Applied Research Ethics National Association (ARENA)
Public Responsibility in Medicine and Research (PRIM&R)
126 Brookline Avenue, Suite 202
Boston, MA 02215 USA
Phone 617.423.4112 | Fax 617.423.1185
info@arena.org | www.primr.org

October 13, 2003

Dockets Management Branch (HFA-305)
Docket No. 00N-1484
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Comments on Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule

To whom it may concern:

On behalf of the Applied Research Ethics National Association (ARENA), we appreciate the opportunity to comment on the *Proposed Rule for Safety Reporting Requirements for Human Drug and Biological Products* published in the Federal Register on March 14, 2003. ARENA is a division of Public Responsibility in Medicine and Research (PRIM&R), and shares with that organization a commitment to advance the highest ethical standards governing research and to foster their consistent application. ARENA's members include administrators, chairs and members of Institutional Review Boards (IRBs) and Institutional Animal Care and Use Committees (IACUCs), representing organizations across the nation with varying volumes and complexities of research.

ARENA supports global harmonization of safety reporting that will enhance the overall system for human research subject protections. The following comments have been prepared from the perspective of those working with Institutional Review Boards (IRBs). We hope you consider the following comments as you prepare the final rule. Thank you for the opportunity to provide this information.

- The proposed rule does not mention the role of an IRB in the reporting process for a suspected adverse drug reaction (SADR). The proposal is silent about sending any information to IRBs although the IRB's charge is to have written procedures for reporting "Any unanticipated problems involving risks to human subjects or others." Therefore, we recommend that the FDA be clear about whether any changes in sections 56.108(b)(1), 56.111(a)(1) and 312.66 are to be proposed. *FDA's Guidance (Continuing Review, Sept 1998)* advises IRBs to have written procedures for receiving and reviewing reports of "adverse reactions and unexpected events" involving risks to subjects or others.

00N-1484

C21

Recommendation: Provide guidance to sponsors, manufacturers, investigators and IRBs that clearly delineates the reporting responsibilities of SADR(s) to the IRB.

- The regulation should specifically and clearly acknowledge that sponsors, manufacturers and applicants are permitted to propose alternatives that will avoid over-reporting of SADRs while assuring that SADR reporting is not compromised. ARENA agrees with the FDA that the proposed definition for a "suspected adverse drug reaction" (SADR) will "result in an increase in safety reporting for clinical studies of investigational and marketed products". We also agree that "the proposed definition of SADR may result in submission of numerous safety reports to the agency for which the reported SADR is not informative as a single report because it is very likely to have been a consequence of the patient's disease." The following comments from a research investigator reflect how the proposed definition of the "SADR" and "unexpected SADR" could lead to over-reporting:

Comment on SADR Definition

The ICH terminology of "reaction" and "response" could be misleading if these terms are taken to imply a direct causal relationship. Under such terminology, neutropenia would be considered as an adverse drug "reaction" or "unintended response," but a consequent infection could be considered as a secondary complication, rather than a "reaction" or "response" to the drug itself. The original term "experience" is broader and would be preferable, since this term clearly embraces secondary complications, as well as direct reactions and responses.

Without additional guidance, the "relationship cannot be ruled out" standard will likely result in expedited reporting of any SADR that is both serious and unexpected, regardless of whether the product caused the response or not. The guidance could be improved by providing additional criteria specifying the circumstances under which a causal relationship can be affirmatively ruled out. This category could include reactions that are most plausibly explained by the subject's underlying medical condition or by concomitant therapy, provided that the reaction has neither a plausible temporal relationship nor a plausible biological relationship to the administration of the product.

Even with additional guidance, the new "relationship cannot be ruled out" standard would almost certainly require expedited reporting of any SADR that is both serious and unexpected in subjects who are seriously ill due to the underlying disease. The complexity of an illness such as cancer and its treatment through administration of multiple transfusions and concomitant medications, including potentially toxic antibiotics and antifungal agents, will make it impossible to satisfy the "relationship cannot be ruled out" standard. In such situations, "over-reporting" is bound to occur under the proposed rules.

Comment on unexpected SADR

As written, the "severity" standard is vague, since product brochures and labels typically define SADRs in qualitative terms rather than quantitative terms. In some cases, quantitative terms are available, as acknowledged in the draft regulation, but these are exceptions rather than the rule. This gap leaves it to the imagination of the

investigator to make a threshold judgment, knowing that all reactions have a range of severity. For example, should infections requiring hospitalization be categorized as "expected" after cancer chemotherapy, since they are known to occur at some frequency?

RECOMMENDATIONS: Inform investigators, sponsors, manufacturers and IRBs that protocols can be written to describe, per study, what will or will not be considered a SADR requiring expedited reporting based on the condition of the research subject under study. This would ensure safety criteria and outcomes are managed appropriately.

The protocols could also detail the role of the Data Safety Monitoring Boards for Phase 3 and 4 studies when reviewing SADR(s) that could help reduce redundancy of SADR reporting evaluations to the IRB. With detailed information about the role of the DSMB and their review of trial wide SADR(s), an IRB could more efficiently focus their attention on local SADRs, knowing that trial wide monitoring was occurring by experts on the DSMB.

Collectively, we consider these suggested approaches will meet the spirit and intent of the safety protections proposed by the FDA and also streamline the reporting efficiencies in a way the reduces redundancy, while at the same time protects the safety of research participants participating in trials involving drugs and biological products.

Thank you again for the opportunity to comment on this proposed rule. We also look forward to and encourage any future harmonization efforts between FDA and NIH, as noted in the summary section of the FDA Proposed Rule. If ARENA can assist you in that effort, we would be willing to provide you input.

Sincerely,

Marianne Elliott,

Karen Hansen

Cc: Drafting Committee: Pat Scannell; Erica Heath; Paul Martin, MD; Phil Ludbrook, MD; Bernard Schwetz, DVM, Acting Director, OHRP; David LePay, FDA