



0575 5 APR 21 A9:31

Date: APR 20 2005

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

Re: Docket Number 2005N-0038  
Response to FDA Call for Comments  
Reporting of Adverse Events to Institutional Review Boards

Dear Sir or Madam:

Reference is made to the February 8, 2005 Federal Register notice announcing the request for comments on Reporting of Adverse Events to Institutional Review Boards.

AstraZeneca has reviewed the Federal Register notice and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Michael Young, Regulatory Affairs Manager, at (302) 885-4196.

Sincerely,

Judith Molt, Director  
Regulatory Affairs  
Telephone: (302) 885-0976  
Fax: (302) 886-2822

Enclosure

2005N-0038

C8

**February 8, 2005, Federal Register Notice [Docket No. 2005N-0038]  
"Reporting of Adverse Events to Institutional Review Boards"**

FDA would like to understand better how the IRB's responsibility with respect to adverse events fits with the roles of these other parties and how the process for reporting adverse events to IRBs can be improved to better enable IRBs to meet their obligation to protect the rights and welfare of human subjects. FDA would like interested parties to address the following issues and questions:

**1. The role of IRBs in the review of adverse event information from ongoing clinical trials.**

**Question:**

Given the number of parties with responsibilities related to adverse events that occur during the course of a clinical trial, what role should IRBs play in the review of adverse events information from an ongoing clinical trial?

**AstraZeneca Response:**

As stated in 21 CFR Part 56, Subpart A, Section 102 (g), the IRB's primary role is to protect the rights and welfare of the study subjects at their institution. However, we do not believe it is necessary for IRBs to review individual adverse event reports in order to accomplish this. The IRB needs sufficient safety information to provide context for its continuing assessment as to whether the risks to the subjects at the IRB's institution are reasonable in relation to anticipated benefits, if any, and in relation to the importance of the knowledge that may be expected to result (as outlined in 21 CFR Part 56, Subpart C, Section 111(2)). The IRB should not attempt to review all safety data in detail, since this is duplicative of the remits of other parties (the study sponsor, scientific review committees, study steering committees, data safety monitoring boards, FDA, etc.) Additionally, most IRBs are not equipped to handle the volume of data involved in such a detailed review. We believe that it is the responsibility of the study sponsor to provide adequate summarized safety information to the investigator, who should then provide this to the IRB according to the local requirements (e.g., periodicity and format) established by the institution.

**Question:**

How does that role differ from the current role of IRBs?

**AstraZeneca Response:**

There is no difference, however, we believe that the operating model for fulfillment of this role needs to be reconsidered. For large, multicenter studies, it is unreasonable to expect IRBs to perform this role without assistance from the study sponsor in terms of providing context for the safety information so that the IRB can make informed decisions regarding benefit and risk for the subjects it seeks to protect. However, this context is most appropriately communicated to the IRB through the investigator(s) participating in the study under the IRB's auspices.

February 8, 2005, Federal Register Notice [Docket No. 2005N-0038]  
"Reporting of Adverse Events to Institutional Review Boards"

**Question:**

Should IRB responsibilities for multi-site trials differ from those for single-site trials? If so, how should they differ?

**AstraZeneca Response:**

The responsibilities of the IRBs should remain the same whether or not the trials are single-site or multi-site, although we believe that, in some instances (eg, for very large studies or studies where a large number of SAEs will be reported), it would be reasonable for the study sponsor to provide the investigators with summarized information that included assessments made by an independent monitoring body such as a DSMB or study steering committee, so that the investigators could then forward this to their respective IRBs. The criteria for reporting adverse events to an IRB from a multi-site trial should not differ depending on whether or not the adverse event occurred at the IRB's site or not, since this information will be relevant to the site subjects. However, the IRB might prefer to receive a full case report for a serious, unexpected, possibly related adverse event experienced by a subject at its site from the investigator of that site, but the IRB would find a line listing with a cumulative summary analysis provided by the study sponsor sufficient for such events from all sites in the study as long as the IRB could determine which events came from their sites. The standard for all studies should be that the investigators are provided summary information from the study sponsor to support actions (or confirm that no action is needed) for the study and the investigator forwards this summary information to their IRB. Of course, the study sponsor should always provide more detailed information to the IRB if requested.

**2. The types of adverse events about which IRBs should receive information.**

**Question:**

Based on your view of the role of IRBs in the review of adverse event information from ongoing clinical trials, what types of adverse events should an IRB receive information about, and what types of information need not be provided to IRBs? For example, should IRBs generally receive information only about adverse events that are both serious and unexpected?

**AstraZeneca Response:**

We believe that the sponsor's assessment of information about serious, unexpected, possibly related adverse events that have occurred on active study drug in the relevant clinical program (study or set of studies) and the sponsor's recommendation of how these events impact the conduct of the study are the most important reports an IRB will receive from the investigators during a clinical trial, and certainly the most time-sensitive. However, we also believe that other information is useful as well, although perhaps not as time sensitive. This would include the following:

- Adverse events from the relevant clinical program that, while not serious, unexpected, and/or possibly related, are the basis for a change to the protocol,

**February 8, 2005, Federal Register Notice [Docket No. 2005N-0038]  
"Reporting of Adverse Events to Institutional Review Boards"**

the informed consent, and/or the investigator's brochure. This should include those that occurred on comparator or placebo, or those that occurred due to study design

- Other safety-related trend information specific to the study, such as an unusually high rate of study subject dropouts due to AEs or an unusually high rate of protocol violations
- Adverse events received from other studies, eg, other than those from the relevant clinical program (in different populations and/or for different indications)
- An explanation of adverse events from commercial marketing experience that may lead to a change in the labeling of the product
- Significant safety information ascertained from pre-clinical studies that might change the way the study is conducted or the investigational product administered.

We believe the information listed above would be most useful to the IRB if it were sent in a summary format on a periodic basis, unless, of course, the information was of an urgent nature (e.g., has the potential for immediate impact to the safety of the study subjects), in which case it should be provided to investigators on an expedited basis for prompt communication to the IRBs. In addition, we believe it would also be useful for the investigator to provide the study sponsor's Investigator's Brochure (IB) along with any subsequent IB updates since the IB captures most of this type of information in a convenient summary format.

**Question:**

Are there circumstances under which IRBs should receive information about adverse events that are not both serious and unexpected (e.g., if the information would provide a basis for changing the protocol, informed consent, or investigator's brochure)?

**AstraZeneca Response:**

Yes, as outlined above.

**Question:**

In a multicenter study, should the criteria for reporting adverse events to an IRB differ, depending on whether the adverse events occur at the IRB's site or at another site?

**AstraZeneca Response:**

No, as stated previously, the criteria for reporting adverse events to an IRB from a multi-site trial should not differ depending on whether or not the adverse event occurred at the IRB's site or not, since this information will be relevant to subjects at all sites. The standard for all studies should be that the IRB receive summary information to support actions (or confirm that no action is needed), not individual adverse event report forms without any assessment. However, we do believe that it is reasonable for the sponsor to provide the information in a format that allows the IRB to distinguish the events by site. For example, the IRB might prefer to receive a full case report for a serious

**February 8, 2005, Federal Register Notice [Docket No. 2005N-0038]  
"Reporting of Adverse Events to Institutional Review Boards"**

unexpected adverse event experienced by a subject at its site from the investigator of the site, but would find a line listing with a summary analysis provided by the study sponsor sufficient for such events from all sites as well as from other studies. As is the case today, IRBs always have the right to request additional details from the sponsor if they feel this is needed for their decision-making.

**3. Approaches to providing adverse events information to IRBs.**

There seems to be a general consensus in the IRB community that adverse event reports submitted individually and sporadically throughout the course of a study without any type of interpretation are ordinarily not informative to permit IRBs to assess the implications of reported events for study subjects (see, e.g., the SACHRP letter, NIH Regulatory Burden v. Human Subjects Protection—Workgroups Report, available at <http://grants2.nih.gov/grants/policy/regulatoryburden/humansubjectsprotection.htm>, which states that data that are neither aggregated nor interpreted do “not provide useful information to allow the IRB to make an informed judgment on the appropriate action to be taken, if any.”).

**Question:**

What can be done to provide IRBs adverse event information that will enable them to better assess the implications of reported events for study subjects? For example, if prior to submission to an IRB, adverse event reports were consolidated or aggregated and the information analyzed and/or summarized, would that improve an IRB’s ability to make useful determinations based on the adverse event information it receives?

**AstraZeneca Response:**

We believe it would be helpful to improve the format of the written IND safety reports that study sponsors send to investigators (which is usually the report that is then forwarded to the IRBs.) Many companies send MedWatch reports, since this ensures fulfillment of the regulatory obligation to inform investigators (and IRBs) of the same information that is sent to the FDA. With the help of a focus group of investigators, study coordinators, and IRB members, we designed a custom form that was more “user-friendly” and concise (thus decreasing the amount of paper and the associated administrative burden), but still contained the same information as the MedWatch. Investigators and IRBs have found the new form to be much more amenable to interpretation and comprehension.

For some large, multi-center, multi-national studies with high rates of SAEs, we have provided investigators and IRBs with a periodic safety summary (in addition to single case reports of serious, unexpected, possibly related events.) Investigators and IRBs indicated that this summary information was very helpful to them. This approach is similar to that recently put into place by the Clinical Trials Directive in the European Union. Preliminary feedback from European investigators and Ethics Committees indicate that they have found receiving summary information on a periodic basis more helpful and less of an administrative burden than receiving individual case reports. The

**February 8, 2005, Federal Register Notice [Docket No. 2005N-0038]  
"Reporting of Adverse Events to Institutional Review Boards"**

Clinical Directive also mandates that annual reports are also provided to investigators and Ethics Committees, and we believe consideration should be given to doing the same in the US with the annual IND report, which currently is only sent to FDA.

We also believe that the Investigator's Brochure is one of the most important vehicles for communication of safety information to investigators and IRBs. These should be updated whenever safety information significantly changes the risk profile of the drug and not less frequently than every year. In addition, we believe it would be helpful for the IRB to inform the study sponsor if a meeting(s) or teleconference would be appropriate to help resolve questions about the study. The study sponsor could also use teleconferences with the investigator and the IRB to communicate urgent safety information.

**Question:**

If so, what kinds of information should be included in consolidated reports?

**AstraZeneca Response:**

We believe that the following information should be included in consolidated reports (although, depending upon significance, there may be exceptions where these need to be communicated in an expedited manner as defined in the study protocol):

- Serious, unexpected, possibly related adverse events that have occurred on active study drug in the relevant clinical program (study or set of studies)
- Adverse events from the relevant clinical program that, while not serious, unexpected, and/or possibly related, are the basis for a change to the protocol, the informed consent, and/or the investigator's brochure. This should include those that occurred on comparator or placebo, or that occurred due to study design.
- An analysis summarizing the new reports appearing in the attached listings, as well as a summary of any other new safety information received during the time period since the last report, including
  1. Adverse events received from studies in other patient populations and/or different indications, eg, other than those from the relevant clinical program
  2. An explanation of adverse events from commercial marketing experience that lead to a change in the labeling of the product (we do not believe including spontaneous reports in the line listing is appropriate or will add value.)
  3. Significant safety information ascertained from pre-clinical studies
  4. Any issues with study design

This analysis should include an assessment of any change to the risk-benefit ratio, and any actions taken or planned based on this safety information.

February 8, 2005, Federal Register Notice [Docket No. 2005N-0038]  
"Reporting of Adverse Events to Institutional Review Boards"

**Question:**

And when should consolidated reports be provided to IRBs (e.g., at specified intervals, only when there is a change to the protocol, informed consent, or investigator's brochure due to adverse events experience)?

**AstraZeneca Response:**

We recommend that FDA consider the approach recently established in Europe where Ethics Committees (which are the European counterparts of IRBs) receive consolidated reports on a quarterly basis, since this allows for internal consistency in the preparation of summaries by the study sponsor. Many trials are conducted on an international basis, so it would be helpful to harmonize reporting procedures across regulatory agencies. Alternatively, frequency could be based on study enrollment (eg, if more than 100 subjects are planned to be included per month, the frequency could be increased to monthly) or based on the number of SAEs (eg, a summary report could be triggered when a certain number of initial SAE reports were received.) However, we are concerned that too many frequency variations will make the process very logistically difficult, and would potentially jeopardize compliance.

**Question:**

Who should provide such reports?

**AstraZeneca Response:**

Due to the diversity of IRB operating procedures at various institutions (different administrative requirements such as formats, receiving entities, frequencies, etc.), and the established working relationship of an IRB with the investigator of that site, we believe that the study sponsor should provide the relevant information to the investigator, and then the investigator should forward this information to his/her respective IRB according to the established procedures of that institution. As is presently done today, the sponsor should monitor the investigational site to ensure that this communication is included as part of that site's study records. Also in accordance with current practice, the IRB may contact the study sponsor directly with questions or requests for additional data.

**Question:**

Should the approach to providing IRB's adverse event reports be the same for drugs and devices?

**AstraZeneca Response:**

We believe it would be more efficient to be consistent (as much as possible) in terms of frequencies and responsibilities in the process. However, we also think that device reports should only list incidents, and not include "near incidents."