DATA INTEGRITY IN THE PHARMACEUTICAL INDUSTRY: ANALYSIS OF INSPECTIONS AND WARNING LETTERS ISSUED BY THE BIORESEARCH MONITORING PROGRAM BETWEEN FISCAL YEARS 2007-2018

by

CLINTON ALLEN ROGERS

(Under the Direction of Michael Bartlett)

ABSTRACT

Warning Letters issued by the Food and Drug Administration's (FDA) Bioresearch Monitoring Program provide insight into data integrity issues and other research misconduct in the premarket side of the pharmaceutical industry. This study presents an analysis of inspections and warning letters related to clinical investigators, institutional review boards (IRBs), sponsors of clinical studies, good laboratory practice (GLP) laboratories, and bioequivalence studies. The most common violations found included failing to follow and maintain procedures and poor documentation practices. Although the number of warning letters has decreased over the past decade and inspection results have been improving, there are still significant data integrity and other regulatory compliance issues found in the premarket side of the pharmaceutical industry.

INDEX WORDS: US Food and Drug Administration, Bioresearch Monitoring Program, Inspections, Warning Letters, Compliance, Data Integrity

DATA INTEGRITY IN THE PHARMACEUTICAL INDUSTRY: ANALYSIS OF INSPECTIONS AND WARNING LETTERS ISSUED BY THE BIORESEARCH MONITORING PROGRAM BETWEEN FISCAL YEARS 2007-2018

by

CLINTON ALLEN ROGERS

BS, University of Georgia, 2018

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2019

DATA INTEGRITY IN THE PHARMACEUTICAL INDUSTRY: ANALYSIS OF INSPECTIONS AND WARNING LETTERS ISSUED BY THE BIORESEARCH MONITORING PROGRAM BETWEEN FISCAL YEARS 2007-2018

by

CLINTON ALLEN ROGERS

Major Professor:	Michael Bartlett
Committee:	Gurvinder Singh Rekhi
	Randall Tackett
	Jennifer Ahearn

Electronic Version Approved:

Suzanne Barbour
Dean of the Graduate School
The University of Georgia
May 2019

ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. Bartlett, for guiding me in my undergraduate and graduate research and helping me explore both the analytical science and regulatory science disciplines. I would like to thank the College of Pharmaceutical and Biomedical Sciences for providing me with the unique opportunities I have been given to be a part of the new BS/MS program. I would like to thank the faculty of the International Biomedical Regulatory Affairs program for stimulating my interest in the regulatory side of the pharmaceutical industry. Finally, I would like to thank my family and my girlfriend for supporting me throughout this journey.

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

CHAPTER 1

INTRODUCTION

1.1 Data Integrity in the Pharmaceutical Industry

Data integrity has become a hot topic in the pharmaceutical industry because of how easily data can be manipulated and compromised in the modern computer-based era. The U.S. Food and Drug Administration (FDA) is especially aware of this, noting in their data integrity guidance that an increasing number of current good manufacturing practices (cGMP) violations involving data integrity have been observed in recent years.[1] Data integrity is typically defined in the pharmaceutical industry using the acronym ALCOA: data must be Attributable, Legible, Contemporaneously recorded, Original, and Accurate. In more recent years, this acronym has been extended to become ALCOA+, with the "+" referring to complete, consistent, enduring, and available, although the "+" does not technically add any new requirements to the original ALCOA and only provides extra emphasis.[2]

According to the FDA, data integrity is important in the pharmaceutical industry for ensuring the safety, efficacy, and quality of drug products.[1] Data integrity issues can lead to poor quality products released on the market, which can have a negative impact on public health. Some examples of regulations in cGMP that are directly related to data integrity involve maintaining original data records (21 CFR 211.180), securing data from alteration or inadvertent erasure (21 CFR 211.68), and reviewing records for accuracy (21 CFR 211.182, 211.186(a), 211.188(b)(11), 211.194(a)(8)). However, data integrity violations are not limited to manipulated

or mishandled data. The validity of data can also be challenged when standard procedures are followed incorrectly, leading to data that is inaccurate in the first place.

A number of pharmaceutical regulatory bodies, including the FDA[1], the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA)[2], and the European Medicines Agency (EMA)[3] have all recently issued major guidances on data integrity practices for the pharmaceutical industry. While data integrity issues can be hard to quantify and study in the real world, a tangible record of data integrity violations in the pharmaceutical industry can exist in the form of FDA-issued inspection citations and warning letters.

1.2 Overview of FDA Inspections

Inspections are the FDA's way of ensuring that firms are complying with cGMP and other applicable regulations. The FDA inspects all drug and device manufacturers that market FDA-regulated products, including foreign manufacturing facilities.[4] At the end of an inspection, the FDA classifies the inspection under one of three categories.[5] A No Action Indicated (NAI) classification indicates that either no compliance issues were found or there were no issues observed that require further action. A Voluntary Action Indicated (VAI) classification indicates that some regulatory violations were found but the FDA does not intend to pursue further regulatory action. An Official Action Indicated (OAI) classification indicates that significant violations were observed in the inspection and the FDA intends to take further regulatory action. The inspector will issue an FDA Form 483 at the end of an inspection that lists the most significant regulatory violations found.[6] If the violations in a 483 are serious enough and not corrected quickly, the FDA may decide to issue a warning letter. Electronic 483s are posted in a database on the FDA website, though these do not represent all 483s issued.[7]

The FDA publishes inspection manuals, known as Compliance Program Guidance Manuals (CPGM), on their website.[8] The CPGMs provide insight into what inspectors look for in inspections and what actions may be taken as a result of an inspection.

1.3 Warning Letters

Warning letters are letters issued by the FDA to firms or individuals who have been caught violating regulations found within the Code of Federal Regulations (CFR), generally as the result of an inspection.[9] These letters contain detailed summaries on major violations found and they identify what must be done to correct the violations, typically with a response deadline of 15 business days. All of these letters are available to the public on the FDA's website.[10] According to the FDA's Compliance Actions dashboard, a website that shows gross data on warning letters, injunctions, and seizures, there were 85,138 warning letters issued between fiscal year (FY) 2009-2018.[11] The majority of these warning letters were issued to tobacco retailers (79,141), while a combined total of 3,538 warning letters were issued within the pharmaceutical industry (1,418 for medical devices, 1,263 for drugs, 108 for biologics, and 749 for veterinary medicines).

Warning letters are issued by the product center (Center for Biologic Evaluation and Research [CBER], Center for Drug Evaluation and Research [CDER], Center for Device and Radiological Health [CDRH], or Center for Veterinary Medicine [CVM]) that has regulatory jurisdiction over the entity that is inspected. If the violations of the warning letter are not addressed properly within the timeframe, the FDA may consider further regulatory penalties, such as injunction or seizure of products.

1.4 The Bioresearch Monitoring Program

While most of the focus has been on data integrity on the marketed products side of the pharmaceutical industry, less focus has been spent on the premarket research side of the industry. This can be problematic because of how important premarket research is to our understanding of how products will work when they reach patients on a large scale. If the decision to allow a product on the market is based on data that is manipulated or not obtained properly, that can lead to unsafe and ineffective products reaching consumers. This is why it is important for premarket studies to be held to a high standard of conduct and data integrity.

In 1977, the FDA developed a task force specifically for investigating clinical studies that would later become known as the Bioresearch Monitoring (BIMO) Program.[12] This task force was created because of congressional hearings between 1975-1976 that determined a need for improved monitoring of investigational research studies. The BIMO Compliance Program Guidance Manuals (CPGM) state that the objectives of the BIMO program are to protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials, to verify the accuracy and reliability of clinical trial data submitted to the FDA in support of research or marketing applications, and to assess compliance with the FDA's regulations governing the conduct of clinical trials.[13] Today, the BIMO program inspects clinical investigators, institutional review boards (IRB), sponsors, monitors, and contract research organizations (CROs) involved in clinical trials, *in vivo* bioavailability/bioequivalence (BA/BE) studies, and nonclinical labs subject to Good Laboratory Practice (GLP) regulations.

Warning letters issued by the BIMO program are typically grouped under 1 of 5 categories: clinical investigator, IRB, sponsor, sponsor-investigator, or GLP. These warning letters made up about 6% of all warning letters issued to the pharmaceutical industry between FY

2009-2018 (205 BIMO program warning letters, 3,538 total warning letters). Warning letters are issued to clinical investigators who are not in compliance with 21 CFR 312 (Investigational New Drug Application) in the case of drugs and biologics or 21 CFR 812 (Investigational Device Exemptions) in the case of medical devices. Clinical investigators are also responsible for compliance with 21 CFR 50, which deals with informed consent. Sponsors need to be compliant with these same CFR Parts as well, though different subsections apply to sponsors rather than clinical investigators. IRBs must follow the regulations in 21 CFR 50 and 21 CFR 56 (Institutional Review Boards), and GLP labs must abide by 21 CFR 58 (Good Laboratory Practice for Nonclinical Laboratory studies).

The penalties for BIMO program warning letters are similar to those of other FDA warning letters. The recipient is required to submit a response within 15 working days detailing how violations will be corrected and how future violations will be prevented. Clinical investigators may be issued a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) instead of or along with a warning letter as the result of a BIMO program inspection. A NIDPOE is used to notify a clinical investigator that the FDA is considering disqualifying them from participating in clinical investigations.[14]

1.5 Closeout Letters

Closeout letters are follow-ups to warning letters that the FDA releases when all of the issues cited in the warning letter have been corrected by the entity that received the warning letter.[9] The FDA closeout letter program was created to keep the public informed about regulatory compliance following warning letters. This program is relatively recent and only warning letters issued on or after September 1, 2009, are eligible to receive closeout letters.

According to the FDA website, a closeout letter may only be issued if the corrective actions have been implemented and have been verified by the FDA. This typically requires the FDA to perform a follow-up inspection to confirm that the proper corrective actions have been taken. Because some warning letters address issues that occurred in the past and can no longer be adequately corrected, not every warning letter is eligible to receive a closeout letter.

Currently, closeout letters are the only publicly available notice on the FDA website that indicate that a firm or individual has corrected the violations mentioned in a warning letter. Closeout letters for all warning letters sent out by the BIMO program were also analyzed as a part of this study.

1.6 Literature Review

Previous studies have been published on the topic of BIMO program warning letters.[15-22] Bramstedt (2004) analyzed 58 clinical investigator warning letters from 2002-2004, finding that these warning letters can serve as an educational tool for helping other clinical investigators learn from the issues cited.[15] In this time period, Bramstedt found the most common violations cited to be related to deviation from the investigational plan, flawed informed consent processes, and deficiencies in adverse event reporting. Bramstedt and Kassimatis (2004) analyzed 52 IRB warning letters issued between 1997 and 2004.[16] Common issues they found included deficiencies related to procedures for research review, documentation of IRB activities, and continuing review of research studies. Gogtay et al. (2011) reviewed both clinical investigator and IRB warning letters from 2005-2010[17] and compared the results with the previous studies by Bramstedt.[15,16] Gogtay et al. found similar occurrence rates for common violations as the previous studies.

While the Bramstedt[15,16] and Gogtay et al.[17] studies analyzed frequency of violations by grouping related regulations together under violation "themes," Knowlton and Wan (2011) analyzed clinical investigators from 1996 through 2011 by tallying total number of infractions by regulation.[18] This study found deviation from investigational plan to be the most common violation, though this study also notes a significant number of violations related to record keeping that was not found in the Bramstedt[15] study. O'Reilly et al. (2013) reviewed sponsor-investigator warning letters from 2007-2012, finding the most common violations to be related to monitoring of investigations, submitting annual reports, and obtaining investigator agreements.[19] Shetty and Saiyed (2015) studied warning letters issued to clinical investigators, IRBs, and sponsors.[20] In comparison to previous studies by Bramstedt[15,16] and Gogtay et al.,[17] Shetty and Saiyed found violations relating to supervising of the study and protecting subject safety to be significantly more common in 2011-2012 clinical investigator warning letters, while IRB violations cited in 2011-2012 warning letters were similar. This was the first study to analyze sponsor warning letters, finding the common violations between 2005-2012 to be related to monitoring of investigations, obtaining investigator agreements, and maintaining records.

The most extensive study to date analyzing clinical investigator warning letters was published by Garmendia et al. (2018).[21] This study analyzed new warning letters between 2012-2015 and also included a meta-analysis of all clinical investigator warning letters issued between FY 2007-2015 (October 1, 2006 to September 31, 2015) using data from the previous studies by Bramstedt,[15] Gogtay et al.,[17] and Shetty and Saiyed.[20] Garmendia et al. found the only statistical difference between these data sets to be a decrease in informed consent violations in the more recent warning letters. Garmendia et al. (2018) also performed an extensive study that analyzed FDA 483s issued by the FDA's BIMO program from FY 2006-2015.[22]

The current study analyzes all of the warning letters issued by the FDA's BIMO program from FY 2007-2018, including the analysis of clinical investigator, IRB, sponsor, sponsor-investigator, and GLP warning letters. To the best of our knowledge, this is the first study that has analyzed warning letters issued to GLP laboratories and is the most extensive study on BIMO program warning letters to date. This study also analyzes closeout letters associated with these warning letters, which has not been studied before. An analysis of the BIMO program's inspection metrics from FY 2007-2017 is included and related to the warning letters issued.

CHAPTER 2

METHODS, RESULTS, AND DISCUSSION

2.1 Methods

This study involved the analysis of 300 warning letters issued by the BIMO Program over the course of 12 FYs (October 1, 2006 through September 30, 2018). Warning letters were obtained from the publicly available warning letter database located on the FDA website.[10] Standardized violation themes (VTs) were created for each category of warning letters in order to tally the frequency of violations found in warning letters, except for clinical investigator warning letters in which the VTs designed by Garmendia et al. were used.[21] VTs were also grouped by which FDA center issued the warning letter (CDER, CDRH, CBER, or CVM).

The categories that BIMO program warning letters are listed as in the warning letter database are clinical investigator, IRB, sponsor/monitor/CRO, sponsor-investigator, and GLP. For the purpose of this study, sponsor/monitor/CRO and sponsor-investigator warning letters were analyzed together due to their similarity. Sponsor-investigator warning letters were also analyzed separately using the VTs for clinical investigators in order to determine common deficiencies cited for their role as an investigator. The 25 closeout letters were also obtained from the FDA website. These letters can be found linked to the original warning letters that they referenced in the FDA warning letter database.

The BIMO program publicly releases inspection metrics for every FY on the FDA website.[23] These reports include the total number of inspections conducted for each category for the FY and what classification they received (No Action Indicated [NAI], Voluntary Action

Indicated [VAI], or Official Action Indicated [OAI]). Data on domestic inspections for clinical investigators, IRBs, sponsors/monitors/CROs, GLP labs, and BA/BE studies from these yearly reports was compiled for FY 2007-2017 in order to compare inspection trends over time. Yearly reports are typically released around May following the end of the FY, so the yearly report for FY 2018 was not available at the time of this study.

Statistical analysis was done using Rstudio software version 1.1.463 (Rstudio, Inc.) to calculate significance using Fisher's exact test at a significance level of 5%.

2.2 Explanation of Violation Themes for IRB Warning Letters

Violations for IRB warning letters were sorted into 12 different categories (VTs) based on subject matter. A complete list of regulations associated with these VTs can be found in Table 1.

Table 1 Sections of 21 CFR Covered by IRB Violation Themes

VT #	Violation Theme	Regulations cited
1	Documentation of Meeting Minutes	56.115(a)(2)
2	Timely review of research	56.109(f)
3	Not following written procedures/ missing written procedures	56.102(g), 56.108(a)(1), 56.108(a)(2), 56.108(a)(4), 56.108(b), 56.109(b), 56.109(c), 56.109(d), 56.115(a)(6), 812.66
4	Informed consent	50.25, 50.27, 56.109(b)-(c)
5	Less than majority in meeting/no nonscientific member present	56.108(c)
6	Membership issues/no accurate roster	56.115(a)(5)
7	Research Documentation	56.115(a)(1)
8	Expedited Review	56.110(b), 56.110(c)
9	Safety/Risk	56.111(a)(1), 56.111(a)(2)
10	Conflict of interest	56.107(e)
11	Children/vulnerable populations	56.109(h), 56.111(a)(3), 56.111(b)
12	Other	50.24, 56.107(a), 56.109(a), 56.109(c),56.109(e), 56.111, 56.113, 56.115(b)

VT1 covered violations relating to documentation of meeting minutes. As per 21 CFR 56.115(a)(2), “Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.” These violations typically involved not recording the minutes of a meeting or leaving out important information about topics that were discussed and voted on in a meeting.

VT2 covered violations relating to the timely review of research. As per 21 CFR 56.109(f), “An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year.” These violations involved not reviewing research studies on a yearly basis.

VT3 covered violations relating to following or establishing written procedures. There are several sections of 21 CFR 56 that specifically mention having and following written procedures for various tasks, including review of research (108[a]) and prompt reporting to the FDA (108[b]). These violations typically involved either not preparing adequate written procedures or not following them properly.

VT4 covered violations relating to informed consent. As per 21 CFR 56.109(b), “An IRB shall require that information given to subjects as part of informed consent is in accordance with §50.25.” These violations typically involved either the IRB neglecting to require informed consent or the informed consent procedures did not meet the requirements listed in 21 CFR 50.25.

VT5 covered violations relating to meeting attendance. As per 21 CFR 56.108(c), “Except when an expedited review procedure is used, [each IRB shall] 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." Most of these violations were due to too few members attending each meeting.

VT6 covered violations relating to the IRB not fulfilling membership requirements or not having a current accurate roster. As per 21 CFR 56.115(a)(5), "[an IRB should prepare and maintain adequate documentation of] A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant." Commonly, IRBs would not maintain an updated roster of members and their employment or experience. Also, according to 21 CFR 56.107, IRBs must have at least 5 members of varying backgrounds and at least 1 member must have primary concerns in a nonscientific area. Occasionally, IRBs would allow non-members (those not listed on their roster) to participate in voting.

VT7 covered violations relating to research documentation issues. As per 21 CFR 56.115(a)(1), "[an IRB should prepare and maintain adequate documentation of] Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects." These violations involved a failure to maintain copies of research reports and other documents relating to research studies.

VT8 covered violations relating to expedited review procedures. According to 21 CFR 56.110, an IRB may use expedited review procedures to quickly review research that involves

minimal risk or research that has been previously reviewed by the IRB and has received no more than minor changes. Most of these violations involved using expedited review procedures in the wrong situations or not keeping all IRB members informed of research studies approved under these procedures.

VT9 covered violations relating to protecting subject safety and minimizing risk. As per 21 CFR 56.111(a)(1-2), an IRB should make sure that risks to research subjects are minimized and that risks to subjects are reasonable in relation to anticipated benefits to the subjects. These violations involved not adequately reviewing the risks and benefits of research studies before approving them.

VT10 covered violations relating to conflicts of interest within the IRB. As per 21 CFR 56.107(e), “No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.” These violations involved allowing members with conflicting interests to vote on the approval of research studies.

VT11 covered violations relating to the protection of children and other vulnerable populations. According to 21 CFR 56.111(b), “When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.” These violations involved not ensuring that special protections required for children and other vulnerable populations were adequately considered in approving research studies.

VT12 covered miscellaneous violations that did not fit into other categories but were not common enough to have their own category. These violations included:

- The IRB failed to request sufficient information to determine whether studies meet the criteria for IRB approval of research at continuing review [21 CFR 56.111]
- Failure to meet the requirements for review of research involving an exception from informed consent for emergency research. [21 CFR §§ 56.109(c) and 50.24].
- The IRB failed to demonstrate its ability to ascertain the acceptability of the proposed research in terms of regulations, applicable law, and standards of professional conduct and practice. [21 CFR § 56.107(a)].
- The IRB failed 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)].
- Failure to report promptly to the FDA any suspension or termination of approval and failure to prepare written procedures [21 CFR 56.113 and 21 CFR 56.115(a)(6)]
- The IRB failed to make all records required by regulation to be fully accessible for inspection and copying by authorized representatives of the Food and Drug Administration (FDA). [21 CFR § 56.115(b)].
- Failure to review all research activities 21 CFR 56.109(a).
- Failure to retain IRB records for at least 3 years after completion of the research. [21 CFR 56.115(b)]

2.3 Explanation of Violation Themes for Sponsor Warning Letters

Violations for sponsor and sponsor-investigator warning letters were sorted into 11 different categories. A complete list of regulations associated with these VTs can be found in Table 2. Sponsor-investigator warning letters often included violations relating to the recipient's role as a clinical investigator, though these were not included in the sponsor VTs in order to better group sponsor and sponsor-investigator warning letters together.

Table 2 Sections of 21 CFR Covered by Sponsor Violation Themes

VT #	Violation Theme	Regulations cited
1	Monitoring of Investigation	312.50, 312.56(a), 812.2(b)(1)(iv), 812.25(e), 812.40
2	Maintaining Records	312.57(a), 812.140(b)(1-2), 812.140(b)(6)
3	Submission of regular reports	312.56(c), 812.150(b)(5)
4	Investigator violations	312.53(c)(1), 312.55(b), 812.40, 812.43(b), 812.43(c)(3), 812.43(c)(5), 812.46(a)
5	FDA/IRB approval	56.103(a), 56.107, 312.20, 312.23, 312.30, 312.40, 812.20(b)(2), 812.25(b), 812.27, 812.40, 812.42
6	Informed Consent/Patient Rights	50.20, 50.25, 812.150(b)(8)
7	Labeling/advertisement	812.5(a-b), 812.7(a), 812.7(d)
8	Adverse event reporting/evaluation	812.46(b)(1), 812.150(b)(1)
9	Provide FDA information/inspection on request	314.3(b), 812.145(a), 812.150(b)(10)
10	Financial disclosure/conflict of interest	312.57(b), 812.43(c)(5)
11	Other	312.42(a), 312.42(e), 314.50(d)(5)(iv), 1271.85(1-2), 1271.85(a)(5)

VT1 covered violations relating to monitoring of clinical investigations. According to 21 CFR 312.50 and 812.40, sponsors are responsible for monitoring clinical studies and ensuring that investigational procedures are properly followed. These violations involved not picking

qualified monitors to monitor investigations or not having written procedures in place for monitoring investigations.

VT2 covered violations relating to maintaining records. 21 CFR 312.57 and 812.140(b) indicate the records that sponsors must keep relating to investigational studies. This includes records of correspondence with investigators or IRBs and records of the shipment and other disposition of investigational products. Violations in this category most commonly involved not keeping adequate records relating to the disposition of investigational products.

VT3 covered violations relating to submission of regular reports. 21 CFR 312.56(c) and 812.150(b)(5) detail annual reporting requirements for sponsors of investigational products. These violations most commonly involved not submitting annual reports to the FDA.

VT4 covered violations relating to the investigators involved in the investigational studies. These violations commonly involved not obtaining signed investigator agreements for each investigator and not providing investigators with all information necessary to carry out studies.

VT5 covered violations relating to obtaining FDA or IRB approval for investigational studies. These violations often involved conducting clinical studies without IRB approval or without submitting the proper applications to the FDA beforehand.

VT6 covered violations relating to informed consent and protecting patient rights. These violations involved inadequate informed consent procedures and not reporting when investigational products were used without obtaining informed consent.

VT7 covered violations relating to investigational product labeling and advertisement. According to 21 CFR 812.5(a), investigational devices must not have false or misleading labeling and must indicate that the device is investigational, and according to 21 CFR 812.7,

medical devices cannot be promoted as safe and effective prior to FDA approval. These violations most commonly involved not indicating that devices were for investigational use only on their labeling.

VT8 covered violations relating to adverse event reporting and evaluation. According to 21 CFR 812.46(b)(1) and 812.150(b)(1), sponsors of investigational medical device studies must conduct immediate evaluations on unanticipated adverse events and must report such adverse events to IRBs and the FDA within 10 working days of initial notice. These violations most commonly involved not reporting adverse events as required.

VT9 covered violations relating to FDA requests and inspections. One violation involved denying the FDA inspection of facilities while the other violations involved not providing the FDA with information they specifically requested from the sponsor.

VT10 covered violations relating to financial disclosure of investigators. According to 21 CFR 312.57(b) and 812.43(c)(5), sponsors must maintain accurate records of financial interests of each investigator. 21 CFR 54 details the necessary financial disclosure information that sponsors must record. These violations involved not keeping adequate records of the financial interests of investigators.

VT11 covered miscellaneous violations that did not fit into other categories but were not common enough to have their own category. These violations included:

- "Failure to provide the FDA adequate descriptions and analyses of any other data or information relevant to the evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic including information derived from clinical investigations [21 CFR 314.50(d)(5)(iv)]."

- "You administered an investigational product in violation of a clinical hold. [21 CFR § 312.42(a) and (e)]."
- "You failed to test a specimen from the donor for evidence of infection due to relevant communicable diseases agents, to adequately and appropriately reduce the risk of transmission of relevant communicable diseases. [21 CFR § 1271.85(a)(5)]."
- "You failed to test a specimen from the donor of viable, leukocyte-rich cells to adequately and appropriately reduce the risk of transmission of relevant cell-associated communicable diseases including Human T-lymphotropic virus (HTLV) types I and II. [21 CFR § 1271.85(b)(1)]"
- "You failed to test a specimen from the donor of viable, leukocyte-rich cells for evidence of infection due to Cytomegalovirus (CMV) to adequately and appropriately reduce the risk of transmission [21 CFR § 1271.85(b)(2)]."
- "You violated a clinical hold by allowing a clinical investigator to give subjects an investigational drug after FDA issued an order to delay a proposed investigation [21 CFR 312.42(a)]."

2.4 Explanation of Violation Themes for GLP Laboratory Warning Letters

Violations for GLP warning letters were sorted into 10 different categories. A complete list of regulations associated with these VTs can be found in Table 3.

Table 3 Sections of 21 CFR Covered by GLP Violation Themes

VT #	Violation Theme	Regulations cited
1	QA unit responsibilities	58.31(c), 58.35
2	Study protocols	58.120, 58.130(a)
3	Inadequate reports	58.185
4	SOPs	58.81
5	Characterization of test article	58.31(d), 58.105, 58.113, 58.185(a)(4)
6	Calibration of equipment	58.63(a)
7	Recording/storage of data	58.33(b), 58.130(e), 58.190(b)
8	Personnel	58.29(a-b), 58.31(f), 58.33
9	Handling unforeseen circumstances	58.33(c)
10	Other	58.31(a), 58.31(g), 58.43(a)(3), 58.45, 58.90(g), 58.107(d)

VT1 covered violations relating to Quality Assurance (QA) unit responsibilities. 21 CFR 58.35 details the requirements for and responsibilities of QA units involved in GLP studies. While most other violations could also technically be considered a failure of the QA unit to carry out their responsibilities, this VT was used whenever the warning letter specifically referenced the QA unit.

VT2 covered violations relating to study protocols. 21 CFR 58 Subpart G details the requirements of GLP study protocols and following them. These violations involved not following established protocols or not having complete protocols.

VT3 covered violations relating to preparing adequate reports. 21 CFR 58.185 details the requirements of reporting results of nonclinical studies, specifically in the format of a final report. These violations involved either not submitting final reports or leaving out important information from the final report.

VT4 covered violations relating to establishing and following standard operating procedures (SOPs). 21 CFR 58.81 details the requirements for establishing SOPs, what SOPs must be established, and how to handle deviations from SOPs. These violations involved not

properly documenting and justifying deviations from established SOPs as well as not establishing the required SOPs.

VT5 covered violations relating to characterization of test and control articles. According 21 CFR 58.105, the test articles used in GLP studies must be adequately tested for identity, strength, purity, and composition. These violations involved not performing required testing to characterize therapeutics used in GLP studies and not putting this information in the final report.

VT6 covered violations relating to maintenance and calibration of equipment. According to 21 CFR 58.63(a), "equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized." These violations involved not cleaning or calibrating equipment used for the GLP study.

VT7 covered violations relating to data recording and storage. According to 21 CFR 58.33(b), 58.130(e), and 58.190, data must be dated and signed, stored in a secure and organized archiving system, and verified by the study director for accuracy. Any changes in data entries must be properly documented and indicate a reason for the change. These violations often cited data that was not verified as accurate by the study director or was changed without justification.

VT8 covered violations relating to personnel. 21 CFR 58.29 details requirements for personnel involved in GLP studies. These violations involved not ensuring that personnel had adequate experience and training and not maintaining adequate records of personnel involved in a study.

VT9 covered violations relating to handling unforeseen circumstances. According to 21 CFR 58.33(c), "The study director shall assure that unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and

corrective action is taken and documented." These violations involved the study director not taking appropriate corrective action and not performing investigations when issues occurred during a GLP study.

VT10 covered miscellaneous other violations that did not occur more than once. These violations included:

a. The receipt and distribution of each batch of test and control articles were not documented, including the quantity and date of each batch distributed and returned [21 CFR 58.107(d)].
b. Failure of testing facility management to fulfill its responsibilities. [21 CFR § 58.31(a) and (g)]. (Appoint study director)
c. Failure to ensure that there is a dedicated storage area for animal feed that is separate from areas housing the test systems. [21 CFR § 58.45].
d. Failure to periodically analyze feed and water used for test animals. [21 CFR § 58.90(g)].
e. Failure to provide a sufficient number of animal rooms or areas to assure proper quarantine of animals. [21 CFR 58.43(a)(3)]

2.5 Violation Themes for Clinical Investigator Warning Letters

This study used the VTs that were used in previous studies of clinical investigator warning letters. These VTs were originally created by Shetty and Saiyed[20] and then subsequently revised by Garmendia et al.[21] For the sake of this study, the numbering of the VTs was adjusted to be sequential. A complete list of regulations associated with these VTs can be found in Table 4 (adapted from Garmendia et al.).

Table 4 Sections of 21 CFR Covered by Clinical Investigator Violation Themes

VT #	Violation Theme	Regulations cited
1	Deviation from investigational plan	312.60, 812.110, 812.150(a)(4)
2	Failure to maintain adequate/accurate source documentation	312.62(b-c), 312.305(c)(4), 812.140(a)
3	Informed consent	50.20, 50.23, 50.25, 50.27, 50.55, 312.60, 812.100, 812.110(a), 812.140(a)(3)(i), 812.150(b)(5)
4	Violations related to investigational product	312.61, 312.62(a), 312.69, 312.305(c)(1), 812.7(d), 812.140(a)(2)
5	Failure to personally supervise the study	312.60, 812.110(c)
6	Failure to protect subject safety/report adverse events to IRBs/communicate with the IRB	56.103, 312.66, 812.150(a)(1-3)
7	Submission of false information to the FDA and sponsor	312.70, 812.119
8	Failure to communicate with the sponsor	312.64, 812.150(a)(6)
9	Financial disclosure	812.110(d)

Adapted from Garmendia et al.[21]

2.6 Warning Letter Results

A combined total of 300 warning letters were analyzed as a part of this study (Table 5). The number of warning letters issued each FY has varied greatly, with more recent FYs seeing much fewer warning letters than 10 years ago. For comparison, 48 total warning letters were issued in FY 2007 while only 1 warning letter was issued in FY 2018. Clinical investigators received the most warning letters during this time period, while GLP laboratories received the least amount of warning letters. CDER issued 149 warning letters, CDRH issued 124 warning letters, CBER issued 26 warning letters, and CVM issued only 1 warning letter.

Table 5 Warning Letters Issued between FY 2007-2018 by Category

	FY07	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	FY16	FY17	FY18	Total
CI	26	28	25	23	13	9	9	13	6	6	3	0	161
IRB	6	8	7	14	8	8	5	4	1	4	0	0	65
S+SI	13	10	2	7	6	5	1	7	4	3	4	0	62
GLP	3	1	4	1	1	0	0	1	0	0	0	1	12
Total	48	47	38	45	28	22	15	25	11	13	7	1	300

CI – Clinical Investigator; S+SI – Sponsor and Sponsor-Investigator Combined

2.6.1 IRB Warning Letters

A total of 65 IRB warning letters were analyzed in this study (Table 6). Of these warning letters, 25 (39%) were issued by CDER, 32 (49%) were issued by CDRH, and 8 (12%) were issued by CBER. The most common VT cited involved written procedures (77% of all warning letters), while the second most common VT involved documentation of meeting minutes (75%). Other common violations involved meeting attendance (51%) and membership issues within the IRB (42%). Using Fischer's exact test for significance, there were no statistically significant differences in violations between warning letters issued by different FDA centers for any VT.

Table 6 Frequency of VTs in IRB Warning Letters

VT #	Violation Theme	CDER n=25	CDRH n=32	CBER n=8	Total n=65	P value
1	Documentation of Meeting Minutes	17(68%)	25(78%)	7(88%)	49(75%)	0.56
2	Timely review of research	5(20%)	12(38%)	1(13%)	18(28%)	0.26
3	Not following procedures/no written procedures	18(72%)	25(78%)	7(88%)	50(77%)	0.77
4	Informed consent	6(24%)	8(25%)	1(13%)	15(23%)	0.84
5	Less than majority in meeting/no nonscientific member present	11(44%)	18(56%)	4(50%)	33(51%)	0.65
6	Membership issues/no accurate roster	9(36%)	14(44%)	4(50%)	27(42%)	0.78
7	Research Documentation	6(24%)	7(22%)	2(25%)	15(23%)	1
8	Expedited Review	5(20%)	6(19%)	1(13%)	12(18%)	1
9	Safety/Risk	5(20%)	1(3%)	0	6(9%)	0.10
10	Conflict of interest	5(20%)	6(19%)	2(25%)	13(20%)	0.91
11	Children/vulnerable populations	6(24%)	3(9%)	2(25%)	11(17%)	0.21
12	Other	8(32%)	4(13%)	2(25%)	14(22%)	0.19

2.6.2 Sponsor Warning Letters

A total of 62 sponsor and sponsor-investigator warning letters were analyzed, with 46 of these letters categorized as "Sponsor" and 16 of them categorized as "Sponsor-Investigator" (Table 7). Even though the BIMO program lumps sponsor, monitor, and CRO inspections into a single category, all warning letters under this category were addressed to sponsors. CDER issued 20 (32%) of these letters, CDRH issued 39 (63%), and CBER issued 3 (5%). The most common VT cited involved ensuring proper monitoring of the investigation (56%), with the next most common issues involving record keeping (50%), lack of investigational application review or IRB review (50%), and problems with investigators of the trials (48%). Unlike other warning letter categories, there were no violations that were present in more than 75% of warning letters.

Table 7 Frequency of VTs in Sponsor Warning Letters

VT #	Violation Theme	CDER n=20	CDRH n=39	CBER n=3	Total n=62	P value
1	Monitoring of Investigation	12(60%)	21(54%)	2(67%)	35(56%)	0.91
2	Record keeping	6(30%)	25(64%)	0	31(50%)	<0.01*
3	Submission of regular reports	0	11(28%)	1(33%)	12(19%)	0.01*
4	Investigator issues	6(30%)	22(56%)	2(67%)	30(48%)	0.11
5	FDA/IRB approval	9(45%)	19(49%)	3(100%)	31(50%)	0.32
6	Informed Consent/Patient Rights	3(15%)	13(33%)	0	16(26%)	0.26
7	Labeling/advertisement	0	7(18%)	0	7(11%)	0.14
8	Adverse event reporting/evaluation	0	7(18%)	1(33%)	8(13%)	0.06
9	Provide FDA information/inspection on request	2(10%)	1(3%)	1(33%)	4(6%)	0.06
10	Financial disclosure/conflict of interest	2(10%)	5(13%)	1(33%)	8(13%)	0.50
11	Other	2(10%)	0	1(33%)	3(5%)	0.02*

*Statistically significant based on P<.05

These letters saw more differences in violations issued by different centers than warning letters in other categories. Based on Fischer's exact test for significance, sponsors of medical device studies received significantly more citations for inadequate record keeping and inadequate reporting than sponsors of drug products. Medical device sponsors were also the only ones to

have labeling and advertising violations. Sponsors of drug products received no violations relating to regular progress reports and adverse event reporting.

2.6.3 GLP Warning Letters

Warning letters issued to GLP labs are the least common type of BIMO warning letter. A total of 12 warning letters were analyzed, with 5 (42%) issued by CDER, 1 (8%) issued by CDRH, 5 (42%) issued by CBER, and 1 (8%) issued by CVM (Table 8). These letters on average cite more violations than any other warning letter type. Every GLP warning letter except for one specifically mentioned deficiencies in the quality assurance unit. Other frequent violations included failure to follow and maintain SOPs (75%) and failure to record or store data properly (75%). Of the 10 VTs devised for GLP warning letters, 6 of them were present in at least half of the warning letters. Because of the small sample size, statistics were not performed on GLP warning letters.

Table 8 Frequency of VTs in GLP Warning Letters

VT #	Violation Theme	CDER n=5	CDRH n=1	CBER n=5	CVM n=1	Total n=12
1	QA unit responsibilities	5(100%)	1	4(80%)	1	11(92%)
2	Study protocols	2(40%)	0	4(80%)	1	7(58%)
3	Inadequate reports	4(80%)	0	3(60%)	0	7(58%)
4	SOPs	3(60%)	1	4(80%)	1	9(75%)
5	Characterization of test article	3(60%)	0	2(40%)	0	5(42%)
6	Calibration of equipment	3(60%)	0	3(60%)	0	6(50%)
7	Recording/storage of data	5(100%)	1	2(40%)	1	9(75%)
8	Personnel	1(20%)	1	2(40%)	0	4(33%)
9	Handling unforeseen circumstances	0	0	2(40%)	1	3(25%)
10	Other	0	1	2(40%)	1	4(33%)

2.6.4 Clinical Investigator Warning Letters

Clinical investigator warning letters are the most common type of BIMO warning letters. A total of 161 warning letters were issued to clinical investigators during this time period, with 99 issued by CDER, 52 issued by CDRH, and 10 issued by CBER.

Only 9 new warning letters have been issued to clinical investigators since Garmendia et al.'s analysis of clinical investigator warning letters, all of which were issued by CDER. In these warning letters, only 3 different VTs were cited: deviation from investigational plan (9 times), failure to maintain source documentation (4 times), and violations related to the investigational product (2 times). The data from the warning letters issued from FY16-FY18 was combined with the data from Garmendia et al. to create a combined dataset from FY07-FY18 (Table 9). The addition of the 9 new warning letters did not have a great effect on the overall dataset. The most common violations for clinical investigators were deviation from investigational plan (94%), failure to maintain source documentation (66%), and violations related to informed consent (46%).

In reviewing the FDA warning letter database, only 151 clinical investigator warning letters were found. One letter that was not available in the FDA database was found on a third-party website.[24] This does not match the 155 warning letters that were analyzed by Garmendia et al.[21] Garmendia was affiliated with the FDA at the time of writing the article, so he may have had access to some warning letters that were never publicly released, which could account for this discrepancy, although all warning letters are supposed to be published on the FDA website. It is also worth noting that one of the warning letters cited in their article was cited twice by accident, which could potentially mean that this letter was analyzed twice. Garmendia et al. also

did not cite the warning letter issued to Dr. Henry Lin in 2010,[25] so it is unclear whether or not this letter was analyzed.

Table 9 Frequency of VTs in Clinical Investigator Warning Letters

VT#	Violation Theme	CDER n=98	CDRH n=56	CBER n=10	Total n=164	P value
1	Deviation from investigational plan	93(95%)	52(93%)	9(90%)	154(94%)	0.55
2	Failure to maintain adequate/accurate source documentation	61(62%)	39(70%)	8(80%)	108(66%)	0.42
3	Informed consent	36(37%)	33(59%)	6(60%)	75(46%)	0.02*
4	Violations related to investigational product	32(33%)	13(23%)	4(40%)	49(30%)	0.35
5	Failure to personally supervise the study	22(22%)	4(7%)	0	26(16%)	0.02*
6	Failure to protect subject safety/report adverse events to IRBs/communicate with the IRB	31(32%)	19(34%)	3(30%)	53(32%)	0.96
7	Submission of false information to the FDA and sponsor	1(1%)	0	0	1(1%)	1
8	Failure to communicate with the sponsor	3(3%)	1(2%)	0	4(2%)	1
9	Financial disclosure	0	1(2%)	0	1(1%)	0.40

*Statistically Significant based on P<.05

The 16 Sponsor-Investigator warning letters were also analyzed using the clinical investigator violation themes (Table 10). Like clinical investigator warning letters, the most common violation was failure to follow the investigational plan (63%) followed by failure to maintain documentation (50%) and informed consent violations (44%). No sponsor-investigator warning letters cited violations related to submitting false information to the FDA, failure to communicate with the sponsor, or financial disclosure. Because of the small sample size, statistics were not performed on sponsor-investigator warning letters.

Table10 Frequency of Clinical Investigator VTs in Sponsor-Investigator Warning Letters

VT#	Violation Theme	CDER n=5	CDRH n=10	CBER n=1	Total n=16
1	Deviation from investigational plan	2(40%)	7(70%)	1	10(63%)
2	Failure to maintain adequate/accurate source documentation	3(60%)	5(50%)	0	8(50%)
3	Informed consent	1(20%)	6(60%)	0	7(44%)
4	Violations related to investigational product	2(40%)	0	0	2(13%)
5	Failure to personally supervise the study	0	0	0	0
6	Failure to protect subject safety/report adverse events to IRBs/communicate with the IRB	1(20%)	0	0	1(6%)
7	Submission of false information to the FDA and sponsor	0	0	0	0
8	Failure to communicate with the sponsor	0	0	0	0
9	Financial disclosure	0	0	0	0

2.7 Inspection Results

Overall, inspection results have improved since FY 2007 (Table 11). The percentage of NAIs went from 51% in FY 2007 to 71% in FY 2017, showing a gradual increase since FY 2010. The percentage of VAIs and OAIs have also been lower in recent years. There are more OAIs issued than warning letters, showing that not every OAI leads to a warning letter.

Table 11 Total Domestic BIMO Program Inspections with Classification

Classification	FY07	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	FY16	FY17	Total
NAI	460 (51%)	557 (49%)	627 (47%)	621 (45%)	577 (50%)	520 (53%)	606 (55%)	746 (56%)	876 (63%)	943 (67%)	937 (71%)	7470 (56%)
VAI	367 (41%)	476 (42%)	630 (47%)	663 (48%)	504 (44%)	423 (43%)	470 (42%)	499 (38%)	444 (32%)	423 (30%)	347 (26%)	5246 (39%)
OAI	70 (8%)	98 (9%)	81 (6%)	107 (7%)	63 (6%)	35 (4%)	33 (3%)	81 (6%)	68 (5%)	49 (3%)	34 (3%)	719 (5%)
Total	897	1131	1338	1391	1144	978	1109	1326	1388	1415	1318	13435
Warning letters	48	47	38	45	28	22	15	25	11	13	7	299

Inspection results broken down by category can be found in Tables 11-15. Clinical investigators received the most inspections, followed by bioequivalence studies, IRBs, sponsors/monitors/CROs, and GLP labs. Sponsors/monitors/CROs typically receive the highest

percentage of OAIs out of all of the categories followed by GLP labs. Although bioequivalence studies received 103 OAIs during this time period, no warning letters were issued in this category. Some years will have more warning letters issued than OAIs issued in a particular category, which is due to warning letters being issued based on inspections from previous years.

Table 12 IRB Inspections

Classification	FY07	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	FY16	FY17	Total
NAI	51% (93)	46% (87)	43% (77)	44% (114)	52% (93)	47% (73)	45% (77)	50% (76)	59% (81)	66% (82)	77% (95)	948 (51%)
VAI	47% (86)	47% (88)	50% (89)	50% (129)	44% (79)	46% (72)	49% (84)	45% (68)	37% (51)	27% (33)	21% (26)	805 (44%)
OAI	2% (4)	7% (13)	7% (13)	6% (15)	4% (7)	7% (11)	6% (10)	5% (8)	4% (6)	6% (7)	2% (3)	97 (5%)
Total	183	188	179	258	179	156	171	152	138	124	124	1850
Warning letters	6	8	7	14	8	8	5	4	1	4	0	65

Table 13 Sponsor/Monitor/CRO Inspections

Classification	FY07	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	FY16	FY17	Total
NAI	51% (36)	61% (55)	64% (74)	50% (62)	55% (70)	64% (51)	54% (53)	57% (79)	61% (72)	65% (73)	64% (67)	692 (59%)
VAI	24% (16)	20% (18)	28% (33)	38% (47)	36% (46)	31% (25)	44% (43)	35% (48)	31% (36)	26% (29)	30% (31)	372 (32%)
OAI	22% (15)	19% (17)	8% (9)	12% (15)	9% (11)	5% (4)	2% (2)	8% (11)	8% (9)	9% (10)	6% (6)	109 (9%)
Total	67	90	116	124	127	80	98	138	117	112	104	1173
Warning letters	13	10	2	7	6	5	1	7	4	3	4	62

Table 14 GLP Inspections

Classification	FY07	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	FY16	FY17	Total
NAI	42% (23)	51% (22)	49% (24)	43% (35)	46% (19)	30% (12)	63% (29)	40% (17)	36% (13)	43% (19)	65% (22)	235 (46%)
VAI	51% (28)	44% (19)	39% (19)	53% (43)	44% (18)	68% (27)	35% (16)	53% (23)	56% (20)	50% (22)	35% (12)	247 (48%)
OAI	7% (4)	4% (2)	12% (6)	4% (3)	10% (4)	2% (1)	2% (1)	7% (3)	8% (3)	7% (3)	0%	30 (6%)
Total	55	43	49	81	41	40	46	43	36	44	34	512
Warning letters	3	1	4	1	1	0	0	1	0	0	0	11

Table 15 Clinical Investigator Inspections

Classification	FY07	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	FY16	FY17	Total
NAI	52% (308)	50% (353)	48% (416)	46% (340)	53% (324)	56% (320)	56% (372)	58% (466)	64% (526)	66% (512)	73% (512)	4449 (57%)
VAI	40% (237)	41% (289)	46% (399)	45% (333)	41% (251)	41% (235)	42% (279)	37% (297)	33% (271)	32% (248)	26% (182)	3021 (38%)
OAI	8% (47)	9% (63)	6% (52)	9% (66)	6% (36)	3% (17)	2% (13)	5% (40)	3% (25)	2% (15)	1% (7)	381 (5%)
Total	592	705	867	739	611	572	664	803	822	775	701	7851
Warning letters	26	28	25	23	13	9	9	13	6	6	3	161

Table 16 Bioavailability/Bioequivalence Study Inspections

Classification	FY08	FY09	FY10	FY11	FY12	FY13	FY14	FY15	FY16	FY17	Total
NAI	38% (40)	28% (36)	37% (70)	38% (71)	49% (64)	58% (75)	57% (108)	67% (184)	71% (257)	68% (241)	1146 (56%)
VAI	59% (62)	71% (90)	59% (111)	59% (110)	49% (64)	37% (48)	33% (63)	24% (66)	25% (91)	27% (96)	800 (39%)
OAI	3% (3)	1% (1)	4% (8)	3% (5)	2% (2)	5% (7)	10% (19)	9% (25)	4% (14)	5% (18)	103 (5%)
Total	105	127	189	186	130	130	190	275	362	355	2049

2.8 Closeout Letter Results

Out of 169 BIMO warning letters issued after September 1, 2009, only 25 (15%) letters received closeout letters as of December 2018 (Table 17). This indicates that only 25 letters have been publicly confirmed to be completely resolved. Using Fischer's exact test, there was no statistically significant difference between the percentage of closeout letters issued for warning letters of each type. The average time to closeout was 518 days, ranging from 26 days to 1729 days.

Table 17 Closeout Letters and Warning Letters

	Clinical Investigator	IRB	Sponsor	Sponsor-Investigator	GLP	Total
Closeout Letters	11(13%)	5(11%)	6(22%)	1(10%)	2(50%)	25(15%)
Warning Letters (After September 1, 2009)	84	44	27	10	4	169

2.9 Discussion

Warning Letters issued by the FDA's BIMO Program provide insight into data integrity issues and other research misconduct in the premarket side of the pharmaceutical industry. This study presents data on the major compliance issues found during inspections of clinical investigators, IRBs, sponsors of clinical studies, and GLP laboratories. This data can provide an understanding of the impact the BIMO program has on ensuring integrity in clinical trials and can help those conducting clinical studies understand what the FDA looks for in inspections based on empirical evidence.

Violations cited in warning letters typically come straight from the BIMO program CPGMs.[13] The CPGMs go into detail on how the inspection process works and all of the criteria the inspected establishment is judged by. One way to prepare for an inspection would be to read through the respective CPGM and make a checklist of the items listed that the inspectors will check. Adhering to these criteria would help the establishment remain in compliance with all major regulations.

Looking at all of the warning letter datasets, documentation was a common issue among all of the categories. This resulted as the second-most cited violation for each category, counting IRB meeting minute documentation. Failure to follow and maintain procedures was another common violation for clinical investigators, IRBs, and GLP labs, being the most common violation for both IRBs and clinical investigators and second-most common for GLP labs. This violation was fairly common for sponsors in the context of failing to maintain and follow procedures for monitoring clinical studies and investigators.

While the number of warning letters issued in the past few years was much lower than the number issued in the latter half of the 2000s, there were still a number of OAIs issued. This

decrease in warning letters could be due to a number of reasons. It is possible that compliance has overall improved where fewer warning letters were needed, though this does not seem likely because the number of OAIs did not decrease nearly as much as the number of warning letters. It is also possible that recipients were better at responding to 483s issued to them and returning to a state of compliance before a warning letter was issued, though it would be impossible to know this without personally working for the FDA and having access to individual responses to 483s. Perhaps the BIMO program changed their practices for when to issue warning letters. A more likely scenario is that the recent restructuring efforts of the FDA's Office of Regulatory Affairs (ORA) and the BIMO program have led to these programs having less time and resources to issue warning letters.[26,27] Regardless, without insider information from the FDA, it would be hard to determine the exact cause of the decrease in warning letters.

2.9.1 IRB Issues in Warning Letters

IRBs play a significant role in reviewing research involving human subjects for their protection of human rights and risks/benefits to the subjects. It is important for IRBs to review research properly and comply with applicable regulations. Failure to follow these regulations can lead to inadequately reviewed research that can potentially harm patients.

Violations related to following and maintaining procedures were the most common, appearing in 77% of warning letters. These violations were sometimes linked with other violations, as violating another regulation such as requirements for research review may also involve failing to follow written procedures that would have prevented the violation. Written procedures are important for ensuring that IRB responsibilities are carried out in a systematic and

thorough manner. Failing to follow and establish necessary procedures can lead to missing important parts of the research review process.

The significant number of IRB violations relating to meeting attendance emphasizes the importance of regularly reviewing and revising the membership of the IRB. According to 21 CFR 56.107, IRBs must have at least 5 members of varying backgrounds and at least 1 member must have primary concerns in "nonscientific areas" (i.e. lawyers, clergy, community representatives, etc.). The regulations also state in 21 CFR 56.108(c) that a majority of IRB members must be present at meetings and at least 1 nonscientific member must be present. Meeting attendance issues are troubling because IRBs are intended to be a third-party entity of people from different professional backgrounds that can provide different perspectives when reviewing research. Given the FDA's emphasis on meeting attendance, it seems that it would be better to restrict IRB membership to fewer people who more actively participate in IRB activities and have the time to regularly attend meetings. It is important that this regulation is followed in order to ensure that IRBs approve research based on review from a diverse group of individuals.

Meeting minutes and documentation were other common IRB issues found that are important to address. It is important that IRB activities are documented in order to provide a record that IRBs are adequately serving their purpose. 21 CFR 56.115(a)(2) sets forth the requirement for IRBs to keep track of all meeting minutes, which is important for showing that research proposals and issues were adequately discussed by the IRB. It is also important that how the members of the IRB vote is well documented in order to show that research approval procedures were followed appropriately and members with conflicting interests did not vote. Good record-keeping is important in cases where clinical research is conducted and found to cause significant harm to humans, where the IRB would be bound to come under scrutiny.

There were no statistically significant differences in violations cited between warning letters issued to IRBs by different centers. This suggests that IRBs violate regulations at a similar rate for drug, medical device, and biologic studies.

2.9.2 Sponsor Issues in Warning Letters

Sponsors are responsible for overseeing clinical trials and making sure they are in compliance with all applicable regulations. It is important that they are aware of all of the regulations that they need to follow to ensure the integrity of the trials and to protect the rights and safety of the patients.

The most commonly cited violation in sponsor warning letters (monitoring deficiencies) was only cited in 56% of warning letters, while other categories have violations that are cited in more than 75% of warning letters. This is interesting because the sponsor violations were less concentrated in the major violation areas than the other categories. Documentation violations were only cited in 50% of sponsor warning letters, while this violation had much higher representation in the other categories.

Failure to obtain IRB or FDA approval was a violation that appeared in 50% of sponsor warning letters. This is alarming because it shows that quite a few clinical studies were initiated without proper review of the risks to patients.

A violation unique to medical devices was experimental labeling of investigational products. It is important that the requirements of 21 CFR 812.5(a) for experimental labeling are met so that patients and device investigators know that the device products are only experimental and have not been approved as safe and effective. This labeling should not include claims that have not been proven and should include all necessary cautionary statements. Another unique

violation for medical device sponsors was the promotional advertisement of investigational devices as safe and effective, which violates 21 CFR 812.7. The fact that these issues only show up in medical device warning letters suggests that sponsors of investigational device studies are more likely to be unaware of these important regulations.

Adverse event reporting and investigation was another issue that did not show up in CDER warning letters but appeared in CDRH warning letters and a CBER letter. This is a significant issue because of how adverse events play into the overall safety and risk of a product. All serious adverse events should be adequately investigated for their relationship to the product. One letter even cited deaths that occurred during a study that were not adequately investigated for their relationship to the investigational device.[28] Serious adverse events like this also play a role in determining if a trial needs to be ended early to reduce risks for other patients enrolled in the trial, which emphasizes the need for investigating these events as soon as possible.

The three statistically significant differences in sponsor violations were in record keeping, submission of regular reports, and other violations. Medical device sponsors received record keeping violations at a significantly higher rate than drug and biologic sponsors. Medical device and biologic sponsors violated report submission requirements at a significantly higher rate than drug sponsors. It should be noted that no drug sponsors violated report submission requirements out of the 20 warning letters issued. This could be an indication that medical device and biologic sponsors are less likely to be aware of the reporting requirements of clinical studies.

2.9.3 GLP Issues in Warning Letters

Nonclinical studies have historically received scrutiny for poor methodology and data integrity practices.[29] The GLP regulations in 21 CFR 58 are in place to ensure that nonclinical

studies, especially those involving animal subjects, are conducted with a high degree of integrity by establishing requirements such as data audit trails and quality assurance procedures. The results of these studies are used to determine if an experimental product is safe and effective enough to test in human subjects, which highlights the importance that these studies are conducted appropriately.

Warning letters issued to GLP labs, on average, cited more violations than warning letters issued in the other categories. It is not entirely clear if this is due to GLP labs having more compliance issues overall or if there are higher violation thresholds for issuing warning letters to GLP labs.

Nearly every warning letter issued to a GLP lab cited problems with the quality assurance unit. The quality assurance unit in a GLP study is responsible for auditing the lab and assuring the integrity of the study. This is one of the major requirements of GLP regulation that separates exploratory animal studies from FDA regulated studies intended to support the application for the use of a drug product in humans. In some cases, no quality assurance unit had been established at all.

Violations relating to the recording and storage of data were cited in 75% of GLP warning letters. This is a violation directly related to data integrity. There were instances of original data records not being signed and dated, data not being verified by the study director, and changes in data records without a documented reason. Although some of these violations are more serious than others, they all represent violations of good data practices that need to be addressed.

Calibration of equipment is an issue only relevant to GLP labs that was quite common. It is important that equipment used in GLP studies is properly maintained so that the data generated is accurate and reliable.

2.9.4 Clinical Investigator Issues in Warning Letters

Clinical investigators are responsible for doing the groundwork of a clinical trial so that data can be collected on the safety and efficacy of a product in human patients. Because of the direct relationship between the clinician and the patient, the investigator plays the most important role in ensuring the safety and wellbeing of patients.

The warning letters issued to clinical investigators in the past two years only covered violations within 3 of the 9 violation themes. It is difficult to determine whether or not this is an indication that the other violations are no longer an issue because of the low sample size of warning letters issued in this time period.

By far the most common violation cited for clinical investigators involved failing to follow the study protocol. The fact that this violation is found in almost every clinical investigator warning letter may indicate that it is one of the primary requirements for receiving a warning letter. Adhering to study protocols is important for ensuring the validity of the data gained from the study, as deviations from the protocol may have an effect on the outcome of the product use. This violation theme also included admitting patients who met exclusion criteria or did not meet inclusion criteria. This poses a potential safety risk to patients, as inclusion and exclusion criteria are designed to ensure only the appropriate patients are enrolled in a study.

Maintaining adequate source documentation was a significant violation that points to clear data integrity issues within clinical trials. These violations were not limited to losing data

files or not holding on to data for the proper retention period. These violations often involved not gathering all the data required by a study protocol or having issues with the documentation of the data such as changing numbers without explanation. A key emphasis was on maintaining the raw data files even after the data had been recorded in the patient's electronic case report form (eCRF). This serves as a true record that proves the tests were done and the results were recorded properly.

Only two violation themes showed statistically significant differences in occurrence rate between warning letters issued by different centers. Informed consent violations occurred significantly more often in medical device and biologic clinical studies than in drug studies. This violation theme did not meet the threshold for a statistically significant difference in Garmendia et al.'s dataset.[21] Failure to personally supervise the study, on the other hand, showed a statistically significant difference in both the previous study and this study, with this violation being more common for drug investigators.

2.9.5 Bioavailability/Bioequivalence Studies

Inspections of BA/BE studies make up a large percentage of the total BIMO program inspections. Bioequivalence studies received more total OAIs than IRBs, sponsors, and GLP labs during FY 2008-2017, but no warning letters were issued based on inspections of these studies. This raises the question of what regulatory actions are taken for out-of-compliance bioequivalence studies. The CPGMs related to BA/BE studies make no mention of warning letters as a potential follow-up to an OAI inspection, unlike the other BIMO program CPGMs.[30,31] These CPGMs do mention that an untitled letter, a letter that is less severe than a warning letter and places no legal obligation on the recipient,[32] may be issued as a follow up to

an NAI or VAI inspection. The BA/BE CPGMs only mention that what comes after an OAI result is up to the Office of Scientific Investigations (OSI) to decide.

Even though we do not have warning letters to show the major violations found in inspections of BA/BE studies, the BIMO program yearly inspections metrics reports list the most common violations found each year for these studies.[23] The past 5 yearly reports have all listed recordkeeping, inclusion/exclusion criteria issues, informed consent issues, dosage issues, and analytical concerns relating to validation and stability as common BA/BE study deficiencies. This shares some similarity with typical clinical studies, as clinical investigator warning letters commonly cite violations relating to recordkeeping, inclusion/exclusion criteria issues, and informed consent issues. The analytical concerns relating to validation of methods are concerning because of how important it is that validated analytical methods are used ensure the reliability of data obtained from clinical samples.

2.9.6 Closeout Letters

The FDA issued a closeout letter for only 15% of the BIMO program warning letters eligible for receiving a closeout letter. It is unclear whether this is a good measure of compliance. Closeout letters are the only publicly-available confirmation that the violations found within a warning letter have been corrected. However, the FDA can typically only confirm that the appropriate corrective actions have been taken through reinspection, which costs the FDA time and resources and requires continued communication between the recipient and the FDA. Because of this, it seems likely that the low number of closeout letters issued does not accurately reflect the number of warning letter violations that have been corrected. The alternative explanation to this would be that 85% of all BIMO program warning letters issued are not

addressed adequately and the recipients remain out of compliance, which would pose a serious risk to public health and bring into question if warning letters are a useful tool for improving compliance.

Closeout letters do not go into specific detail on what corrective actions were taken to fix the violations stated in a warning letter. This is problematic because it does not help other warning letter recipients know how to respond to a warning letter properly and effectively fix compliance issues. Closeout letters, as they are now, only show that warning letter violations have been corrected and offer little else of value.

Analyzing a list of all FDA warning letters issued between January 1, 2013, and August 15, 2018, generated from the FDA website, 1131 (32%) of 3491 warning letters received closeout letters. This suggests that even the post-market side of the pharmaceutical industry receives a fairly low number of closeout letters.

2.9.7 Comparison to Previous Studies

Comparing the violations cited in more recent warning letters to older warning letters can potentially determine if there have been any notable changes in compliance or what the FDA inspectors focus on during inspections. While many of the previous studies covered warning letters within a time period encompassed by the current study, some studies were able to look at warning letters from earlier time periods.

Bramstedt and Kassimatis (2004) analyzed 52 IRB warning letters between 1997 and 2004.[16] This study found the most common violations to be related to following and maintaining procedures (96%), documentation of IRB activities (including meeting minutes, membership lists, and protocols and consent forms) (90%), and providing adequate continuing review of

approved studies (69%). Comparing these numbers to the current study, there were much higher percentages of violations relating to procedures and documentation, though these are still the top two violations in more recent warning letters. Failing to provide adequate continuing review of approved studies seems to be a violation that has decreased in recent years, as this was not even a top issue found in the current study.

Knowlton and Wan (2011) analyzed 273 warning letters issued to clinical investigators between 1996 and 2011.[18] Instead of using violation themes to group individual violations together, this study recorded the frequency of violations relating to individual regulations within the CFRs. The most common violations cited in this study involved not following the investigational plan (21 CFR 312.60, 812.100) and record keeping (21 CFR 312.62, 812.140). These are the same as the most common violations found in the current study.

2.10 Conclusion

The findings of this study suggest that there are significant data integrity and other regulatory compliance issues in all aspects of the premarket side of the pharmaceutical industry. Inspections conducted by the BIMO program show that many clinical investigators, IRBs, sponsors, and GLP laboratories have issues with documentation and following defined procedures. However, inspection results have seen overall improvement during the past 12 years, potentially indicating improvement in compliance. While this study assessed some of the activity of the BIMO program, more work is required to understand the overall impact of this program for improving compliance in the industry.

CHAPTER 3

FUTURE WORK

The results of this study bring up questions about the overall impact of the BIMO program in ensuring compliance in the pharmaceutical industry. While this study analyzed warning letters and what common violations can be found in them, this study did not address what effects these warning letters can have on the success of products studied or how warning letters can affect compliance in the industry.

Warning letter and inspection analyses like this study can be conducted regularly to see how regulatory compliance is changing over time. While it is unlikely for there to be significant differences in compliance issues from year to year, analyzing multiple years at a time can show potential trends in inspection results and warning letters issued. Seeing that very few warning letters were issued in the last couple of years compared to 10 years ago, it will be interesting to see how many BIMO program letters will be issued in the following years. It is possible that the BIMO program is deciding to move away from issuing as many warning letters as they have in the past, or perhaps warning letters will be on the rise after FDA realignment has been completely finished.

3.1 Warning Letters and Effect on Product Lifecycle

An analysis of how warning letters related to premarket studies of drug and device products potentially affect the lifecycle of the product would help us understand how premarket compliance translates to the final marketed product. If significant data integrity violations are

found in the clinical studies of a product, the studies may not accurately predict the safety and efficacy of the product in the real world. It would also be interesting to determine if there is a correlation between warning letters issued for a product while it is in the premarket stage and warning letters issued related to the product when it is on the market. The challenge of this, though, is that the FDA typically redacts information related to specific clinical studies and products used in them, making it hard to determine which warning letters may pertain to a specific product.

It would also be interesting to see how often a specific product receives multiple warning letters in the premarket phase. There are several examples of related organizations receiving warning letters from the BIMO program. One particular instance of this involved the infamous cancer researcher Stanislaw Burzynski. Burzynski himself and the Burzynski Research Institute both received warning letters on December 3, 2013, related to the use of potential brain cancer therapeutics.[33,34] The Burzynski Research Institute IRB also received a warning letter on October 5, 2009, though information related to specific clinical studies has been redacted from this letter.[35]

3.2 Foreign BIMO Program Inspections

The BIMO program also conducts foreign inspections of studies conducted to meet U.S. regulatory requirements. The results of these inspections are released in their yearly metrics reports along with domestic inspections.[23] Analyzing these foreign and domestic inspection metrics side-by-side would show how compliance with FDA regulations is different between studies conducted within the U.S. and studies conducted outside of the U.S. It would also be

interesting to see how BIMO program foreign inspection results compare to other foreign FDA inspection programs.

3.3 BIMO Program 483s

Garmendia et al. conducted an analysis of Form FDA 483s issued by the BIMO program from FY 2006-2015.[22] A direct comparison of 483s and warning letters could show what violations cited in 483s typically lead to warning letters. It would also be important to see how often 483s lead to warning letters and what this means as far as how effective 483s are at ensuring future compliance.

3.4 Warning Letters and Further Enforcement Action

Warning letters themselves do not carry too much legal significance. Typically, warning letters only require the recipient to respond within 15 working days with what corrective and preventive actions will be taken to fix violations cited and ensure they do not happen again in the future. Because of this, warning letters can usually be taken care of quickly and help a firm reach a better state of compliance. However, if a warning letter is not handled properly, the recipient may be subject to further legal action initiated by the FDA, such as injunction. An analysis of further regulatory action taken as the result of warning letters issued by the BIMO program can help show how often the FDA takes further action on these warning letters. This would possibly be a better measure of how well warning letters are responded to than closeout letters, although the lack of further regulatory action may not necessarily mean that the violations within a warning letter have been corrected.

REFERENCES

1. U.S. Food and Drug Administration. Data Integrity and Compliance with Drug CGMP Questions and Answers Guidance for Industry. https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf Updated December 2018. Accessed January 23, 2019.
2. Medicines and Healthcare Products Regulatory Agency. 'GXP' Data Integrity Guidance and Definitions. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf Updated March 2018. Accessed February 16, 2019.
3. European Medicines Agency. Guidance on good manufacturing practice and good distribution practice: Questions and answers. https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/guidance-good-manufacturing-practice-good-distribution-practice-questions-answers#section16 Updated July 2018. Accessed February 16, 2019.
4. U.S. Food and Drug Administration. What does FDA inspect? https://www.fda.gov/aboutfda/transparency/basics/ucm194888.htm Updated August 22, 2018. Accessed March 13, 2019.
5. U.S. Food and Drug Administration. HCT/P Inspection Information. https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformati

on/ComplianceActivities/ucm136342.htm Updated April 26, 2018. Accessed March 13, 2019.

6. U.S. Food and Drug Administration. FDA Form 483 Frequently Asked Questions. https://www.fda.gov/iceci/inspections/ucm256377.htm Updated July 24, 2017. Accessed March 13, 2019.
7. U.S. Food and Drug Administration. Inspection Citation. https://www.fda.gov/iceci/inspections/ucm346077.htm Updated March 7, 2019. Accessed March 13, 2019.
8. U.S. Food and Drug Administration. Compliance Programs. https://www.fda.gov/ICECI/ComplianceManuals/CompliancePrograMManual/ucm2005382.htm Updated December 19, 2018. Accessed March 13, 2019.
9. U.S. Food and Drug Administration. About Warning and Close-Out Letters. https://www.fda.gov/iceci/enforcementactions/warningletters/ucm278624.htm Updated January 29, 2018. Accessed January 23, 2019.
10. U.S. Food and Drug Administration. Warning Letters. https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm Updated December 27, 2018. Accessed January 23, 2019.
11. U.S. Food and Drug Administration. Data Dashboard: Compliance Actions. https://datadashboard.fda.gov/ora/cd/complianceactions.htm Accessed February 25, 2019.
12. U.S. Food and Drug Administration. Bioresearch Monitoring. https://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/bioresearchmonitoring/default.htm Updated September 25, 2018. Accessed January 23, 2019.

13. U.S. Food and Drug Administration. Bioresearch Monitoring Program (BIMO). https://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/ucm160670.htm Updated September 21, 2018. Accessed February 25, 2019.
14. U.S. Food and Drug Administration. Clinical Investigators - Disqualification Proceedings. https://www.fda.gov/ICECI/EnforcementActions/ucm321308.htm Updated March 31, 2016. Accessed February 26, 2019.
15. Bramstedt KA. A study of warning letters issued to clinical investigators by the United States Food and Drug Administration. *Clinical And Investigative Medicine*. 2004;27(3):129-134.
16. Bramstedt KA, Kassimatis K. A study of warning letters issued to institutional review boards by the United States Food and Drug Administration. *Clinical And Investigative Medicine*. 2004;27(6):316-323.
17. Gogtay NJ, Doshi BM, Kannan S, Thatte U. A study of warning letters issued to clinical investigators and institutional review boards by the United States Food and Drug Administration. *Indian Journal Of Medical Ethics*. 2011;8(4):211-214.
18. Knowlton JA, Wan JY. An Analysis of United States Food and Drug Administration Warning Letters Issued to Clinical Investigators from 1996 through 2011. *Journal of Clinic Research and Bioethics*. 2011;8(2). DOI: 10.4172/2155-9627.1000122
19. O'Reilly EK, Blair Holbein ME, Berglund JP, Parrish AB, Roth M-T, Burnett BK. Warning letters to sponsor-investigators at academic health centres - the regulatory "canaries in a coal mine." *Clinical And Investigative Medicine*. 2013;36(6):E290-E296.
20. Saiyed AA, Shetty YC. Analysis of Warning Letters Issued by the US Food and Drug Administration to Clinical Investigators, Institutional Review Boards and Sponsors: A

Retrospective Study. *Journal of Medical Ethics*. 2015;41(5):398-403. doi:10.1136/medethics-2013-101829.

21. Garmendia CA, Bhansali N, Madhivanan P. Research Misconduct in FDA-Regulated Clinical Trials: A Cross-sectional Analysis of Warning Letters and Disqualification Proceedings. *Therapeutic Innovation & Regulatory Science.* 52(5):592-605. doi:10.1177/2168479017749514.
22. Garmendia CA, Epnere K, Bhansali N. Research Deviations in FDA-Regulated Clinical Trials: A Cross-Sectional Analysis of FDA Inspection Citations. *Therapeutic Innovation & Regulatory Science*. 52(5):579-591. doi:10.1177/2168479017751405.
23. U.S. Food and Drug Administration. BIMO Inspection Metrics. https://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/ucm261409.htm Updated May 1, 2018. Accessed March 1, 2019.
24. U.S. Food and Drug Administration. Warning Letter Addressed to Daniel Potter. http://www.circare.org/fdawls3/potter_fdawl_20091102.pdf November 2, 2009. Accessed March 9, 2019.
25. U.S. Food and Drug Administration. Warning Letter Addressed to Daniel Potter. http://wayback.archive-it.org/7993/20170112063022/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm204453.htm March 8, 2010. Accessed March 10, 2019.
26. U.S. Food and Drug Administration. FDA Program Alignment Bioresearch Monitoring Program FY2016 Action Plan. https://www.fda.gov/AboutFDA/CentersOffices/ucm477078.htm Updated March 28, 2018. Accessed March 14, 2019.

27. U.S. Food and Drug Administration. Program Alignment and ORA. https://www.fda.gov/aboutfda/centersoffices/officeofglobalregulatoryoperationsandpolicy/ora/ucm549087.htm Updated August 31, 2017. Accessed March 14, 2019.
28. U.S. Food and Drug Administration. Warning Letter Addressed to Boston Scientific Cardiovascular. http://wayback.archive-it.org/7993/20170112201031/http:/www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076492.htm August 30, 2007. Accessed March 17, 2019.
29. Carroll EE. Going GLP: Conducting Toxicology Studies in Compliance with Good Laboratory Practices. *US Army Medical Department Journal*. October 2016:64-69.
30. U.S. Food and Drug Administration. Procedures for FDA Staff: In Vivo Bioavailability/Bioequivalence Studies (Clinical). https://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/UCM605601.pdf Updated May 1, 2018. Accessed March 18, 2019.
31. U.S. Food and Drug Administration. Procedures for FDA Staff: In Vivo Bioavailability/Bioequivalence Studies (Analytical). https://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/UCM605600.pdf Updated May 1, 2018. Accessed March 18, 2019.
32. U.S Food and Drug Administration. Issuance of Untitled Letters. https://www.fda.gov/iceci/enforcementactions/ucm511995.htm Updated November 28, 2017. Accessed March 18, 2019.
33. U.S. Food and Drug Administration. Warning Letter Addressed to Stanislaw R Burzynski, M.D.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm378237.htm December 3, 2013. Accessed March 19, 2019.

34. U.S. Food and Drug Administration. Warning Letter Addressed to the Burzynski Research Institute. https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm378233.htm December 3, 2013. Accessed March 19, 2019.
35. U.S. Food and Drug Administration. Warning Letter Addressed to the Burzynski Research Institute IRB. https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm378233.htm October 5, 2009. Accessed March 19, 2019.