An Audit of Warning letters [WLs] issued to Sponsors, Institutional Review Boards [IRBs] and Investigators by the United States Food and Drug Administration (US FDA) over a six-year period

Unstructured Abstract

The present audit was carried out with an objective of evaluating WLs issued to Sponsors, Clinical investigators and IRBs during a six-year period and compare it with two similar earlier audits**.** WLs were reviewed and classified as per stakeholder and further classified according to pre-defined themes. The chi-square test was performed for trend analysis of WLs. A total of N=62 WLs were issued to the three stakeholders. The maximum number of WLs were issued to Clinical investigators (35/62, 58.06%) followed by Sponsors (19/62, 11.29%) followed by IRBs (7/62, 11.29%). Among Sponsors lack of SOPs for the monitoring, receipt, evaluation and reporting of post-marketing adverse drug events (8/19; 42.1%) was the most common. Among Clinical investigators, deviation from investigational plan was the most common (31/36; 86.11 %.). An inadequate documentation was commonly noted for IRBs (6/7; 85.71%). We saw an overall reduction in the number of WLs to three stakeholders. Hence, identification of areas where there was no improvement that need to be addressed by individual stakeholders.

Key words: investigational plan, informed consent, Monitoring, Documentation

**Introduction:**

The United States Food and Drug Administration (FDA) periodically conducts inspections to ascertain data integrity and participant safety and inspects alike the three key stakeholders- sponsors, Institutional Review Boards [IRBs] and investigators. Subsequent to these inspections, if the inspector finds something that is objectionable in his/her opinion, a Form 483 [also called Inspectional Observations] is issued. While it does not constitute a final determination by the FDA, the stakeholder is expected to respond in writing expeditiously and also document corrective action. Lack of a response or an inadequate response from any stakeholder leads to the issuing of a Warning Letter [WL] which represents an escalation of the Form 483. These WLs are available under the Freedom of Information Act in the public domain. [[1](file:///C:\Users\Debdipta%20Bose\Downloads\%5b1)].

WLs issued by the FDA have been evaluated earlier as well [2,3]. Two previous audits have shown that among clinical investigators, deviation from the investigational plan was the most common deviation while among IRBs, failure to maintain adequate documentation and retain IRB records was the most common finding. Amongst sponsors, inadequate monitoring of the clinical investigations was the most common deviation seen. A follow up study to the two earlier audits would help to assess whether the continued issuance of WLs has improved the functioning of the three stakeholders and hence the present study was envisaged. [2, 3]

**Methodology**

### *Ethics:* The study was exempted from review by Institutional Ethics Committee [EC/OA-27/2019] as it involved analysis of data available electronically in public domain.

*Study design, time frame, selection criteria and study sample*: This audit was a retrospective analysis and included all FDA WLs issued to Clinical investigators, Sponsors and IRBs during the period January 2014-December 2019 which formed the study sample. The WLs unrelated to clinical research such as GMP Deviations, Adulterated Animal Food, Labelling/False and Misleading/New Drug/Misbranded, Unapproved and Misbranded New Drugs, Adulterated Dietary Supplement, Family Smoking Prevention and Tobacco Control Act/Adulterated/ Misbranded, and Illegal Drug Residue were excluded.

*Methodology: All WLs* were hand searched and downloaded from the FDA database [1]. These were reviewed and data was extracted by four authors [US, SS, DB and ND] independently. The data was further verified by the two senior authors [NG and UMT]

*Classification of WLs and themes* - Each WL was classified per defined stakeholder. Various violation themes were predefined for individual stakeholders based on methodology from the two previous studies [2,3]. These included a) *Violation themes [Clinical Investigators]* – deviation from investigational plan, inadequate conduct or supervision of clinical investigations, inadequate documentation of drugs and participants case history, failure to obtain informed consent, violations related to investigational products and non-adherence to regulatory guidelines. b) *Violation themes [Sponsors]* – inadequate monitoring of study sites, lack of standard operating procedures (SOPs) for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences, failure to submit IND application, failure to maintain required records, non-adherence with FDA regulations, inadequate reporting of adverse events, failure to obtain IRB approval, and failure to include essential elements in informed consent. c) *Violation themes [IRBs]-* inadequate documentation, inadequate monitoring, non-declaration of conflict of interest, failure to review proposed research at convened meetings, lack of SOPs, and deviation in including essential elements in informed consent document (ICD).

*Outcome measures*: These included 1) The total number of WLs issued to Sponsors, Investigators, IRBs, 2) Nature (violation themes) of WLs issued to all stakeholders, and 3) Trend Analysis of WLs with previously conducted two studies.

*Statistical Analysis:* Categorical variables like number of WLs issued to each of the stakeholders, and number of WLs issued under each of the violation themes were expressed as proportions. Chi-square test was used for trend analysis of WLs issued over a six-year period and comparison with two previous studies and post hoc analysis was done using Bonferroni test. All analyses were performed at 5% significance level using Statistical Package for the Social Sciences (SPSS) version 24.

**Results**

1. *Demographics*: A total of N=62 WLs were issued to the three stakeholders over the study period. The maximum WLs were issued to Clinical investigators (35/62, 58.06%); followed by Sponsors (19/62, 11.29%) while the least number of WLs were issued to IRBs (7/62, 11.29 %). Overall, there was a significant reduction in the issuance of WLs seen in this study relative to the two previous audits (p<0.001). This difference was significant between Clinical investigators [n= 129 in *Gogtay et al.,* 20 in *Shetty et al.,* and 36 in current study] and sponsors[ n=46 in *Shetty et al.,* and 19 in current study] but not with respect to IRBs[n=32 in *Gogtay et al.,* 18 in *Shetty et al.,* and 07 in current study] [Table 1].
2. Analysis of WLs issued to individual stakeholders

* *Clinical Investigators*

Of the n = 36 WLs, issued , the common themes seen were - deviation from the investigational plan (31/36; 86.11 %), followed by inadequate documentation related to the Investigational product (11/36; 30.55%), inadequate documentation of participants case history (10/36; 27.77%), inadequate conduct or supervision of the clinical investigations (7/36; 19.44%), and failure to obtain informed consent (4/36; 11.11%).

* *Sponsors*

Of the total n = 19 WLs issued to sponsors, the most common violation was - lack of SOPs for the surveillance, receipt, evaluation and reporting of post-marketing adverse drug experiences (8/19; 42.1%), followed by inadequate monitoring of the clinical investigations (6/19; 31.573%) , failure to submit IND applications (5/19; 26.31%), inadequate reporting of adverse events (4/19; 21.05%), failure to maintain required records (4/19; 21.05%), non-adherence with FDA regulations(4/19; 21.05%), failure to obtain IRB approval (3/19; 15.78%), and failure to include essential elements in informed consent (1/19; 5.26%).

* *IRBs*

Of the total n = 7 WLs issued, “inadequate documentation” (6/7; 85.71%) was the commonest, followed by lack of SOPs (5/7; 71.42%), failure to review proposed research at convened meetings (4/7; 57.14%), inadequate monitoring (3/7; 42.85%), non-declaration of conflict of interest (1/7; 14.28%), and deviation in informed consent document (1/7; 14.28%).

Details of WLs issued to all three stakeholders are depicted in Table 2

1. *Trend analysis - comparison of WLs issued in present study with WLs seen in previous studies [2,3] [Table 2]*

* *Clinical Investigators*: A significant reduction (p<0.05) was seen in the areas of record keeping, informed consent, IP related violations and compliance with regulatory guidelines relative to the previous studies. On the other hand, areas such as deviation from investigational plan and supervision of the clinical investigations did not show any improvement (p>0.05).
* *Sponsors:* There was a significant reduction in the area of inadequate monitoring of the clinical investigations indicating improved monitoring (p<0.05). There was improvement seen with regards to adherence to the FDA’s regulatory guidelines (p<0.05). Other , domains such as failure to a) submit IND application, b) obtain IRB approval, c) maintain records, d) include essential elements in informed consent and e) report adverse events, did not show any improvement (p>0.05) over the previous studies.
* *IRBs:* There was a significant difference (p<0.05) in inadequate documentation and records of projects submitted to IRBs for review, lack of SOPs and inadequate monitoring while areas such as non-declaration of conflict of interest and deviation in informed consent document events did not show any improvement (p>0.05).

Table 1: Total WLs issued to three Stakeholders

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Stakeholders | Gogtay *et al.,* [2005-2010]  N | Shetty *et al.,* [2011-2012]  n | Saxena *et al.,* [2014-2019]  n | p-value# |
| Clinical Investigator | 129 | 20 | 36 | <0.001\* |
| Sponsors | - | 46 | 19 | <0.001\* |
| IRBs | 32 | 18 | 07 | 0.18 |

Chi square for trend, \* p<0.05 considered as statistically significant

Table 2: Violation themes among WLs issued to Clinical Investigators, IRBs and Sponsors

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Violation Themes** | Gogtay *et al.,* [2005-2010]  (N=129) | Shetty *et al.,* [2011-2012]  (N=20) | Saxena *et al.,* [2014-2019]  (N=36) | p-value# |
| n (%) | n (%) | n (%) |
| **Clinical Investigators** | | | | |
| Deviation from Investigational Plan | 104 (80.6) | 19 (95) | 31(86.11) | 0.24 |
| Failure to maintain accurate, complete, and current records of each subject’s case history and exposure to the device | 75(58.1) | 8 (40) | 10(27.77) | 0.003\* |
| Failure to personally conduct or supervise the clinical investigations | 27(20.9) | 6 (30) | 7(19.44) | 0.96 |
| Failure to obtain informed consent | 62(48) | 7 (35) | 4(11.11) | 0.0002\* |
| Violations related to investigational product | 38 (29.4) | 3 (15) | 3(8.33) | 0.019\* |
| Failure to comply with Regulatory guidelines | 50(38.8) | 8 (40) | 3(8.33 | 0.002\* |
| Failure to maintain adequate records of drug and the disposition of the drug and failure to retain records | Not reported | Not reported | 11(30.55) | - |
| **IRBs** | | | | |
| Inadequate documentation | 30 (93.8) | 8 (44.44) | 6(85.71) | 0.002\* |
| Lack of SOPs | 30 (93.8) | 8(44.44) | 5(71.42) | 0.005\* |
| Failure to review proposed research at convened meetings | Not reported | 10 (55.56) | 4(57.14) | - |
| Inadequate Monitoring | 2(6.7) | 7 (58.33) | 3(42.85) | 0.0007\* |
| Non-declaration of conflict of interest | 3 (9.4) | 5 (27.78) | 1(14.28) | 0.22 |
| Deviation in informed consent | 15 (46.9) | 5(27.78) | 1(14.28) | 0.16 |
| **Sponsors** | | | | |
| Inadequate monitoring of the clinical investigations | Not reported | 27 (58.69) | 6(31.57) | 0.046\* |
| Lack of SOPs for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences | Not reported | Not Reported | 8(42.1) | - |
| Failure to Submit IND application | Not reported | 13 (28.26) | 5(26.31) | 0.87 |
| Inadequate reporting of adverse events | Not reported | 11 (23.91) | 4(21.05) | 0.803 |
| Failure to obtain IRB approval and failure to comply with IRB | Not reported | 6 (13.04) | 3(15.78) | 0.77 |
| Non-adherence with FDA regulations | Not reported | 2 (4.35) | 4(21.05) | 0.034\* |
| Failure to maintain required records | Not reported | 14 (30.43) | 4(21.05) | 0.591 |
| Failure to include essential elements in informed consent | Not reported | 4 (8.69) | 1(5.26) | 0.636 |

# Chi-square test for statistical significance \* p<0.05 considered as statistically significant

**Discussion**

The present study found that N = 62 WLs were issued to the three stakeholders in clinical research (Clinical investigators, Sponsors, and IRBs) over a six-year period, out of which more than 58% were issued to Clinical investigators. There was overall reduction in the number of WLs issued to all three stakeholders as compared to previous two studies. That difference was significant with regards to Clinical investigators and sponsors but not with respect to IRBs.

Among Clinical investigators, the most common violation theme was deviation from investigational plan. When this finding from the current study was compared with the two previous audits, [2,3], it was seen that there was a significant reduction in violations related to the informed consent process, errors in documentation of case history and non–adherence to regulatory guidelines [2,3]. This implies greater awareness and a significant spread of both the letter and spirit of GCP over the years. However, there was no significant difference in deviation from investigational plan, inadequate conduct and supervision of the clinical investigation. There could be several reasons for this. It is possible that some investigators who are more experienced are shouldering a greater burden of studies leaving them with inadequate time for oversight and supervision. Staff attrition and inadequate attention to training new recruits could be yet another reason. The conduct of clinical research is a humungous task with myriad responsibilities resting with the PI [4-5]. The FDA has issued a guidance document entitled “Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects [2009][6] to assist investigators and sponsors. This document was the result of increasing issuing of WLs by the US FDA. The contents of this document will always remain relevant. Some aspects in this document include delegation of authority and the use of standard operating procedures, both of which can guide the investigators to plan and conduct studies better. Frequent internal reviews, online or offline, and early detection of errors and addressing them quickly will help address this aspect of the WLs

With IRBs, inadequate documentation was most common violation theme. When the current study was compared with the previously conducted two studies [2, 3], there was a significant difference in inadequate documentation [i.e., improvement in this area], monitoring and adherence to SOPs. The number of WLs issued to IRBs decreased to seven (7) in current study[from 32 in the study by Gogtay *et al*]. This finding could be attributed to that fact that some IRBs may be more burdened than the others similar to investigators. There was no difference with regards to non-declaration of conflict of interest [COI] and deviation in informed consent document. Appreciation and understanding the importance of COI is a key aspect of IRB functioning [7].The Cancer Council New South Wales from Australia laid down guideline [2016] to address COI amongst Ethics Committee members which states that a member must disclose his/her COI in writing when a potential or perception for conflict exists. This guideline further states that the disclosure should be prompt and complete [8]. Accreditation by the national accreditation bodies is likely to play an important role in reducing violations and strengthening the functioning of IRBs. In India, agencies such as the National Accreditation Board for Hospitals and Health Care [NABH] have begun accreditations of IRBs all over the country and as on date 22/Oct/2020 a total of 156 IRBs have been accredited by them. [9-11] and COI is an area that they review during the accreditation process.

Among sponsors, lack of SOPs for the surveillance, receipt, evaluation and reporting of post-marketing adverse drug experiences and inadequate monitoring of the clinical investigations (33.33%) were the most common violations themes. When current study result was compared with the previously conducted study [3], however, there was a significant improvement seen in inadequate monitoring of the clinical investigations. One of the approach that could improve the oversight is risk-based monitoring (RBM) which has also been given importance in recent E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry,2018 [12,13]. This will not only improve the quality of oversight but also reduce the number of site visits with real time monitoring of data from a central system.

The present study is limited by the fact that it included analysis of WLs from a solitary regulatory agency from a developed country and individual therapeutic areas of the WLs like oncology were not analysed.

Conclusion

There was an overall reduction in WLs issued by the US FDA to Investigators, IRBs and sponsors over the last six years. Key areas such as Deviation from investigational plan and failure to supervise the clinical investigations for investigators, non-declaration of conflict of interest and deviation in inclusion of essential element in informed consent for IRBs, failure to submit IND application, obtain IRB approval, maintain records, include essential elements in informed consent and report of adverse events for sponsors need significant strengthening.

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