ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

October 14, 2003

Dockets Management Branch (HFA-305)
Docket Number 02N-0475
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 00N-1484

Proposed Rule – "Safety Reporting Requirements for Human Drug and Biological Products"

Dear Sirs:

Clinical research organizations (CROs) assist pharmaceutical, biotechnology and medical device companies with the conduct of thousands of clinical trials each year, and are a key participant in the development of new drugs and new treatments. The Association of Clinical Research Organizations (ACRO) was formed in 2002 to represent this key segment of the clinical research enterprise to legislative and regulatory bodies. ACRO member companies employ more than 40,000 people worldwide, conduct research in 60 countries, and represent a multibillion-dollar industry. ACRO is pleased to submit the following comments regarding several key proposals in the above-referenced proposed rule.

The safety of human participants in clinical research is a core issue for ACRO members, and the Association applauds the FDA's interest in modifying current safety reporting requirements to address the potential for the under-reporting of adverse drug reactions, and to provide additional data to the agency to better evaluate the relationship between specific drug and biological products and adverse events that may be associated with their use. Further, we support the implementation of safety reporting standards consistent with those recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

While we believe that there is very little under-reporting of serious adverse events (SAEs) in clinical trials that are conducted under FDA regulations, ACRO recognizes that the degree of 'discretion' left to investigators under the "reasonable possibility" standard for determining that a drug or biological may have caused an adverse event may, in some instances (including clinical research that is conducted under the Common Rule,)

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result in a 'premature' decision that the probability of causality is sufficiently low that the adverse event need not be reported. Thus, even as we note the potential for a significant increase in adverse event reporting and a consequent exacerbation of potential noise-to-signal problems, ACRO can support a change that would define "reasonable possibility" as meaning that "the relationship cannot be ruled out." However, since the common-sense meanings of "reasonable possibility" and "cannot be ruled out" are not, in fact, synonymous, we believe that the potential for definitional confusion will remain under the language in the proposed rule, and we would support the suggested 'alternative' definition for a SADR offered in the NPRM: "A noxious and unintended response to any dose of a drug product for which a relationship between the product and the response to the product cannot be ruled out" [FR Vol. 68, No. 50, p. 12417].

As the agency notes in the proposed rule, "with regard to clinical studies of investigational and marketed drugs and biological products, the proposed definition of SADR is likely to result in an increase in the number of safety reports that are currently submitted to the FDA..." [FR p. 12417]. In the proposed rule the agency goes on to suggest that it would be open to proposals from sponsors or applicants for alternative methods of adverse event reporting during clinical studies that would minimize 'over-reporting' while still assuring that the agency can develop an adequate picture of "suspected" adverse experiences. For example, the study protocol and other documentation could list known consequences of a disease relevant to a particular study, which would not be submitted to the FDA in an expedited manner as individual case safety reports, but would be monitored by the sponsor or applicant and reported to the agency if, in aggregate, it appears that the product in use in the clinical study may be causing an increase in events sufficient to consider product administration changes. ACRO believes that providing expanded opportunity for sponsors and applicants to discuss beforehand the 'ground rules' for SADR reporting for specific studies offers the potential for positive improvements in protocol design.

Consistent with current safety reporting regulations, the proposed rule requires prompt reporting of SADRs that are serious and unexpected, which must be submitted in writing within 15 calendar days (or seven days for SADRs that are fatal or life-threatening). The proposed rule stipulates that written notification of serious and unexpected SADRs would flow to participating investigators as well as the FDA, and those investigators will be required to notify the relevant institutional review board (IRB), as is true today. Notwithstanding the possibility that alternative methods for SADR reporting will be devised in consultation with the agency before a trial begins, the potential remains that IRBs could be inundated by written IND safety reports of serious SADRs that were unexpected, especially in large, multicenter, phase III trials. Since a SADR relationship to study drug, under the proposed definition, "cannot be ruled out" the vast majority of what are today called serious adverse events (SAEs) will be assessed as possibly related to study product. That is, the process of causality assessment outlined in III.B.2.b [FR p. 12424] will in most cases default to 'related' and thus generate the potential to dramatically increase the number of written IND safety reports.

What is needed is an approach that assures the agency of adequate safety oversight and improved decision making while, at the same time, not overburdening review boards. An

approach to consider that would allow IRBs to focus on trends rather than isolated events would be to decrease the number of isolated IND safety reports from clinical trials by requiring sponsors of large studies (for example, of greater than 150 total patients) to submit to review boards regular (monthly, bimonthly, quarterly, other) blinded, tabular summaries of all serious SADRs, sorted using standard coding dictionaries. Under this approach the agency could still define certain individual events as requiring immediate IRB notification when they result in an IND safety report. For example, the agency could require that the same list of "medically significant" SADRs defined as "always expedited reports" in the post-marketing environment [FR p. 12432] must be reported to investigators and IRBs within the same timeframe as the report to the FDA.

While there is much to commend in the proposed rule, ACRO is concerned about the introduction of medication error reporting into the safety reporting system, especially in regard to the requirement to report "potential" as well as actual medication errors, and always on an expedited basis. As the proposed rule's definition of medication error makes clear, the preventable events "that may cause or lead to inappropriate medication use or patient harm" are almost always related to human factors and do not represent "a noxious or unintended response" to a properly administered drug product. While ACRO recognizes the need to develop new mechanisms for tracking and addressing the hundreds of thousands of medication errors that occur each year in hospitals alone, the Association is concerned that expedited reporting of even a small percentage of these events would quickly overwhelm the resources available to the FDA and could begin to detract from the capacity of the safety reporting system to identify and address SADRs as new drugs and biologicals are in development. If reporting of medication errors is retained in further versions of the proposed rule, ACRO suggest that "potential" medication errors or those that do not result in a SADR should not be reported to the FDA on an expedited basis but rather made part of other periodic reports to the agency.

Since its inception, ACRO has advocated for the development of uniform human research subject protection requirements that would apply to all research subject to Federal oversight, regardless of the source of funding for the research or the site where the research is conducted. In light of that basic principle, ACRO urges the FDA to request that the NIH and the other Federal agencies that have agreed to the Common Rule also adopt the proposed changes to current safety reporting requirements. We believe that all participants in the research enterprise must be fully committed to the protection of research participants, and fostering better and more complete safety reporting will support that commitment.

On behalf of the Association of Clinical Research Organizations (ACRO), I am pleased to submit these comments.

Sincerely,

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