NOTIFICATION OF INTERESTED PARTIES WHEN A BIORESEARCH MONITORING INSPECTION IS CLASSIFIED AS OFFICIAL ACTION INDICATED DUE TO POTENTIAL REJECTION OF DATA

I. PURPOSE

This document describes the procedure under which the Center for Veterinary Medicine (CVM) Office of Surveillance and Compliance (OSC) will classify certain bioresearch monitoring (BIMO) inspections as Official Action Indicated (OAI) and the manner in which it will notify certain interested parties.

II. BACKGROUND

A. Legal Authority

FDA has the responsibility and administrative authority to make decisions on a variety of applications and other submissions that are supported with bioresearch data.[1] FDA has commensurate inspectional authority to "ensure the accuracy and reliability of studies and records or other information [and] to assess compliance with applicable requirements."[2] The "facilities, equipment, written procedures, processes, and conditions [under which bioresearch information is] generated, held, processed, analyzed, or transferred"[3] can bear directly on FDA's decisions. Although FDA has defined specific regulatory requirements for certain aspects of the bioresearch process for FDA-regulated products for use in animals,[4] there are a variety of areas

[1] Examples of bioresearch data submitted to CVM may include data submitted in support of new animal drug applications (NADAs), abbreviated new animal drug applications (ANADAs), requests for designation of a new animal drug for a minor use or a minor species (i.e., requests for Indexing), and Food Additive Petitions for animal food.

[2] See Food Drug and Cosmetic Act (FD&C Act), Section 704(a)(5), 21 U.S.C. § 374(a)(5).

[3] See Food Drug and Cosmetic Act, Section 704(a)(5)(D)(III), 21 U.S.C. § 374(a)(5)(D)(III).

[4] See, e.g., FDA's Good Laboratory Practice for Non-Clinical Studies regulation, 21 CFR Part 58, which sets forth detailed requirements for certain safety studies and the New Animal Drugs for Investigational Use regulation, 21 CFR Part 511, which sets forth a variety of requirements, such as those related to the labeling of investigational drugs, recordkeeping for drug shipments, and monitoring of studies by sponsors.

not covered by a regulation. For example, there are no regulations which specifically govern the conduct of clinical investigators (CIs) when performing studies generating bioresearch study data that is intended to demonstrate the effectiveness of animal drugs in support of new animal drug applications (NADAs) or abbreviated new animal drug applications. Similarly, there are no regulations governing the manner in which bioresearch data is transferred from CIs to sponsors, and how that data is held, analyzed, and processed into a submission to FDA. The conditions or practices of any firm involved in bioresearch can affect the validity or integrity of data submitted to FDA, and thus, affect FDA's administrative decisions.[5]

In areas where no affirmative regulatory requirement exists, certain conditions or practices adversely impacting the validity or integrity of bioresearch data do not themselves always constitute a violation of the law, and therefore do not necessarily warrant an advisory action.[6] However, FDA has the authority to take a variety of adverse administrative actions in these cases, all of which can have a significant negative impact on those conducting bioresearch or using it as part of a submission to FDA. Adverse administrative actions that can be taken by FDA due to BIMO inspection findings include:

1. data rejection[7] as part of FDA review of pending applications;
2. initiation of disqualification proceedings against clinical investigators;[8]
3. termination of the sponsor's investigational exemption;[9] and
4. actions under the Application Integrity Policy (AIP).[10]

B. Classification of Inspections

Inspections are ordinarily classified as No Action Indicated (NAI), Voluntary Action Indicated (VAI), or Official Action Indicated (OAI). Classification is an internal FDA procedure which allows the agency to categorize inspectional findings for use in a variety of regulatory functions. An OAI classification generally indicates that objectionable conditions were found, and regulatory (advisory, administrative, or judicial) action is recommended.[11] Data rejection, disqualification of a clinical

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[5] See the OSC overarching standard operating procedure on case review. 1244.000.006 Regulatory Case Review and Clearance Process

[6] FDA issues advisory actions (Warning Letters and Untitled Letters) only to address violations of the law. (See Regulatory Procedures Manual, 4-1-1 and 4-2-1). For conduct subject to the FD&C Act, violations generally refers to conduct that can result in the commission of a Prohibited Act and/or for which the Act or FDA's regulations impose a penalty. (See FD&C Act, Section 301, Prohibited Acts.) By contrast, an animal drug clinical investigator conducting an efficacy study (which is not subject to a specific regulation governing the matter in which research must be conducted) who unknowingly and accidentally (e.g., solely due to poor research / data handling practices) submits false data to a sponsor does not commit a violation of the act. Nevertheless, this could result in data rejection and, if repeated, could result in disqualification.

[7] For the purposes of this procedure, data rejection means discounting or otherwise declining to consider data, ranging in scope from individual datapoints to one or more studies.

[8] 21 C.F.R. § 511.1(c).

[9] 21 C.F.R. § 511.1(d).

[10] FDA Compliance Policy Guide, Sec. 120.100, Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities.

[11] See FDA's webpage Inspection Classifications for general information. CVM has final classification authority for CVM BIMO inspections.

investigator, termination of a sponsor's investigational exemption, and proceeding under the API are all administrative actions that may warrant an OAI classification.

FDA posts most inspection classifications online, and, in most cases where an inspection is classified OAI, FDA posts a corresponding written document detailing the Agency's concerns.[12]

C. Relationship of Inspectional Classification with Application-related Decisions

OSC's classification of a BIMO inspection may be considered as part of the decision by the Office of New Animal Product Evaluation (ONAPE) or the Office of Generic Animal Drugs (OGAD) to accept or reject data, or to approve an application. OSC makes classification decisions in a consistent manner across all BIMO inspections, including Good Laboratory Practice inspections, where FDA's policy is that noncompliance with the applicable regulation is not determinative of data rejection.[13] There are a variety of ways in which inspectional classification differs from approval-related decision-making.

FDA may reject data and/or be unable to approve an application without classifying the underlying inspections OAI, for example:

1. OSC will not classify an inspection as OAI if FDA did not gather sufficient evidence to affirmatively establish the existence of objectionable conditions or practices and determine the inspected firm is responsible. Applicants bear the burden of proving their drugs are effective by substantial evidence consisting of one or more adequate and well-controlled studies.[14] Similarly, FDA may not approve a drug application if there is insufficient information to establish safety.[15] Therefore, an inspection may not warrant an OAI classification, but the data may be inadequate to support a specific approval decision because the applicant did not meet their burden.

2. Inspections are classified based solely on the objectionable conditions or practices of the inspected firm, whereas data rejection can be based, in whole or in part, on scientific concerns. For example, an inspection may reveal that some study subjects contracted an illness during the study. The inspection's classification will consider factors such as whether the adverse events were documented and reported, and whether the protocol was followed, whereas the decision to accept or reject data will consider additional factors, such as the nature of the illness and its effects on the data.

[12] See, e.g., FDA's Data Dashboard - Inspections (inspectional classifications), FDA's Warning Letter database (written OAI advisory actions), and FDA's "Clinical Investigators – Disqualification Proceedings database (including written Notice of Initiation of Disqualification Proceeding And Opportunity to Explain).

[13] 43 Fed. Reg. 59986, 59989 (Dec. 22, 1978) (The preamble to the final GLP regulation states that "the agency may evaluate the effects of the noncompliance and take one of the following actions: (1) Determine that the noncompliance did not affect the validity of the study and accept it, or (2) determine that the noncompliance may have affected the validity of the study and require that the study be validated by the person submitting it, or (3) reject the study completely. The standard of review applied to studies that contain data adverse to a product is no different. That is, a study that failed to comply with these regulations might, nonetheless, contain valid and significant data demonstrating a safety hazard.")

[14] See, e.g., Food Drug and Cosmetic Act, sections 512(d)(1)(E), 512(d)(3) and 21 CFR § 514.4(a).

[15] See, e.g., Food Drug and Cosmetic Act, section 512(d)(1)(D).

3. FDA may collect information that bears on approval decision-making from multiple sources (e.g., multiple inspections, direct communications between the sponsor and reviewers, etc.) but classifies inspections individually. Thus, an individual inspection may not warrant an OAI classification, but the totality of the information before CVM may indicate that the data is unacceptable. This may include, for example, the cumulative effect on the reliability of the same data due to the conduct of separate entities (e.g., the cumulative effect on the reliability of data due to practices at contract laboratories, study sites, contract research organizations, and sponsor), or the cumulative effect of inspectional findings and (non-inspectional) scientific concerns about the study.

4. OSC's classification of an inspection is an overall assessment of the firm being inspected, whereas data rejection is necessarily a study and/or application-specific decision. An isolated error may permanently affect a specific study or datapoint, but the inspected firm may be in an overall satisfactory state of compliance (e.g., the inspection revealed numerous other studies that were performed correctly, and the firm detected the isolated error and prevented it from reoccurring.)

5. OSC considers a firm's post-inspectional commitments and corrective actions when assigning a classification, but data collected before the corrective actions may still be unacceptable to support an application's approval (i.e., rejected). Even if data is rejected, OSC may still assign a VAI classification based on a firm's post inspectional corrective actions and commitments.

However, when significant objectionable conditions are observed and there is a potential causal relationship with data rejection, this can be a major factor in classification. Inspectional classification considers, among other things, the regulatory significance of the inspectional finding. As the purpose of research is to gather valid data with sufficient integrity that it can be used to support a regulatory decision, objectionable conduct that undermines that goal is inherently significant. This is particularly true when research is conducted under an investigational exemption and the use of the product would otherwise be unlawful. Thus, conduct which may cause FDA to take an adverse administrative action (e.g., data rejection) can support an OAI classification.

III. SCOPE

A. OAI Classifications Included in this Procedure

This procedure describes the circumstances where CVM will classify individual BIMO inspections as OAI due to significant concerns which may result in future adverse administrative action by FDA, including those that may result in rejection of data; those which do not immediately warrant disqualification proceedings, but if repeated, could lead to disqualification proceedings; those which do not immediately warrant termination of the sponsor's investigational exemption, but if repeated, could lead to termination; and those which do not immediately warrant consideration under the

Application Integrity Policy (AIP), but if repeated, could lead to consideration under the AIP.[16]

B. OAI Classifications Excluded from this Procedure

This procedure does not cover OAI classification of inspections where the classification is due to violations of the FD&C Act or FDA's regulations, including the GLP regulations (21 CFR Part 58) and the regulations governing New Animal Drugs for Investigational Use (21 CFR Part 511). These inspections and associated regulatory actions (e.g., Warning Letters, termination of investigational use exemption, etc.) will continue to be classified and processed according to other procedures. FDA may incorporate language from this procedure into those actions, if appropriate.[17]

This procedure does not cover situations where FDA classifies a BIMO inspection as OAI due to suspected criminal conduct (Office of Criminal Investigations (OCI) referral), initiation of disqualification proceeding, initiation of proceedings to terminate an investigational exemption, or invocation of the AIP.

Neither this procedure nor an inspection's classification governs FDA's determination whether studies/data will be accepted or rejected, or whether an application will be approved.[18]

IV. OAI CLASSIFICATION AND WRITTEN CORRESPONDENCE

A. OAI Classification

CVM OSC may classify an inspection as OAI when the inspected firm bears responsibility for:

1. conditions or practices that directly impacts the validity or integrity of study data, and which may result in significant portions of study data being rejected (if submitted to FDA);[19]

[16] Both clinical investigator disqualification and AIP have provisions that bring unknowing/unintentional conduct into their scope if it is repeated. Clinical investigators can be disqualified for unintentionally but repeatedly submitting false data. See 21 C.F.R. § 511.1(c)(1). Similarly, FDA's AIP procedure defines a "wrongful act" to include "submitting data that are otherwise unreliable due to, for example, a pattern of errors whether caused by incompetence, negligence, or a practice such as inadequate standard operating procedures or a system-wide failure to ensure the integrity of data submissions." AIP is generally invoked when there is "pattern or practice of wrongful conduct". See also 56 Fed. Reg. 46191, 46194 (September 10, 1991) ("Decisions to conduct validity assessments and defer substantive data review need not be based on a finding of intentional misconduct. Data may be unreliable due to sloppiness and inadvertent errors. A pattern of errors by an applicant involving material subject matter may raise a significant question regarding the general reliability of data in applications from that applicant.")

[17] Where there is an established office (e.g., OSC letterhead) or division template for any documents we are preparing, templates should be used to create these documents. Internal information redacted.

[18] See, e.g., CVM Policies and Procedures Manual 1240.3101 - Review of Animal Safety and Effectiveness Data which directs a case-by-case review of the pertinent facts. See also discussion above regarding noncompliance not being determinative of data rejection.

[19] For example, labeling, dispensing, or storing the investigational product in a manner that may have resulted in a mix-up or improper dosing directly impacts the validity of any associated data. The existence of multiple sets of study records with conflicting information which directly impacts the integrity of the study data.

2. conditions or practices that do not immediately warrant disqualification proceedings, but if repeated, could result in disqualification proceedings;[20]

3. conditions or practices that do not immediately warrant termination of the sponsor's investigational exemption, but if repeated, could result in termination;[21] or

4. conditions or practices that do not immediately warrant consideration under the AIP, but if repeated, could result in invocation of AIP;[22]

unless the inspected firm has taken adequate corrective action.

Data rejection by ONAPE/OGAD solely due to scientific reasons/deficiencies will not result in an OAI classification by OSC. Purely scientific deficiencies (e.g., inadequate study design) are intentional scientific choices made by entities in the bioresearch process which are also immediately apparent (i.e., explicitly stated in the study plan/protocol, clearly disclosed to FDA as part of a submission, etc.). ONAPE and OGAD are responsible for addressing scientific deficiencies solely through the application review and decision-making process.

OSC will not classify an inspection as OAI based on an inspected firm's decision not to adopt FDA's recommendations set forth in a guidance document.[23]

OSC will not classify an inspection as OAI if the inspection reveals significant issues, but the inspected firm was not responsible.[24]

B. Written Correspondence

OSC will draft written correspondence about OAI inspections and notify the inspected firm. OSC will draft the written correspondence such that it:

1. transparently describes agency processes and conclusions;

2. provides an additional opportunity for the inspected firm to prevent future adverse findings that may result in administrative action;

3. provides the inspected firm the opportunity to respond directly to FDA's assessment, including the opportunity to provide other contrary evidence or justifications;

4. provides awareness for regulated industry regarding the types of inspectional findings FDA considers to be of regulatory significance with sufficient detail so as to enhance industry's ability to prevent those from occurring in the future;

5. gives sponsors–including those who may have studies occurring at the inspected firm, but which were not reviewed during the inspection–awareness of ongoing or recent issues at contract research sites (e.g., with contract

[20] See 21 C.F.R. § 511.1(c)(1).
[21] 21 C.F.R. § 511.1(d).
[22] See FDA's AIP procedure.
[23] See FDA's Good Guidance Practices Regulation, 21 C.F.R. § 10.115.
[24] OSC will make classification decisions with the understanding that sponsors, clinical investigators, nonclinical laboratories, contract research organizations all have different roles and responsibilities in the bioresearch process.

clinical investigators) that may impact their own ongoing research or implicate the sponsor's oversight obligations;[25] and

6. facilitates research into the past history of potential contractors, such that sponsors can evaluate the inspected firm's suitability for future studies.

Unless the inspected firm will receive a Warning Letter or Untitled Letter, FDA will notify the firm of its concerns via a Data Concerns Letter. The letter will inform the inspected firm, at minimum, that:

1. FDA has classified their inspection as OAI;
2. the conditions or practices identified in the letter appear to directly impact the validity or integrity of study data and may result in significant portions of data being rejected if the data is submitted to FDA as part of an application or other submission;
3. the letter does not constitute a decision to accept or reject any data, and any such determinations will be made separately during the applicable review process; and
4. due to confidentiality requirements,[26] FDA is unable to publicly disclose whether an application containing the data was submitted, or to share its decision regarding data acceptance/rejection, so the inspected firm should provide the sponsor and/or FDA with any additional information supporting the suitability of the data and should implement appropriate corrections to ensure current or future studies generate suitable data.

The written correspondence may also inform the inspected firm that:

1. (If applicable) the conditions or practices noted in the letter, if repeated, may lead to initiation of disqualification proceedings against the clinical investigator;
2. (If applicable) the conditions or practices noted in the letter, if repeated, may constitute grounds for termination of the sponsor's investigational exemption; and
3. (If applicable) the conditions or practices noted in the letter, if repeated, may implicate FDA's Application Integrity Policy.

CVM OSC will address the letter to the most responsible person at the inspected firm, and will carbon copy (with redactions, where appropriate) the sponsors of any studies specifically identified in letter.

V. REFERENCES

FDA Regulatory Procedures Manual

https://www.fda.gov/inspections-compliance-enforcement-and-criminal- investigations/compliance-manuals/regulatory-procedures-manual

[25] See, e.g., 21 C.F.R. § 511.1(b)(7)(i), and 21 C.F.R. § 511.1(b)(8)(ii).
[26] See, e.g., 21 C.F.R. § 514.11(b).

FDA Application Integrity Policy Procedures

https://www.fda.gov/media/71236/download

CVM Policies and Procedures Manual

1240.2040 – CVM's Implementation of the Agency's Fraud, Untrue Statements of Material Facts, Bribery and Illegal Gratuities Policy

Internal information redacted.

Internal information redacted.

Internal information redacted.

Internal information redacted.

VI. VERSION HISTORY

March 4, 2025 – Original version.