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October 17, 2002

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

Re: Docket No. 02D-0320; Draft Guidance, *The Use of Clinical Holds Following Clinical Investigator Misconduct*, 67 Federal Register 55025 (August 27, 2002)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2001 alone, Bristol-Myers Squibb dedicated \$2.1 billion for pharmaceutical research and development activities. The company has nearly 6,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises more than 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on this FDA proposed guidance on the use of clinical holds following clinical investigator misconduct.

Summary of BMS Comments on Proposal

We commend the U.S. FDA for proposing guidance on the circumstances for the use of FDA's authority to impose a clinical hold if FDA finds that a clinical investigator conducting the study has committed serious violations of the regulations. We feel this guidance will provide sponsors with direction in reporting investigators who commit serious violations of FDA regulations. Also, through FDA's early notification, it will make sponsors aware of pending actions against clinical investigators.

However, there are several aspects of the draft guidance that need clarification, which we have noted below.

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General Comments

This guidance refers to clinical hold resulting from investigator misconduct. The term “clinical hold” is already in use by the FDA and as it is currently used, it means stopping an entire study and not just a study site. Since many of our studies are multi-center trials, it is not clear from this guidance whether it is investigator-specific or it applies to all clinical investigators in a given program. While we do not believe that the Agency’s intention is that a clinical hold applies to all clinical investigators, it is not clear to us from reading this guidance. Therefore, we recommend to change the term from “clinical hold” to “clinical investigator hold”.

Also, the scope of “clinical trials” needs to be defined, i.e. IND studies only, Phase I-III, Phase IV, medical device studies, studies not conducted under an IND but are used to support a US application.

Clarification of the process for notification of a clinical hold is needed. For example, will all Sponsors and IRBs who are working with an investigator be notified when an investigator is placed on clinical hold? The order and timing of notification also needs to be mentioned. For example, if multiple sponsors are using an investigator when the investigator is placed on clinical hold, will all sponsors be notified at the same time?

In addition, the guidance should address whether or not the listing of investigators who are placed on clinical hold will be made public and posted on the FDA Home Page. The role of the sponsor in the clinical hold process needs to be addressed as well as the timeframe for implementation of FDA’s use of clinical hold following clinical investigator misconduct. The scope of the FDA investigation into clinical investigator misconduct should be defined, e.g. would sponsors be investigated? Would FDA need to conduct their own inspection to verify information that may have been provided by the sponsor?

Specific Comments

I. Purpose

- *“This guidance provides information on the Food and Drug Administration’s (FDA’s) use of its authority to impose a clinical hold on a study or study site if FDA finds that a clinical investigator conducting the study has committed serious violations. ...”*

Recommendation: In order to clearly define the intent of this guidance, we recommend this sentence be changed to indicate a clinical hold will be placed on a study site and not on an entire study. Even though this is clarified on page 4 of the draft guidance, it should be mentioned up front. Also, the terms “study” and “study site” need to be defined. It should be determined whether or not it is necessary to state a clinical hold will be imposed if FDA finds that personnel under the supervision of the clinical investigator commit serious violations of FDA regulations, e.g. sub-investigator, study coordinator.

- *“Where the investigator’s misconduct appears to pose an ongoing threat to the safety and welfare of such subjects, imposition of a full or partial clinical hold on ongoing or proposed studies of human drugs or biological products may be appropriate.”*

Recommendation: Clarification of “partial clinical hold” is needed. Also, this sentence should be reworded to indicate “ongoing or proposed studies conducted by or to be conducted by a clinical investigator.....”. It should be clarified whether or not the clinical hold applies to IND studies only, Phase I-III, Phase IV, medical device studies, studies not conducted under an IND but are used to support a US application.

III.B. Under What Circumstances Would FDA Consider Imposing A Clinical Hold Following Discovery Of Clinical Investigator Misconduct?

- *“In this section, FDA provides guidance on the circumstances in which the agency could reach such a conclusion and impose a clinical hold on the study or study sites in which an investigator is involved.”*

Recommendation: It should be clarified that an entire multi-center study would not be placed on hold due to the actions of one site. Also, clarification of how the sponsor will be notified of this hold is needed.

III.B.1. Before an enforcement action is initiated.

- *“For example, FDA may conclude that suspending the trial is necessary to protect subjects from a significant and unreasonable risk of illness or injury, if FDA finds evidence of one or more of the following””*

Recommendation: It should be clarified that an entire multi-center trial would not be placed on hold due to the actions of one site. Also, it is not clear what the question marks mean in this section. We suggest adding to the list falsification of any data and significant protocol changes unless to eliminate a safety concern that impact on safety of human subjects. There should be a statement indicating this list is not intended to be all-inclusive.

- *“Nonetheless, protecting the safety of patients at imminent risk is of great importance, and even preliminary (e.g., pre-inspectional), but credible evidence raising concerns that patients may be placed at substantial risk may warrant a hold while further information is being obtained.”*

Recommendation: Credible evidence needs to be defined.

III.B.2. After an enforcement action is initiated.

- *“One or more of the following types of violations may give rise to NIDPOE letters, and may also give rise to clinical holds if the circumstances show that the violations pose a significant risk to subjects:”*

Recommendation: We suggest adding to the list failure to adequately supervise the study that would jeopardize the safety of the subjects. Also, it is not clear what the question marks mean in this section.

III.C. What Steps Will FDA Take Before Imposing a Clinical Hold to Protect Subjects from Investigator Misconduct?

- *“If possible, as in all cases where a clinical hold is considered, FDA contacts the sponsor....”*

Recommendation: Examples should be provided for when it would not be possible to contact the sponsor.

III. D. When Will FDA Lift a Clinical Hold That Was Imposed to Protect Subjects from Investigator Misconduct?

- *“FDA will lift a clinical hold imposed to protect subjects from investigator misconduct when the grounds for the hold no longer apply.”*

Recommendation: It should be noted how sponsors that are directly involved are notified of the holds and hold releases.

- *“The sponsor of the affected study may, during the pendency of the clinical hold, present evidence to FDA to show that it has taken steps....”*

Recommendation: It should state the investigator may present evidence also. Also, the role of the sponsor in a investigation should be clarified.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

A handwritten signature in cursive script that reads "Laurie Smaldone". The signature is written in black ink and has a fluid, connected style.

Laurie Smaldone, MD
Senior Vice President
Global Regulatory Sciences