

April 21, 2005

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

Re: **Docket No. 2005N-0038**; Request for Comment - "*Reporting of Adverse Events to Institutional Review Boards*" (70 Federal Register 6693, February 8, 2005)

Dear Sir/Madam:

The following comments on the above-captioned topic are submitted on behalf of Pfizer Inc. Pfizer discovers, develops, manufactures, and markets leading prescription medicines for humans and animals and many of the world's best-known consumer brands. Our innovative, value-added products improve the quality of life of people around the world and help them enjoy longer, healthier, and more productive lives. The company has three business segments: health care, animal health, and consumer health care. Our products are available in more than 150 countries.

Pfizer appreciates the opportunity to comment on the questions raised by the FDA on the reporting of adverse events to Institutional Review Boards (IRBs), which were discussed at a public hearing held on March 21, 2005 (70 Federal Register 6693; February 8, 2005). Pfizer strongly supports the Agency's stated goal of providing appropriate and effective communications to Investigators and IRBs regarding patient safety in clinical trials. The need to provide the most appropriate, effective communications to investigators and IRBs regarding safety is clear. On the other hand, conservatism regarding assessment and reporting of serious, unexpected, related events provides a large influx of individual case reports to IRBs that can be difficult to put into context.

While considering the many good suggestions that will be received via the Docket, we urge the Agency to adopt a common sense approach that optimizes the benefits and minimizes the negative consequences of any new requirements. Undesirable outcomes would be to provide too great a burden of safety data in addition to what IRBs already receive, to delay studies due to prolonged discussions regarding type and feasibility of aggregate reports for individual IRBs, or to overburden sponsors with providing customized reports for every IRB and study. Any new regulation or guidance being contemplated by FDA should clearly support any new requirements, and updates to existing regulations would be required to support many of the current proposals. Changes in requirements must support the ultimate goal to provide IRBs and investigators with more meaningful information to enable them to assess and ensure the safety of their clinical trial subjects.

Each individual IRB cannot be responsible to determine the whole risk profile of a drug. Not only would this require extremely in-depth involvement with the program, but this responsibility would then be duplicated by every IRB in the program. However, the IRB has two key responsibilities: monitoring the safety of the trial subjects at their site, and evaluating the implications of safety findings from other sites and studies for the safety of the trial subjects at their site. For monitoring the safety of the IRB site subjects, the IRB should receive all reports of serious unexpected related adverse events occurring at their site, either from the sponsor or directly from the investigator. For evaluating implications of safety findings from other sites and studies, both the IRB and the investigator, in addition to periodic updates of the Investigator's Brochure, should receive aggregated reports of serious unexpected related adverse events. If the investigator also received only those case reports occurring at his/her site, as well as aggregate reports, or if all but ad hoc reporting was replaced by aggregate reporting, changes would be required to federal regulations such as 312.32 on IND Safety Reports. Changes in reporting requirements that would reduce expedited reporting to investigators and IRBs seem unlikely in the current risk environment. However, periodic reporting to investigators and IRBs could be implemented as a supplement to the current expedited reporting regulations.

A distinction is needed between IRBs responsible for a single site in multi-site trials ("local/ institutional IRBs") and IRBs responsible for multiple sites ("central IRBs"). In the first case, responsibilities should be as described above. In the second case, if there is also a local/ institutional IRB responsible for subject safety at each of the sites overseen by the central IRB, the local IRBs should receive reports as described above, while the central IRB might receive only the aggregate reports. If the central IRB is/were the sole IRB covering multiple sites, then the IRB would receive both the aggregate reports and all serious unexpected related adverse event reports for covered sites.

The proposed aggregate reports should be provided by the sponsor directly to investigators and either directly or indirectly (via the investigator) to the IRB. The reports should include adverse events that are serious and unexpected that have a reasonable causal association with the drug, in the opinion of either the reporting investigator or the sponsor. Device-related events should be included in this reporting. In general, these reports would provide aggregate incremental data since the last Investigator's Brochure or aggregate report, and would provide program-wide and not

study-specific data. Where multiple indications or special protocol conditions exist that would lead to clinically significantly different rates and types of reports, supplemental indication-specific or protocol-specific information could be provided as appropriate. The data would be provided in line listing and summary format, with counts of events per treatment group. These reports should be provided yearly, at a minimum, and should be linked with the timing of regulatory reports, such as IND Annual Reports or post-marketing aggregate reports, to ensure consistent information is being provided to investigators, IRBs, and regulators. Harmonization of aggregate reports with ICH guidance would also ensure consistency and global applicability, a key need where many larger clinical trials are global in nature. Recommendations, guidances, or regulations on the frequency of these aggregate reports should take into careful consideration the impact on subject safety, IRB resources, and other potential consequences. Although there needs to be flexibility based on a drug's risk profile, there also needs to be enough guidance to prevent the situation where IRBs in a program or even in one multi-site trial have significantly different requests for aggregate reporting. On a yearly basis, the sponsor should provide some summary text regarding the impact to the risk profile (premarketing) or benefit risk profile (postmarketing) of the drug either in the Investigator's Brochure, if appropriate, or in the appropriate aggregate report. For blinded controlled trials, the protocol should state whether such aggregate reports ~~will~~would contain blinded or unblinded information.

If ad hoc individual case reports were to be provided under certain circumstances, clear criteria for those circumstances would have to be agreed in advance and consistent with federal regulations since, given uncertainty, the conservative route would generally be taken and lead to reporting of many events whose medical relevance could not be completely disproved. The details of ad hoc reporting criteria would require considerable thought to develop appropriately. However, if aggregate report analysis reveals significant new safety information or if any safety information results in changes to the protocol, informed consent, or Investigator's Brochure, this information would be provided in a letter from the sponsor to all investigators, IRBs, and regulators.

In summary, we agree that providing consolidated or aggregate reports of appropriate adverse events by the sponsor on at least an annual basis, with an annual analysis or summary of the drug risk profile (pre-approval) or benefit risk profile (post-approval) by the sponsor, would improve the ability of an IRB to make useful determinations based on the adverse event data received. We emphasize that consideration of ethics, science, equity and efficiency dictate the importance of providing the same information in the same format to both the investigator and IRB, and preferably in a format that could be used globally. Any exceptions to this rule (i.e. providing information to the IRB and not to the investigator) would require a strong justification, such as prevention of scientific bias on the investigator's part, should the information unblind patient assignment to drug therapy. When exceptions are justified, it may be appropriate for the IRB to receive the aggregate safety reports directly from the sponsor rather than from the investigator.

We reiterate that a practical approach, one that thoughtfully considers both intended and unintended consequences, is extremely important in contemplating possible new requirements. We have particular concerns regarding potential negative impacts, such as additional burden on IRBs, study start-up delays, and unnecessary burdens on sponsors from multiple nonharmonized aggregate reports. Any new Regulation or guidance being contemplated by the Agency should clearly support any new requirements and we should always maintain sight of the ultimate goal, which is to provide IRBs and investigators with more meaningful information to enable them to assess and ensure the safety of their clinical trial subjects.

In closing, Pfizer recognizes and commends FDA's commitment to the safety of clinical trial subjects, continuous improvement of the clinical trial process, and effective communications among agency, sponsor, investigator, and IRB. We thank FDA for the opportunity to comment and we look forward to working with the Agency, the IRB community, investigators, and other stakeholders as improvements are made in the current system for notification of IRBs regarding safety information. We would be pleased to respond to any questions that the Agency might have.

Sincerely,

Deborah Kirby  
Vice President

cc: <http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm>