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April 21, 2005

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

Re: Docket No. 2005N-0038 -- Request for Comment: Reporting of Adverse Events to Institutional Review Boards

Dear Madam/Sir:

AdvaMed is pleased to provide comments in response to FDA's request for comments regarding the process by which institutional review boards (IRBs) obtain and review information on adverse events that occur during the conduct of clinical investigations.

AdvaMed, the Advanced Medical Technology Association, is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's more than 1,300 members and subsidiaries manufacture nearly 90 percent of the \$75 billion in health care technology products purchased annually in the United States, and more than 50 percent of the \$175 billion purchased annually around the world. AdvaMed members range from the smallest to the largest medical technology innovators and companies. Nearly 70 percent of our members have fewer than \$30 million in sales annually.

AdvaMed has a number of comments both general and specific, as well as responses to the questions posed in the FDA notice. These are discussed below.

General Comments

FDA's current IDE regulations appropriately reflect important differences between devices and drugs. For instance, drug and device mechanisms of action are different. Drugs are chemical entities that are metabolized and have pharmacokinetic and systemic effects. Drugs can also react with other drugs in unanticipated ways. By contrast, devices typically act locally and provide physical effects. Device development is conducted under design control regulations (21 CFR 820.30) which require that products meet specific design requirements. This design control process involves the evaluation and mitigation of risk. Thus, unlike a chemical metabolic entity, the device development process and device modes of action facilitate the

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prospective determination of anticipated adverse device effects as well as the device risk/benefit ratio expected during the trial. Similarly, the incidence of unanticipated adverse device effects (UADEs) is far lower for devices than for drugs. As a result, device reporting needs are different from pharmaceutical reporting needs.

Concerns about IRBs being inundated by large volumes of individual adverse event reports (AERs) were outlined in the notice for this request for comments, and were reiterated by many of the presenters during the Part 15 hearing as well as in a recent letter from the Secretary's Advisory Committee on Human Research Protections (SACHRP). However, the genesis for many of these individual AERs appears to arise from studies involving pharmaceutical products, not devices. AdvaMed is not aware of similar concerns existing for individual adverse event reporting for device trials. Reporting individual adverse events to IRBs is not common in the device industry, except for the reporting of unanticipated adverse device effects which is required by the IDE regulations.

In fact, none of the hearing presenters complained of being overwhelmed by device-related individual adverse event reports. One presenter at the hearing, Dr. Alfano, reported that "we do not receive a burden of reports on devices."¹ Another presenter, Dr. Reese, suggested that the current regulations are effective, noting that:

"Commonly, for multi-site studies, the reports we receive that do suggest increased risk have already been massaged. They come accompanied by the consent form changes that are recommended and the protocol revisions. In other words, evaluation of the problem and the determination of the action needed are made independent of input from an IRB. In many cases, it's apparent the FDA has been involved in the process of determining the action to be taken by the sponsor. This really calls into question the utility of having the IRB review these reports at all."

Dr. Reese's statement supports the view that the current regulations are working as intended.

Under the device IDE regulations, investigators are required to report unanticipated adverse device effects (UADEs) to sponsors and the reviewing IRB "as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect" (21 CFR 812.150(a)(1)). An unanticipated device effect is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device,

¹ Dr. Alfano made two other statements that we would like to address directly. First, she noted that she finds it "problematic" that the IDE regulation requires sponsors to notify the IRB directly because "sometimes when we receive those reports, we don't even know what protocol it's in relation to." AdvaMed member companies have advised us that to accommodate IRBs, they frequently submit their evaluations to the IRB through the principal investigator to avoid any such confusion. Sponsors then require the IRB to confirm they received the evaluation.

Secondly, Dr. Alfano reported that her institution does "not always receive assessments." This concern was also reiterated during the question period for Dr. William Hendec. We believe these comments may unfairly and inaccurately suggest that medical device companies routinely underreport adverse events. Nevertheless, AdvaMed would be happy to co-sponsor a workshop with the FDA to provide guidance to IRBs, investigators and to device companies regarding device AE reporting.

if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects” (21 CFR 812.3(s)). Historically, UADEs are typically rare events and many device trials have none.

The IDE regulations require sponsors to “immediately conduct an *evaluation* of any unanticipated adverse device effect” (21 CFR 812.46(b)(1)). Further, sponsors are required to *submit the results of any UADE evaluations to “FDA and to all reviewing IRBs and participating investigators within 10 working days* after the sponsor first receives notice of the effect” (21 CFR 812.150(b)(1)). The regulations require a sponsor “who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects” to “terminate all investigations or parts of investigations presenting that risk as soon as possible” but in no case, “later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect” (21 CFR 812.46(b)(2)). Other adverse events are required to be reported “at regular intervals, and at least yearly” in “progress reports to all reviewing IRBs.” For significant risk devices, progress reports must also be submitted to FDA (21 CFR 812.150(b)(5)). Such progress reports include a summary of unanticipated and anticipated adverse effects occurring in the trial.

In short, the IDE regulations reflect the potential seriousness associated with unanticipated device effects by requiring that UADEs be reported to IRBs on a case-by-case basis. More important, the IDE regulations clearly and appropriately place adverse event analysis and decision-making responsibilities (including the decision to terminate all or parts of an investigation) with the sponsor – not the IRB.

We note that several presenters at the hearing stated that “IRBs were never intended to be either scientific review or data monitoring committees” and are “ill-equipped to deal effectively with safety information on their own.” AdvaMed concurs with these comments. Most IRBs lack the engineering or specialized technical expertise required to make evaluations about particular devices. Again, to restate, the IDE regulations appropriately place this responsibility on the sponsor.

In summary, we disagree with the argument made by at least one presenter that the device regulations are part of the problem. To the contrary, we believe the device regulations provide a rational and effective adverse event reporting process for device trials. The current IDE regulations appropriately place the responsibility of evaluating and reporting adverse events across the entire study – both anticipated and unanticipated – with the sponsor.

For these and other reasons, AdvaMed strongly recommends **against** making any changes to the current IDE regulations. If FDA nevertheless feels compelled to respond to the issue of individual drug adverse event reports to IRBs, we would support the view articulated by at least one of the presenters that a “remedy could be quickly accomplished through guidance issued by FDA.” We concur that FDA guidance to drug manufacturers clarifying which drug events are reportable to IRBs would more quickly and effectively remedy the drug AE reporting problem. Most importantly, we strongly oppose any proposition which seeks to

combine drug and device clinical trial reporting requirements into a single regulation. The medical device adverse event reporting process is effective and efficient in its current state – it should not be compromised by efforts to correct the known problems with adverse event reporting for drugs.

Specific Comments on Statements Made During the Part 15 Hearing

We would also like to address a recommendation made by several of the presenters during the hearing that data monitoring committees (DMCs) or data safety monitoring boards (DSMBs) should be required for all clinical trials or, at a minimum, for all multi-site trials. With respect to device trials, AdvaMed disagrees. Although DMCs are comprised of experts, they still may not possess the same level of technological expertise and familiarity with the device and its design as the sponsors who are required by the regulations to provide adverse event evaluations.

Furthermore, most device trials do not warrant a DMC because of the relatively low risk to participants (e.g., non-significant risk device studies) or because the technology is not novel. This is particularly true with devices because of the iterative nature of device development. FDA's draft "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees" appropriately states that "a DMC is not needed or advised for every clinical study." AdvaMed believes the draft guidance lays out the appropriate criteria for determining when a DMC may be needed.

Finally, we note the comment of P. Pearl O'Rourke, Chair of the Board of Directors of Public Responsibility in Medicine and Research (PRIM&R) presented by David Borasky: "Finally – make proposed solutions achievable – please consider the logistics and the necessary resources. For example, if more Data Monitoring Committees will be required – consider the fact that even now, investigators have difficulty identifying people willing to serve on DSMBs or even to serve in lesser oversight roles. If more independent monitoring is required - how will these people be found? Be paid? Be vetted as free of conflict of interest?"

Responses to Questions Posed in the FDA Notice

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

- a. 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?**

Response: AdvaMed concurs with the comments made by many of the presenters that IRBs are not appropriately constituted to conduct a scientific analysis of individual adverse event reports and should not be required to conduct such evaluations. The responsibility for this evaluation appropriately resides with the device sponsor in the IDE regulations. The IDE requirement that evaluations of UADEs be provided to FDA within 10 working days also highlights the important role of FDA oversight in assuring that needed changes in the consent or protocol are taken along with any steps needed to ensure the safety of human subjects.

IRBs serve an important role in reviewing and approving clinical studies and in protecting the rights, safety and welfare of human research subjects by ensuring subjects are provided with appropriate consent information and by ensuring risks to subjects are minimized and reasonable in relation to anticipated benefits. The IRB should remain focused on providing oversight for research conducted under their jurisdiction at their respective institutions.

The IRB role in “continuing review” of ongoing research should include a review of the frequency and trends in adverse events at their institution. Sponsor’s progress/annual reports, such as those required to be submitted to FDA and IRBs by 21 CFR 812.150(b)(5), can be used to review trends across the study. In addition, the regulations also allow the IRB to ask the sponsor for more tailored information. 21 CFR 812.150(b)(10) says “a sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete and current information about any aspects of the investigation.”

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

Response: This role is consistent with current IDE regulations and typical practice for device studies.

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

Response: The primary responsibility of IRBs is to ensure the protection of the rights, safety and welfare of human subjects at their own institution, regardless of whether the study is single-site or multi-site study. When reviewing multi-site studies, the IRB should rely on other mechanisms of oversight to determine whether sufficient safety precautions are in place given the risk/benefit ratio of the study. These other mechanisms include:

- The clinical monitoring group
- Steering Committees
- Endpoint Assessment/Adjudication Committees
- FDA review and oversight
- the use of sponsor medical monitors, and
- the use of independent clinical event committees or data monitoring committees when appropriate

Some studies use “commercial IRBs” that oversee multiple sites within a given study. These IRBs should function essentially the same as an institution-based IRB. Of course, IRBs should also rely on sponsor evaluations of UADEs, sponsor progress or annual reports, or sponsor requests for changes to the consent form or protocol to make determinations about the safety and welfare of human subjects at their institution.

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

a. 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?

Response: AdvaMed advocates continuing the current practice of the IDE regulations. This requires sponsors to submit UADE reports to IRBs on an individual basis and to submit progress reports summarizing adverse events occurring across the study on an annual basis, at a minimum.

- b. 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)?**

Response: We support providing the information as a basis for changing the protocol or informed consent when the change is related to adverse event information identified during the course of the study. We believe this is standard practice within the device industry. Also as noted above, sponsor's progress/annual reports, such as those required to be submitted to FDA and to IRBs, can be used to review trends across the study, including events that are not both serious and unanticipated.

- c. 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?**

Response: Sponsor reporting should be consistent across sites. We support the current regulations that require expedited reporting of UADEs to all centers, regardless of where the event occurred. Other types of adverse events are best summarized in an aggregate format in periodic progress reports submitted to IRBs for continuing review (per 21 CFR 812.150(b)(5)).

As stated previously, we are aware of the drug industry practice of sending individual adverse event reports to IRBs throughout the course of a study. Other than for UADEs (as discussed above), this is not required by the IDE regulation and we do not believe it is a common practice in the device industry. Sending IRBs individual reports of adverse events from other investigational sites can be counterproductive for the reasons noted in the notice and by the hearing presenters. It is difficult for IRB members to review adverse events out of any context and it is easy for IRBs to reach mistaken conclusions without all the information.

3. Approaches to providing adverse events information to IRBs.

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

Response: As we have previously noted, the IDE regulations require sponsors to provide IRBs with evaluations of all UADEs within 10 working days. The IDE regulations do not require submission to the IRB of other adverse events except as part of the progress/annual report. These progress/annual reports typically contain the following type of consolidated or aggregated information:

- Nature of event, including an assessment of relatedness to the study device or related study procedures or tests.
- Whether the event is unanticipated as described in the investigational plan and informed consent documentation.
- Seriousness of the event
- Degree of frequency

b. 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)?

Response: Consolidated reports should be provided: (1) as part of progress/annual reports sent to IRBs for the purpose continuing review and (2) when needed to support changes to study protocols or consent or documents.

c. Who should provide such reports?

Response: This is the Sponsor's responsibility. The sponsor consolidated progress/annual report may include statements of review by an independent adverse events committee or a data monitoring committee, if used by the study due to the novelty of the technology or risk inherent to the study.

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

Response: As noted in our general comments, there is no evidence that IRBs are concerned about the number of device-related individual adverse event reports they receive. This is a result of the IDE regulations where only UADEs – the highest risk situation – are required to be reported on a case-by-case basis. Given this, we believe the current IDE regulations provide a rational and effective adverse event reporting process for devices. We are concerned that any revision of the regulations that made drug and device requirements identical could inadvertently eliminate those aspects of the IDE regulations that respond to the unique characteristics of device development and innovation or could inadvertently impact current IDE regulations which work effectively for device studies.

For example, the risk-based approach of the IDE regulations in terms of significant risk and non-significant risk device studies and the role of IRBs in terms of non-significant risk device studies are unique to the device regulations. Any revisions to the regulations to make drug and device requirements identical could inadvertently compromise the current approach to regulating non-significant risk devices, which is predicated on maintaining IRB approval of non-significant risk device studies (21 CFR 812.2(b)(1)(ii)). Thus, reporting device UADEs – the highest risk situation – to IRBs and to FDA is consistent with the risk-based approach of the IDE regulations in terms of abbreviated requirements for non-significant risk device studies, and provides further support for maintaining the current approach for devices. For these reasons, AdvaMed opposes any effort to combine drug and device clinical trial adverse event reporting requirements into a single regulation.

Conclusion

In conclusion and as noted in our General Comments above, if FDA feels compelled to address drug-related individual AE reports to IRBs, AdvaMed believes this could be managed through FDA guidance to drug manufacturers clarifying which drug events are reportable to IRBs.

Sincerely,



Tara Federici
Associate Vice President
Technology and Regulatory Affairs