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**AMERICAN
SOCIETY of
GENE
THERAPY**

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May 24, 2002

Food and Drug Administration
Dockets Management Branch (HFA-305)
5600 Fishers Lane
Rockville, MD 20857

Dear Sirs:

The American Society of Gene Therapy (**ASGT**) has reviewed the Proposed Rules related to 21 CFR Part 56 [Docket No. 01N-0322] appearing in the Federal Register: March 6 2002 (Volume 67, Number 44). Responding to the request for comments, the Society would like to address the following points raised in the proposal.

First, the Society wishes to express its support of any measure that can be shown to protect the rights and welfare of research subjects participating in clinical trials. While the Society supports new requirements that further this goal, we are also aware that regulations which do not provide added protection can inhibit the development of gene therapy and other novel treatment approaches. Therefore, any new requirements should be enacted on an evidence-based need and provide for a measurable decrease in "IRB shopping".

Issue 1: How significant is the problem of IRB shopping? Few hard data at this time support the allegation that IRB shopping occurs at a significant frequency or that it adversely affects the safety of subjects participating in research studies.

If IRB shopping is occurring, the Society believes more information is required to determine the reasons such shopping occurs. For example, shopping may occur because IRBs with less expertise or rigor will approve studies, and are therefore sought by sponsors seeking approval of questionable trials. But of course in the current climate within IRBs, it is just as likely that the opposite is true: IRBs inexperienced in certain areas may chose to disapprove trials which they are uncomfortable reviewing. Any regulation is likely to be ineffective if the reasons for "IRB shopping" are not understood.

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Issue 2: who should make these disclosures? The Society believes it impractical to require investigators to make such disclosures. If an investigator submits a study on behalf of a sponsor, and the study is not approved, the FDA will be placing regulatory and financial responsibilities on an investigator who has no professional, financial or other interests in the study. As the sponsor is the only source for determining all sites where a study is under review, the sponsor (specifically the IND holder) should be responsible for disclosure.

Issue 3: who should receive the disclosures? If the FDA determines that disapproval of a study must be disclosed, the implied (or stated) reason for disclosure is the identification of important issues relevant to the safety of research subjects. Therefore, IRBs will be faced with the onerous task of re-reviewing studies each time they receive notification of disapproval at another institution. While the Proposed Rule suggests that IRBs might not need to act on disapproval immediately (for example, the IRB could wait until the study comes up for continuing review), such a delay is not consistent with the spirit of the rule. If the FDA considers it important to share disapprovals to minimize risk to research subjects, an IRB would be considered negligent if the information is not acted on expeditiously.

IRB disclosure may also lead to concerns regarding liability. Will an IRB and/or institution feel at risk in allowing a study to move forward knowing that another site disapproved the trial? The IRB or institution may be concerned that disapproval at another site could be used in legal proceeding against the institution should an adverse event occur. In this case, innovative studies may be inhibited due to financial rather than scientific concerns.

Issue 4: what information should be disclosed? Informing an IRB only when studies are disapproved assumes that the disapproving IRB's conclusions were well founded. To our knowledge there are no data to support this contention. Also, a study might have been favorably reviewed at many sites and such information would be valuable to an IRB dealing with a single report of disapproval. Therefore, consideration of an unfavorable review by an IRB should be done with full knowledge of all reviews, not only those that are unfavorable.

Issue 5: If a proposal would not require disclosure of all prior IRB decisions, what information should be disclosed? Initial IRB reviews of complex protocols rarely result in an immediate approval or disapproval. An IRB may mandate significant changes to a study but later reverse that mandate after the investigator has responded to the IRB's comments. Providing information prior to the conclusion of the IRB's final decision could therefore be misleading. Should disclosure be deemed necessary, such communications should only occur after the IRB has reached a final decision regarding the study.

Issue 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? Stipulating that IRBs detail reasons for study approval will alter the goals of the IRB. Currently, the default decision for IRBs is to approve research unless the potential risks outweigh the potential benefits. Therefore, when evaluating a study they do not assess why they should approve a study. Forcing IRBs to evaluate why a study is worth approving will change the focus of the review process and will result in increased workload for sponsors, investigators, and the IRB.

Issue 7: How should FDA enforce the requirement? Enforcement issues appear premature until the scope and consequences of IRB shopping are understood.

Issue 8: Are there other ways to deal with IRB shopping other than disclosure of prior IRB reviews? Until the reasons for IRB shopping are determined, regulation appears premature.

In addition to the issues raised in the Federal Register, there are points that are not discussed which will be critical to any subsequent ruling. Most notably, the notice does not define what a "study" is. For example, if the sponsor changes the dose, route of administration, or duration of treatment, does this constitute a "new" study? If the rule aims to regulate sponsor supported protocol open at multiple sites, reporting may be feasible. If the rule included a drug or device utilized in distinct, investigator initiated trials, reporting appears impractical.

In summary, attempts to require sponsors to inform IRB of prior review will be an onerous task and will significantly add to the work required of IRBs, sponsors and investigators. The Society supports additional investigation of the scope and frequency of "IRB shopping". If shopping does occur, it will be critical to determine the reasons for such occurrences and determine if there were any compromise to the safety of research subjects. Mandating remedies appear premature until the scope, reasons and impact for "IRE3 shopping" are known.

Sincerely,



Malcolm Brenner, MD, PhD, President
American Society of Gene Therapy



Kenneth Cornetta, MD, Chair, ASGT
Clinical & Regulatory Affairs Committee

cc: ASGT Clinical & Regulatory Affairs Committee

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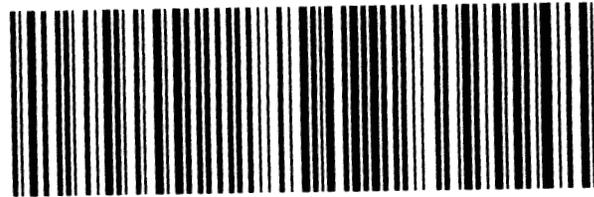
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