Original Investigation

Research Misconduct Identified by the US Food and Drug Administration
Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature

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IMPORTANCE Every year, the US Food and Drug Administration (FDA) inspects several hundred clinical sites performing biomedical research on human participants and occasionally finds evidence of substantial departures from good clinical practice and research misconduct. However, the FDA has no systematic method of communicating these findings to the scientific community, leaving open the possibility that research misconduct detected by a government agency goes unremarked in the peer-reviewed literature.

OBJECTIVES To identify published clinical trials in which an FDA inspection found significant evidence of objectionable conditions or practices, to describe violations, and to determine whether the violations are mentioned in the peer-reviewed literature.

DESIGN AND SETTING Cross-sectional analysis of publicly available documents, dated from January 1, 1998, to September 30, 2013, describing FDA inspections of clinical trial sites in which significant evidence of objectionable conditions or practices was found.

MAIN OUTCOMES AND MEASURES For each inspection document that could be linked to a specific published clinical trial, the main measure was a yes/no determination of whether there was mention in the peer-reviewed literature of problems the FDA had identified.

RESULTS Fifty-seven published clinical trials were identified for which an FDA inspection of a trial site had found significant evidence of 1 or more of the following problems: falsification or submission of false information, 22 trials (39%); problems with adverse events reporting, 14 trials (25%); protocol violations, 42 trials (74%); inadequate or inaccurate recordkeeping, 35 trials (61%); failure to protect the safety of patients and/or issues with oversight or informed consent, 30 trials (53%); and violations not otherwise categorized, 20 trials (35%). Only 3 of the 78 publications (4%) that resulted from trials in which the FDA found significant violations mentioned the objectionable conditions or practices found during the inspection. No corrections, retractions, expressions of concern, or other comments acknowledging the key issues identified by the inspection were subsequently published.

CONCLUSIONS AND RELEVANCE When the FDA finds significant departures from good clinical practice, those findings are seldom reflected in the peer-reviewed literature, even when there is evidence of data fabrication or other forms of research misconduct.

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Editorial

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As part of the drug approval process, the US Food and Drug Administration (FDA) regularly inspects clinical trial sites involved in FDA-regulated research to determine the degree to which these sites conform to regulations. The FDA regulations intend to ensure, among other things, that scientists adhere to good clinical practice and that they protect the rights of human participants. Such inspections often yield useful information about the reliability and quality of the clinical data produced at a clinical trial site.

An FDA inspection typically involves officials visiting a trial site and auditing the records kept at that site. During the course of several days, the inspectors verify that, among other things, the investigators adhered to the trial protocol, the participants had given informed consent, and the research had been duly approved by an institutional review board. The inspectors may also audit the data comparing, for example, an investigator's progress notes in hospital records with data reported to the study sponsor to ensure that there are no irregularities.[1]

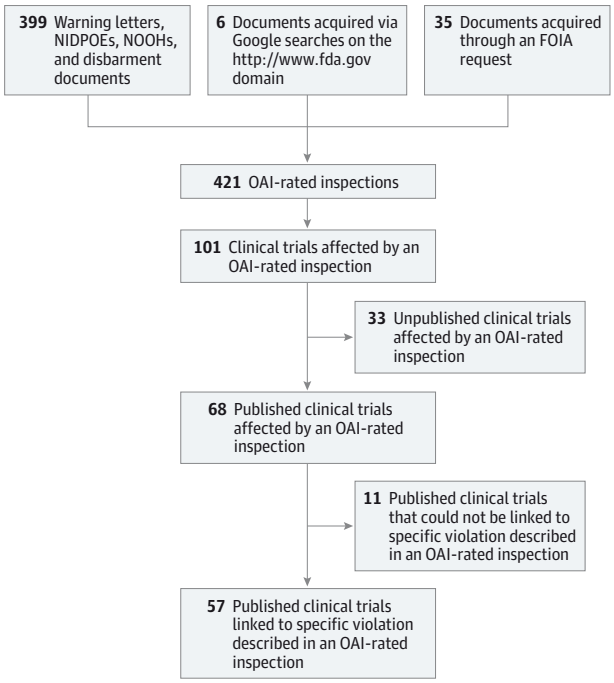
The FDA classifies its inspections in 1 of 3 ways, depending on the gravity of violations found. *No action indicated* indicates that there were no substantial violations. *Voluntary action indicated* means that inspectors have found violations of good clinical practice, but the nature and extent of those problems are not serious enough to require sanction. The most severe classification, *official action indicated* (OAI), is reserved for cases in which the inspection identified objectionable conditions or practices significant enough to warrant regulatory action.[2] In the 2013 fiscal year, approximately 2% of the 644 inspections of trial sites carried out by the FDA's Bioresearch Monitoring organization were classified as OAI.[3] The nature and extent of the OAI violations, which include submission of false information and failure to report adverse events to the appropriate bodies, often raise questions about the validity and accuracy of the clinical trial site's data. Consequently, the FDA typically excludes data from a site that received an OAI when judging the safety or efficacy of a new drug.

The goals of the present study were to identify publications describing clinical trials that the FDA had determined had an OAI violation, to describe the violations, and to determine whether the published article or any subsequent correction acknowledged the violation.

Methods

A multipronged approach was used to identify clinical trials with an OAI violation (**Figure**). The process began by attempting to identify clinical trial sites and principal investigators who had received an OAI violation. Although there is no public canonical list of OAI inspections, the FDA maintains a database containing the results of some of its inspections.[4] In July 2012, the database was searched for clinical investigators who had received an OAI. To obtain documents (form 483s and Establishment Inspection Reports) that provide details about a given inspection, Freedom of Information Act requests were made to the FDA. The request yielded documents related to 20 OAI-rated inspections, all dated before August 8, 2012, when the Freedom of Information Act request was submitted.

Figure. Relevant Clinical Trials



Identification of relevant clinical trials linked to specific violations described in an official action indicated (OAI)–rated inspection. Between October 7 and December 9, 2013, all warning letters that were issued to a clinical investigator after January 1, 1998, as well as all Notices of Disqualification Proceedings and Opportunity to Explain (NIDPOEs), Notices of Opportunity for a Hearing (NOOHs), and disbarment decisions that were on the US Food and Drug Administration's website, were reviewed. FOIA indicates Freedom of Information Act.

To supplement the data obtained from the searches of the FDA database, Google searches of the http://www.FDA.gov domain were performed. The most effective searches used combinations of phrases and their variants that were contained in documents describing OAI-rated inspections of clinical sites (eg, *classified as OAI*, *inspection summary*, *received an OAI*, *inspected*, *OAI classification*, and *inspection*). This strategy yielded documents related to 21 OAI-rated inspections.

The best source of documentation of OAI-rated inspections came from instances in which the FDA took regulatory action against clinical investigators. Such actions occur only when the failure to adhere to research regulations is considered particularly grave. In such cases, the FDA often issues 1 or more documents that detail the problems found in an inspection: warning letter, Notice of Disqualification Proceedings and Opportunity to Explain, Notice of Opportunity for Hearing, and official notification of disbarment or sanctions. Between October 7 and December 9, 2013, all warning letters that were issued to a clinical investigator after January 1, 1998 (letters regarding 298 inspections), as well as all Notices of Disqualification Proceedings, Notices of Opportunity for Hearing, and disbarment decisions that were on the FDA's website (documents concerning 82 inspections), were reviewed.

The 3 methods of search yielded 421 OAI-rated inspections. We then attempted to link the sites and investigators described in the related inspection documents to specific clinical trials. Heavy redactions in most of these documents prevented this linkage in most cases (eAppendix in the Supplement). However, whenever we were able to identify a clinical trial that received an OAI finding, we searched the peer-reviewed literature for any resultant publications. If such publications were found, they were independently reviewed by the author and by a second reader with the goal of identifying any written acknowledgment about the violations identified by the FDA. Agreement between the 2 reviewers was high (κ = 0.85). One article noted that data "were either missing, or were considered unreliable by the investigator due to problems collecting accurate data."[5(p3)] The 2 reviewers disagreed about whether the unreliability might have been an oblique reference to problems found during an inspection. However, the inspection documents[6] detailed failures to obtain informed consent, falsified information, misreporting the dosage of drugs for at least 7 patients, and failure to record data on 10 patients. After discussion, the reviewers concurred that the language in the article was not an acknowledgment of the inspection findings.

PubMed and Thomson-Reuters' Web of Science were searched for any corrections, retractions, expressions of concern, or other comments in which those violations might have been aired after the article was published. Food and Drug Administration-related documents obtained in this investigation are available.[7]

Results

General Findings

There were approximately 600 clinical trials mentioned in the documents we gathered; owing to redactions, most of these trials could not be identified. However, in some cases, key information was not redacted from the documents, allowing us to identify 101 trials in which at least one clinical trial site received an OAI grade on an inspection (Figure).

Of those 101 clinical trials, we identified 68 for which results had been published in the peer-reviewed literature, resulting in a total of 95 publications. For 11 of the clinical trials that had been published, the documents were not sufficiently detailed for us to prove that the violations described in the document were specific to the trial in question, so they were excluded from the primary analysis (**Table 1**).* For example, 1 warning letter[8] and 1 Notice of Disqualification Proceedings and Opportunity to Explain[9] detailed violations in 7 clinical trials of stem cell therapies, which then resulted in 4 publications.[10,35-37] Because of the redactions in those documents, there was ambiguity about which of the 7 trials was linked to which violation described in the documents. It was possible to tie specific violations to only 3 of the 4 published trials[38-40]; the fourth trial[41] was therefore excluded from analysis.

For each of the 57 remaining trials, 1 or more FDA inspections of a trial site had uncovered evidence of significant departures from good clinical practice, such as underreporting of adverse events, violations of protocol, violations of recruitment guidelines, and various forms of scientific misconduct.

In 22 of these trials (39%), the FDA cited researchers for falsification or submission of false information; in 14 (25%), for problems with adverse events reporting; in 42 (74%), for failure to follow the investigational plan or other violations of protocol; in 35 (61%), for inadequate or inaccurate recordkeeping; in 30 (53%), for failure to protect the safety, rights, and welfare of patients or issues with informed consent or institutional review board oversight; and in 20 (35%), for violations not otherwise categorized. Examples of uncategorized violations include cases in which the investigators used experimental compounds in patients not enrolled in trials, delegated tasks to unauthorized personnel, or otherwise failed to supervise clinical investigations properly.

The 57 clinical trials in our analysis resulted in 78 articles published in the peer-reviewed literature (**Table 2**). Of these 78 articles, only 3 publications (4%) included any mention of the FDA inspection violations despite the fact that for 59 of those 78 articles (76%), the inspection was completed at least 6 months before the article was published. Researchers are usually given a form 483 within a day of the inspection, with the form detailing any problems found by the inspector.

For the 3 articles that mentioned the inspection violations, 1 stated that 1 of the trial sites "was found to have allegedly entered fraudulent data and was dropped from participation."[121(p390)] (References 76 through 184 are listed in the eReferences in the Supplement.) The research misconduct involved falsified laboratory test results in a phlebotomy trial. In the second instance, the article noted that the data from 1 clinical trial site were excluded owing to "protocol adherence and data quality issues."[111(p78)] According to the FDA documents, the researcher apparently eliminated the blinding in a randomized protocol so she "could control drug treatment assignments"[168(p7)] of her patients; she was also cited for falsification of data in 2 other protocols. In the third instance, an article explained that data from several patients were excluded from the efficacy analysis because "site monitoring raised questions in regard to certain data at 1 study site."[65(p431)] The FDA documents[64] allege that none of the individuals enrolled at 1 study site had met the inclusion criteria and that the responsible researcher had fabricated chest radiographs of participants and committed other forms of misconduct.

In no other instance did we find acknowledgment of problems found during an FDA inspection. In addition, we were unable to identify any corrections, retractions, comments, or notifications of concern published after FDA identification of the violations.

Examples of Unreported Violations

To illustrate the importance of the unreported inspection violations, 4 cases cut examples are provided herein.

Case 1

A publication describing a stem cell trial in 26 patients with ischemic limbs stated that "all patients recognized and were aware of major clinical improvements in the treated (more is-

*References 12-16, 18-21, 24-26, 28, 29, 33, 34

Table 1. Clinical Trials and Publications With Possible but Not Definitive Instances of OAI-Rated Violations Excluded From the Primary Analysis[a]

Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name	Source Document/ Publication Affected	Falsification[b]	Protocol[c]	Record-keeping[d]	Safety[e]	Other[f]
Autologous stem cells	NCT00548613	2007-02-I	NIDPOE,[8] warning letter[9]/ Lasala et al[10]	...	...	...	P	Y
Bevacizumab	NCT00109070/ NCT00109226	AVF2107g/ AVF2192g	NIDPOE[11]/Scappaticci et al[12]	P	...	...	P	P
Bevacizumab	NCT00109070/ NCT00109226	AVF2107g/ AVF2192g	NIDPOE[11]/Kabbinavar et al[13]	P	...	...	P	P
Bevacizumab	NCT00109070/ NCT00109226	AVF2107g/ AVF2192g	NIDPOE[11]/Kabbinavar et al[14]	P	...	...	P	P
Docetaxel	...	TAX326	NIDPOE[11]/Belani et al[15]	P	...	...	P	P
Docetaxel	...	TAX326	NIDPOE[11]/Fossella et al[16]	P	...	...	P	P
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Gibofsky et al[18]	...	...	P	P	...
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Weaver et al[19]	...	...	P	P	...
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Markenson et al[20]	...	...	P	P	...
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Gibofsky et al[21]	...	...	P	P	...
Lumiracoxib	NCT00366938	...	NIDPOE,[22] form 483[23]/ Dougados et al[24]	P	P	...	...	...
Lumiracoxib	NCT00366938	...	NIDPOE,[22] form 483[23]/ Sheldon et al[25]	P	P	...	...	...
Naproxcinod	NCT00504127	...	NIDPOE,[22] form 483[23]/ Schnitzer et al[26]	P	P	...	...	...
Quetiapine	NCT00090324	112	Clinical Review[27]/ Findling et al[28]	...	...	...	...	...
Quetiapine	NCT00090311	149	Clinical Review[27]/ Pathak et al[29]	...	...	...	...	...
Telithromycin	...	3005	Form 483 and EIR,[30] NIDPOE,[31] NOOH[32]/ Luterman et al[33]	P	P	...	...	...
Telithromycin	...	3007	Form 483 and EIR,[30] NIDPOE,[31] NOOH[32]/ Zervos et al[34]	P	P	...	...	...

Abbreviations: ADE, adverse drug event; ellipses, not applicable; OAI, official action indicated; P, violation identified but no definitive link; Y, definitive link.

[a] None of the clinical trials listed herein had violations having to do with reporting of ADEs.

[b] Falsification and/or submission of false information.

[c] Protocol issues included failure to follow investigational plan and/or other violations of protocol.

[d] Record-keeping issues included inadequate and/or inaccurate records.

[e] Safety issues included failure to protect rights, safety, and welfare of patients and/or issues related to informed consent or institutional review board notifications.

[f] Other issues were violations not otherwise categorized.

chemic) leg, despite no significant clinical changes in the control (less ischemic) leg."[37(p381)] However, an FDA document[169] revealed that 1 patient had a foot amputated 2 weeks after administration of the stem cells. We found no correction or retraction.

Case 2

Eight of 16 FDA inspections of sites involved in a clinical trial of rivaroxaban,[170] a novel anticoagulant, had been rated OAI. These inspections had uncovered evidence of various transgressions, such as "systemic discarding of medical records,"[171(p3)] unauthorized unblinding, falsification, and "concerns regarding improprieties in randomization."[172(p211)] Consequently, the entire study, RECORD 4 (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep-Venous Thrombosis and Pulmonary Embolism 4), was deemed unreliable by the FDA.[171] These problems are not mentioned in the article describing the study's results[142] or in other publications associated with the trial.[144,145]

Case 3

A researcher was caught falsifying documents in a number of trials,[173-176] in part because those falsifications led to the death of a patient undergoing treatment in a clinical trial comparing 2 chemotherapy regimens. The researcher had falsified laboratory test results to hide the patient's impaired kidney and liver function, and the first dose of the treatment proved to be fatal. The researcher pleaded guilty to fraud and criminally negligent homicide and was sentenced to 71 months in prison. Although this episode is described in detail in FDA documents[11,67] as well as court documents,[177] none of the publications in the peer-reviewed literature associated with the chemotherapy study in which the patient died[70-72,178] have any mention of the falsification, fraud, or homicide. The publications associated with 2 of the 3 other studies for which the researcher falsified documents also do not report on the violations.[68,73]

Case 4

A clinical site in China taking part in a large trial of apixaban, a novel anticoagulant, had apparently altered patient records. If one were to exclude the data from the patients at that site, the claim of a statistically significant mortality benefit disappears.[179] For this reason, among others, the FDA wrestled with whether it was appropriate to allow the manufacturer to claim a mortality benefit. None of this discussion appears in the literature. The claim for the mortality benefit, which has

Table 2. Clinical Trials and Publications Affected by Official Action Indicated–Rated Inspections

No.	Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name(s)	Source Document No./ Publication Affected[a]	Falsification[b]	ADE Reporting[c]	Protocol[d]	Record-keeping[e]	Safety[f]	Other[g]
1[h]	Alogliptin	NCT00707993	SYR-322_303	Clinical inspection summary[42]/ Rosenstock et al[43]	...	...	Y	Y	Y	...
2	Amoxicillin/ clavulanic acid extended-release	...	25000/592	NIDPOE,[44] NOOH,[45] debarment order[46]/ File et al[47]	Y	...	Y	...	...	...
3	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Granger et al[38]	Y	Y	...	...	...	...
4[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Lopes et al[50]	Y	Y	Y	Y	Y	
5[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/McMurray et al[51]	Y	Y	Y	Y	Y	
6[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Wallentin et al[52]	Y	Y	Y	Y	Y	
7[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Garcia et al[53]	Y	Y	Y	Y	Y	
8[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Alexander et al[54]	Y	Y	Y	Y	Y	
9[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Alexander et al[55]	Y	Y	Y	Y	Y	
10[h]	Asenapine	NCT00145470	A7501008, P05844	Warning letter[56]/Szegedi et al[57]	...	...	Y	Y	...	...
11[h]	Autologous dendritic cells	...	1997-064	NOOH[58]/Redman et al[59]	...	...	Y	Y	...	...
12	Autologous stem cells	NCT00518401	2007-01-I	NIDPOE,[8] warning letter[9]/ Lasala et al[35]	...	...	...	...	Y	Y
13[h]	Autologous stem cells	NCT00721006	2008-01-II	NIDPOE,[8] warning letter[9]/ Lasala et al[37]	...	Y	...	...	Y	Y
14	Autologous stem cells	NCT00643981	2007-03-I	NIDPOE,[8] warning letter[9]/ Lasala et al[36]	...	...	Y	...	Y	Y
15	Autologous tumor cells	...	1995-243	NOOH[58]/Chang et al[60]	...	...	Y	Y	...	...
16[h]	Budesonide/ formoterol	NCT00206167	D5899C00001	NIDPOE[61]/Bleecker et al[62]	...	...	...	Y	...	...
17	Budesonide/ formoterol	NCT00206167	D5899C00001	NIDPOE[61]/Rennard et al[63]	...	...	...	Y	...	...
18[h]	Cd34+ Cells	NCT00300053	ACT34-CMI	NIDPOE[64]/Losordo et al[65]	Y	Y	Y	Y	...	Y
19[h]	Cd34+ cells	NCT00300053	ACT34-CMI	NIDPOE[64]/Povsic et al[66]	Y	Y	Y	Y	...	Y
20[h]	Dfmo	NCT00003814	ILEX-DFMO341	NIDPOE,[67] NOOH[11]/Messing[68]	Y	...	Y	P	P	Y
21	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Ajani[70]	Y	...	Y	Y	Y	...
22	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Ajani[70]	Y	...	Y	Y	Y	...
23[h]	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Ajani et al[71]	Y	...	Y	Y	Y	...
24[h]	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Van Cutsem et al[72]	Y	...	Y	Y	Y	...
25[h]	Docetaxel	...	TAX327	NIDPOE,[11] NOOH,[67] NOOH [69]/ Tannock et al[73]	Y	...	Y	Y	Y	...
26	Erlotinib	NCT00081614	AVF2938	Warning letter [74]/ Bukowski et al[75]	...	...	Y	...	Y	...
27[h]	Esomeprazole/ naproxen	NCT00527787	PN400-301	NIDPOE,[22] form 483[23]/ Goldstein et al[76]	Y	P	P	Y	...	...
28	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Gibofsky et al[18]	...	...	Y	Y	Y	...
29	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Weaver et al[19]	...	...	Y	Y	Y	...
30[h]	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Markenson et al[20]	...	...	Y	Y	Y	...
31[h]	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Gibofsky et al[21]	...	...	Y	Y	Y	...
32	Faropenem daloxate	...	100288	Form 483 and EIR,[77] warning letter,[78] warning letter[79]/ Upchurch et al[80]	...	...	Y	Y	P	...
33[h]	Ferric carboxymaltose	NCT00982007	1VIT09031	Warning letter[81]/ Onken et al[82]	...	...	Y	...	...	...
34[h]	Fondaparinux	NCT00038961	APOLLO	NIDPOE[83]/Turpie et al[84]	...	...	Y	Y	Y	Y

(continued)

Table 2. Clinical Trials and Publications Affected by Official Action Indicated–Rated Inspections (continued)

No.	Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name(s)	Source Document No./ Publication Affected[a]	Falsification[b]	ADE Reporting[c]	Protocol[d]	Record-keeping[e]	Safety[f]	Other[g]
35	Ibuprofen	NCT00225732	008a, CPI-CL-008	Warning letter,[85] clinical inspection summary[86]/ Southworth et al[87]	...	Y	Y	Y	...	Y
36[h]	Ibuprofen	NCT00225732	008b, CPI-CL-008	Warning letter,[85] clinical inspection summary[86]/ Kroll et al[88]	...	...	Y	Y	...	Y
37[h]	Indiplon	...	NBI34060-MR-0212	NIDPOE[89]/Lydiard et al[90]	Y	...	Y	Y	...	...
38[h]	Leuprolide acetate	...	...	Form 483,[91] EIR,[92] letter,[93] NIDPOE[94]/ Crawford et al[95]	Y	...	Y	Y	Y	Y
39[h]	Ly518674	NCT00133380	H8D-MC-EMBF	Warning letter[96]/ Nissen et al[97]	...	...	Y	P	P	Y
40[h]	Modified lymphocytes	...	1990-489	NOOH[58]/Chang et al[98]	...	...	Y	Y	Y	...
41	Modified lymphocytes	...	1995-318	NOOH[58]/DeBruyne et al[99]	...	...	Y	Y	...	...
42[h]	Nebivolol	NCT00200460	NEB302	NIDPOE[100]/Weiss et al[101]	Y	Y	Y	Y	...	Y
43	Ofloxacin	...	PRT002/ PRT003	NIDPOE,[102] NOOH,[103] proposal to debar/ NOOH,[104] debarment,[105] warning letter,[106] warning letter[107]/ Jones et al[108]	Y	...	Y	Y	Y	...
44[h]	Olanzapine	...	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/Tunis et al[111]	...	...	Y	...	P	...
45[h]	Olanzapine	...	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/ Ascher-Svanum et al[112]	...	...	Y	...	P	...
46[h]	Olanzapine	...	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/Faries et al[113]	...	...	Y	...	P	...
47[h]	Olanzapine	NCT00103571	F1D-US-HGLS	Warning letter[114]/Kinon et al[115]	...	...	Y	P	Y	...
48[h]	Oxycontin extended-release	NCT01559701	PTI-821-CM	NIDPOE[116]/Friedmann et al[117]	P	...	Y	Y	Y	...
49[h]	Paliperidone palmitate	NCT00111189	CR004198, R092670PSY300	Warning letter[56]/ Kozma et al[118]	...	Y	Y	Y	Y	...
50[h]	Paliperidone palmitate	NCT00111189	CR004198, R092670PSY300	Warning letter[56]/ Hough et al[119]	...	Y	Y	Y	Y	...
51[h]	Paroxetine	...	704	NIDPOE,[109] proposal to debar, NOOH[110]/Geller et al[120]	Y	...	Y	Y	Y	...
52[h]	Phlebotomy for atherosclerosis	NCT00032357	FeAST	NIDPOE,[11] NOOH,[67] NOOH[69]/ Zacharski et al[121]	Y	...	...	...	...	...
53[h]	Pomalidomide	NCT00072722	...	Warning letter [122]/ Amato et al[123]	...	...	P	P	Y	...
54[h]	Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Googe et al[127]	Y	...	Y	...	...	Y
55[h]	Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Gangaputra et al[128]	Y	...	Y	...	...	Y
56	Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Bhavsar et al[129]	Y	...	Y	...	...	Y
57[h]	Ranibizumab	NCT00891735	HARBOR	Warning letter[130]/ Busbee et al[131]	...	...	Y	Y	Y	...
58[h]	Reduced glutathione	...	...	Warning letter[132]/ Bishop et al[133]	...	...	...	...	Y	Y
59	Rivaroxaban	NCT00329628	RECORD 1	Compliance review,[134] medical review,[135] other review[136]/ Eriksson et al[137]	...	Y	Y	Y	...	...
60[h]	Rivaroxaban	NCT00332020	RECORD 2	NIDPOE,[48] Compliance review,[134] medical review,[135] other review[136]/ Kakkar et al[138]	Y	Y	Y	Y	Y	...

(continued)

Table 2. Clinical Trials and Publications Affected by Official Action Indicated–Rated Inspections (continued)

No.	Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name(s)	Source Document No./ Publication Affected[a]	Falsification[b]	ADE Reporting[c]	Protocol[d]	Record-keeping[e]	Safety[f]	Other[g]
61	Rivaroxaban	NCT00361894	RECORD 3	Compliance review,[134] medical review,[135] other review[136]/ Lassen et al[139]	...	Y		Y	Y	...
62[h]	Rivaroxaban	NCT00362232	RECORD 4	Compliance review,[134] medical review,[135] other review,[136] form 483,[140] EIR[141]/ Turpie et al[142]	Y	Y	Y	Y	Y	Y
63[h]	Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894	RECORD 1, 2, 3	Compliance review,[134] medical review,[135] other review[136]/ Eriksson et al[143]	Y	Y	Y	Y	Y	...
64[h]	Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894/ NCT00329628	RECORD 1, 2, 3, 4	NIDPOE,[48] compliance review,[134] medical review,[135] other review,[136] form 483,[140] EIR[141]/ Eriksson et al[144]	Y	Y	Y	Y	Y	Y
65[h]	Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894/ NCT00329628	RECORD 1, 2, 3, 4	NIDPOE,[48] compliance review,[134] medical review,[135] other review,[136] form 483,[140] EIR[141]/ Lassen et al[145]	Y	Y	Y	Y	Y	Y
66[h]	Rocuronium	NCT00124722	P05797	Warning letter,[146] letter[147]/ Pirotta et al[5]	...	...	...	P	Y	Y
67[h]	Rofecoxib	NCT00060476	2006_414, Formally P30A03LD, MK0966-201	NIDPOE[83]/ van Adelsberg et al[148]	...	...	P	...	...	Y
68[h]	Roflumilast	NCT00297102	BY217/M2-124	NIDPOE[61]/Calverley et al[149]	...	...	Y	Y	Y	Y
69[h]	Ropinirole	...	SKF-101468/ 191	NIDPOE[89]/Allen et al[150]	Y	...	Y	Y	...	...
70	Sodium oxybate	...	OMC-GHB-2	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrema Multicenter Study Group[154]	P	P	...	P	P	Y
71[h]	Sodium oxybate	...	OMC-GHB-3	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrema Multicenter Study Group[155]	P	P	...	P	P	Y
72[h]	Sodium oxybate	...	OMC-SXB-21	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrema Multicenter Study Group[156]	P	P	...	P	P	Y
73[h]	Thrombo-spondin-1	NCT00073125	...	Warning letter[122]/ Ebbinghaus et al[157]	...	...	P	P	Y	...
74[h]	Tramadol extended-release	NCT00348010	...	NIDPOE,[158] NOOH[159]/ Babul et al[160]	Y	Y	Y	Y	Y	...
75[h]	Tramadol extended-release	NCT00347685	...	NIDPOE,[158] NOOH[159]/ Pascual et al[161]	Y	Y	Y	Y	Y	...
76[h]	Valsartan	NCT00154271	CVAH631DUS02	NIDPOE[162]/ Everett et al[163]	Y	Y	Y	Y	Y	...
77[h]	Velimogene aliplasmid	NCT00044356	VCL-1005-208	Warning letter[164]/ Bedikian[165]	...	Y	Y	...	Y	...
78[h]	Zolpidem modified-release	...	EFC4529/ ZOLADULT	NIDPOE,[89] medical review[166]/ Roth et al[167]	Y	...	Y	Y	...	...

Abbreviations: ADE, adverse drug event; ellipses, not applicable; P, violation identified but no definitive link; Y, definitive link.

[a] References 76 through 167 are listed in the eReferences in the Supplement.

[b] Falsification and/or submission of false information.

[c] Violations having to do with reporting of ADEs.

[d] Protocol issues included failure to follow investigational plan and/or other violations of protocol.

[e] Record-keeping issues included inadequate and/or inaccurate records.

[f] Safety issues included failure to protect rights, safety, and welfare of patients and/or issues related to informed consent or institutional review board notifications.

[g] Other issues were violations not otherwise categorized.

[h] The article was published at least 6 months after the inspection was completed.

appeared in the literature since 2011,[50,52,180] consistently relies on the full data set, including data from the site at which the research misconduct allegedly occurred. This is true even for an article that was published[52] nearly 18 months after the alleged research misconduct was discovered. In addition, the mortality benefit analysis of the FDA-approved drug label as of August 31, 2014, is also based on the full data set[181] despite a recommendation from the FDA's Office of Scientific Investigation that data from not just the problematic site but 23 additional suspect Chinese sites be excluded.[182] Despite the fraudulent data, when all the suspect Chinese sites are excluded rather than just the one at which the evidence of alleged research misconduct was found, the mortality benefit becomes statistically significant at the $P = .05$ level once again.[182] One FDA analyst, commenting on the "data quality issues" in this clinical trial, complained about the agency's lack of transparency and poor handling of evidence of problems with trial data: Some of the responsibility for the data quality issues rests with us, the FDA: We have approved drugs ignoring similar data quality issues, granting superiority claims, and not discussing in the labels the data quality issues. We must stop doing this.[182(p19)]

Discussion

Our study has some limitations. The data are descriptive rather than quantitative. We do not know how many publications derive from trials that received an OAI finding or whether a full sample of such publications would show a higher or lower rate of acknowledging inspection violations. Our search strategy was limited by the information publicly available. For example, the FDA database of clinical inspections is infrequently updated. In addition, documents from certain time periods and certain regions of the country were harder to locate than others, indicating that our search was biased. Moreover, the records that the FDA makes available are incomplete and often heavily redacted. The nature of the redactions—and thus, our likelihood of linking a given document to a specific clinical trial—also varied depending on which FDA officer was performing the redaction and the year in which the redactions were performed. All of these limitations prevent generalization of our findings to the entire population of clinical trials. Finally, problems uncovered during inspections of clinical trial sites represent only a fraction of the departures from good clinical practice of which the FDA becomes aware. For example, the FDA sometimes learns of departures from good clinical practice through communications with and inspections of organizations sponsoring and responsible for conducting clinical trials; these instances were not part of our investigation.

Even though several inspection documents reviewed here described major violations of good clinical practice, including allegations of fabrication and other forms of research misconduct, it was rare that objectionable conditions or practices uncovered by the FDA were reflected in the peer-reviewed literature.

Of course, not all violations are of equal severity. When a clinical trial site receives an OAI, it does not mean that the violations need be acknowledged in an article or, if discovered after publication of the study, warrant a correction. Even in the case of data fabrication, there is occasional ambiguity. For example, in a clinical trial[183] of a drug administered via intravitreal injection, a researcher apparently fabricated images of patients' retinas. Although one might argue that an article in which those images were used as data[128] might require a correction, it is unclear whether another article that addresses the study's infection rates associated with intravitreal injections,[129] without relying on the retinal images to support the findings, would be similarly affected. Furthermore, data are sometimes excluded from peer-reviewed publications, occasionally without explanation. Consequently, in some of the articles (Table 2), tainted data might be handled properly, even if not explicitly remarked upon in the publication; it was not possible in the present study to determine how often this occurred.

Conclusions

The findings presented in this study should give us pause. This investigation has found numerous studies for which the FDA determined there was significant evidence of fraudulent or otherwise problematic data. Such issues raise questions about the integrity of a clinical trial, and mention of these problems is missing from the relevant peer-reviewed literature. The FDA does not typically notify journals when a site participating in a published clinical trial receives an OAI inspection, nor does it generally make any announcement intended to alert the public about the research misconduct that it finds. The documents the agency discloses tend to be heavily redacted. As a result, it is usually very difficult, or even impossible, to determine which published clinical trials are implicated by the FDA's allegations of research misconduct.

The FDA has legal as well as ethical responsibilities regarding the scientific misconduct it finds during its inspections. When the agency withholds the identity of a clinical trial affected by scientific misconduct, it does so because it considers the identity to be confidential commercial information, which it feels bound to protect.[184] However, failing to notify the medical or scientific communities about allegations of serious research misconduct in clinical trials is incompatible with the FDA's mission to protect the public health. Such allegations are relevant to include in the peer-reviewed literature on which physicians and other medical researchers rely to help them choose treatments that they offer to patients and other research participants.

To better serve the public health, the FDA should make unredacted information about its findings of research misconduct more readily available. The agency should make sure that any substantial evidence of misconduct is available to editors and readers of the scientific literature. One possible mechanism for this would be to use the national clinical trials database: any OAI inspection affecting a trial site should be promptly noted at http://www.clinicaltrials.gov. The FDA should also create a website or a publicly available database that lists all OAI-rated inspections of

clinical sites and provides links to copies of the relevant, unredacted, inspection-related documents.

The FDA should be more transparent about its findings of research misconduct; however, most of the burden for ensuring the integrity of the research in the peer-reviewed literature falls to the authors of the articles submitted to peer-reviewed journals. Currently, there is no formal requirement for authors seeking to publish clinical trial data to disclose any adverse findings noted during FDA inspections. Journals should require that any such findings be disclosed. Voluntary disclosures are never foolproof, but, as with conflict-of-interest statements, requiring authors and journals to be forthcoming about significant departures from good clinical practice will help raise the standard for the reporting of research toward greater transparency.

ARTICLE INFORMATION

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Supplementary Online Content

Seife C. Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature. *JAMA Intern Med*. Published online February 9, 2015. doi:10.1001/jamainternmed.2014.7774.

eAppendix. Two Examples of FDA Redactions

eReferences. References 76 through 184 from the main article

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Two Examples of FDA Redactions

Inspections, Compliance, Enforcement, and Criminal Investigations

Alexander, Elmore, D.O. 1/27/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

JAN 27, 2012

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Elmore Alexander, D.O.
(b)(6)

Dear Dr. Alexander:

Between November 13, 2009, and October 20, 2010, Ms. Stephanie Hubbard and Mr. LaReese Thomas, representing the U.S. Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigations of the investigational drug **(b)(4)**, performed for **(b)(4):**

- Protocol **(b)(4)**
- Protocol **(b)(4)**
- Protocol **(b)(4)**

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Hubbard and Ms. Thomas attempted multiple times to present you witl a Form FDA 483, Inspectional Observations. However, you refused to review the Form FDA 483 with FDA investigators. Consequently, and because your medical office had closed during the course of the inspection, the FDA investigators left a copy of the Form FDA 483 at your residence, and observed that you retrieved it.

We have reviewed the inspection report and the documents submitted with that report. We note that you did not provide a written response to the Form FDA 483. Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately submitted false information to the sponsor or FDA in required reports, and repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products, as published under Title 21, Code of Federal Regulations (CFR), part 312 (copy enclosed).

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR 312.70. A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. You repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report [312.70(a)].

Based on the information obtained during the course of the inspection, the FDA has determined that you submitted falsified subject records for three subjects enrolled in your clinical trials. The FDA inspection reveale that all of the subjects you enrolled in Protocol **(b)(4)** and Protocol **(b)(4)** were, in fact, study coordinators whom you enrolled under fictitious names.

a. Protocol **(b)(4)**: You enrolled your study coordinator (**(b)(6)**) into the study as Subject 1012 under a fictitious name (DCJ). In addition, you signed study records that showed the fictitious name for this subject.

(b)(6) completed the following study related documents for himself/herself while falsely claiming to be subjec DCJ:

- Patient medical history questionnaire for the December 3, 2008, visit date.
- Inclusion/exclusion form on December 3, 2008.
- Screening records for Visit 1 on December 3, 2008. On the same date, you signed the physical examination portion of these records as the physician completing the examination.
- Informed consent document (ICD) showing falsified subject DCJ's signature on December 22, 2008. (This date was later crossed out and changed to January 23, 2009, and was initialed on February 3, 2009.) You also signed this subject's ICD on February 3, 2009.
- Visit 2 esophagogastroduodenoscopy (EGD) report dated December 22, 2008. You signed this document on December 31, 2008.
- Study records for Visit 3 on December 23, 2008. In addition, you signed the Investigator Symptom Assessment for this visit on the same date.
- Study records for Visit 4 on January 23, 2009.
- Visit 4 EGD report dated January 22, 2009. Your subinvestigator, **(b)(6)**, signed this report.

Furthermore, study records note that you signed an informed consent document executed by falsified subject DCJ; you conducted physical examinations for subject DCJ at both the screening visit on December 3, 2008, and Visit 3 on December 23, 2008; and you signed a laboratory report for laboratory samples drawn from subject DCJ on January 23, 2009. These records indicate that you were aware that you enrolled your study coordinator into Study **(b)(4)** under a fictitious name.

b. Protocol **(b)(4)**: You enrolled your study coordinator (**(b)(6)**), who was also the Chief Executive Officer of the Site Management Organization (SMO), Clinical Trial Providers Inc., into the study as Subject 1011 under a fictitious name (MD). You and **(b)(6)** also signed study records that showed the fictitious name for this subject. Specifically:

- ICD (August 13, 2008, version) showing falsified subject MD's signature on November 26 and December 10, 2008. You also signed these ICDs on November 26 and December 10, 2008.
- ICD (October 30, 2008, version) showing falsified subject MD's signature on January 13, 2009. Your study coordinator **(b)(6)** signed as the person obtaining consent on the ICD for subject MD on this date
- Screening records for Visit 1 on November 26, 2008. You completed and signed a physical examinatior form for subject MD at the screening visit on November 26, 2008. Your study coordinator **(b)(6)** also completed and signed screening records for Visit 1 on this date.
- Screening records for Visit 2 on December 10, 2008 (later crossed out and changed to December 9, 2008). Your study coordinator **(b)(6)** completed and signed these study records on December 16, 2008
- Visit 2 EGD report for subject MD, dated December 9, 2008. You and your subinvestigator, **(b)(6)**, signed this report on December 9, 2008.
- Visit 3 study records dated December 10, 2008. Your study coordinator **(b)(6)** completed and signed these study records on December 10, 2008, and you signed the Investigator Symptom Assessment section of these records on the same date.
- Visit 4 EGD report dated January 13, 2009. The signature at the bottom of this endoscopy report was not his/her true signature.
- Visit 4 EGD CRF (visit date January 13, 2009). Your study coordinator **(b)(6)** completed and signed the Visit 4 EGD CRF for subject MD on January 13, 2009.
- Study records for Visit 6 on January 30, 2009. Your study coordinator **(b)(6)** completed and signed Visit 6 study records for subject MD on January 30, 2009.

As noted above, in addition to enrolling your study coordinator under a fictitious name, you signed study records that showed the fictitious name for this subject. These records indicate that you should have been aware that you enrolled your study coordinator, **(b)(6)**, into Study **(b)(4)** under a fictitious name.

c. Protocol **(b)(4)**: You enrolled your study coordinator (**(b)(6)**) into the study as Subject 1012 under a fictitious name (DCJ). You also signed study records that showed the fictitious name for this subject. Furthermore, your study coordinator, **(b)(6)**, completed these study-related documents for himself/herself while falsely claiming to be subject DCJ:

- ICD dated January 23, 2009. Your study coordinator **(b)(6)** completed and signed her/his own informed consent document under the false identity of DCJ, originally on December 22, 2008. On February 3, 2009, your study coordinator, using the initials DCJ, crossed out the original date and changed it to January 23, 2009.

- Inclusion/exclusion criteria form on January 23, 2009. Your study coordinator **(b)(6)** completed and signed this study record on June 8, 2009, using his/her true identity as the person completing the form but using the false identity of DCJ as the subject.
- Visit 1 study records for January 23, 2009, visit date. You signed the Investigator Symptom Assessment study record for this visit, originally on December 23, 2009, then crossed out that date and changed it to January 23, 2009. You initialed this change on February 5, 2009.
- Visit 4 study records on February 26, 2009.

As noted above, in addition to enrolling your study coordinator into Study **(b)(4)** under a fictitious name, you signed study records that showed the fictitious name for this subject. These records indicate that you should have known that you enrolled your study coordinator into Study **(b)(4)** under a fictitious name.

As the clinical investigator, it was your ultimate responsibility to ensure that these studies were conducted properly and that subjects' true identities were used on study records.

d. The signature of your subinvestigator, **(b)(6)**, was falsified on the following documents:

- Financial disclosure form, signed and dated April 20, 2009.
- Endoscopy report dated January 13, 2009, for Subject 1011 in Study **(b)(4)**.
- Memo dated February 4, 2009, which was attached to the November 21, 2008, endoscopy report for Subject 1004 in Protocol **(b)(4)**.

As the clinical investigator, it is your responsibility to ensure that the data collected from study subjects are accurate and can be relied upon in all analyses of the study endpoints. As all of the collected data were based on falsified subjects, none of the data collected in support of the referenced studies are considered reliable. When you signed the Statement of Investigator, Form FDA 1572, you agreed to provide accurate information to the sponsor, and to assure that you will comply with FDA regulations related to the conduct of the clinical investigations of the investigational drugs. You also agreed to ensure that all associates, colleagues, and employees assisting in the conduct of the studies would be informed of their obligations in meeting their commitments. Furthermore, your signature constitutes both your affirmation that you are qualified to conduct the clinical investigation, and your written commitment to abide by FDA regulations in the conduct of the clinical investigations. The use of fictitious information significantly compromises the integrity of your studies, as well as the reliability and validity of the data.

2. You failed to personally conduct or supervise the clinical investigations [21 CFR 312.60].

When you signed the Statement of Investigator (Form FDA 1572) for the above referenced clinical trials, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trials are conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60]. By signing the Form FDA 1572, you specifically agreed to personally conduct the clinical trials or to supervise those aspects o the trials that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequat to ensure that the clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare o human subjects.

Specifically, you failed to adequately supervise the study coordinators to whom you delegated tasks. Your failure to adequately supervise the conduct of the studies referenced above led to many of the violations noted in this letter. These violations include, for example, the fabrication of records by your study coordinators; their enrollment under fictitious names in Protocols **(b)(4)** (Protocol **(b)(4)**) and **(b)(4)** (Protocol **(b)(4)**); and falsified signatures. Had you provided adequate oversight, you would have been able to prevent many of these violations from occurring.

As the clinical investigator, it was your ultimate responsibility to ensure that the studies were conducted properly and in compliance with FDA regulations, in order to protect the rights, safety, and welfare of study subjects and ensure the integrity of the study data. Your lack of supervision and oversight of the clinical studies raises significant concerns about the protection of study subjects enrolled into the studies, and the integrity of the data from your site.

3. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, you are required to ensure that investigations are conducted according to the signed investigator statement, the investigational plan, and applicable regulations. You failed to conduct Protocols **(b)(4)** and **(b)(4)** according to the investigational plans. Examples of this failure include, but are not limited to, the following:

a. A sponsor newsletter, dated July 2008, prohibited the enrollment of "site staff associates" in your studies at the sites where the staff were employed. The purpose of this requirement was to avoid the introduction of bias into the study data. You violated this requirement by enrolling your study coordinators into the studies at your site. Specifically, you enrolled **(b)(6)** into Protocol **(b)(4)** in November 2008; you enrolled **(b)(6)** into Protocol **(b)(4)** in December 2008; and you enrolled **(b)(6)** into Protocol **(b)(4)** in January 2009, all of which were after the publication date of the sponsor newsletter. By enrolling your study coordinators into your studies, you introduced bias and compromised the study data.

b. Exclusion criteria for Protocol **(b)(4)** (version of March 24, 2008, exclusion criterion 7) and Protocol **(b)(4)** (version of February 11, 2008, exclusion criterion 3), require that subjects with current **(b)(4** be excluded from enrollment into the study. Contrary to these exclusion criteria, you enrolled Subject 1012/DCJ (your study coordinator, **(b)(6)**, using a fictitious identity) into Studies **(b)(4)** and **(b)(4)** despite two screening endoscopic evaluations on December 22, 2008, and January 22, 2009, documenting **(b)(4)**. Based on these endoscopy results, this subject should have been excluded from enrollment into both studies.

We emphasize our concern that you failed to fully evaluate the eligibility criteria, designed specifically for each clinical investigation by the sponsor to optimize the interpretability of the data to the disease process under study, and to minimize foreseeable harm to enrolled subjects due to comorbidities. Enrollment of subjects who do not meet eligibility criteria jeopardizes subject safety and welfare and compromises the interpretation and validity of the investigational endpoints.

4. You did not obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60, 21 CFR 50.20, and 21 CFR 50.27].

As a clinical investigator, you are required to obtain legally effective informed consent prior to involving a subject in research. An investigator shall seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. In addition, the regulations require that information given to the subject or the subject's legally authorized representative (LAR) shall be in language understandable to the subject or the LAR, and that the consent document be signed and dated by the subject or the subject's LAR at the time of consent. You failed to obtain informed consent from subjects in accordance with these provisions of 21 CFR part 50. Examples include, but are not limited to, the following:

a. You failed to ensure that the consent documents were signed and dated by the subject or the subject's LAR at the time of consent. Specifically, you failed to obtain signatures that reflected the subjects' true identities on informed consent documents in that you permitted your study coordinators, **(b)(6)** and **(b)(6)**, to enroll into studies under fictitious identities and to sign consent documents using these fictitious identities. You permitted your study coordinator, **(b)(6)**, to sign consent documents as falsified subject DCJ in Studies **(b)(4)** and **(b)(4)**, and you permitted your study coordinator, **(b)(6)**, to sign consent documents as falsified subject MD for Study **(b)(4)**.

b. You failed to obtain legally effective informed consent from Subject 1007 in Study **(b)(4)** in that you failed to ensure that the information given to the subject or the subject's LAR was in a language understandable to the subject or the LAR. Both you and your study coordinator told the Contract Research Organization (CRO) that the subject only spoke Spanish. The SMO administrator had to translate the consent form orally for this subject at the time of consent. You did not provide a Spanish version of the consent form to this subject or his/her LAR. You also did not provide a short form written consent document in Spanish to the subject, which states that the elements of informed consent required by §50.25 have been presented orally to the subject or the subject's LAR. In addition, there was no written documentation that a witness was present during the oral presentation of informed consent.

Subject 1007 signed the ICD for Study **(b)(4)** on November 17, 2008, and had the endoscopy procedure with gastric biopsy for screening purposes on December 12, 2008. Endoscopy and biopsy are both invasive procedures with potential adverse events for the study subject. By not providing the subject with proper informed consent, you jeopardized this subject's safety by not assuring that he/she understood all the risks associated with screening for the study, including but not limited to the endoscopic procedure and biopsy.

c. You failed to obtain informed consent prior to involving subjects in research. Specifically, for Study **(b)(4)**, Subject 1012 completed the patient medical history questionnaire, inclusion/exclusion form, and subject screening records on December 3, 2008. However, you did not obtain informed consent from Subject 1012 until December 22, 2008. In addition, Subject 1012's informed consent form was signed under a fictitious name.

d. You failed to obtain legally effective informed consent from your study coordinators, **(b)(6)** and **(b)(6)**, in that their enrollment raised concerns regarding coercion and undue influence. As your study site staff, **(b)(6)** and **(b)(6)** were not free to give informed consent that was independent of their status as employees. You did not minimize the potential for coercion and undue influence by enrolling them as subjects in your studies.

Your failure to ensure that informed consent documents were properly signed and dated by the subject or the subject's LAR; your failure to provide subjects with informed consent documents in a language that is understandable to the subject; and your failure to obtain informed consent prior to involving subjects in research jeopardize the safety and welfare of subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

5. You failed to prepare and 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)].

As clinical investigator, you were required to prepare and maintain adequate and accurate case histories that recorded all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include case report forms and supporting data, including, for example, subject medical records and signed and dated informed consent forms

As discussed above, you enrolled two members of your study staff into your study under fictitious names. Thus, you did not maintain accurate case histories for these subjects because their medical records, case report forms, and informed consent forms contained false names.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational products. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations

On the basis of the above-listed violations, FDA asserts that you have failed to protect the rights, safety, and welfare of subjects under your care; repeatedly or deliberately submitted false information to the sponsor; and repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks to human subjects and jeopardized the integrity of data; and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above-stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70

Within fifteen (15) days of receipt of this letter, write or call me at 301-796-3150 to arrange a conference time or to indicate your intent to respond in writing.

Should you choose to respond in writing, your written response should be forwarded within thirty (30) days of receipt of this letter.

Your reply should be sent to:

Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5342
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above-listed violations. You should bring with you all pertinent documents, and a representative of your choice may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The FDA's Center for Drug Evaluation and Research (the Center) will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you with notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products.

You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

To enter into the enclosed consent agreement with FDA, thereby terminating this disqualification process, you must:

(1) Initial and date each page of this Agreement,
(2) Sign and date the last page of this Agreement, and
(3) Return this Agreement initialed, signed, and dated to the signer below.

A copy of the fully executed Agreement will be mailed to you.

Sincerely yours,
{See appended electronic signature page}
Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosures:
#1 - Consent Agreement
#2 - 21 CFR 16
#3 - 21 CFR 312.70

Page Last Updated: 04/22/2012
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL – RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

Kim C. Hendrick, M.D.
Flushing Family Care PC and
Flushing Research Center PC
6429 West Pierson Road, Suite 12
Flushing, Michigan 48433

Dear Dr. Hendrick:

Between July 29, 2002 and August 28, 2002, Ms. Laureen F. Kononen, representing the Food and Drug Administration (FDA), conducted an inspection and met with you to review your conduct of the following clinical investigations:

Protocol[ ]entitled: "An Open, Non-Comparative Multicenter Study to Assess the Efficacy and Safety of Oral[ ]125mg Twice Daily for 10 Days in the Treatment of Acute Bacterial Sinusitis in Adults;" and

25000/092
Augmentin XR

Protocol[ ]entitled: "A Randomized, Double-Blind, Double Dummy, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Oral[ ]320 mg Once Daily for 7 Days Compared with Oral Cefuroxime Axetil 250 mg Twice Daily for 10 days in the Treatment of Acute Bacterial Sinusitis (ABS) Infections," performed for[ ]

009
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This inspection is part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research involving investigational products.

At the conclusion of the inspection, Ms. Kononen presented and discussed with you the items listed on the Form FDA 483, Inspectional Observations. We have reviewed your letter of September 10, 2002, in response to the inspectional observations, and accept your response regarding protocol[ ]that subjects 19343[ ]and 19289 [ ]met the inclusion criteria. We also acknowledge that the same radiologist was not required to assess sinus X-rays for study subjects and screen failures. However, we

do not find your explanation acceptable in addressing the remaining matters under complaint.

Based on our evaluation of the information obtained by the agency, FDA's Center for Drug Evaluation and Research (the Center) believes that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational drugs as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed) and that you submitted false information to the sponsor or FDA in a required report.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational drugs as set forth under 21 CFR 312.70.

A list of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You submitted false information to the sponsor or FDA in a required report [21 CFR 312.70(a)].**

   a. The sinus X-ray assessments for subjects enrolled in Protocol[ ]and Protocol[ ]which were used, in Case Report Forms or other documents you submitted to the sponsor, to confirm that the subjects met the inclusion criteria, were false. These false x-ray assessments provided the basis for the submission of false information to the sponsor or FDA in a required report.

   Both protocols required that the diagnosis of acute bacterial sinusitis (ABS) be confirmed by an independent radiological evaluation of the involved sinus(es) for subjects to qualify for inclusion in the studies. Protocol[ ]requires screening procedures at visit 1 including a sinus x-ray (Water's view) or a CAT scan, with the results of either study "consistent with a diagnosis of ABS of a maxillary sinus" for the patient to be enrolled (see Protocol Section 5.4.1). No CAT scan was purported to have been conducted in protocol[ ]Protocol [ ]requires that the radiologist "radiologically confirm ABS of the affected sinus(es) via a Water's view X-ray" at the screening visit (see Protocol Section 5.3.1). You falsely represented that sinus X-ray assessments were performed by radiologist[ ]M.D. for at least 129 subjects that you enrolled in these protocols. These reports were purportedly from two sources: (1) [ ]and (2)[ ] although all were allegedly completed by Dr.[ ]Dr.[ ]worked only for [ ]

The X-ray reports found in your case files that were used to confirm that subjects met the inclusion criteria for the studies and identified as being from[ ]and completed by Dr. [ ]were visibly different from[ ]X-ray reports verified as authentic. The letterheads and format of authentic reports from[ ]were not the same as other reports

identified as being from[ ] In addition, all authentic[ ]X-ray reports have an assessment date under the electronic signature, most contain subject identifiers (i.e., birth date, social security number), and some are initialed by the radiologist performing the assessment. Of the assessments that we reviewed for enrolled subjects at your site, all lack the subjects' social security number and the majority lack an assessment date and the subjects' birth date. Those with birth dates depict the dates in a different position and format than that found on an authentic[ ]report. In addition, during an interview with Dr.[ ]on August 8, 2002, she stated to Ms. Kononen, the FDA investigator, that all assessments that did not document the date of the electronic signature, i.e., assessment date, were not performed by her.

Other X-ray reports in your files that were used to confirm inclusion criteria contained the following identifier: "Flushing Research Center, P.C. Interpreted by[ ]and listed Dr.[ ]as evaluator. Dr.[ ] stated in sworn testimony that she provided radiological interpretations for[ ] she had no agreement with you to perform assessments outside of[ ]and that she was "not a member of[ ]" Furthermore, our personnel could not confirm the existence of[ ]

Protocol[ ]

1) There were 22 sinus X-ray assessments for 12 subjects[ ](7/3/01, 7/24/01),[ ](5/8/01, 5/30/01),[ ](5/14/01, 5/31/01),[ ] (3/13/01)[ ](7/11/01, 7/31/01)[ ](2/27/01, 3/20/01),[ ] (12/27/00, 1/18/01),[ ](1/4/01, 1/26/01),[ ](2/27/01, 3/23/01),[ ] (3/26/01),[ ](12/8/00, 12/27/00), and[ ](12/7/00, 12/26/00)) that were reported on[ ]letterhead and listed Dr.[ ]as the evaluator. In sworn testimony, Dr.[ ] stated that she did not interpret these X-rays.

   During the course of the FDA inspection, our personnel requested[ ]staff to search its database (by subject name, requesting physician, and requesting group) for evidence that sinus X-rays were performed or interpreted at[ ] for the above subjects.[ ]could find no evidence in their database to indicate that these X-rays or assessments were done at[ ]

2) There were 22 sinus X-ray assessments for 12 subjects[ ](12/4/01),[ ](12/6/01),[ ](11/28/01, 12/17/01),[ ](12/20/01, 1/8/02),[ ](12/20/01, 1/7/02),[ ](12/26/01, 1/15/02),[ ](1/8/02, 1/25/02),[ ](1/8/02, 1/29/02),[ ](1/10/02, 1/28/02),[ ](2/12/02, 3/5/02),[ ](2/28/02, 3/18/02)), and[ ](3/19/02, 4/11/02) that were printed on stationery bearing the letterhead "Flushing Research Center, P.C... Interpreted by[ ] and listed Dr.[ ]as the evaluator.

As stated above, Dr.[ ]stated that she was not "... a member of[ ]' and our personnel could not confirm the existence of [ ]

3) FDA personnel compared the list of X-ray interpretations verified as generated by[ ]for the time period 12/1/00-12/31/01 with your study log listing the sinus X-rays that you reportedly sent to Dr.[ ]for evaluation for the same time period. Only two of the 195 X-ray assessments that you claim were performed by Dr.[ ]were performed at[ ]and neither of these assessments were performed by Dr.[ ]Specifically, Dr.[ ]confirmed that she did not perform the 3/7/01 assessment for subject[ ]corroborated that another of their radiologists performed this assessment, with the finding of clear paranasal sinuses.[ ]also confirmed that a radiologist other than Dr.[ ]evaluated the sinus X-rays for subject[ ]on 12/28/00, with the finding of mucosal thickening. The protocol required radiologically confirmed ABS of a maxillary sinus, and specifically stated that mucosal thickening alone was not sufficient to make a subject eligible, so neither of these subjects met the inclusion criteria for the study. However, you enrolled both subjects in the study. Note that this is also a protocol violation under item 2, set forth below.

To support your claim that Dr.[ ]reviewed and signed sinus X-ray reports for subjects enrolled in Protocol[ ][as set forth in items 1.a.1), 1.a.2), and 1.a.3) above], you submitted to the sponsor a memorandum dated 8/29/01 that Dr.[ ]purportedly signed. This memorandum reads, "This is to certify that I received copies of previously read and electronically signed sinus x-ray reports from Flushing Family Care, PC on August 27, 2001. I reviewed the reports and signed all such copies provided me on August 28, 2001, as requested by Dr. Hendrick." You also presented this memorandum to Ms. Kononen during the FDA inspection in July/August 2002 when she questioned the different format of the sinus X-ray assessments for the enrolled subjects. Dr.[ ]has given sworn testimony that she did not write or sign this memorandum. We note that the signature on the 8/29/01 memorandum is markedly different from other documents that Dr.[ ]has confirmed that she signed.

Protocol[ ]

4) There were 25 sinus X-ray assessments for 13 subjects[ ]that were reported on[ ]letterhead and listed Dr.[ ]as the evaluator. In sworn testimony, Dr.[ ]reported that she did not interpret these X-rays.

During the course of the FDA inspection, our personnel requested[ ]staff to search its database (by subject name, requesting physician, and requesting group) for evidence that sinus X-rays were performed or interpreted at[ ]

for the above subjects. [ ]could find no evidence of these X-rays in their database.

2. **You failed to conduct the study in accordance with the investigational plan [21 CFR 312.60].**

Protocol[ ]

You failed to adhere to the protocol in that you did not perform a screening sinus puncture for subject[ ] As a result of this failure, the primary efficacy measure could not be determined for this patient. In addition, as noted in item 1.a.3) above, the protocol required radiologically confirmed ABS of a maxillary sinus, and specifically stated that mucosal thickening alone was not sufficient to make a subject eligible. The radiological assessment for subject[ ]found clear paranasal sinuses and the radiological assessment of subject[ ]found mucosal thickening, so neither subject was qualified for the study. However, you enrolled both subjects in the study.

3. **You failed to prepare and maintain adequate and accurate records [21 CFR 312.62(b)].**

Protocol[ ]

You failed to document in the case report forms the reasons why 41 subjects were considered screen failures. The protocol required that you record the reason for exclusion of any patient from the study to document the lack of systemic bias in selecting patients.

4. **You failed to report adverse events to the sponsor [21 CFR 312.64].**

Protocol[ ]

As you acknowledged in your September 10, 2002, response to the 483, you failed to report to the sponsor the diarrhea and yeast infection experienced by subject[ ] during the study.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations. On the basis of the above listed violations, the Center asserts that you have submitted false information and repeatedly or deliberately failed to comply with the cited regulations for investigational new drugs and it proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at (301) 594-0020 to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Joseph Salewski
Director (Acting)
Division of Scientific Investigations (HFD-45)
Food and Drug Administration
7520 Standish Place, Suite 103
Rockville, Maryland 20855

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and you may be accompanied by a representative of your choosing. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products.

You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,

{See appended electronic signature page}

Joseph Salewski
Director (Acting)
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosures:
21 CFR 312
21 CFR 16
Consent Agreement

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph Salewski
5/11/2006 02:50:59 PM

eReferences. References 76 through 184 from the main article

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