April XX, 2005

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 (AEs) to Institutional Review Boards.
Commentary submitted by MedImmune, Inc.

Dear Sir or Madam,

Thank you for the opportunity to comment on the Reporting of Adverse Events to Institutional Review Boards. MedImmune Inc. regards the safety of patients as paramount and welcomes a thoughtful dialogue on how industry, regulatory authorities, institutional review boards and clinical investigators can work together to implement an efficient system for communication of significant new safety information during clinical trials.

- **What role should IRBs play in the review of adverse events information from an ongoing clinical trial?**
  IRBs are responsible for performing continuing review of ongoing research and have an obligation to protect the rights and welfare of human subjects enrolled in clinical trials at their institutions (21 CFR 56). This responsibility requires efficient safety monitoring and early detection of signals which indicate significant risk for human subjects. Access to all adverse event data and epidemiology information is necessary for objective safety assessment (analysis and evaluation of safety data). IRBs however do not have access to all adverse event data or their membership often does not include individuals with expertise for undertaking safety assessment. IRBs should therefore not generally be expected to perform initial safety assessment of adverse event data i.e. initial analysis and evaluation of individual case safety reports (ICSRs). Sponsors of clinical trials should be accountable for providing to IRBs initial safety assessment of adverse event data.

- **What types of adverse events should an IRB receive information about?**
  IRBs should receive adverse event information that indicates significant risk for human subjects. As previously noted, this requires initial analysis and evaluation of all other similar events and background event rates by sponsors prior to communication to IRBs. The following issues are impeding achievement of the goal of communicating significant safety information to IRBs:

FDA Regulations:

Issue: Current regulations do not support communication of significant risk information.

Current regulations require investigators to promptly report to the IRB all unanticipated problems involving risk to human subjects (21 CFR 66) or sponsors to expedite all serious, unexpected, and associated adverse reactions (SUARs) to investigators (21 CFR 312.32). "Unanticipated problems" or "SUARs" do not necessarily indicate significant risk situations and expedited reporting of all such events to clinical investigators and IRBs is inefficient and contributes to increased noise to signal ratio in the safety surveillance system. Further clarification on "unanticipated problems" to indicate situations of significant risk, should be provided to investigators (21 CFR 66). The linked requirement for expedited reporting of all SUARs to both FDA and investigators should be revised (21 CFR 312.32). Only SUARs that represent new significant risk information should be expedited to investigators and IRBs but expedited reporting of all SUARs to the FDA should be maintained due to the agency's shared responsibility with sponsors in signaling adverse event data.

Expectedness Assessment:

Issue: Varied thresholds are applied by sponsors when determining AE expectedness.

21 CFR 312.32 (IND safety reports) defines "unexpected adverse drug experience" as an adverse drug experience that has not been previously observed (e.g. mentioned in the investigator brochure). Specific guidance on the interpretation of "mentioned in the investigator brochure (I.B)." is not available to sponsors of clinical trials. This situation has led to a spectrum of approaches by sponsors in identifying thresholds for expectedness of adverse experiences, ranging from events that have been observed in animals and mentioned in the I.B., to the CIOMS III/V recommended approach for listing expected events in developmental core safety information (DCSI). Adoption of the DCSI approach by all sponsors of clinical trials would introduce consistency in assessment of adverse event expectedness during clinical trials i.e. an event is expected when the event is included (listed) in the DCSI list which corresponds to a threshold of established causal relationship between the drug and the event. Waivers for expedited adverse drug reaction (ADR) reporting should be prospectively agreed with the FDA for adverse events that are associated with the disease or patient population under investigation or are clinical efficacy endpoints in the trial. When this proposal is considered in the context of other proposals submitted here, there is no adverse impact on IRBs and there is benefit to regulatory agencies such as the FDA who have a shared responsibility with sponsors in signaling adverse event data.

Causality Assessment:

Issue: Causality assessments of individual case reports do not necessarily indicate significant risk.

"Associated with the use of the drug" (CFR 312.32) is currently interpreted by sponsors as meaning "there is reasonable possibility that the experience may have been caused by the drug". This level of interpretation of causal association corresponds to "possible" on causality scales and other alternative etiologies or risk factors for the adverse event in question are potentially present by definition. Upgrading the causality threshold for expedited reporting from "possible" to "probable" or "definite" in an effort to reduce the volume of distributed SUARs and enhance communication of significant risk information, would have the following effects:

- Negative effect of reducing the number of expedited reports to the FDA.
- Added complexity in global safety surveillance operations due to divergence from the ICH standard of "possible".
- False sense of enhanced prediction from ICSRs since objective safety assessment always requires consideration of all adverse event data and epidemiology information irrespective of causality of individual cases.

- **What approaches should be used to provide adverse events information to IRBs?** MedImmune Inc. proposes the following approaches for communicating significant risk information to IRBs (see attachment for details):
    - Individual SUARs: ICSRs should be provided to IRBs only when such information dictates need for an update to the Informed Consent Form (ICF) or protocol amendment.
    - Aggregate SUARs: Monthly case listings should be provided to IRBs for their ongoing awareness of all such events.
    - Aggregate SAEs: Quarterly reports including the sponsor's safety assessment of data/information in the report should be provided to IRBs to enable them undertake ongoing review of adverse event information.
    - Data Monitoring Committee (DMC) Reports: These reports should be provided to IRBs when available.

Closing Comments

MedImmune Inc. believes that the current crisis situation with excessive volume of expedited reporting to investigators and IRBs and attendant high noise to signal ratio can be corrected by consideration and implementation of the proposed approaches. The FDA should also carefully take into consideration approaches in other ICH regions (e.g. EU Clinical Trials Directive) in the interest of global harmonization, efficiency and reduced complexity for sponsors' global safety systems.

Regards,

Samuel Yonren, M.D.
Vice President,
Product Safety

Attachment

What	Format/Content	Schedule	Rationale
Individual SUARs	**Expedite Report** ▪ CIOMS report including sponsor's summary analysis and evaluation.	7/15 calendar days	▪ Expedite SUAR report is only sent to IRBs when such information represents significant risk i.e. update to ICF or protocol amendment is required. ▪ This approach will reduce the volume of expedited reports to IRBs and minimize "noise" in the safety surveillance system involving investigators and IRBs.
Aggregate SUARs	**Periodic Monthly Listings** ▪ CIOMS II line (case) listings	Monthly	▪ Certain IRBs want to be aware of all SUARs (internal and external) on an ongoing basis. ▪ This approach will ensure ongoing awareness of all SUARs by all IRBs and reduce the paper burden resulting from distribution of individual case reports.
Aggregate SAEs	**Periodic Quarterly Report** ▪ SUAR (IND Safety Reports) listings ▪ Other SAE listings ▪ Summary Analysis and evaluation of information in the report.	Quarterly	▪ This report provides IRBs with the sponsor's safety assessment for adverse event information reported during the interval period. ▪ The quarterly report should include analysis and evaluation of ALL SAEs and not only SUARs. ▪ This format is similar to NDA postmarketing quarterly report. ▪ This approach also accommodates the EU Clinical Trials Directive requirement for quarterly reports of SUSARs and therefore supports global harmonization.
Data Monitoring Committee (DMC) Reports	**DMC Report**	When available	▪ Provides independent scientific review and opinion on accumulating safety data.

SUAR: serious unexpected associated reaction
SUSAR: serious unexpected suspected adverse reaction
SAE: serious adverse event