International Journal of Research in Medical Sciences
Shetty YC et al. Int J Res Med Sci. 2025 Apr;13(4):1587-1593
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20250986

Original Research Article

A follow up study of warning letters issued by US Food and Drug Administration to clinical investigators, institutional review boards and sponsors: a situational analysis during COVID-19 pandemic

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Received: 25 February 2025
Revised: 18 March 2025
Accepted: 25 March 2025

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ABSTRACT

Background: United States food and drug administration (FDA) is the apex body governing and regulating clinical research. FDA issues warning letters (WLs) to individuals and institutions for significant regulatory violations. Our study aimed to evaluate the WLs issued to various stake holders during COVID-19 pandemic.
Methods: A web-based analytical study was employed to analyse WLs issued between 01 January 2020 to 31 December 2022 to clinical investigators, institutional review board (IRB) and sponsors. The outcome measures were: total number of WLs, violation theme and trend analysis in comparison with the previous study.
Results: A total of 241 WLs were analyzed which included 232 (96.27%) letters to sponsors, 9 (3.73%) to clinical investigator and none to IRB. Device-related violations were failure to comply with current good manufacturing practice (CGMP) (26/39, 66.67%; 8/14, 57.14%), adulterated/misbranded products (19/39, 48.71%; 7/14, 50%) and failure to follow monitoring schedule (16/39, 41.02%; 5/14, 35.71%) in 2020 and 2022 respectively. While in 2021, failure to submit investigational device exemption (50/61, 81.87%) was the commonest theme. In the drug-related group, violation trends were similar for 2020, 2021 and 2022. The frequent violations were misbranded/unapproved drug (24/26, 92.3%; 15/21, 71.43%; 40/57, 70.17%) and failure to comply with CGMP (8/26, 30.77%; 8/21, 38.09%; 19/57, 33.33%). Our previous study of 2015 is at variance, highlighting deviations as failure to follow monitoring schedule, failure to obtain investigator agreement and failure to maintain data record.
Conclusions: Majority warning letters were issued to sponsors, pertaining to quality and process of drug and device related research.

Keywords: CGMP, COVID-19, Sponsors, Warning letters

INTRODUCTION

Researchers conducting studies must not forget their moral obligations towards the safety and well-being of their study participants. In the United States of America (USA), federal regulations govern research involving human participants. It is the legal responsibility of authorized officials in regulated organizations to follow the required procedures and ensure that their products, practices and other activities comply with the regulations. The US food and drug administration (FDA) issues warning letters (WLs) for violations of significant regulations to individuals and organizations, to encourage voluntary compliance through deliberate and rapid corrective action before any enforcement action is initiated. The FDA defines a warning letter 'as an informal advisory to a firm communicating the agency's position on a matter but does not commit the FDA to taking enforcement action'.[1,2]

Hence, warning letter is post-inspectional correspondence between the FDA and stakeholders with scope for improvement within a specified time frame.

Fair and appropriate procedures for handling violations during clinical trials need to be developed and implemented globally in order to protect human rights, wellbeing and safety and to raise awareness of ethical behavior.[3] Very few authors have studied the violations during the COVID-19 pandemic. We attempted to review the violations noted by FDA during COVID-19 pandemic at the level of various stakeholders. A study was undertaken to evaluate the warning letters issued to clinical investigators, institutional review boards (IRB) and sponsors and also to assess the trends in violations and deviations if any from those previously observed by Shetty et al.[4]

METHODS

Web based analytical study was conducted after approval by the institutional ethical committee vide letter number IEC III/ OUT/ 798/2022. Our dataset involved online retrieval of WLs issued by FDA from the web site http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.html between 01 January 2020 to 31 December 2022 by Department of Pharmacology and Therapeutics, Seth GS Medical College and KEM Hospital, Mumbai. The warning letters were divided into three categories, namely clinical investigators, IRBs and sponsors and further the violation themes were recorded. The various themes included for different stakeholders is mentioned below.

For sponsors

Misbranded/ unapproved drug use, failure to comply with current good manufacturing practices (CGMP), failure to seek prior permission for advertisement, failure to follow monitoring schedule and failure to ensure proper labelling of device.

For investigators

Deviation from investigational plan, failure to protect subject safety, informed consent, failure to maintain case records and regulatory non-compliance.

For IRBs

Failure to follow standard operating procedures and maintain documentation, non-declaration of conflict of interest (COI), failure to inform institutional officials regarding study status, failure to ensure that the essential elements were included in an informed consent document (ICD), failure to review proposed research at convened meetings and lack of standard operating procedures (SOPs). In addition, within each category medical drug-related, device-related and biologic-related violations were enlisted. Record was maintained separately for each year of the three years 2020, 2021 and 2022.

The warning letters received for veterinary products, dietary supplements and homeopathic and herbal products were excluded.

Outcome measures

Total number of WLs issued to sponsors, investigators and IRBs. Nature (violation themes) of WLs issued to all stakeholders. Trend analysis of WLs with previously conducted studies.

Statistical analysis

Descriptive statistics was performed using GraphPad V.3.06. Chi square test was used for comparative analysis and to determine statistical significance, with $p<0.05$ being considered as statistically significant.

RESULTS

The total number of global inspections and warning letters issued is depicted in Figure 1 along with comparative analysis with the 2015 study of Shetty et al. A total of 241 WLs were analyzed over the three-year study period which was inclusive of only those issued by centre for drug evaluation and research, center for devices and radiological health and center for biologics evaluation and research.

Out of 241 WLs issued, 232 (96.27%) were to sponsors, 9 (3.73%) to clinical investigator and no letter was issued to IRB. The year-wise distribution of WLs is projected in Table1. Maximum WLs were issued to device-related category 114 (49.14%) and least to biologic 14 (6.02%). Maximum warning letters were issued to sponsors and none to IRB.

Warning letters issued to sponsors

In the current study 232 letters were issued to sponsors; 114 (49.14%) were issued for device-related violations, 104 (44.84%) for drug-related violations and 14 (6.02%) for biologic-related violations.

Within the device-related group, in the years 2020 and 2022 the most frequent violations were failure to comply with current good manufacturing practice (26/39, 66.67%; 8/14, 57.14%), adulterated/misbranded products (19/39, 48.71%; 7/14, 50%) and failure to follow monitoring schedule (16/39, 41.02%; 5/14, 35.71%).

While in 2021, failure to submit investigational device exemption (IDE)/investigational new drug application to FDA/pre-market approval (50/61, 81.87%), failure to seek prior permission for advertisement (50/61, 81.87%) and failure to ensure proper labelling of device were the commonest themes (17/61, 26.23%). Table 2 enlists the

device-related warning letters. The following violations were not observed in the present study failure to obtain investigator agreement, failure to ensure informed consent document received from study participants, failure to submit progress report to institutional review board, failure to ensure institutional review board review, failure to notify the FDA of termination of an investigation, failure to allow FDA inspection and failure to provide current investigator list.

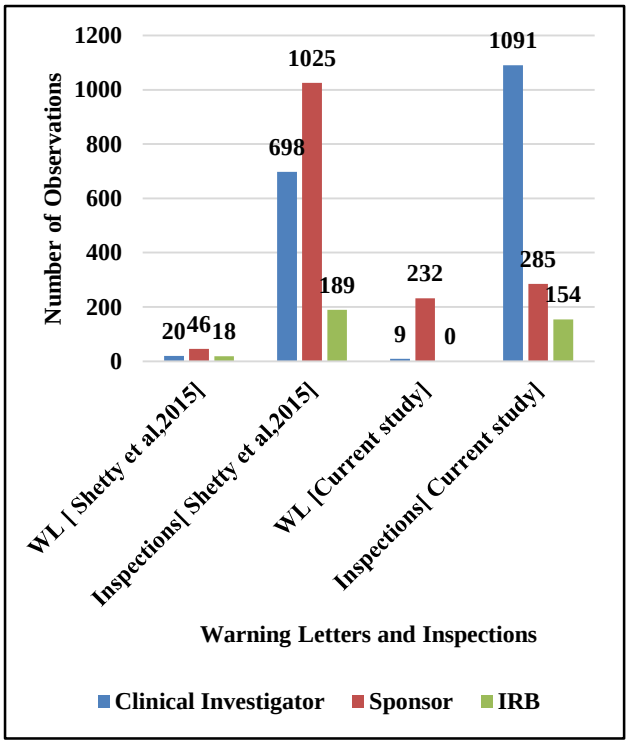

Figure 1: Year wise distribution of warning letters to stakeholders.

In the drug-related group (Table 3), we documented similar violation trends across 2020, 2021 and 2022. The most frequent violations were misbranded/unapproved drug (24/26, 92.3%; 15/21, 71.43%; 40/57, 70.17%), failure to comply with CGMP (8/26, 30.77%; 8/21, 38.09%; 19/57, 33.33%). In addition, failure to ensure proper labelling was observed in 2021 (7/21, 33.33%) and 2022 (7/57, 12.28%).

Our current study did not document the following warnings: failure to secure investigators' compliance, failure to ship/maintain records of investigational product to investigator, failure to ensure informed consent document received from study participants, failure to ensure institutional review board review and failure to include elements in informed consent document. Comparative trend analysis of the current study by author with her previous study of 2015 is depicted in Figure 2.

In the biologic-related group, over the three study years 2020, 2021, 2022, failure to comply with CGMP (4/4, 100%; 2/5, 40%, 3/5, 60%) and failure to follow monitoring schedule were the most common violations (3/4, 75%; 3/5, 60%, 4/5, 80%) noted respectively.

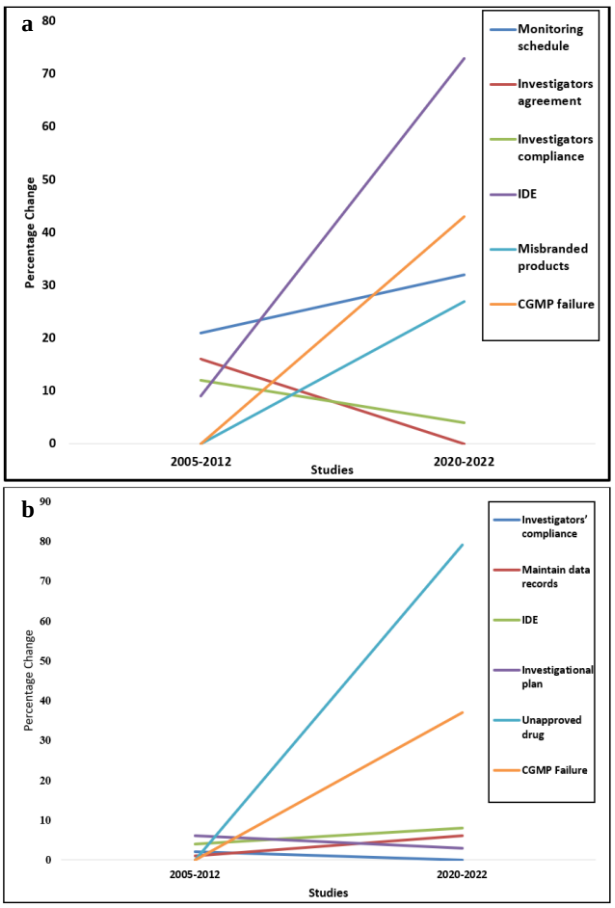

Figure 2: (a) Trend analysis for device-related warning letters issued to sponsors; (b) trend analysis for drug-related warning letters issued to sponsors.

Other violations noted were; failure to maintain data records (3/4, 75%; 2/5, 40% 2/5, 40%), failure to ship/maintain records of investigational product to investigator (2/5, 40% in 2022), failure to adhere to investigational plan (1/5, 20% in 2022), failure to use trained monitors (2/5, 40% in 2022), failure to investigate unexplained discrepancy or batch/ component failure (1/4, 25% in 2020 and 1/5, 20% in 2022), failure to submit investigational device exemption or investigational new drug application to FDA/pre-market approval (2/5, 40% in 2021), failure to provide investigators with necessary information (3/5, 60% in 2021), failure to ensure proper labelling of device (1/5, 20% in 2021), failure to seek prior permission for advertisement (1/5, 20% in 2021) and adulterated/misbranded/unapproved drug (1/4, 25% in 2020 and 1/5, 20% in 2021).

Warning letters issued to clinical investigator

Nine warning letters were issued to clinical investigators, out of which 1 (11.11%) was issued to device-related study and 8 (88.89%) were drug-related.

The sole observation for device-related study was inability to maintaining adequate and accurate case records and histories and failure to retain records or produce records for inspection. Whilst a range of warnings were noted for drug-related research as depicted in table 4 which also provides comparison with our previous study.

COVID-19 related warning letters

In view of the COVID-19 pandemic numerous products intended to diagnose, cure, treat, prevent and mitigate COVID-19 were available and the WLs issued by FDA to such players were also evaluated by us. The number of WLs issued to sponsors in drug-related category were 24 (92.3%), 17 (80.95%) and 12 (21.05%) for the years 2020, 2021 and 2022 respectively. The number of warning letters issued to sponsors in device-related category were 17 (43.58%), 38 (62.29%) and 7 (50%) for the years 2020, 2021 and 2022 respectively. Failure to submit an investigational device exemption or investigational new drug application to the FDA was the most frequent violation. For biologics 4 (100%) letters were issued in 2020 and no letter was issued in 2021 and 2022. And for clinical investigator 1 (20%) letter was issued in 2022, no letter was issued in 2020 and 2022.

Table 1: Year wise distribution of warning letters to stakeholders.

Stakeholder category		2020 N (%)	2021 N (%)	2022 N (%)
Sponsor (n=232)	Device-related (n=114)	39 (16.81)	61 (26.29)	14 (6.03)
	Drug-related (n=104)	26 (11.2)	21 (9.05)	57 (24.56)
	Biologic-related (n=14)	4 (1.72)	5 (2.15)	5 (2.15)
Clinical investigator (n=9)	Device-related (n=1)	1 (11.11)	0	0
	Drug-related (n=8)	0	5 (55.56)	3 (33.33)
	Biologic-related (n=0)	0	0	0
Institutional review board (n=0)	Device/Drug/ Biologic-related	0	0	0

Table 2: Comparison of warning letters issued to sponsors (device-related) between 2005-2012 and 2020-2022.

Sponsors violation theme	Device-related (2020-2022) n=114 (%)	Device-related (2005-2012) n=35 (%)	P value
Failure to follow monitoring schedule	32 (28.07)	21 (60)	0.0005
Failure to secure investigators' compliance	4 (3.5)	12 ((34.29)	< .00001
Failure to maintain data records	23 (20.17)	13 (37.14)	0.0402
Failure to ship/maintain records of investigational product to investigator	2 (1.75)	12 (34.29)	< 0.00001
Failure to submit an investigational device exemption or investigational new drug application to the FDA	73 (64.03)	9 (25.71)	0.00006
Failure to review, evaluate and submit adverse drug event reports to the FDA	11 (9.65)	9 (25.71)	0.0147
Failure to adhere to investigational plan	1 (0.88)	1 (2.86)	0.3732
Failure to provide investigators with necessary information	14 (12.28)	5 (14.28)	0.7557
Failure to use trained monitors	4 (3.5)	3 (8.57)	0.2156
Failure to ensure proper labelling of device	21 (18.42)	4 (11.43)	0.3328
Failure to inform reviewing institutional review board and the FDA of new information	8 (7.02)	3 (8.57)	0.7584
Failure to seek prior permission for advertisement (online)	50 (43.86)	3 (8.57)	0.0001
Failure to obtain institutional review board approval	1 (0.88)	1 (2.86)	0.3732
Failure to include reports of prior testing of the device	7 (6.14)	1 (2.86)	0.451

Table 3: Comparison of warning letters issued to sponsors (drug -related) between 2005-2012 and 2020-2022.

Sponsors violation theme	Drug-related (2020-2022) n=104 (%)	Drug-related (2005-2012) n=11 (%)	P value
Failure to follow monitoring schedule	10 (9.61)	6 (54.54)	0.000042
Failure to maintain data records	6 (5.78)	1 (9.09)	0.661251
Failure to submit an Investigational Device Exemption or Investigational New Drug application to the FDA	8 (7.69)	4 (36.36)	0.003096
Failure to review, evaluate and submit adverse drug event reports to the FDA	1 (0.96)	2 (18.18)	0.000656
Failure to adhere to investigational plan	3 (2.88)	6 (54.54)	<0.00001
Failure to provide investigators with necessary information	1 (0.96)	1 (9.09)	0.049833
Failure to use trained monitors	2 (1.92)	2 (18.18)	0.005131

P<0.05 statistically significant by chi-square test

Table 4: Comparison of warning letters issued to clinical investigators (drug/device-related) between 2011-2012 and 2020-2022.

Clinical investigator violation theme	Device-related (2020-2022) n=1 (%)	Device-related (2011-2012) n=4 (%)	Drug-related (2020-2022) n=8 (%)	Drug-related (2011-2012) n=16 (%)	P value
Deviation from investigational plan	0	4 (100)	4 (100)	15 (93.75)	0.012851
Maintaining adequate and accurate case records and histories and failure to retain records or produce records for inspection	1 (100)	1 (25)	3 (37.5)	7 (43.75)	0.769698
Informed consent	0	2 (50)	3 (37.5)	5 (31.25)	0.759463
Regulatory non-compliance	0	4 (100)	2 (25)	4 (25)	1.000
Violations related to investigational product	0	0	2 (25)	3 (18.75)	0.722283
Failure to personally supervise the study	0	0	1 912.5)	6 (37.5)	0.204008
Failure to protect subject safety or report adverse events to institutional review boards	0	3 (75)	5 (62.5)	8 (50)	0.562343
Failure to obtain institutional review board approval	1	0	2 (25)	2 (12.5)	.438578
Submission of false information to the FDA and sponsors	0	0	0	1	

DISCUSSION

Analysing warning letters provides vital information pertaining to the scale and type of violations and the remedial actions that need to be taken so as to ensure ethical standards. Our study provides comprehensive analysis of the violations based on various categories. Paucity of studies in this field is noted. The possible explanation is implementation of FDA's Bioresearch Monitoring (BIMO) program. BIMO is a comprehensive program of on-site inspections, data audits and remote regulatory assessments designed to monitor all aspects of the conduct and reporting of FDA regulated research. In addition BIMO metrics are published for each fiscal year which is the inspectional data covering all aspects of FDA's BIMO program (i.e., clinical investigators, IRBs, sponsors, bioequivalence and good laboratory practices) for all Centers.[5]

For sponsors, in comparison to study by Shetty et al, (2015), failure to obtain investigator agreement was the second most common violation reported in device-related group[4] but was not observed in the present study. We noted failure to secure investigators' compliance in 4/39 (10.25%) letters while Shetty et al, documented a higher frequency (34.29%). In the drug-related group the common violation themes were at variance, although authors in the previous study have document a wider spectrum of observations which were absent in the current study namely; failure to secure investigators' compliance, failure to ship/maintain records of investigational product to investigator, failure to ensure informed consent document received from study participants, failure to ensure IRB review and failure to allow FDA inspection.

An interesting observation is that, the two most common violation themes (sponsor) of our present study were not reported in the previous one i.e., misbranded/unapproved drug use and failure to comply with CGMP. Failure to comply with CGMP was noted for device-related, drug-related and biologic-related violations. Manufacturing standards needs to maintained in the research study setting also, because quality control and assurance are both responsibility of the sponsor as per ICH –GCP E6, if not followed duly it can harm the participants.[6]

This can defeat the ethical pursuit of the study of maintaining beneficence and non-maleficence. In the present study there were no WLs for IRB vis-a-vis in the prior study highlighting inadequate documentation. This variation can be attributed to the COVID-19 pandemic which changed the research dynamics focusing largely on developing and marketing COVID-19 related products. Bramstedt et al, studied WLs from March 2020 to July 2020 and concluded that 98 (3.14%) of the WLs included regulatory violations pertaining to COVID-19 products. Apart from drugs, devices, biologics she also focused on dietary supplements.[7] Study by Cooper et al, concluded that to expedite diagnosis and treatment of COVID-19 response time was short for academic-sponsored trials for investigational drugs.[8]

In concordance with our study, an Indian study of 14 years period reported, 85.87% violations were related to failure of compliance with the CGMP guidelines.[9] Kavyashree et al, reviewed warning letters issued for medical device between 2008 to 2018 and reported a declining trend in CGMP warning letters with the time. Whilst CGMP violations were predominant in our study.[10]

In the present study highest warning letters were for sponsors contrasting with the observation by Saxena et al, where maximum WLs were to clinical investigator. Among sponsors common violation theme in drug-related study was misbranded and unapproved drugs while in device-related category was failure to submit investigational exempt device to FDA, whereas in Saxena et al, study violation theme was lack of standard operating procedure for monitoring and they did not compare drug and device separately. Among clinical investigator, a common theme of deviation from investigational plan was observed in both studies. Although higher frequency (6/7, 85.71%) was reported by Saxena et al, and the study period was variable, from 2014 to 2019.[11]

Being a web based study possibility of bias can be entertained and data variation may be noted based on the criteria or methods for compiling the information.

CONCLUSION

The WLs are maximally issued to sponsors as compared to investigators or IRBs over a period of three-years. Device-related studies have been issued more WLs as compared to drug-related studies. Failure to follow CGMP requirements as per FDA was the major violation theme found with sponsor in device-related, drug-related and biologic-related studies. Deviation from investigational plan was the most statistically significant violation for clinical investigator in the author's current and previous study. There is increase in number of WLs issued to sponsors and decrease in WLs to clinical investigators and none to IRBs as compared to the previous study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Shetty YC, Sethi M, Barsinge T, Kamath Y, Kulkarni AS. A follow up study of warning letters issued by US Food and Drug Administration to clinical investigators, institutional review boards and sponsors: a situational analysis during COVID-19 pandemic. Int J Res Med Sci 2025;13:1587-93.