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This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 56

[Docket No. 01N-0322]

Institutional Review Boards: Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is considering whether to amend its institutional review board (IRB) regulations to require sponsors and investigators to inform IRBs about any prior IRB review decisions. These disclosures could help ensure that sponsors and clinical investigators who submit protocols to more than one IRB will not be able to ignore an unfavorable IRB review decision and that IRBs reviewing a protocol will be aware of what other IRBs reviewing similar protocols have concluded. FDA seeks information on IRB practices to determine whether it should draft a regulation and, if a regulation is to be drafted, to help determine the regulation's contents.

DATES: Submit written or electronic comments by June 4, 2002.

ADDRESSES: Submit written or electronic comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Philip L. Chao, Office of Policy, Planning, and Legislation (HF-23), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-3380.

SUPPLEMENTARY INFORMATION:

I. Introduction

IRBs are boards, committees, or other groups formally designated by an institution to review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects (see 21 CFR 56.102(g)). An IRB's primary purpose during such reviews is to assure the protection of the rights and welfare of human subjects (id.). FDA's IRB regulations are at 21 CFR part 56 and apply to clinical investigations involving FDA-regulated products such as human drugs, biological products, medical devices, and food additives. (While section 520(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360j(g)) refers to "institutional review committees" rather than IRBs, FDA considers institutional review committees to be IRBs and to be subject to the IRB regulations).

In 1998, the Department of Health and Human Services, Office of the Inspector General (OIG) issued several reports on IRBs. The OIG sought to identify the challenges facing IRBs and to make recommendations on improving Federal oversight of IRBs. One recommendation was that sponsors and clinical investigators be required to notify IRBs of any prior review (see Office of the Inspector General, Department of Health and Human Services, *Institutional Review Boards: A Time for Reform*, p. 14, June 1998). The OIG report stated that the OIG had:

* * * heard of a few situations where sponsors and/or research investigators who were unhappy with one IRB's reviews switched to another without the new IRB being aware of the other's prior involvement. This kind of IRB shopping deprives the new IRB of information that it should have and that can be important in protecting human subjects. The ground rules should be changed so that sponsors and investigators have the clear obligation to inform an IRB of any prior reviews (footnote omitted). The obligation should be applied to all those conducting research funded by HHS or carried out on FDA-regulated products. It will have particular importance for those sponsors and investigators working with independent IRBs. Id.

It is important to note that the OIG never suggested that it was inappropriate to challenge a negative decision or to seek another IRB's review. What the OIG found troubling was the possibility that the second IRB would be unaware of the first IRB's concerns and reservations.

After reviewing the OIG's recommendation, FDA is considering whether to revise its IRB regulations to require such disclosures and, in this advance notice of proposed rulemaking (ANPRM), has identified several issues on which it invites public comment. The public comments will help FDA decide whether a regulation is needed and, if so, what the regulation's requirements should be.

The issues, in no particular order, are as follows:

1. How significant is the problem of IRB shopping? The OIG report refers to "a few situations" where IRB shopping supposedly occurred, but does not offer any quantitative estimate. FDA seeks information on how frequently IRB shopping occurs, the circumstances in which it occurs, and the nature of the different conclusions reached by the IRBs. For example, what number or percentage of sponsors and investigators engage in IRB shopping? What issues lead to IRB shopping? Is IRB shopping more prevalent where certain FDA-regulated products are involved or more likely to occur in certain types of research or under certain other situations? What sorts of differences in IRB conclusions are observed? Are there particular areas of disagreement that suggest a wider issue, such as review of certain trial practices or standards? Is IRB shopping more prevalent when the protocol includes or excludes certain populations (such as women and minorities)? Information on specific occurrences of IRB shopping and disagreement would be useful to help determine the seriousness of the problem.

2. Who should make these disclosures? The OIG report recommended that sponsors and investigators inform IRBs about any prior reviews, but FDA's experience suggests that there is some variation as to the person who seeks IRB review. In some instances, a sponsor, rather than an investigator, will seek IRB review, especially in the case of devices. One way to deal with these variations could be to require the person who sought the prior review, whether he or she is a sponsor, investigator, or both a sponsor and investigator, to make the required disclosures.

As FDA considered this issue further, questions arose as to whether sponsors and investigators should have a duty to

inform IRBs about any prior reviews, even if the sponsor or investigator had not sought the prior review, but somehow knew about it. For example, if investigator X and investigator Y were using the same protocol, and if investigator X knew that an IRB had disapproved investigator Y's protocol, should investigator X inform his or her IRB about that disapproval even though it involved a different investigator? If the sponsor knew that an IRB had disapproved investigator Y's protocol, should it notify investigator X so that he or she could inform his or her IRB? FDA invites comment on these issues.

3. Who should receive the disclosures? The OIG report states that IRB's that are reviewing or are going to review a protocol should be informed about prior IRB reviews. This assumes that the prior IRB's decision is known at the time the second IRB is asked to review the protocol. But what happens if the new IRB has already approved the protocol at the time the prior IRB's decision becomes known? Would information about prior IRB reviews still be helpful? One could argue that sponsors and investigators should inform new IRBs about prior IRB reviews, even if the new IRB has already approved the protocol, because the prior reviews might be relevant to the new IRBs continuing review of a protocol.

4. What information should be disclosed? The type of information to be disclosed depends on the purpose of the disclosure. If the purpose is solely to be certain that an IRB is aware of a prior adverse conclusion, perhaps only unfavorable prior reviews would need to be disclosed. If the purpose of the disclosure is to ensure that IRBs receive all relevant information about a study, it might be appropriate to disclose all prior IRB decisions, both positive and negative. Should all prior IRB reviews, including approvals, be disclosed?

5. If a proposal would not require disclosure of all prior IRB decisions, what information should be disclosed? Even if the purpose of disclosure is solely to be sure an IRB is aware of an unfavorable IRB review, there could be different degrees of disclosure. An unfavorable IRB decision could encompass complete disapproval of a protocol, a decision to approve a protocol with stipulations, and a request for significant changes to a protocol. Even a decision to require additional reviews by the IRB could be considered as an unfavorable decision.

A requirement to disclose only prior unfavorable IRB reviews may presume that an unfavorable review is more likely to be correct than a favorable review. If one presumes that the earlier

IRB correctly disapproved, or requested modifications of, a protocol, then a new IRB could, indeed, benefit from knowing about that decision. This could be the case, for example, if the earlier IRB disapproved a protocol because one of its scientific members recognized that the investigational product would present a greater risk of harm to research subjects than was acknowledged in the informed consent document, based on that member's knowledge of certain animal studies. This information would be helpful to a new IRB, particularly if its scientific members did not possess the same expertise as the earlier IRB. On the other hand, a favorable decision by a prior IRB with superior expertise in a particular case could also be of value to a subsequent IRB as well.

Conversely, in cases where an initial review, either favorable or unfavorable, was not well-founded, information about the earlier IRB's review decision may offer little or no value to a new IRB and might lead to an ill-considered, "defensive" acceptance or rejection of a satisfactory proposal. For example, if an IRB was associated with an institution, and the institution was well-known or had a good reputation, a subsequent IRB might be inclined to follow the first IRB's decision even if the first IRB's decision was not well-founded.

6. To permit a subsequent IRB to assess the value of a prior IRB decision, should information about the basis for the prior decision be disclosed? Currently, IRBs are not generally required to document the reasons for approving a study, so if a proposed rule would require all IRB decisions to be disclosed, IRBs might have to explain their reasons for approving a study. Should the disclosed information include information about the composition and expertise of the prior IRB's members? What would be the additional burden on IRBs if FDA required the disclosure of the basis for all or even some IRB review decisions? How would this affect the time needed to conduct an IRB review?

7. How should FDA enforce the requirement? The OIG report did not suggest any method for enforcing a requirement that these disclosures about prior IRB reviews occur. What would be an appropriate sanction to impose on an investigator or sponsor for failure to comply with a disclosure requirement?

FDA must learn about a violation before it can consider what sanctions might be imposed. The OIG report did not recommend that sponsors and investigators inform FDA about any prior IRB reviews; it only recommended that sponsors and investigators inform IRBs. If FDA has no knowledge about

the prior IRB review, the agency might find it difficult to detect noncompliance. FDA invites comment on how it might enforce the requirement efficiently.

8. Are There Other Ways to Deal with IRB Shopping Other Than Disclosure of Prior IRB Reviews? Although the OIG report recommended requiring disclosure of prior IRB reviews, there may be other ways to deal with IRB shopping. Therefore, if the problem of IRB shopping is significant enough to warrant Federal regulatory action, are there other requirements that could be employed to address the problem besides mandating disclosure of prior IRB reviews?

II. Request for Comments

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments regarding the issues presented in this ANPRM by June 4, 2002. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments should be identified with the docket number found in brackets in the heading of this document. Received comments may be seen at the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: October 23, 2001.

Margaret M. Dotzel,

Associate Commissioner for Policy.

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[W1104-01-7334; FRL-7153-8]

Approval and Promulgation of Air Quality Implementation Plans; Wisconsin; Excess Volatile Organic Compound Emissions Fee Rule

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: The EPA is proposing to approve a rule that revises Wisconsin's State Implementation Plan (SIP) for ozone. The rule requires major stationary sources of volatile organic compounds (VOC) in the Milwaukee nonattainment area to pay a fee to the state if the area fails to attain the one-hour national ambient air quality standard for ozone by 2007. The fee must be paid beginning in 2008 and in each calendar year thereafter, until the