



June 3, 2002

Margaret M. Dotzel
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Management Branch (HFA-305)
Food and Drug Administration
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Re: Docket No. 01N-0322
Advance Notice of Proposed Rulemaking
Institutional Review Boards: Requiring Sponsors and Investigators to Inform IRBs of
Any Prior IRB Reviews

Dear Ms. Dotzel,

We are writing in response to the Food and Drug Administration's advance notice of proposed rulemaking on March 6, 2002 entitled, "Institutional Review Boards: Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews" (*Federal Register* 67: 10115-10116, March 6, 2002). The notice invited comments to Docket No. 01N-0322 by June 4, 2002.

GlaxoSmithKline is one of the largest pharmaceutical companies in the United States, as well as worldwide. We discover, develop, manufacture, and distribute prescription and nonprescription drug and biologic products for the prevention and treatment of many diseases. In our work, we sponsor numerous clinical investigations in the United States as well as in other countries. These investigations are conducted in accordance with all applicable laws and regulations. Our comments on this notice of proposed rulemaking are based on our extensive experience and knowledge of this field.

Although we fully support the conduct of clinical trials in a manner that protects the interests and welfare of human research participants, GlaxoSmithKline has several concerns regarding the proposal for a new rule requiring sponsors and investigators to inform IRBs about any prior IRB review decisions. These concerns are described below.

- The notice is based on very limited, mostly anecdotal, information from an Office of the Inspector General (OIG) Report that summarized observations from a survey of a limited and non-representative sample of IRBs. We do not believe that rulemaking should be considered in the absence of substantive information derived from a representative sampling of IRBs in the United States.

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- The notice describes a proposed rule that would place substantial administrative burden on investigators and industry sponsors. Since it is not uncommon to conduct a clinical study at many different clinical centers spread across a broad range of geographic locations (sometimes 100 or more sites for a specific protocol), tracking and summarizing all prior IRB decisions for a specific multicenter protocol would require creation of an extensive new infrastructure. Communicating these review decisions and keeping this information current would likewise require significant administrative support and would impose a substantial burden on investigators and sponsors. Pending substantiation that the current regulatory requirements do not adequately protect the interests and welfare of research participants, we do not believe such an additional and substantial administrative burden is presently justified. As an alternative, we suggest that the *potential* for possible "IRB shopping" could be addressed by a specific and focused regulatory change involving the interactions between a specific investigator, at a specific research site, and the IRB(s) with which he/she interacts.
- An IRB already may require that an investigator advise it of prior IRB reviews if it believes this information is pertinent to its review of the protocol. The regulations require and empower IRBs to initiate inquiries deemed necessary to assure that the interests and welfare of research participants are being protected. Accordingly, we believe that an IRB can and should have the discretion to decide whether information about prior IRB decisions will be requested. However, mandatory requirements in every case, for every investigational site, adds questionable value while substantially increasing the administrative burden to investigators and sponsors.
- We do not believe that an investigator should be responsible for summarizing for his/her IRB all of the interactions between other investigators and their respective IRBs for the same protocol being considered at other geographically distinct locations.
- We do not believe that FDA should consider unilateral action on matters involving protection of research participants. At the time of enactment of 21 CFR Part 56 (46 FR 8958 January 27, 1981), FDA noted its agreement that the Agency's regulations and those of the Department of HHS should be as consistent as possible. Accordingly, 21 CFR 56 was enacted following FDA participation with other affected Federal agencies of the Public Health Service in order to establish a uniform standard.

The following specific comments are provided on the advance notice:

Page 10115, 2nd column: The genesis of this notice of proposed rulemaking is a comment in a 1998 OIG Report ("*Institutional Review Boards: A Time for Reform*"; OEI-01-07-00193) which cited "a few situations" described to OIG where a research investigator and/or sponsor who was unhappy with one IRB's reviews switched to another IRB, without the new IRB being aware of the other's prior involvement. We believe it is shortsighted to consider rulemaking without substantive information on the incidence and impact of alleged "IRB shopping," as it is called in the OIG report.

The OIG Report is based on very limited information. Specifically, the OIG based its report on visits to 6 IRBs (all at academic medical centers) and discussions with representatives of about 75 IRBs. These samples are very small (considering the approximately 4,000 IRBs in the United States) and no information is provided to show that the samples are representative of IRBs in the United States.

We acknowledge that one of the specific purposes of the notice of proposed rulemaking is to solicit public comment about the frequency of "IRB shopping" noted in the OIG Report. In our experience, so called "IRB shopping" is rare due to current safeguards in the regulatory system. These safeguards include the local requirement for an investigator with an institutional affiliation to use the IRB in that institution, as well as the FDA requirement for any change in IRB to be reported to FDA on Form FD 1572. Despite these safeguards, if additional information from a representative sample of IRBs documents "IRB shopping", we urge the Agency to take action to investigate this practice and to propose a regulatory change that will counteract this practice while avoiding the creation of a costly and time consuming communication infrastructure to inform IRBs about any prior review at geographically distinct study centers.

Page 10116, 2nd column: The notice suggests that information about a review decision from one IRB review would be valuable to a subsequent IRB if the first IRB contains committee members with superior expertise in a particular case. The notice raises the possibility that disclosed information should include information about the composition and expertise of the prior IRB membership and the basis on which the prior IRB reached a conclusion. We believe that such a requirement is unnecessary, impractical, and would substantially increase the administrative burden to investigators and sponsors. This is particularly true of large, multicenter clinical trials.

We believe that it will be impractical for a sponsor to obtain and summarize in any meaningful way the expertise of committee membership of one IRB for subsequent IRB review consideration. Such a new requirement would be extremely burdensome and would require investigators and sponsors to obtain information to which they do not presently have ready access.

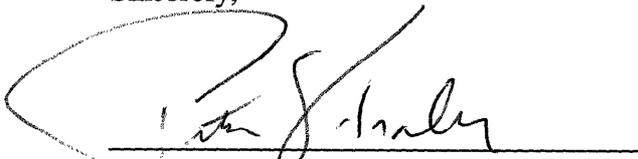
The current regulations that define the requirements for IRB membership (21 CFR 56.107) require that "The IRB shall be sufficiently qualified through experience and expertise of its members..." The regulations also require appropriate considerations of race, gender, cultural backgrounds and sensitivities to such issues as community attitudes. We believe that existing regulations require each individual IRB to be sufficiently constituted to independently assess proposed investigations. Local sensitivities that may have played an important role in a decision at one center may be irrelevant at a geographically distant site.

General Comments:

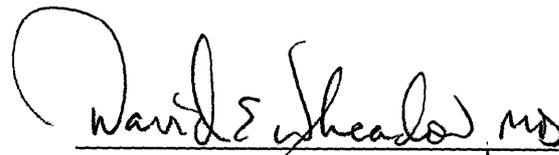
- The notice suggests a number of possible steps for the future (e.g., all prior IRB reviews could be disclosed or IRBs to explain their reasons for approving a study). These comments in the notice are open ended and unfocused. To our knowledge, there is no evidence in the OIG Report or from other sources to suggest, let alone prove, that such changes in regulations will yield measurable improvements in the protection of human subjects. We urge FDA to insist that any future proposed revisions to the regulations in Parts 56 and 312 be accompanied by specific and detailed evidence of the need for the change and how the proposed changes will yield measurable improvements in the protection of research participants.
- As noted above, in the absence of substantive evidence that current safeguards are inadequate, we believe that no new rulemaking is necessary with regard to disclosure of prior IRB decisions. However, in the event that the Agency determines that additional requirements are necessary to protect the interests and welfare of research participants, we believe that the information disclosed regarding prior IRB reviews should be limited to only past rejections of the protocol. We are opposed to disclosing information about approvals with stipulations or negative opinions that are not related specifically to the protocol. Some hypothetical examples might include an IRB in Southern California that did not approve a protocol until the associated consent document had been offered in both English and Spanish. Such a stipulation may not be germane to the review of the same protocol in Vermont. Under another hypothetical situation, a sponsor might be placed in a position of conflict with the investigator's privacy rights (real or perceived). For example, in response to a direct question by IRB#1, Investigator might disclose that he was censored 10 years previously by the state medical board following allegations of sexual misconduct. IRB#1 may reject Investigator as an investigator for the study based on this information. By comparison, IRB#2 may ask only if Investigator is currently licensed in good standing with no restrictions by the medical board, or even ask other questions that would not reach the information on which IRB#1 based its decision. A rule that would require the sponsor to disclose the decision by IRB#1 to IRB#2, against the wishes of Investigator places the sponsor in a position of disclosing personal information about the investigator. In our view, such mandatory disclosures add no value with respect to subsequent IRB decisions.

Thank you for the opportunity to comment on this notice.

Sincerely,



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 Senior Vice President
 Clinical Development & Medical Affairs
 Chief Medical Officer, GSK



 David E. Wheadon, M.D.
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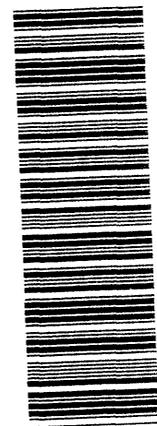
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