

# HOGAN & HARTSON

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November 25, 2002

Dockets Management Branch  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 2052

Re: *Clinical Hold Following Clinical Investigator Misconduct*  
(Docket No. 02D-0320), Comment

Dear Sir or Madam:

We are writing on behalf of a leading pharmaceutical company to provide comments on the draft document, *Guidance for Industry and Clinical Investigators: The Use of Clinical Holds Following Clinical Investigator Misconduct* (April 2002), published by the Food and Drug Administration (FDA) on August 27, 2002 (67 FR 55025) (the "Draft Guidance"). The Draft Guidance describes the circumstances under which FDA may suspend a study in the face of possible misconduct by a clinical investigator.

Our client depends on the safe and reliable conduct of clinical trials and appreciates the efforts of FDA to address clinical investigator misconduct. We recognize that, in certain circumstances, FDA may need to act quickly to protect the welfare of human subjects from rogue investigators. We are concerned, however, that the Draft Guidance lacks adequate procedural protections to ensure that studies are not disrupted based on an inadequate factual record. In addition, the Draft Guidance does not include a mechanism for notifying sponsors in advance as to those investigators who have been found by FDA to have engaged in misconduct. Without such notice, sponsors may inadvertently engage an investigator who has been determined to present a risk to patients.

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## I. BACKGROUND

The legal standard for the entry of a clinical hold order is set forth in section 505(i) of the Food, Drug, and Cosmetic Act (21 USC 355(i)(3)) and in regulations issued by FDA, found at 21 CFR 312.42. Under section 505(i)(3), the agency may issue a clinical hold order if it determines that:

[T]he drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved . . . .

21 USC 355(i)(3). The statute also provides that FDA may by regulation establish additional grounds for the imposition of a clinical hold. *Id.*

In addition, the statute requires that FDA specify in writing the basis of the clinical hold order, including the specific information or evidence available to the agency. *Id.* A written request from the sponsor to remove a clinical hold must be decided within thirty days after its receipt. *Id.* That decision and its basis must be rendered in writing. *Id.*

The agency's regulations for imposing a clinical hold essentially follow the statutory standard. The regulations repeat the statutory standard that a hold may be imposed upon a finding that human subjects "are or would be exposed to an unreasonable and significant risk of illness or injury" or upon a finding that the clinical investigators "are not qualified by reason of their scientific training or experience." 21 CFR 312.42(b). FDA has not issued regulations regarding the use of clinical holds to address possible (but unproven) clinical investigator misconduct.

A separate rule governs the disqualification of clinical investigators who have "repeatedly or deliberately" failed to meet standards for human subject protection (*see* 21 CFR Parts 50 and 56) or have submitted false information to FDA. *See* 21 CFR 312.70. The disqualification rule requires notice and an opportunity for an evidentiary hearing where an investigator is suspected of having breached his or her responsibilities. Only after the completion of this process may the agency enter an order "disqualifying" the investigator from receiving an investigational drug for study in an ongoing investigation. 21 CFR 314.70(b). There is no provision in the

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regulation (21 CFR 314.70) for making a preliminary determination of disqualification pending, or in lieu of, notice and an opportunity to be heard.

## II. COMMENTS

The stated purpose of the Draft Guidance is to provide information on the use of clinical hold where an investigator has been found to have violated FDA standards or falsified information. Draft Guidance at 1. The novel issue raised in the Draft Guidance is the use of this mechanism *before* the agency has initiated a disqualification proceeding under 21 CFR 312.70. In fact, the agency states that it may impose a clinical hold *before* the agency has “had an opportunity to assess the significance of the alleged violations” and *before* it has even attempted to hear the investigator’s response to the allegations. Draft Guidance at 6.

We share FDA’s concern that patients not be put at risk by investigators who have engaged in misconduct. We are equally concerned, however, that the agency not disrupt ongoing studies based on allegations, speculation, and hearsay. And, we are concerned that sponsors will not be given adequate real-time notice as to which investigators have been determined by FDA to be “at-risk.”

### A. Timing and Process

The Draft Guidance allows FDA to conclude that an investigator has “committed serious violations of FDA regulations on clinical trials of human drugs and biologics . . . or has submitted false information to FDA or the sponsor . . . .” (Draft Guidance at 1) without any apparent procedural safeguards. Such a finding exposes the investigator to personal liability and should not be made with adequate notice and process.

For this reason, we recommend that if a clinical hold is to be imposed based on investigator misconduct, it should be imposed only in conjunction with the issuance of a NIDPOE letter. The NIDPOE letter provides a procedural check upon the agency; it requires that the agency reduce its concerns to writing, discuss the relevant legal standard, and identify all relevant evidence. It also provides an opportunity for interested persons, including the sponsor, to quickly schedule an informal conference to test the weight of the agency’s evidence. See 21 CFR 312.70(a). Indeed, we believe the Guidance should state that the agency will agree to schedule an informal conference with a sponsor within 5 business days of the entry of a clinical hold based on alleged investigator misconduct.

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In addition, where the agency concludes that clinical hold is needed because of investigator misconduct, the NIDPOE letter should be signed by the Center Director. The Draft Guidance proposes an extraordinary remedy – *i.e.*, imposition of a hold before the investigator (or the sponsor) has had an opportunity to see or respond to the allegations. Because of the extraordinary nature of this remedy, the matter should be presented for Center Director review, rather than review at the division or office level. The Center Director is in a better position to weigh the strength of the allegations, on the one side, against the impact that a hold will have on patients and on the drug or biological product sponsor, on the other.

#### **B. Real-Time Notice**

Clinical hold orders are disruptive; they can have a detrimental impact on patient care and safety and can undermine a sponsor's development program. For this reason, the Draft Guidance should be amended to include a mechanism for publishing the names of clinical investigators whose studies have been placed on hold. The list should be kept current, with names removed if the agency later determines that the investigator did not engage in misconduct. And, the list should be easily accessible on the FDA website. In this way, a sponsor who initiates a new study will be able to consult the list and ensure that no person whom the agency has determined to be at-risk is associated with the study.

#### **C. Quality and Quantity of the Evidence**

The Draft Guidance is silent as to the quality and quantity of evidence the agency intends to rely upon when ordering a clinical hold based on possible investigator misconduct. For example, the Draft Guidance would allow for clinical hold based on the uncorroborated assertions of a disgruntled employee or the relative of a patient enrolled in the study, as well as the subjective opinions of a single IRB panel member. Indeed, the Guidance states that the agency would halt a trial prior to conducting an in-person inspection to confirm the basic facts. Draft Guidance at 6. Once a study is on hold, the Guidance places the burden *on the sponsor* to come forward with evidence that patients are adequately protected.

Some consideration must be given as to how the agency intends to assess the weight and credibility of the allegations to determine that an investigator has engaged in misconduct. Again, the basis stated in the Draft Guidance for putting a study on hold is a finding that an investigator has engaged in misconduct and has put patients at "unreasonable and significant risk of illness or injury."

Draft Guidance at 1. Before the agency proposes to make such a finding, and to do so without an evidentiary hearing, it needs to engage in a much more searching analysis of the quality and quantity of evidence needed.

#### **D. Scope**

According to the Draft Guidance, a clinical hold order based on misconduct may halt all studies under an IND, as well as all studies in which the suspect investigator is participating. To protect patients, including those who may depend on the continuation of a study, we believe the Guidance must clearly state that (a) only studies directly associated with instances of alleged investigator misconduct will be subject to a clinical hold; and (b) clinical hold orders will be sustained only so long as there remains credible evidence of significant risks to human subjects. The Guidance should state that the narrowest hold possible will be entered, to address the precise risk posed by the investigator's misconduct. For example, the Guidance should clearly state that an entire multi-site study will not be placed on hold where investigator misconduct at one site has been found.

### **III. CONCLUSION**

In the interest of patient safety, the agency must be able to take rapid action. On behalf of our client, however, we are concerned that the Draft Guidance all but eliminates the procedural safeguards associated with clinical investigator disqualification (*see* 21 CFR 312.70). As the agency concedes, disqualification has become a lengthy process, often taking years to complete. Through this Guidance, the agency would establish a policy that virtually eliminates the need for a disqualification proceeding. Once a suspect investigator's study is put on hold, sponsors will have no choice but to terminate the investigator. The investigator, in effect, will be unable to receive investigational products – the very same remedy described in 21 CFR 312.70.

In this light, the agency must narrow the Draft Guidance substantially, to be sure that it applies the new policy only where there is very clear evidence that patients *are being harmed*. In the alternative, the agency should proceed through notice and comment rulemaking to create the preliminary remedy outlined in the Draft Guidance.

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We thank the agency for initiating this proceeding and look forward to working closely with FDA on developing an appropriate approach to the problem of investigator misconduct.

Sincerely,

DM Fox by FDC

David M. Fox