Warning Letters Issued to Sponsors, IRBs and Investigators from 2010 to 2019

By

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Abstract

The Bioresearch Monitoring Program, administered by the Office of Scientific Investigations, ensures the integrity of safety and efficacy of clinical trial data that is submitted to the U.S. Food and Drug Administration. Any objectionable findings discovered during an inspection may result in a Warning Letter to the responsible organization. This study examined 91 Warning Letters issued to sponsors, IRBs and investigators from 2010 to 2019 and compared these findings with those of previous studies. The most critical observation made was the repetitive nature of the types of violations being cited to all three organizations, not only over the last decade but also prior to 2010. Findings also demonstrated an overall decrease in the number of Warning Letters and violations cited between 2010 and 2019. Furthermore, the number of Warning Letters issued to investigators during this time revealed a meaningful decrease from the previous decade.

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Introduction

The most important element of clinical research is the quality of the clinical trials. Clinical trials are conducted to obtain the data required to assess the safety and efficacy of drugs in support of new drug approvals. It is thus important that clinical trials are conducted in accordance with the principles of the Declaration of Helsinki (1964), which aims at protecting the safety, rights and well-being of human subjects. Clinical trial sponsors, investigators, IRBs and monitors are required to comply with the International Conference on Harmonization Good Clinical Practice (ICH GCP), which is an international quality standard for the rights and safety of human trial subjects, and following ICH GCP guidance ensures the quality, integrity and reliability of data collected (U.S. Food & Drug Administration, 2018c). The U.S. Food and Drug Administration (FDA) conducts on-site inspections and data audits through the Bioresearch Monitoring Program (BIMO) to oversee various aspects of a study. Violations of the 21 CFR 312 (Investigational New Drug Application) regulations identified during BIMO inspections may generate Warning Letters to the responsible organizations.

Office of Scientific Inspections (OSI)

The Office of Scientific Inspections (OSI), which operates within the Office of Compliance in the Center for Drug Evaluation and Research (CDER), is responsible for verifying the integrity of safety and efficacy data that is submitted to the FDA in support of new drug applications and also for ensuring that the rights and safety of human participants in clinical trials are protected (U.S. Food & Drug Administration, 2018e).

History of OSI. The Federal Food, Drug, and Cosmetic (FDC) Act was passed by the U.S. Congress in 1938, for the first time requiring new drugs be proven safe (U.S. Food & Drug

Administration, 2014a). Thus, the results of testing on any new drugs would need to be submitted to the FDA in a new drug application (NDA) before that drug could be marketed to the public. A few decades later in 1960, a new drug application was received by the FDA for a sedative called thalidomide, which had been used for years in other countries to treat various maladies, including morning sickness in pregnant women. The William Merrell Company was keen on bringing the drug to the U.S. market; however, FDA medical officer Frances Oldham Kelsey denied the new drug application, citing insufficient safety data. Lacking an approved new drug application, the company decided instead to distribute the drug for investigational use, effectively putting more than 2 million tablets of it into the hands of physicians and pharmacists for the treatment of their patients (U.S. Food & Drug Administration, 2014a).

By 1962, the drug was being linked to severe birth defects in thousands of newborns in other countries, and the William Merrell Company had no choice but to recall the distributed tablets back from U.S. clinics and pharmacies. As a result, a 1960 bill to strengthen the drug provisions of the FDC Act was reintroduced into Congress, becoming the Drug Amendment of 1962 and that same year being signed into law by President John F. Kennedy. This law mandated that drug manufacturers submit efficacy as well as safety data to the FDA prior to marketing and that all human subjects in clinical trials sign informed consent. Importantly, the law also gave the FDA the authority to regulate investigational use of unapproved new drugs (U.S. Food & Drug Administration, 2014a).

As a consequence of the new law, the Division of New Drugs was restructured, and Dr. Frances Kelsey was given direction of its Investigational Drug Branch, which was responsible for assessing how well proposed clinical trials comply with regulations on investigational drugs

and would eventually be reorganized and become today's OSI (U.S. Food & Drug Administration, 2014a).

Functions of OSI. As mentioned previously, the OSI aims to ensure the rights and safety of human trial participants as well as the quality of clinical research data submitted for new drug approvals with the FDA (U.S. Food & Drug Administration, 2018d). All of this is done through inspection of the organizations involved in research studies. Primarily, the OSI monitors research investigators, sponsors, and IRBs to confirm that they are operating in accordance with federal regulations on good clinical practice and good laboratory practice. The OSI is charged with implementing the Bioresearch Monitoring Program (BIMO) (U.S. Food & Drug Administration, 2018d).

Bioresearch Monitoring Program (BIMO)

The Bioresearch Monitoring Program (BIMO) is an essential aspect of the FDA pre-approval process for new medical drugs, biologics and devices, food and color additives, and veterinary products being considered for use among the general population in the United States (U.S. Food & Drug Administration, 2019c). It provides extensive guidelines for on-site inspections and data audits for clinical research studies submitted to the FDA for the approval of new products. The BIMO Program supports more than 1000 inspections each year through its compliance programs, of which this study will focus on the following three:

- Sponsors
- Institutional Review Board; and
- Clinical Investigators (U.S. Food & Drug Administration, 2019a).

The BIMO Program guidelines not only aim to ensure the quality of reported data regarding new products submitted for FDA approval, but also to assure that studies are done in

accordance with GCPs for the ethical and safe treatment of the human subjects who participate in FDA-regulated studies. When any organization—sponsor, investigator, or IRB—is found to be in major violation of a federal regulation, the OSI is responsible for issuing the appropriate Warning Letters and/or following up with further actions (U.S. Food & Drug Administration, 2018d).

What are Warning Letters?

Major violations of one or more FDA regulations discovered during an inspection are reported to the responsible organization in the form of a Warning Letter. According to the FDA, a Warning Letter is defined as "an informal advisory to an organization communicating the Agency's position on a matter but does not commit the FDA to taking enforcement action" (U.S. Food & Drug Administration, 2018c). Essentially, Warning Letters serve as a tool for post-inspectional correspondence between the FDA and stakeholders (Talele & Bowalekar, 2012).

Form 483. An FDA investigator issues a Form 483 to organization management whenever any conditions or conduct deemed objectionable is observed that may be in violation of the Food Drug and Cosmetic Act and/or related acts. All observations noted on Form 483 are to be clear, specific and significant to merit inclusion, and they must indicate that the safety or efficacy of a food, drug, device, or cosmetic has been compromised or is likely to become compromised as a direct result of how it is being prepared, packaged or stored (U.S. Drug & Food Administration, 2020b).

According to the Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors (U.S. Drug & Food Administration, 2019d), after the completion of an FDA inspection, the inspector conducts an exit interview with the responsible organizations to discuss inspection findings. A response to the Form 483 may be given orally during the interview or in writing to

the FDA. The FDA inspector then prepares a written Establishment Inspection Report (EIR). The EIR along with Form 483 (if applicable) and other documents collected during the inspection are sent to the FDA Center to evaluate and classify the inspection outcome. Upon this review, a Warning Letter will be issued if any major violations have been identified. If no objectionable findings were noted during the inspection, a general letter may be issued indicating the noncompliance observed; however, this letter is not always issued when the FDA does not observe any significant violations. Additionally, in some cases, an informational or untitled letter may be issued stating any deviation that does not meet the threshold to issue a Warning Letter. A written response will be requested in such cases.

In the event of major objectionable conduct being observed, there are different types of violations that may be cited, and these are categorized based on the regulation being violated. It is evident from previous studies that a few particular regulations have been repeatedly violated over the years by IRBs, sponsors, and investigators (Shelley, 2004). For example, according to Bramstedt and Kassimatis (2004), the most common violation cited to IRBs during the years 1997 to 2004 was “failure to have and follow adequate written procedures on the way IRB was conducting its review of research”. These findings were similar to those of a later study conducted by Talele and Bowalekar (2012), who identified the same violation as being cited most frequently during the years 2002 to 2009.

Similarly, FDA inspections tend to uncover specific types of citations for sponsors, as well. According to Shetty and Saiyed (2014), the most common violation cited for sponsors during the years 2011 to 2012 was the failure to follow the monitoring schedule. An example of this type of violation was cited to Oeyama Moto Medical Group Foundation in 2016, with the explanation that there was a lack of monitoring records associated with the inspected study.

Failure to obtain investigator agreement was the second most common violation issued to sponsors during that period (Shetty & Saiyed, 2014).

According to Bedadala (2014), the most common violation cited to investigators during the years 2002 to 2011 was failure to conduct the study according to investigational plan and conditions put forth by IRB. On the other hand, there was no significant trend observed in the number of Warning Letters issued to investigators over that same period (Bedadala, 2014). These studies mentioned here sought to determine trends in the Warning Letters and violations issued to one of the three organizations—either sponsors, investigators or IRBs—but did not consider comparing Warning Letter data across all three organizations. Moreover, because of the dates of publication for these studies, each lacks the inclusion of the most recent Warning Letter data available. This study examined Warning Letters published on the FDA website from 2010 to 2019 which were issued to sponsors, IRBs and investigators, and then compared the results with previous studies to identify potential trends.

Purpose of this Study

Primary objective. To determine whether trends exist in the violations issued to clinical trial sponsors, IRBs or investigators during the years 2010 to 2019.

Secondary Objectives. To identify the most common violations cited to clinical trial sponsors, IRBs and investigators during the years 2010 to 2019 and to identify the frequency of commonly cited violations.

Methods

This study utilized the FDA Warning Letters archive as a data source of Warning Letters issued to sponsors, IRBs and investigators between the years of 2011 and 2019. All Warning Letters are listed on the FDA Warning Letter index page by their year of issue (U.S. Food & Drug Administration, 2020d). These letters were searched manually based on the year of issue and then categorized for the purpose of this study. First, all Warning Letters were placed in three categories for those issued to sponsors, IRBs and investigators, then within each category the Warning Letters were further divided based on their year of issue. Each Warning Letter was reviewed thoroughly, and the citations in each letter were noted. A list of citations was prepared separately for sponsors, IRBs and investigators. These citations were further categorized based on the type of violation and regulation that was violated. Finally, trends in the number of Warning Letters issued, violations cited over the 10-year period for each of the three organizations, and the most commonly cited violations and their frequencies were analyzed to observe how they had evolved over the last decade.

Results

The OSI conducted inspections each year of sponsors, IRBs and investigators during the period of 2010-2019. Inspections of sponsors led to Warning Letter issuance 0-3.4% of the time. For IRBs, inspections resulted in a Warning Letter being issued as little as zero and as much as 5.4% of the time, and anywhere from zero to 4.3% of inspections of investigators led to a Warning Letter. Annual numbers for inspections and Warning Letters, as well as the percentage of inspections resulting in a Warning Letter, are listed below (see Table 1). Data on inspections for the year 2019 were not available at the time of this study; however, the FDA had published data on the Warning Letters issued during that year.

Table 1: Inspections & Warning Letters for Sponsors, IRBs and Investigators

Year	Sponsors			IRBs			Investigators			Total WL's
	Inspections	WL's	% with WL's	Inspections	WL's	% with WL's	Inspections	WL's	% With WL's	
2010	61	2	3.3%	97	3	3.1%	403	12	3.0%	**17**
2011	45	0	0%	103	3	2.9%	322	14	4.3%	**17**
2012	65	0	0%	92	5	5.4%	404	2	0.5%	**7**
2013	62	1	1.6%	90	4	4.4%	370	8	2.2%	**13**
2014	83	2	2.4%	91	0	0%	469	9	1.9%	**11**
2015	66	2	3.0%	83	1	1.2%	451	5	1.1%	**8**
2016	58	2	3.4%	81	3	3.7%	432	5	1.2%	**10**
2017	55	1	1.8%	79	0	0%	521	4	0.7%	**5**
2018	85	0	0%	95	0	0%	547	0	0%	**0**
2019		1			0			2		**3**

Sponsors

In total, 11 Warning Letters (WL's) to sponsors were published on the FDA webpage during the years 2010-2019. Twelve different types of violations (see Table 2) were cited to sponsors over this period. Of these 12 types of violations, "failure to ensure proper monitoring of the clinical investigations [21 CFR 312.50; 312.56(a)]" was the most common violation (see Table 3). A description for each type of violation and the number of citations for that violation are provided below (see Tables 2 and 3).

Table 2: Classification of Violations Issued to Sponsors.

Type	Description	Code of Federal Regulations
1	Failure to ensure proper monitoring of the clinical investigations	21 CFR 312.50; 312.56(a)
2	Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND	21 CFR 312.50
3	Failure to secure investigator compliance with the investigational plan and applicable FDA regulations	21 CFR 312.56(b)
4	Failure to ensure that only investigators who were qualified by training and experience were selected as appropriate experts to investigate a drug	21 CFR 312.53(a)
5	Failure to keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use	21 CFR 312.55(b)
6	Failure to comply with the requirements for use of an investigational new drug in a clinical investigation by administering the investigational new drugs Compounds 1, 2, and 3 to subjects without an IND in effect	21 CFR 312.40
7	Failure to obtain prior written authorization from FDA prior to charging for an investigational drug	21 CFR 312.8(a)(3)

8	Failure to maintain adequate records showing the receipt, shipment or other disposition of an investigational drug	21 CFR 312.57(a)
9	Failure to obtain informed consent in accordance with the provisions of 21 CFR part 50, as required by 21 CFR 312.60	21 CFR 312.60
10	Failure to ensure that an IRB complying with the requirements set forth in 21 clinical studies	21 CFR 312.66
11	Failure to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects	21 CFR 312.62(a)
12	Failure to obtain from an investigator sufficient financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR part 54	21 CFR 312.53(c)(4)

Table 3: Number of Sponsor Violations During the Years 2010 to 2019.

Violation	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Type 1	0	0	0	1	2	2	0	0	0	0
Type 2	2	0	0	1	2	1	0	0	0	0
Type 3	0	0	0	0	0	0	0	0	0	0
Type 4	0	0	0	0	0	0	0	0	0	0
Type 5	1	0	0	0	0	0	0	0	0	0
Type 6	1	0	0	0	1	1	1	1	0	0
Type 7	1	0	0	0	0	0	0	0	0	0
Type 8	1	0	0	0	1	0	0	0	0	0
Type 9	1	0	0	0	0	0	0	0	0	1
Type 10	1	0	0	0	0	0	0	0	0	0
Type 11	1	0	0	0	0	0	0	0	0	0
Type 12	T	0	0	1	0	0	0	0	0	0

IRBs

The FDA published a total of 19 Warning Letters to IRBs on its webpage between 2010 and 2019. Nineteen different types of violations (see Table 4) were cited to investigators over this period, out of which "failure to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings [21 CFR 56.115(a)(2)]" was the most common violation (see Table 5). A description for each type of violation and the number of citations for that violation are provided below (see Tables 4 and 5).

Table 4: Classification of Violations Issued to IRBs.

Type	Description	Code of Federal Regulations
1	Failure to follow its written procedures for conducting its initial and continuing review of research	21 CFR 56.108(a)(1)
2	Failure to conduct continuing review of research at intervals of not less than once per year	21 CFR 56.109(f)
3	Failure to prepare and maintain written procedures for the IRB and failed to follow written procedures as required by 21 CFR 56.108(a) and (b)	21 CFR 56.115(a)(6)
4	Failure to prepare and maintain a list of IRB members identified by name; earned degrees; representative capacity; indications of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution	21 CFR 56.115(a)(5)
5	Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas	21 CFR 56.108(c)
6	Failure to notify investigators and the institution in writing of its decision to approve or disapprove proposed research activities, or of modifications required to secure IRB approval of the research activity	21 CFR 56.109(e)
7	Failure to follow its written procedures for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and	21 CFR 56.108(a)(4)

	approval except where necessary to eliminate apparent immediate hazards to the human subjects	
8	Failure to determine that risks to subjects are minimized	21 CFR 56.111(a)(1)
9	Failure to follow FDA regulations regarding expedited review procedures	21 CFR 56.110(b)
10	Failure to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings	21 CFR 56.115(a)(2)
11	Failure to ensure that information given to subjects as part of informed consent is in accordance with 21 CFR Part 50.25	21 CFR 56.109(b)
12	Failure to ensure that no member participated in the initial or continuing review of a project in which the member had a conflicting interest, except to provide information requested by the IRB	21 CFR 56.107(e)
13	Failure to demonstrate its ability to ascertain the acceptability of the proposed research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice	21 CFR 56.107(a)
14	Failure to determine at the time of initial review that studies involving children are in compliance with 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations	21 CFR 56.109(h)
15	Failure to prepare and maintain adequate documentation of IRB activities, including copies of all research proposals reviewed, approved consent documents, and progress reports submitted by investigators	21 CFR 56.115(a)(1)
16	Failure to maintain copies of all correspondence between the IRB and investigators	21 CFR 56.115(a)(4)
17	Failure to ensure that informed consent would be sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by 21 CFR Part 50	21 CFR 56.111(a)(4)
18	Failure to fulfill membership requirements	21 CFR 56.107
19	Approval of research without determining that risks to subjects were reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result	21 CFR 56.111(a)(2)

Table 5: Number of IRB Violations During the Years 2010 to 2019.

Violation	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Type 1	2	2	2	0	0	0	0	0	0	0
Type 2	1	1	1	0	0	0	1	0	0	0
Type 3	1	0	5	3	0	0	2	0	0	0
Type 4	1	0	3	0	0	0	0	0	0	0
Type 5	1	0	3	1	0	1	1	0	0	0
Type 6	1	0	1	1	0	0	1	0	0	0
Type 7	1	0	0	0	0	0	0	0	0	0
Type 8	1	2	0	1	0	0	0	0	0	0
Type 9	0	2	2	1	0	0	0	0	0	0
Type 10	0	2	4	2	0	1	2	0	0	0
Type 11	0	2	0	1	0	0	0	0	0	0
Type 12	0	1	1	0	0	0	0	0	0	0
Type 13	0	1	0	0	0	0	0	0	0	0
Type 14	0	0	1	3	0	1	0	0	0	0
Type 15	0	0	2	0	0	0	0	0	0	0
Type 16	0	0	2	1	0	0	0	0	0	0
Type 17	0	0	1	0	0	0	0	0	0	0
Type 18	0	0	0	2	0	0	0	0	0	0
Type 19	0	0	0	1	0	0	0	0	0	0

Investigators

Overall, a total of 61 Warning Letters to investigators were issued and published by the FDA from 2010 to 2019. Twenty different types of violations (see Table 6) were cited to sponsors over this period. The most commonly cited violation was "failure to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]" (see Table 7). A description for each type of violation and the number of citations for that violation are provided below (see Tables 6 and 7).

Table 6: Classification of Violations Issued to Investigators.

Type	Description	Code of Federal Regulations
1	Failure assure that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 was responsible for the initial review and approval of Protocol (b)(4)	21 CFR 312.66
2	Failure to ensure that the investigation was conducted according to the investigational plan	21 CFR 312.60
3	Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation	21 CFR 312.62(b)
4	Failure to maintain adequate records of the disposition of the drug, including the dates, quantity, and use by subject	21 CFR 312.62(a)
5	Failure to retain records required to be maintained under 21 CFR Part 312 until 2 years after the investigation was discontinued and FDA was notified	21 CFR 312.62(c)
6	Failure to ensure proper monitoring of the clinical investigations	21 CFR 312.50; 312.56(a)
7	Failure to obtain a signed investigator statement, Form FDA 1572, before permitting an investigator to participate in an investigation	21 CFR 312.53(c)(1)
8	Failure to give each participating investigator an investigator brochure containing the information described in 312.23(a)(5)	21 CFR 312.55(a)

9	Failure to review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator	21 CFR 312.56(c)
10	Failure to submit to the FDA an annual report of the investigation	21 CFR 312.33
11	Failure to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug	21 CFR 312.57(a)
12	Failure to maintain complete and accurate records showing any financial interests of investigators subject to 21 CFR Part 54	21 CFR 312.57(b)
13	Failure to retain records and reports for two years after shipment and delivery of the drug is discontinued and FDA has been so notified	21 CFR 312.57(c)
14	Failure to comply with the requirements for use of an investigational new drug in a clinical investigation by administering the investigational new drugs Compounds 1, 2, and 3 to subjects without an IND in effect	21 CFR 312.40
15	Failure to obtain prior written authorization from FDA prior to charging for an investigational drug	21 CFR 312.8(a)(3)
16	Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation	21 CFR 312.62(b)
17	Failure to return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59	21 CFR 312.59
18	Repeated or deliberate submission to FDA or to the sponsor false information in any required report	21 CFR 312.70(a)
19	Failure to adhere to requirements for all expanded access uses with respect to maintaining accurate case histories and retaining records in a manner consistent with 21 CFR 312.62	21 CFR 312.305(c)(4); 21 CFR 312.62(b) and (c)
20	Failure to take adequate precautions to prevent theft or diversion of an investigational drug that is subject to the Controlled Substances Act	21 CFR 312.69

Table 7: Number of Investigator Violations During the Years 2010 to 2019.

Violation	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Type 1	6	5	1	1	1	0	0	0	0	0
Type 2	17	24	2	11	10	4	5	3	0	3
Type 3	6	7	1	4	4	1	2	1	0	1
Type 4	4	3	0	0	0	1	1	1	0	1
Type 5	1	1	0	0	1	0	0	2	0	1
Type 6	1	0	1	1	0	1	0	0	0	0
Type 7	1	0	0	0	0	0	0	0	0	0
Type 8	1	0	0	0	0	0	0	0	0	0
Type 9	1	1	0	0	0	0	0	0	0	0
Type 10	1	0	0	0	0	0	0	0	0	0
Type 11	2	0	0	0	0	0	0	0	0	0
Type 12	1	0	0	0	0	0	0	0	0	0
Type 13	1	0	0	0	1	0	0	0	0	0
Type 14	1	0	0	0	0	1	0	0	0	1
Type 15	1	0	0	0	0	0	0	0	0	0
Type 16	0	1	0	0	0	0	0	0	0	0
Type 17	0	1	0	0	0	0	0	0	0	0
Type 18	0	0	1	0	0	0	0	0	0	0
Type 19	0	0	0	1	0	0	0	0	0	0
Type 20	0	0	0	0	1	0	0	0	0	0

Discussion

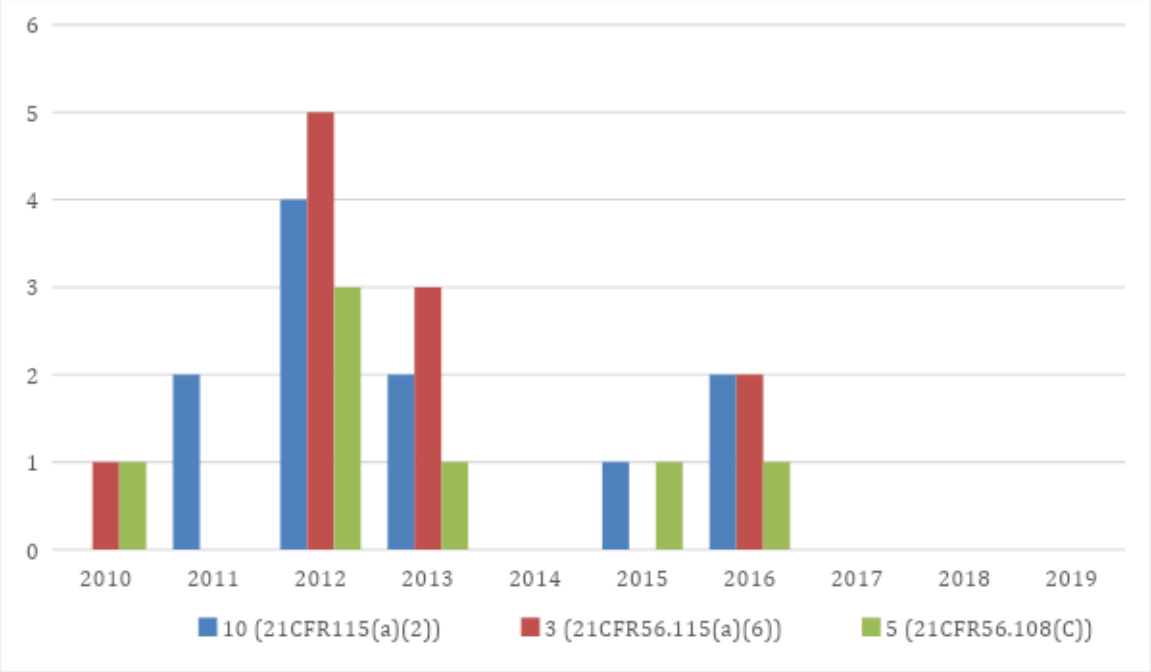
A total number of 91 Warning Letters issued by the OSI to sponsors, IRBs, and investigators from 2010 to 2019 were analyzed for this study, 11 of which were issued to sponsors, 19 to IRBs, and 61 to investigators. Trends in the violations cited over the 10-year period and the most commonly cited violations and their frequencies were analyzed to see how these evolved over the years.

Between the years of 2010 and 2019, there was no significant change observed in the number of Warning Letters issued to sponsors. In comparison to the number of Warning Letters issued to IRBs and investigators, sponsors received significantly fewer Warning Letters over this time period. From 2010 to 2019, the maximum number of letters issued to a sponsor per year never exceeded two, with failure to ensure that the study was conducted as per investigational plan (50%) being the most commonly cited violation. According to Shah (2011), a similar trend in the number of sponsor citations was observed prior to 2010, with failure to ensure proper monitoring of the investigational study accounting for 40% of sponsor violations cited from 2006 to 2009. Other common violations were administration of an investigational new drug to human subjects without an IND in effect and failure to ensure proper monitoring. For example, in 2015 the FDA issued a Warning Letter to CXL-USA in which it was stated that the sponsor had failed to conduct proper monitoring of the protocol. It was also mentioned that the sponsor neither reviewed the investigation records nor conducted site monitoring, relying on the site's self-audits instead (Center for Drug Evaluation and Research, 2015).

For IRBs, failure to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings and failure to prepare, maintain and follow written procedures governing the functions and operations of the IRB were the most common citations.

For instance, in a Warning Letter issued to Oeyama Moto Cancer Research Foundation IRB in 2016, it was stated that the IRB had failed to prepare, maintain and follow procedures for conducting initial and continuing review of research and also for reporting the findings of the IRB and the required actions to the investigator (Shetty & Saiyed, 2014). Regarding failure to maintain adequate documentation, Pikeville Medical Center IRB was issued a Warning Letter in 2016 stating that their meeting minutes did not adequately document IRB member votes on actions, including the number of members voting for, against and abstaining (Bramstedt & Kassimatis, 2004). It was also common for IRBs to receive citations noting a failure to review proposed research at convened meetings. Figure 1 illustrates the frequency of the top three violations cited to IRBs.

Figure 1: Frequency of Top Three Violations Cited to IRBs.



The number of Warning Letters issued to IRBs from 2017 to 2019 significantly decreased from the number issued over the seven years prior. IRBs received a total of thirteen Warning Letters in 2009, and that number dropped to three Warning Letters in 2010. According to Mundy

(2010), this decline could be due to a sting operation led by the Government Accountability Office (GAO) in early 2009. GAO created a fictitious company named Device Med-Systems of Virginia and a fake surgical adhesive gel called Adhesiabloc to be investigated through a trial, and Coast IRB of Colorado Springs, Colorado, approved the study while all the other IRBs declined. The nonexistent Adhesiabloc study was approved for abdominal surgery patients, and only five months later did the IRB discover that neither the company nor the product existed. As a result of the Warning Letter, many big companies moved their business from the Coast IRB. After 2012, the number of Warning Letters issued to IRBs continued to decrease from four letters in 2013 to three in 2016, and no Warning Letters were issued to IRBs for the last three years. This would appear to indicate a higher level of compliance to FDA regulations, although further research would be necessary to determine if this was the cause for the lack of Warning Letters.

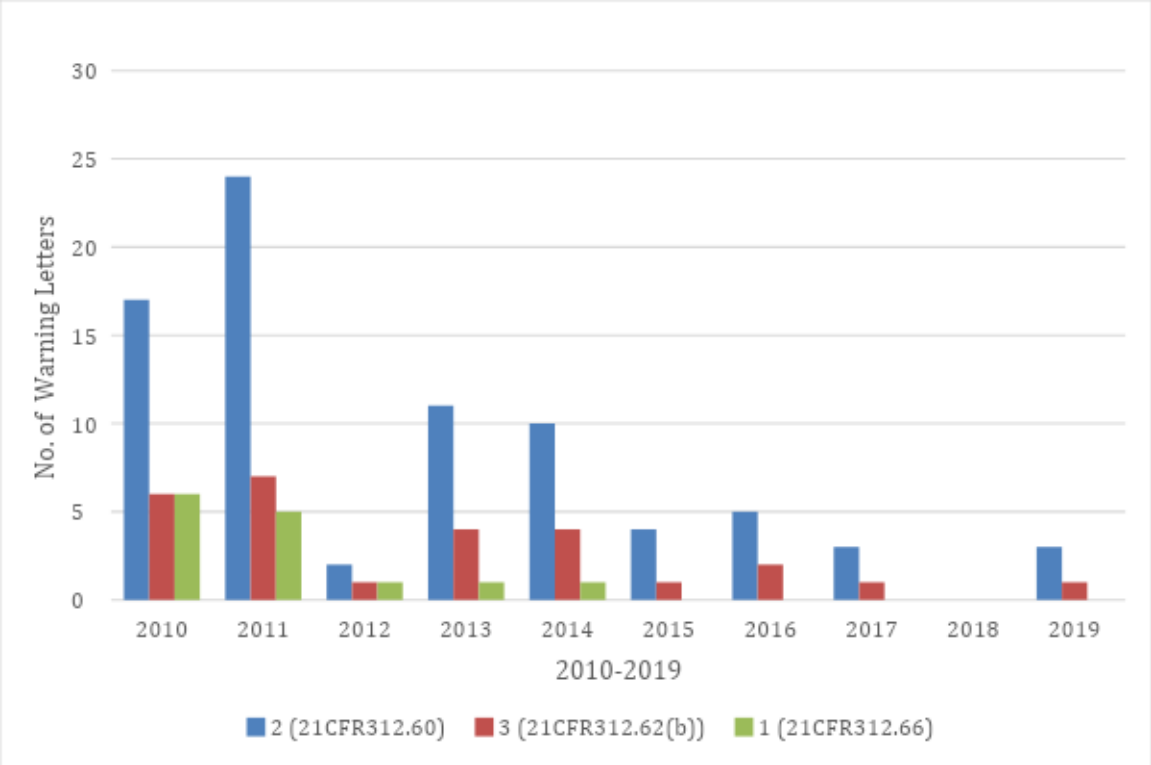
For investigators, failure to ensure that the study was conducted according to the investigational plan was the most commonly cited violation in the last decade, and this type of violation includes observations such as a lack of investigator oversight on the inclusion/exclusion criteria. For example, one of the Warning Letters issued to an investigator in 2017 cited that a patient was enrolled in the study and received the study drug despite meeting the exclusion criteria (Center for Drug Evaluation and Research, 2017). In another Warning Letter from 2017, it was noted that subjects were not treated per protocol in case of adverse events (Center for Drug Evaluation and Research, 2017).

Failure to maintain adequate and accurate case histories of study participants was the second most commonly observed violation. An example of this was cited in a Warning Letter issued in 2016, and the following information was summarized in the letter:

> "On worksheets for medical history, physical examinations, and neurological examinations, you personally hand-printed the name of your sub investigator to indicate that these study procedures were conducted by your sub investigator. However, in fact, you or another study employee actually conducted these study procedures, not your sub investigator" (Center for Drug Evaluation and Research, 2016).

Figure 2 illustrates the frequency of the top three violations cited to investigators.

Figure 2: Frequency of Top Three Violations Cited to Investigators.



The number of Warning Letters issued to investigators increased in 2011 but then exhibited a sharp decline in 2012 and maintained a gradual decline after that. By the end of the decade, there was an overall decrease in the number of violations cited per year to investigators from 45 in 2010 to 7 in 2019. Across the decade, the peak number of Warning Letters issued to

investigators was observed in 2011, and no letters were issued later in 2018. A previous study that looked at investigator Warning Letters from 2002-2011 found a similar trend, which showed that the most Warning Letters were issued in 2004 (n=31) and the least in 2010 (n=13) (Bedadala, 2014). Moreover, the top two violations cited between 2002 and 2011 were similar to those observed from 2010 to 2019 in this study. Ascertaining an explanation for this trend was not within the scope of this study.

Conclusion

This study examined the inspections and Warning Letters issued to sponsors, IRBs and investigators that were published on the FDA website from 2010 to 2019. Of all the three organizations, investigators consistently received the highest number of Warning Letters (67%) when compared to IRBs (20%) and sponsors (12%) during the period of 2010-2019. It should be noted, however, that the number of Warning Letters issued to each organization appears to be correlated with the number of their inspections. One important finding of this study was that despite the similarities observed in Warning Letters issued to investigators during 2002-2011 and 2010-2019, a significant decrease in the overall number of Warning Letters was observed in the latter decade. Furthermore, while the number of inspections of investigators increased overall from 2010 to 2019, the number of Warning Letters decreased. In fact, the total number of all Warning Letters has exhibited a downward trend since 2010, and all three organizations achieved maximum compliance in 2018 with zero Warning Letters being issued that year. This decrease in the number of Warning Letters suggests a higher level of compliance to FDA regulations over time, with the greatest differences observed among investigators. The most critical observation made was the repetitive nature of the types of violations being cited to sponsors, IRBs and investigators, not only over the last decade but also prior to 2010. Using this data, measures could be taken to develop adequate training methods targeted at investigators, sponsors and IRB's specific to these repetitive errors. In addition, a more detailed investigation may be necessary in order to identify additional parameters that might support the minimization of violations and thereby produce more accurate and reliable clinical trial data.

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