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US Regulatory Affairs



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

Re: Docket No. 02D-0320; Draft Guidance for Industry and Clinical Investigators on the Use of Clinical Holds Following Clinical Investigator Misconduct; 67 Federal Register 55025 (August 27, 2002)

Dear Sir or Madam:

The following comments on the above noted draft Guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2001, our members invested over \$30 billion in the discovery and development of new medicines.

PhRMA supports the efforts of FDA to restrict a clinical investigator from either recruiting new subjects or conducting studies where the Agency has found subjects are at risk due to the investigator committing serious violations of FDA regulations or has submitted false data. Although the vast majority of clinical investigators conduct clinical research in accordance with existing regulations there are examples of cases where subjects have been placed at risk or compromised data was unknowingly submitted in an NDA because of falsification of data.

Implementation of this guidance would provide a more effective and timely process to make sponsors aware of significant problems with an investigator. The overall effect would be to meet unmet medical needs by reducing the potential of delaying valuable new medicines by allowing sponsors to make adjustments in their research programs should data be deemed suspect. It will also provide added protection for research subjects, ensuring that they are receiving appropriate medical care.

Recognizing the benefits of this guidance, PhRMA requests clarification on some issues and provides some suggestions for FDA to consider that will improve this guidance and increase its acceptance by industry.

The "Purpose Section" states that the clinical hold would only apply to investigators conducting trials on human drugs and biologics. Many device investigators also conduct studies on drugs and biologics but there does not appear to be any restriction

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*Pharmaceutical Research and Manufacturers of America*

to prevent them from continuing to conduct trials on devices even if they were placed under a clinical hold. It would seem logical that if the trial related activity were fraudulent or significant non-compliance was found these practices might have carried over to other studies. Similarly, it would seem that any outcome would apply to all clinical trials conducted by that investigator regardless of the type of product or therapeutic area.

Considering the purpose and intent of this guidance, it appears FDA would consider a clinical hold if falsification of data or significant scientific misconduct that could harm subjects in a trial were discovered or revealed. As stated in "Section A" of the guidance a partial hold would apply to a site or a study, but not the complete IND. However, the regulations do not define the term "partial" hold, only clinical hold and PhRMA believes clarification is necessary. If an investigator were the source of the problem it would seem logical that FDA would impose a "partial" hold related to that investigator rather than a complete clinical hold on the entire development program. Also, the "partial" clinical hold against the specific investigator should be applied to any other INDs the investigator is working on.

Information regarding an investigator under a clinical hold needs to be communicated in a timely manner to all sponsors actively conducting studies with that. In the guidance it is not clear how or to whom information regarding a clinical hold on an investigator will be communicated. All sponsors who are currently using the investigator should be notified. The guidance should also include a statement that FDA will notify all sponsors who have included data from a suspect investigator in a submission under review by the agency. These actions will ensure that the sponsor can take appropriate action in a timely manner as deemed necessary to ensure that the agency is not reviewing submissions with suspect data that would impact study conclusions and/or to protect the human subjects participating in a trial. These actions may include the reanalyzes of the data without the suspect investigator data, initiation of new studies or the transfer of patients from the suspect investigator in cases of ongoing studies.

Also while an investigator is under a clinical hold for other sponsors' studies, they may be in the process of being considered for new studies by new sponsors that may be totally unaware of the clinical hold. FDA should consider a mechanism to alert these new sponsors, while protecting the confidentiality of existing sponsors and the investigator's right to privacy and due process.

Section III, B.1 states "even preliminary (e.g., pre-inspected) but credible evidence where subjects are at substantial risk could warrant a hold until further information is obtained." PhRMA recognizes the need for FDA to act quickly to protect the subjects participating in a trial when allegations of scientific misconduct are made. Additionally, we also recognize the need to protect the rights of all parties involved including the investigator against whom allegations of misconduct may have been made. Therefore, we urge the FDA to balance the rights of all parties involved and only act to institute a

clinical hold once the Agency has sufficient evidence that may be generated from several sources, including the sponsor and that of FDA.

PhRMA recommends that the FDA provide clear examples of what would be considered to be "credible evidence" PhRMA is concerned about the appropriateness of FDA relying solely on outside information to apply a clinical hold without evidence from their own investigations. PhRMA recommends that the FDA expedite any inspection assignments when a clinical hold is being considered. Our concern is that, should the FDA act solely on third party information it may have the unintended detrimental effect of potential reporters delaying reports until they have total certainty and/or not reporting at all for fear of potential litigation by the investigator for slander, loss of business or defamation of character. For this reason, the need exists for a transparent process whereby FDA clearly defines how it will evaluate and use information it receives to implement a clinical hold, but more importantly we recommend that final clinical hold decisions should be based primarily on FDA's own inspection program results rather than on information from sources external to the FDA.

Regarding Section III.B.1, examples of evidence needed to impose a partial clinical hold on a clinical investigator includes "Failure to obtain IRB review and approval for significant protocol changes". PhRMA believes it important that the guidance add "sponsors" to the IRB, as a sponsor's review and approval is also needed for significant protocol changes, as these may impact the safety of research participants or the evaluability of their data when combined with those data from other investigators' patients for statistical analyses.

PhRMA trusts that these comments are useful to FDA as they move forward to finalize this Guidance.

Sincerely,

A handwritten signature in cursive script, appearing to read "Alan Feldheim".