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GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

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

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

Dear Sir/Madam:

Enclosed please find comments from GlaxoSmithKline (GSK) in response to FDA's request for comments concerning the reporting of adverse events to Institutional Review Boards (IRBs), and suggestions for improving the process to best meet the purposes of IRB review – the protection of human clinical trial subjects.

As FDA notes in the Federal Register notice, the current regulatory framework regarding reporting of adverse events from clinical trials to investigators and IRBs was implemented at a time when most clinical trials involved a single site or a small number of sites, and is not well suited to the current situation, where a clinical development program often includes several very large studies involving multiple sites. As a multinational research-based pharmaceutical company, GSK sponsors many clinical trials of various designs, durations, and complexity, many of which involve investigational sites in multiple countries. We recognize the issues identified by the IRB community and share the concerns of FDA and IRBs that the current system is not an optimal mechanism for providing IRBs with the information they need to ensure the protection of the rights and welfare of clinical trial subjects. We appreciate the opportunity to provide comments on this important issue.

- In the Federal Register notice, the Agency requested information on three topics:
1. The role of IRBs in the review of adverse event information from ongoing clinical trials.
 2. The types of adverse events about which IRBs should receive information.
 3. Approaches to providing adverse events information to IRBs.

Our comments are primarily directed to the second and third topics, and focus on adverse event information provided to investigators and IRBs by sponsors.

Related points for consideration:

1. The issues identified by the IRB community related to receipt of large volumes of individual expedited case safety reports, without adequate information to enable the IRB to fully assess the implications for study subjects, are equally applicable to investigators, who also receive these reports. We urge the Agency to consider including reporting of adverse events to investigators in whatever guidance or regulations are developed for reporting to IRBs.

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2. We also urge that wherever possible, the Agency harmonize their requirements and guidance with international initiatives in this area, such as the ICH E6 Guideline for Good Clinical Practice, the European Union Clinical Trial Directive and the CIOMS VI report on Management of Safety Information from Clinical Trials.

With regard to the types of adverse event information required by IRBs and methods for providing this information to IRBs, we believe that periodic reporting to IRBs and investigators by sponsors would provide the appropriate information in a much more meaningful, effective and less burdensome manner than the current practice of sponsors sending individual case safety reports to investigators who then forward the reports to their IRBs. Such a periodic report is described in the EU Clinical Trial Directive guidance document ENTR/CT 3, and was also recommended by the recent CIOMS VI Working Group. GSK supports the CIOMS VI recommendations, and we strongly urge FDA to consider these recommendations in their deliberations regarding adverse event reporting to IRBs and investigators.

As outlined in the CIOMS VI report, a periodic report to investigators and IRBs/Ethics Committees would include:

- an unblinded line listing of all cases from clinical trials that were submitted to regulatory authorities in an expedited manner during the report period,
- a copy of the current Development Core Safety Information (DCSI) with an explanation of any changes, and
- a brief summary of the emerging safety profile of the compound, taking into account all accumulating data. The summary could also include information on any significant safety issue arising from spontaneous reports, as well as a statement regarding the impact of any changes in the safety profile on the risks to the trial subjects.

The report would be based on the compound in clinical development, rather than on an individual clinical study. For unapproved products, in most cases reports would be submitted quarterly, but there may be circumstances where more or less frequent reports would be appropriate. For approved products, timing of reports would depend on the extent to which new indications are being investigated, (e.g., quarterly for products in Phase II trials, less frequently for well-established products). The CIOMS VI Working Group recommends that for Phase IV investigators and their IRBs, communication of changes to the Company Core Safety Information (CCSI) for marketed products is sufficient, and periodic reports would not be required. We suggest that if periodic reports are required for approved products, the line listings would be limited to clinical trials involving new indications or formulations.

Significant safety issues, defined as those that impact the course of the clinical trial or development program (including suspension of the trial or amendments to protocols), or that warrant immediate update of the informed consent, should be reported to investigators and IRBs in an expedited manner, whether they arise from a single individual case report or analysis of aggregate data.

It is important to note that we are not recommending any changes to the current requirements for investigators to report all adverse reactions to the sponsor, nor to the requirements for expedited reporting to regulatory authorities of serious, unexpected adverse events with a reasonable possibility of a causal relationship to the trial medication by sponsors.

Additionally we suggest that the application of paper-free technology, such as study-specific secure web sites containing both individual and aggregate data, may also have a role in communicating safety information to investigators and IRBs in an effective manner, and urge the Agency to consider this possibility in their deliberations.

In summary, we agree that the current system of providing individual expedited case reports to investigators and IRBs does not provide investigators or IRBs with the optimal information that they need to ensure the protection of clinical trial subjects. We believe that periodic reporting of aggregate information will enable sponsors to provide more meaningful information to investigators and IRBs, and we thank the Agency for their consideration of these comments on this important issue.

Sincerely,



Edward N. Pattishall, MD, MPH
Vice President
Global Clinical Safety and Pharmacovigilance