Information Sheet Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

Clinical Investigator Administrative Actions – Disqualification

FDA is issuing this guidance document for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). If you choose to submit comments on this guidance document, submit your comments to the Division of Dockets Management (HFA-305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This Guidance document is intended to inform institutional review boards (IRBs), clinical investigators, and sponsors about the administrative action of disqualifying a clinical investigator from participating in studies involving investigational new drugs (including biologics) or devices.[1] FDA may disqualify a clinical investigator from receiving investigational drugs (including biologics) and devices if FDA determines that the investigator has repeatedly or deliberately violated the agency's regulations, or has repeatedly or deliberately submitted false information to the sponsor or FDA in any required report.[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA's guidance documents means that something is suggested or recommended, but not required.

[1] This guidance document was prepared primarily to address issues related to FDA-regulated research involving human subjects; however, disqualification actions may also be initiated for investigators who conduct studies in support of Investigational New Animal Drug Applications (INAD) or New Animal Drug Applications (NADA) under 21 CFR 511.1.

[2] See 21 CFR 312.70 and 812.119. Disqualification of clinical investigators conducting studies to support INADs or NADAs is authorized in 21 CFR 511.1(c).

II. DISCUSSION

A. The Disqualification Process

1. Notice of Initiation of Disqualification Proceedings and Opportunity to Explain

FDA's field staff conduct on-site inspections of clinical investigators involved in the investigation of FDA-regulated products. FDA performs these inspections of clinical investigators to evaluate their practices and procedures to determine compliance with applicable regulations. FDA conducts many such routine (i.e., "surveillance") inspections each year. In addition, FDA may receive information about potential misconduct, and typically conducts an inspection of an investigator's site to determine the investigator's compliance.[3]

If, as a result of the inspection, FDA notes repeated or deliberate violations or potential repeated or deliberate violations, the FDA Center[4] having jurisdiction over the product used in the study may initiate the investigator disqualification process by issuing a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE). Generally, the Center will consider issuing a NIDPOE when (1) subjects under the care of the investigator would be or have been exposed to an unreasonable and significant risk of illness or injury; or (2) subjects' rights would be or have been seriously compromised; or (3) data integrity or reliability is or has been compromised. The NIDPOE describes the alleged noncompliance and/or alleged submission of false information and offers the investigator an opportunity to explain in writing or, at the option of the investigator, at an informal conference with FDA. The NIDPOE specifies certain time frames for the investigator to respond to FDA.

If the investigator requests an informal conference, it will be held at the Center as soon as possible following the request. The investigator may bring an attorney. The informal conference may be transcribed, but the meeting is informal, and no prescribed format is required or suggested. After the meeting, the Center will review any new evidence or explanation and decide whether to proceed with the matter. In the event the Center accepts the investigator's explanation, the Center will notify the investigator in writing of this decision.

2. Consent Agreement

[3] See Information Sheet Guidance, "FDA Inspections of Clinical Investigators" http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf.

[4] Center for Drug Evaluation and Research, Center for Devices and Radiological Health, or Center for Biologics Evaluation and Research.

The Center provides a consent agreement to the investigator with the NIDPOE. Rather than contest the allegations set forth in the NIDPOE, the clinical investigator may opt to enter into a consent agreement. In general, the terms of a consent agreement provide that the investigator agrees that he or she will no longer conduct studies with investigational products. The investigator may sign the consent agreement at any time during the disqualification process including up to the issuance of a Commissioner's decision.[5]

Consent agreements generally take one of two forms: (1) the investigator agrees to be disqualified and is no longer eligible to receive investigational products. This agreement has the same effect as a disqualification after a Part 16 hearing and terminates the disqualification administrative proceeding; or, (2) the investigator, after discussions with the FDA, including an explanation of the alleged violations in writing or at an informal conference, agrees to specific restrictions in the use of investigational products, such as oversight of the investigator's conduct of an investigational study by an individual acceptable to both the investigator and FDA. If the investigator violates the restricted consent agreement, FDA can reinitiate the disqualification proceeding.

3. Notice of an Opportunity for Hearing on Proposed Disqualification

If the investigator's explanation (either in writing or during an informal conference) is not accepted by FDA or if the investigator fails to respond to the NIDPOE within the specified time period, FDA will offer the investigator an opportunity for an informal regulatory hearing under 21 CFR part 16 (Part 16 hearing) to determine whether the investigator should remain eligible to receive certain investigational products. FDA initiates a Part 16 hearing by sending the investigator a Notice of Opportunity for Hearing (NOOH).

The NOOH specifies the facts and other relevant information that are the subject of the Part 16 hearing. If the investigator does not respond within the time period specified in the NOOH, FDA considers the offer for a hearing to have been waived, and no informal Part 16 hearing will be held (see 21 CFR 16.22(b)). The Commissioner will consider the information in the administrative record to determine whether to disqualify the investigator.

[5] The Commissioner issues his or her decision pursuant to 21 CFR 16.95, and 21 CFR 312.70 or 812.119.

4. Part 16 Hearing and Final Decision on Disqualification

If the investigator requests a Part 16 hearing and there is a genuine and substantial issue of fact that warrants a hearing,[6] the Commissioner will designate a presiding officer to schedule and conduct the hearing.

Once the hearing is granted, either party (i.e., the Center or the clinical investigator) may move for summary decision on any or all of the issues. The presiding officer reviews any motions filed, issues a summary decision on the issues raised, and determines whether there exists any genuine and substantial issue of fact to be decided at a hearing. (See 21 CFR 16.26(b)). The summary decision issued will be incorporated into a presiding officer's report.

In the alternative, if a hearing is scheduled pursuant to 21 CFR 16.24, the Center and the investigator will, if feasible, exchange written notices of any published articles or written information to be presented or relied upon at the hearing (21 CFR 16.24(g)).

Part 16 hearings are informal, and the rules of evidence do not apply. This means any participant may comment upon or rebut all data, information, and views presented (21 CFR 16.60(c)). The hearing begins with Center staff/counsel giving a full and complete statement of the action that is the subject of the hearing and describing the information and reasons supporting disqualification. Center staff/counsel may present any oral or written information relevant to the hearing. The investigator, who may be represented by legal counsel, then may present any oral or written information relevant to the hearing. The hearing consists primarily of the presentation of oral or written information, and direct and reasonable cross-examination. (See 21 CFR 16.60(b)).

After the hearing, the presiding officer prepares a written report of the hearing (see 21 CFR 16.60(e)). All written material presented at the hearing will be attached to the report and becomes part of the

[6] "A request for a hearing may be denied, in whole or in part, if the Commissioner or the FDA official to whom authority is delegated to make the final decision on the matter determines that no genuine and substantial issue of fact has been raised by the material submitted." (21 CFR 16.26(a)). A hearing will not be granted on issues of policy or law; or, mere allegations or denials of the moving party's evidence but must present evidence of its own that establishes a genuine issue of fact. If there are no genuine disputes of fact, summary decision is appropriate.

An example of a genuine and substantial issue of fact that might warrant a hearing is whether an investigator's repeated changes to data were legitimate corrections as asserted by the investigator or whether the changes were made fraudulently to alter the outcome of the clinical trial. In this example, the presiding officer might assess during the part 16 hearing the veracity of the investigator's statements about the legitimacy of changes to the data.

administrative record along with the hearing transcript (see 21 CFR 16.80). The presiding officer's report includes a recommended decision and the reasons for the recommendation. When time permits, the parties are given the opportunity to review and comment on the presiding officer's report (21 CFR 16.60(e)).

The report and any comments of the parties are transmitted to the Commissioner who considers them as part of the administrative record to determine whether the investigator should be disqualified. The Commissioner then issues a written decision giving the basis for the final action taken. (See 21 CFR 16.95(b)).

5. Actions upon Disqualification

If the Commissioner or his or her designee determines that the investigator has repeatedly or deliberately failed to comply with the applicable regulatory requirements, and/or has repeatedly or deliberately submitted false information to the sponsor or FDA in any required report, the Commissioner will disqualify the investigator, and:

(a) Notify the investigator and the sponsor(s) of any investigation(s) in which the investigator has participated that the investigator is not eligible to receive certain investigational products. The notification will include a statement explaining the basis for this determination. (21 CFR 312.70(b) and 812.119(b)).

(b) Notify the sponsor(s) of studies involving the investigational drug or device, and the sponsors of each approved or cleared application submitted under 21 CFR parts 314, 814, or 807, subpart E, containing data reported by the disqualified investigator, that each investigational new drug application (IND), investigational device exemption (IDE), and each approved and cleared application will need to be examined to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval or clearance of any marketing application (21 CFR 312.70(c) and 812.119(c)).

(c) Determine whether the studies involving the investigational drug or device may continue.[7] If the Commissioner determines, after unreliable data submitted by the disqualified investigator are

[7] FDA may determine that further use of the investigational product should be suspended at the investigator's site (or a more broad suspension, depending on the circumstances). However, if this suspension could create a life-threatening situation for a subject under the disqualified investigator's care, FDA may permit that subject to continue to receive or use an investigational product. Matters where a subject may be at risk if the study is suspended, among other relevant matters, may be brought to the agency's attention during the regulatory hearing.

eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor who will have an opportunity for a regulatory hearing under 21 CFR part 16. If a danger to public health exists, however, the Commissioner will terminate the IND or IDE immediately and notify the sponsor of the determination.[8] The sponsor will then have an opportunity for a Part 16 regulatory hearing to determine whether the IND or IDE should be reinstated. (21 CFR 312.70(d) and 21 CFR 812.119(d)).

(d) Determine whether the continued marketing approval of the product is justified (e.g., any approved product for which the investigator's data were pivotal to FDA decision-making). If continued approval is not justified, the Commissioner will proceed to withdraw approval in accordance with applicable provisions of the Federal Food, Drug, and Cosmetic Act. (21 CFR 312.70(e) and 812.119(e)).

B. Criminal Prosecutions

A disqualification does not preclude initiation of criminal proceedings against an investigator. Those investigators referred for criminal investigation are generally clinical investigators who have knowingly or willfully violated the regulations or statutes.

C. Disclosure of Information Regarding Disqualification Proceedings

When FDA issues a NIDPOE to a clinical investigator, the agency provides a copy of the letter to the reviewing IRB and study sponsor. In addition, if the clinical investigator is disqualified, FDA will disclose the disqualification action to the IRB and sponsor.[9] IRBs and sponsors play a significant role in ensuring that clinical investigators meet applicable statutory and regulatory requirements. This disclosure is necessary and appropriate for IRBs and sponsors to be aware of findings indicating violations or potential violations of the laws and regulations enforced by FDA.

In some cases, evidence of a violation or potential violation may implicate more than one of the clinical investigator's studies. If so, FDA may, where appropriate, share information concerning a violation or potential violation with the sponsors and IRBs of any of the clinical investigator's studies.

In accordance with the above, FDA posts on FDA's Web page lists of investigators who:

[8] Note: A danger to public health includes not only the subjects' safety in any study in question, but also the safety of subjects in other studies in which the investigator is involved.
[9] See 63 Federal Register, October 19, 1998, at 55873.

- are ineligible to receive FDA-regulated investigational products or have agreed to some restricted use of FDA regulated investigational products,[10, 11]
- have had restrictions removed,[12]
- were issued NIDPOEs,[13]
- were issued NOOH letters,[14] and
- were the subject of presiding officer reports and Commissioner's decisions in clinical investigator disqualification proceedings.[15]

These lists are available to the public in FDA's Electronic Freedom of Information Reading Rooms. The lists are updated regularly. FDA encourages IRBs and study sponsors to consult these lists for information about clinical investigators' compliance with FDA regulations.

D. Reinstatement of a Disqualified Investigator

An investigator who has been disqualified may be reinstated if the Commissioner determines that the investigator has presented adequate assurances that he or she will employ the particular investigational products in compliance with FDA regulations. The agency's reinstatement guidelines, entitled "Procedures for Reinstating Eligibility of Disqualified Clinical Investigators to Receive Investigational Articles"[16] are available by writing to the FOI Staff at the address given below.

Freedom of Information Staff (HFI-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

[10] The lists of all investigators who have been disqualified or "totally restricted" may be viewed at http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/ucm131681.htm.
[11] The restricted list for clinical investigators is available at http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/ucm131684.htm.
[12] Access to the lists of "Disqualified/Restricted/Restrictions Removed/Assurances Lists for Clinical Investigators" is available at http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/default.htm.
[13] See http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm092185.htm.
[14] See http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm143240.htm.
[15] See http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm143242.htm.
[16] See 47 Federal Register 52228, November 18, 1982. An update of this reinstatement procedure is in progress.

III. REFERENCES

1. FDA/ORA Compliance Program Guidance; Program 7348.811, Chapter 48 – Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators, issued December 8, 2008; available at http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133773.pdf.

2. Regulatory Procedures Manual, Chapter 5 – Administrative Actions, section 9 – Disqualification of Clinical Investigators; available at http://www.fda.gov/ora/compliance_ref/rpm/chapter5/ch5-9.html#toppage.

3. Staff Manual Guide, Volume IV – Agency Program Directives; Compliance Activities; SMG 7711 – Disqualification of a Clinical Investigator: The Hearing Process, effective June 20, 2008, available at http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm052928.htm.