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July 10, 2007

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

***Re: Docket No. 2007N-0155 – Defining and Implementing Quality in Clinical Investigations:
From Design to Completion; Request for Comments***

Dear Madam/Sir:

AdvaMed was pleased to participate in both the development of the May 10-11 public workshop entitled “Defining and Implementing Quality in Clinical Investigations: From Design to Completion” and to have device industry representation on key workshop panels. We are also pleased to provide these comments in response to FDA’s solicitation for constructive information to help identify attributes of quality in clinical investigations, approaches to quality from trial design to completion, and methods for measuring quality and ensuring data integrity during the conduct of clinical trials.

AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed’s members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent of the health care technology 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. These are discussed below.

General Comments

There is a tendency to assume that what will work for drugs and biologics will also work for medical devices. It is important to understand the key differences between drugs and medical devices that may affect certain regulatory approaches. These differences can result in substantially different inherent risk profiles between drugs and devices. This section provides a brief overview of key drug and device differences as they relate to clinical trials. Medical technology evolves in an iterative progression, with innovation occurring through a process of continual, incremental improvements made over time. A drug on the other hand, is a stable, unchanging molecular entity.



Similarly, drug and device mechanisms of action are different. Many devices which undergo clinical trials are designed to replace or augment a function of the body and typically act locally, providing readily identifiable and relatively immediate physical effects. The risks associated with medical devices can be more predictable. By contrast, drugs are chemical entities that are metabolized and often have systemic effects. Long-term use of the drug may also present risks that are not immediately apparent.

In addition, many device clinical trials may involve a surgical procedure which may complicate the design of the clinical trial (e.g., the ability to develop an effective control arm for the trial or the ability to blind the trial) and data collection and evaluation. This in turn may increase the complexity of the consent form. The technical nature of devices also requires greater involvement by the sponsor in educating and training the investigator or surgeon in the use of the device. Training of the physician (or even the patient) may be key to the success or failure of a medical device clinical trial. Some medical device trials may also require the involvement of multiple physician specialties at a single site (e.g., surgeon, radiologist, specialty doctors).

Finally, medical device trials require accurate tracking and evaluation of all adverse device effects, which may or may not include clinical adverse events. Coding systems for medical device trials must accurately capture both adverse device effects and clinical adverse events. Evaluation of a device clinical trial may also require evaluation of data collection from the device itself as well as remote data capture (e.g., programming of implantable pacemaker thresholds or blood glucose monitoring records). Capture of these data adds complexity to the clinical trial monitoring, to the identification of the source data, and to the quality plans.

Specific Comments

In response to FDA's solicitation for constructive information on quality in clinical investigations, AdvaMed submits the following specific comments. AdvaMed supports the concepts described below to improve quality in medical device clinical trials. Specific caveats are also noted along with specific recommendations.

Quality Plans

AdvaMed welcomes comments made by FDA representatives at the public workshop that recognized that "quality" should not be defined as "zero errors." Toward this end, FDA reported a willingness to review clinical trial quality plans if they were submitted by companies and suggested that mutual company and FDA agreement on such a plan could potentially reduce required monitoring in certain instances and reduce the risk of Good Clinical Practice (GCP) non-compliance. AdvaMed believes the submission and review of quality plans is an important concept that should be further explored. However, the issue raises a number of implementation concerns that need to be resolved in order to ensure that review of such plans actually streamlines and improves the clinical trial process and does not simply add requirements.

For example, companies who have availed themselves of FDA's offer to review quality plans have reported that it has been unclear which elements of the quality plan FDA representatives had actually reviewed and further, which elements FDA accepted. Companies have learned only after the fact that certain aspects of the plan did not meet with FDA's acceptance. If quality plan submission and review is to add value and improve quality, submission and review must occur at the earliest stages of the clinical trial or investigational device exemption submission. FDA's

review of the plan must also be timely. Any delay in clinical trial startup is expensive and it can be challenging to sponsors to reinvigorate site interest after delays in the trial.

Importantly, FDA must commit to review the entire plan and clearly specify which elements of the plan may not be acceptable along with reasons and suggestions. The sponsor should have an opportunity to discuss and revise portions of the plan in order to reach a common "acceptance" of the entire plan.

As suggested by FDA at the workshop, mutual company and FDA agreement on a quality plan may ultimately result in a potential for reduced required sponsor monitoring for certain agreed-upon trial data collection efforts and the potential for reduced BIMO auditing. For example, FDA's review and acceptance of the quality plan should include review of the data monitoring plan including the rules for cleaning data, the acceptable data error rate for certain elements, and whether source document verification could be less than 100%.

It is also important that all sections and personnel scheduled to review the submission from FDA review and reach consensus with the sponsor on FDA's acceptance of the quality plan. If, for example, the Division of Bioresearch Monitoring (BIMO) is not a party to the FDA review, there will be reduced willingness on the part of companies to submit quality plans for FDA review.

AdvaMed also has several additional recommendations in this area. FDA should develop and publish a clinical trial quality plan guidance document and potential templates with examples of acceptable quality plans. Such guidance would be especially useful for small device companies. FDA should also develop a risk management matrix to describe the level of monitoring that is considered acceptable by FDA for a particular trial. This should include identification of acceptable methods to establish confidence levels for expected or estimated data errors to manage the requirement for the percent of Case Report Form or patient data monitoring.

Finally, before FDA embarks on wholesale review of quality plans, AdvaMed recommends that FDA first conduct a pilot program to help define the typical elements of a quality plan, and to assess and ensure that such a program would indeed result in efficiencies and demonstrable benefits for both sponsors and FDA.

Site Certification

Site certification was also raised at the public workshop. A certification process for clinical trials could eliminate much repetitive work in training and qualifying personnel and sites and thus ensure a higher confidence level in the investigative staff and their processes. However, it is not clear to us whether certification should be at the site level, the site coordinator level, the investigator level or all levels. For example, given the high turnover rate for clinical trial coordinators, how will site certification be related to certification of specific personnel at the site?

Further, many device trials, including in vitro diagnostic (IVDs) trials, are conducted at very small sites (e.g., hospital laboratories, doctor's clinics, and outpatient surgery centers). Trials may be short-term (of four or five month's duration) and several trial sites may be used, depending upon the product, the expertise or the trial location. It is unrealistic to assume that all device clinical trial sites would have the resources or inclination to pursue a costly certification process that would presumably require regular renewal.

Any site certification must also be voluntary and should not prejudice FDA against clinical trial sites that are not certified. For example, in the case of IVDs, in order for the sponsor to petition FDA for waived device status under the Clinical Laboratory Improvement Act (CLIA), operators are required to be untrained in the use of the device, thus certification of these personnel would be impossible. These untrained operators would also change from one IVD application to another, so any certification would be a one-time occurrence.

Device companies do not currently have a large pool of clinical investigators from which to draw and given the growing difficulties in finding sites that are willing to conduct device trials, it is critically important that any site certification not limit the types or numbers of investigational sites available for device trials.

In short, site certification is a significant undertaking and should be a long-term objective that remains voluntary and includes a diligent evaluation of the connection between certification and quality performance (e.g., reduction in deviations and errors in data collection). Certification associated with individuals may in the end prove more valuable than site certification.

Clinical Data Acquisition Standards Harmonization (CDASH)

AdvaMed is generally supportive of CDASH with several caveats. First, it is our understanding that the current CDASH initiative has few device industry participants. As a result, we are concerned that the final content standards for the global data collection fields for the Case Report Form may only be appropriate for drug trials and may not accurately capture elements which may be common to all or most medical device trials. Secondly, given the diversity and differences among the thousands of device types, it is unlikely that any one CRF could adequately capture all the elements needed for device trials other than the most common data elements, such as demographic information, adverse events, etc. For these reasons, AdvaMed would recommend that any FDA application of the final CDASH output only be linked to drugs initially. There must be discussion with the device industry prior to applying CDASH to devices. In the interim, AdvaMed is encouraging device industry representatives to participate in the CDASH initiative.

Electronic Data Capture Technologies

AdvaMed commends FDA on the recent issuance of final guidance on *Computerized Systems Used in Clinical Investigations* which provides valuable guidance to companies. However, we must make several important points. First, electronic data capture (EDC) technology is evolving rapidly and it will be difficult for a guidance to adequately cover all EDC issues. For example, there are several difficult issues device manufacturers are currently encountering including: source documentation changes and monitoring effects, investigator control of data with electronic medical records, subject or patient use of EDC, and ownership of data among others. Secondly, it is important for FDA to understand that EDC technology and the related technical support that it requires can be extremely costly in relation to relatively smaller device trials, especially for small medical device companies. Use of EDC technology for device trials may not be a cost-effective option in many instances. In addition, clinical trials associated with devices that are specifically developed for use in developing countries with small healthcare budgets may have limited or no access to computers or even electricity. These same limitations may apply generally to trials conducted in developing countries. For these reasons, FDA should not

mandate the use of computerized systems for medical device trials and paper systems must remain available.

Need for Updated Monitoring Guidance

Beginning in June 2004, AdvaMed's Clinical Trials Working Group participated in a CDRH-sponsored stakeholder meeting to develop new guidance for medical device manufacturers regarding best practices for the monitoring of medical device clinical trials. Our understanding was that the guidance would replace the out-dated "Guideline for the Monitoring of Clinical Investigations." The working group spent numerous hours developing recommendations, participating in the stakeholder meeting, and providing detailed and specific comments to CDRH. At the request of FDA, we also developed a series of suggested questions that we felt would be beneficial to device manufacturers and which we understood would be included in a Frequently Asked Questions (FAQ) section of the guidance. Despite the time and energy of many individuals, to our knowledge, a draft of the guidance has still not been issued for public comment. We believe updated monitoring guidance would provide valuable information to device manufacturers.

Web-Based Investigator Training Modules

Beginning in March 2004, at the request of CDRH, AdvaMed's Clinical Trials Working Group worked collaboratively with CDRH staff to provide comments on a series of web-based investigator training modules. Again, the working group spent considerable time providing detailed recommendations and comments on the 10-part training module for investigators. Unfortunately, to our knowledge, this program was never completed. A critical element of clinical trial quality continues to be ensuring that investigators understand basic medical device clinical trial requirements including informed consent, IRB reporting requirements, and required trial record maintenance among others. While such training will not supplant sponsor responsibility for ensuring appropriate conduct of clinical trials, it can certainly help communicate to and train investigators on the basic requirements FDA expects for FDA-regulated trials. In short, access to an effective yet inexpensive training program, such as the one proposed by FDA in 2004, would be a valuable addition to ensuring the conduct of quality clinical trials.

ISO 14155

FDA is also actively involved in the important work of updating ISO 14155 which defines procedures for the conduct and performance of clinical investigations of medical devices including general requirements intended to protect human subjects and ensure the scientific conduct of the clinical investigation among other items. Importantly, the revision of ISO 14155 will include certain harmonized elements of ICH E6, Consolidated Guideline for Good Clinical Practice, that are applicable to medical devices. Currently, many in the device industry refer to ICH E6 for guidance on the conduct of clinical trials. Unfortunately, ICH E6 was designed for pharmaceutical clinical trials and some parts of it are not relevant to device trials or must be modified when applied to device trials. The updating of ISO 14155 will provide an important up-to-date reference for good clinical practice for medical device trials around the world.

Pharmaceutical Research and Manufacturers of America (PhRMA) Recommendations

Finally, we are aware that PhRMA has recommended the modernization of the Good Laboratory Practices Regulation and the application of risk management to Good Clinical Practices

requirements. AdvaMed endorses these recommendations. AdvaMed also endorses the PhRMA recommendation of further harmonizing regulatory inspection authorities but recognizes the challenges and resources that are consumed by negotiating mutual recognition agreements (MRAs) as well as the statutory limitations that may prevent full harmonization in some instances. Nonetheless, these efforts – such as the Harmonization by Doing initiative – are critical in the global environment of clinical trials. AdvaMed supports continued dialogue in this area and where possible identification of specific action items that can keep the momentum going.

Closing

In closing, AdvaMed has a lengthy history of working collaboratively with FDA to achieve shared objectives. Should FDA be interested and committed to further developing any of the ideas or recommendations referenced above, AdvaMed would be pleased to work cooperatively and collaboratively with FDA.

Sincerely,

A handwritten signature in cursive script that reads "Tara Federici".

Tara Federici,
Vice President, Technology and Regulatory Affairs