

Alan Goldhammer, PhD

Associate Vice President,
US Regulatory Affairs



April 21, 2005

Dockets Management Branch
Food and Drug Administration
HFA-305
5600 Fishers Lane
Room 1061
Rockville, MD 20857

Re: Docket No. 2005N-0038; Reporting Adverse Events to Institutional Review Boards; Public Hearing; 70 Federal Register 6693, February 8, 2005

Dear Sir/Madam:

The following comments on the above topic supplement those presented by the Pharmaceutical Research and Manufacturers of America (PhRMA) at last month's public meeting. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2004, our members invested over \$38 billion in the discovery and development of new medicines.

1. Introduction and background:

PhRMA commends the FDA for organizing a dialogue to discuss issues surrounding reporting of drug safety information to sites, particularly for multi-center studies. The issues summarized in the Federal Register notice regarding the current practice of sending large numbers of individual case reports to IRBs via Investigators, which were further reinforced during the presentations at the Public Hearing, are clearly recognized by PhRMA companies. As highlighted in the presentations, the issues are complex and driven by various requirements impacting the current practices in reporting of safety information to sites and IRBs. The community at large would benefit from harmonization of regulatory directives and clearer guidance from Federal agencies.

The current regulatory framework and guidance documents, including FDA IND regulations and the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use E6 consolidated guidance on Good Clinical Practice, require the expedited submission of clinical study adverse events case reports that are serious, unexpected and at least possibly related to the product(s) under investigation. These reports are to be submitted to Regulatory Authorities, as well as Investigators involved in the study, in most situations within 15 calendar days from the receipt of the information by the Sponsor. It is in turn the responsibility of the Investigators to inform their IRB(s). Sponsors routinely monitor to assure Investigators fulfill their responsibilities.

Currently PhRMA companies take a conservative approach in their assessment of which reports are to be sent to Investigators and for Investigators in turn to send all reports they receive to their IRBs. This process ensures timeliness of notification, but does not best address completeness or meaningfulness of the information. Clinical trial programs often require large

Pharmaceutical Research and Manufacturers of America

1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3533 • FAX: 202-835-3597 • E-Mail: agoldham@phrma.org

numbers of participants and protocols involving multiple Investigators and IRBs. The high number of cases and disaggregated nature of the individual reports make it difficult for the Investigators and IRBs to fully evaluate the significance and implication for study participants at their site.

2. Potential approaches to improve the situation:

During the presentations at the March 21 Public Hearing, several alternatives to the current situation were described, including PhRMA's proposals, which emphasized that more meaningful information would facilitate the IRBs' activities in their role of protecting participants in clinical research studies.

The proposals put forth by PhRMA focus on addressing FDA's question #3 (Approaches to providing adverse events information to IRBs), but we also provide elements that may be relevant to question # 2 (The types of adverse events about which IRBs should receive information). These proposals leverage changes in the current regulatory framework (including concepts included in the newly implemented European Union Clinical Trial Directive), the implementation of Industry Sponsors' best practices, and the recent concepts outlined in the recommendations of the Council for International Organizations of Medical Sciences (CIOMS) VI Working Group.

The core concepts proposed by PhRMA include the following:

- Replace the current process of reporting all serious, unexpected and associated reports to investigators with:
 - Sponsors to provide periodic aggregate safety information to investigators and IRBs.
 - Sponsors to provide 15 day notification for ad-hoc reports of meaningful safety information to investigators and IRBs.

Periodic Aggregate Safety Information:

Information provided to the IRBs should be complete, timely and meaningful. Aggregate safety information should be provided at periodic intervals together with an evaluation of the evolving safety profile of the product under investigation. These summary reports would be best suited for multi-center studies (usually phase II-IV studies), and may not be required for single-center trials. The summary reports should cover the safety profile at the compound level, not just at the study level. The high-level format of such documents is proposed by PhRMA to include the following:

- Line listing containing all serious, unexpected, possibly related adverse events for the reporting period. Note that the line listing would preferably be unblinded, unless unblinding would invalidate the trial (such as endpoint events) – In such cases the rationale for a waiver for the unblinding should be clearly explained.
- Serious adverse event counts (regardless of expectedness and blinding) for active drug, comparator (including placebo) This would be a summary tabulation sorted by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Terms (PT) for the reporting period, as well as a cumulative summary.

- Narrative summary of the safety information covered for the period, taking into consideration any safety issue relevant to the conduct of the trial(s). This narrative would be a critical discussion and interpretation of the evolving safety profile of the investigational product and the impact, or lack thereof, on the risks to the trial participants.

Timeframe for such reports would be documented in the protocols for the program or in protocol appendices, and would be justified based on the target patient population, known safety profile of the product, and expected potential issues based on the similar products or mechanism of action. For most products under development, the frequency would usually be quarterly or every six months, depending on the type of product/study (including considerations for the mechanism of action, emerging or known safety profile of the product, targeted patient population, etc.). For products that are already marketed, a less frequent update (e.g., yearly) or simplified report (e.g., updates to the Investigators Brochure/Company Core Safety Information or other simple notification) may be acceptable. In any case, the reporting frequency should be based on a pre-specified "birth date", which would be the same for the entire development program (equivalent to the Periodic Safety Update Report "International Birth Date"). The protocol section/addendum covering safety reporting should also describe the plans, including scope and frequency, for any Data Safety Monitoring Boards (DSMB) / Data Monitoring Committees (DMC) safety reviews, as well as how the outcome of the review would be communicated to the sites. It should be clarified that DSMB/DMCs do not perform overall product safety surveillance. They typically see only focused data from a single trial or a small number of related trials for the purpose of applying pre-specified early stopping rules for safety or efficacy endpoints. They may also recommend protocol amendments. In either case, any protocol modifications/actions carried out by the sponsor are to be promptly notified to the Investigators and IRBs.

PhRMA companies also strongly recommend that the format of such aggregate documents be harmonized in the context of ICH guidance, so that these documents could be used to meet requirements across the ICH regions.

15 day Ad-Hoc Reports of Meaningful Safety Information:

In addition to the aggregate safety information, ad-hoc reports of meaningful safety information (e.g., information that has implications for the conduct of the trial or warrants immediate revision to the informed consent) should be provided to investigators and IRBs, as these are received by Sponsors.

- Only meaningful single reports would be communicated on an expedited basis (e.g., single events which due to their nature bring significant new safety information which has implications for the conduct of the trial or warrants immediate revision to the informed consent).
- Additional aggregate information that is meaningful, but not in the form of single reports (e.g., pre-clinical or clinical study results which bring significant new safety information and have implication for the conduct of the trial) would also qualify for ad-hoc, expedited reporting (consistent with current regulations).

The criteria proposed by PhRMA companies to help guide the identification of such meaningful events are as follows:

- Event or series of events that have a significant impact on the course of the clinical trial or program (e.g., protocol amendment, change in patient monitoring, enrolment hold or discontinuation of the trial).
- Any issue that indicates an increased risk to trial participants/subjects (new safety issue, results of lack of activity in another trial, etc...) and hence warrants immediate revision to the informed consent.

3. Additional Important Elements for Consideration:

The difficulty in managing individual case reports does not impact just IRBs, but also Investigators. Focus on providing only relevant reports on an expedited basis to sites, with periodic reporting of aggregate safety information together with an evaluation of the accumulating safety information will provide both Investigators and IRBs with better information to help them fulfill their obligation of oversight of the trial at their sites.

Current expedited reporting to Regulatory Health Authorities would remain unchanged (as directed by the harmonized ICH E2A Guideline).

As FDA re-evaluates the process of reporting safety information to IRBs, PhRMA urges the Agency to also evaluate the value of more meaningful reporting to Investigators. In this respect the proposals outlined in the recently completed CIOMS VI report are considered extremely valuable.

Preparation of Guidance within the ICH process is also planned to include the concepts of the CIOMS VI reports. PhRMA would also like to re-emphasize the value of the harmonization of reporting approaches across the sites involved in the research activities (including sites outside of the US).

During the public hearing, the FDA asked a number of additional questions of the presenters. PhRMA companies would like to take the opportunity in these written comments to provide their perspective on some of these additional questions.

- 1) What is PhRMA's position on providing information to Investigators only vs. both Investigators and the IRBs vs. the IRBs only?

PhRMA companies believe that the proposed new format for ongoing reporting of safety information will benefit both the Investigators and the IRBs. PhRMA therefore supports having this information sent to both constituents in parallel. This would facilitate timely distribution of the information to both the Investigators and IRBs and ensure the receipt of consistent information of both groups.

- 2) Should independent Data Safety Monitoring Boards (DSMB) or Data Monitoring Committees (DMC) be implemented for every study?

PhRMA companies do not believe that independent DSMBs or DMCs should be required for every study or for every multi-center study. Independent DSMBs/DMCs should be established when the study methodology or product-specific issues need such an approach. PhRMA recommends that the approach to be followed for a study be described for the study (e.g., within the protocol or an addendum thereof). Again, it is important to delineate that

DSMB/DMCs are not in a position to perform overall product safety surveillance activities. They are commissioned to oversee ongoing trials for the purpose of applying early stopping rules for efficacy or safety endpoints and/or to make recommendations for protocol amendments. It is the responsibility of Sponsors, with oversight from Regulatory Agencies, to provide ongoing product safety surveillance.

4. Conclusions:

PhRMA appreciates the opportunity to comment on this topic and commends the FDA for initiating the dialogue around these issues and possible solutions. PhRMA companies recognize the issues identified by the IRB community and agree that the current system for notification of safety information to IRBs can and should be improved. PhRMA recognizes that more meaningful information to the IRBs will help in their role to protect the public, thereby improving the overall Clinical Research process and PhRMA is committed to actively participate in activities aimed at such improvements. Finally, PhRMA urges FDA to take the opportunity of this review to also address the issue of individual case reporting to Investigators.

Sincerely,

A handwritten signature in cursive script, appearing to read "Alan Helleman".