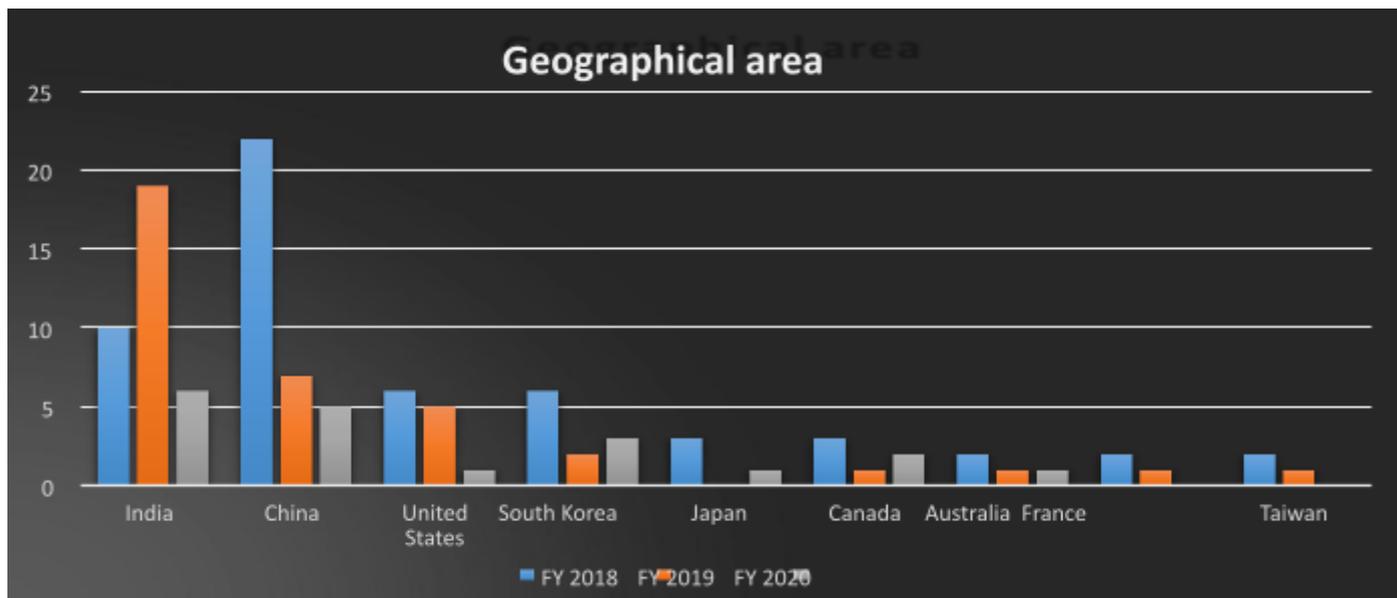


Fig 4.1.a: Frequency Plot for analysing the warning letters in the FY 2018, FY 2019, FY 2020 based on geographical area

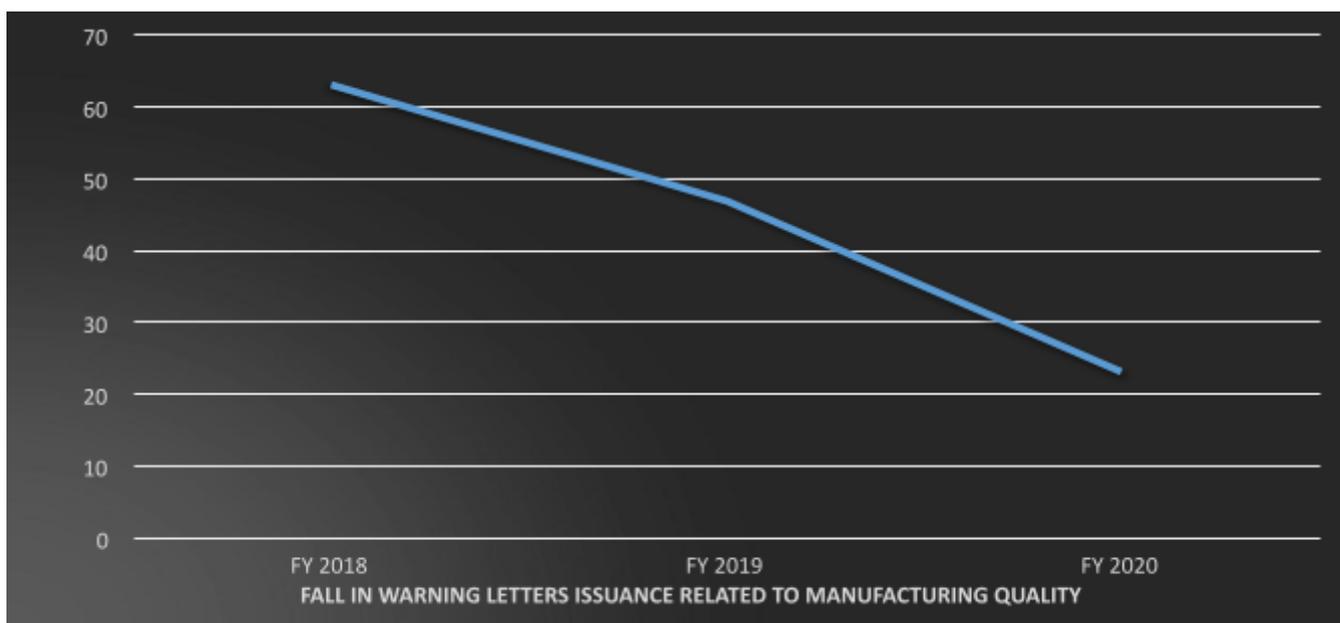


Fig 5.a: Plot for frequency of warning letters issued by FDA related to manufacturing quality in the FY 2018, FY 2019, FY 2020

IV. CONCLUSION

- Warning letters issued by FDA in the year 2018,2019,2020 related to manufacturing quality was issued due to deviations in cGMP of API & Finished pharmaceuticals.
- From the above study it is concluded that, it is concluded that in the FY 2018, **63** number of warning letters were issued related to manufacturing from the total of **91** warning letters issued by FDA. Out of **63** warning letters, china received **22** warning letters, whereas **10** warning letters were issued to India by FDA related to manufacturing quality.
- In the FY 2019, from the total of **88** warning letters issued by FDA, **47** warning letters were issued

related to manufacturing quality issued by FDA. Majority of the warning letters were issued to India due to deviations in cGMP of API & Finished pharmaceuticals. Out of 47 warning letters, 19 warning letters were issued to India related to manufacturing quality due to deviations in cGMP.

- Whereas in FY 2020, though the total number of warning letters was increased to 154, out of 154 letters, 23 warning letters were issued by FDA related to manufacturing quality.
- When compared with FY 2018, the number of warning letters issued by FDA related to manufacturing quality was gradually decreased in FY 2019, FY 2020.
- From the above Research it is concluded that from FY 2018- FY 2020 the number of warning letters issued by FDA to India was more when compared to other countries
- From this research, the preventive measure for avoiding the issuance of warning letter is The manufacturing quality area should be considered by implementing the strict cGMP rules.

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