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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Draft Guidance for Industry and Clinical Investigators - The Use of Clinical Holds Following Clinical Investigator Misconduct (Federal Register: August 27, 2002 [Volume 67, Number 166], Docket No. 02D-0320)

Dear Sir or Madam,

The draft guidance titled "Guidance for Industry and Clinical Investigators - The Use of Clinical Holds Following Clinical Investigator Misconduct" (Federal Register: August 27, 2002 [Volume 67, Number 166], Docket No. 02D-0320), represents an expansion in the scope of the use of clinical holds by FDA from what is currently described in 21 CFR 312.42. The intent of the guidance is sound, valuable and worthy of support; however, there are some fundamental issues in the current rendering of the document that should be amended. The following is a list of these issues and the corresponding recommendations for change proposed by AstraZeneca Pharmaceuticals LP:

1. Revision should be considered for the issue of how the clinical hold is applied, i.e., who receives the hold. The principal interactions in instituting, continuing and resolving a clinical hold as described in the guidance are with the sponsor. The only exception is the investigation by FDA into potential clinical investigator misconduct. All other actions and responses are directed toward the sponsor. Although some interaction with sponsors is clearly needed (e.g., notification or requests related to the FDA inspection), the guidance should require that the clinical hold be enacted upon the clinical investigator and not the sponsor. In this way, the progression of the investigation into misconduct and any subsequent interactions designed to address the concerns of FDA can be orchestrated directly with the clinical investigator. This would then parallel the FDA inspectional process currently in effect that addresses inspectional findings with the inspected party whether it is with the sponsor, clinical investigator or IRB. To require sponsors to become the representative for the investigator in cases relevant to misconduct is inconsistent with the normal inspectional practices of FDA. This is not to deny the need to notify sponsors of clinical holds, so that appropriate measures can be taken to end subject participation or prevent subject enrollment. But, this currently proposed type of clinical hold makes the sponsor the responsible party for communication and resolution of the issues with an investigator as evidenced in the guidance when it states that "...FDA contacts the sponsor and attempts to resolve the matter...before imposing a clinical hold" (page 7). A better

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approach would be to create a clinical hold directed at the investigator, so that he/she is the responsible party. Sponsors and IRBs would then be notified and informed of the details, so that they could respond as necessary.

Most likely a change to 21 CFR 312.42 would be required to allow for the clinical hold to be directed to the clinical investigator. The merits of implementing such a clinical hold in terms of protecting human subjects in these cases justify the effort of a rule change.

2. The concept of partial clinical hold needs clarification. The guidance indicates that the FDA might institute a full or partial clinical hold in cases where the investigator's misconduct appears to pose an ongoing threat to the safety and welfare of study subjects. However, Section III.A., second paragraph of the guidance states:

A clinical hold may be complete or partial. Delay or suspension of all clinical work under an IND is considered a complete clinical hold. Delay or suspension of only part of the clinical work under an IND is considered a partial clinical hold. A partial clinical hold could, for example, be imposed to delay or suspend one of several protocols in an IND, a part of a protocol, or a specific study site in a multi-site investigation.

As described, the guidance could only utilize a partial clinical hold since all clinical work under an IND would not usually be stopped based upon the misconduct of a single investigator. Therefore it is recommended, that if the aforementioned changes to make the investigator the principal recipient of the clinical hold are not made, then partial clinical hold should be used as the primary term in this guidance document.

3. It is recommended that information be added that speaks to situations where foreign inspections indicate clinical investigator misconduct. Specifically, please provide guidance describing the differences in application of the clinical hold process for cases involving foreign investigators.
4. Section III.B.1, second paragraph presents examples of evidence that might lead to the imposition of a clinical hold, e.g., failure to report serious adverse events, serious protocol violations. In order to be consistent with other parts of the document and to add context to the examples, it is recommended that the following change (bolded below) be made to this paragraph:

First, FDA would look at the nature of the violation and its significance for the safety and rights of human subjects. Certain types of violations may pose such a significant threat to subjects in the trial that suspending that part of the trial under the investigator is justified, even where the investigation into the violations is at an early stage. **These would involve serious violations of the investigator's obligations.** For example, FDA ...

5. The guidance needs to make clear whether the findings from one IND study would result in the notification of all sponsors and IRBs for whom the person is participating as a clinical investigator. Making this type of notification of a clinical hold a requirement is recommended and would be consistent with the intent of the guidance, i.e., to protect human subjects from unreasonable and significant risk of illness or injury.

In summary, AstraZeneca supports the goal of increasing human subject protection in clinical research as presented in this draft guideline. To that end, adoption of the changes recommended herein would support a significantly better process whereby this goal could be achieved.

Sincerely,



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