510(k)

Current Status & Considerations:

Conducting a Well-Controlled Clinical Study When Clinical Data is Required

Introduction

In an effort to promote innovation while protecting the population at large, the FDA has been on a path to revise the existing regulatory pathway surrounding the 510(k) process for medical devices for several years. One area of concern revolves around the area of clinical data and the lack of clarity that has historically plagued device manufacturers who risk submitting their 510(k) only to find out afterwards that clinical data will be required, or that perhaps even if they submitted clinical data, it was not enough. The goal is that the FDA's efforts to review the current status of the program will result in changes that will provide prospective answers to device manufacturers regarding whether or not clinical data is required, and if so, to what extent. The purpose of this whitepaper is to establish the current status of the 510(k) process with regard to clinical data requirements, and then to begin to define some considerations that should be given to conducting a well-controlled clinical study, if, indeed, clinical data is required.

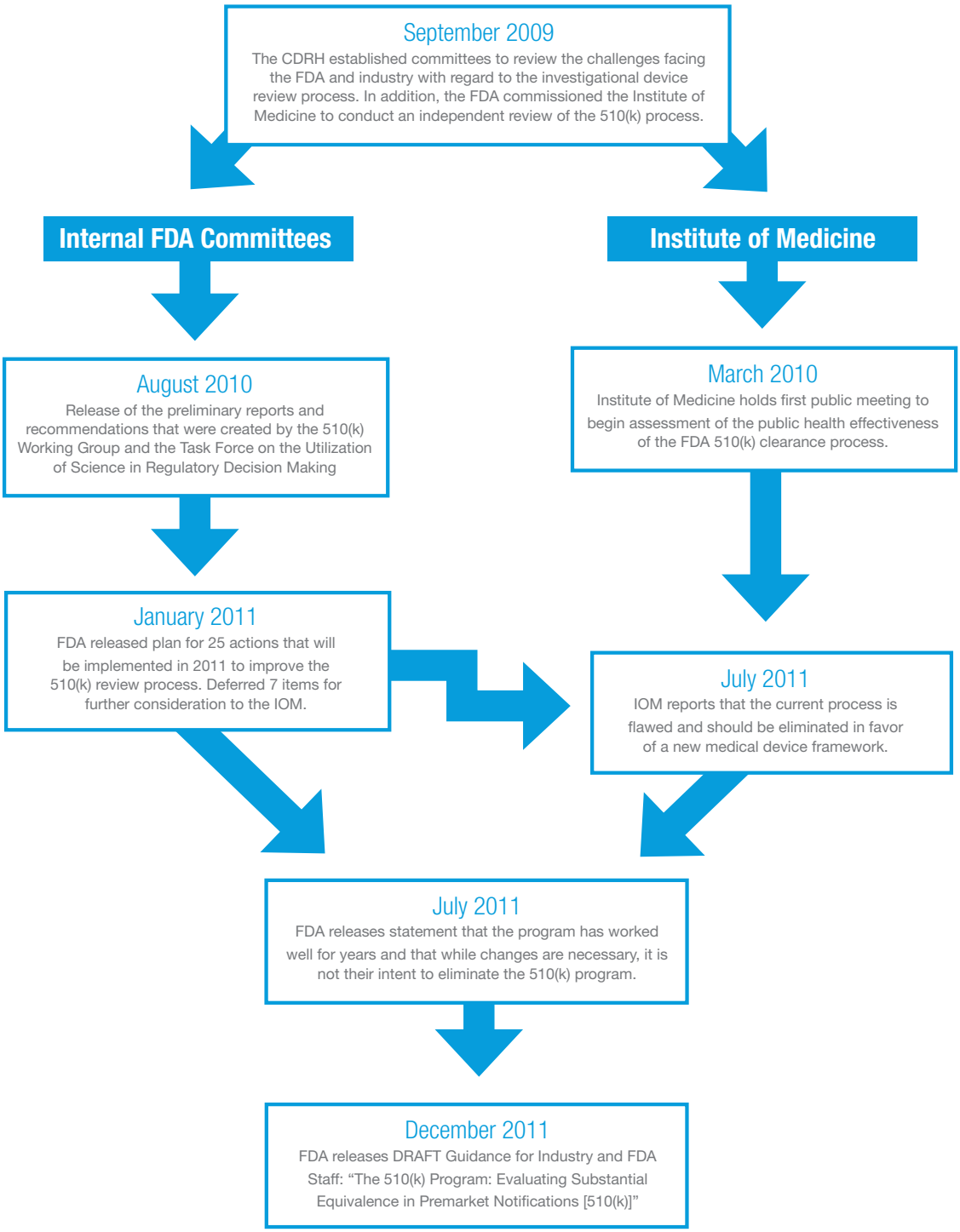
Current status of 510(k) clinical data requirements

Beginning in September 2009, the CDRH established 2 internal committees to review the 510(k) program, including the 510(k) Working Group and the Task Force on Utilization of Science in Regulatory Decision Making. In addition, they commissioned the Institute of Medicine (IOM) to conduct an independent review of the 510(k) process in parallel to their own investigation.

In August 2010, the internal committees released their preliminary reports and recommended actions, including recommendations surrounding the requirements for clinical data. Taking those recommendations along with public comment into account, the FDA released its plan for implementing 25 actions steps in January 2011. Within that plan was a recommendation to develop a guidance document called the "510(k) Paradigm Guidance," a draft of which is targeted to be released by October 31, 2011. This guidance is intended "To provide greater clarity regarding when clinical data should be submitted in support of a 510(k)," (FDA, 2011) among other goals.

In that report, the FDA deferred for further independent evaluation by the Institute of Medicine (IOM) 7 areas that needed additional consideration, including the concept of whether or not to establish a "Class IIb" classification of medical devices for which clinical information would typically be required to support a submission. While lack of time did not permit the IOM to fully investigate this area, in July 2011, Dr. David R. Challoner, Chair of the IOM's committee, sent a letter to Dr. Jeffrey Shuren, Director of the CDRH, recommending that the 35-year old program be eliminated in favor of "a more rationale medical device framework." A timeline of these important dates is located in *Figure 1*.

Figure 1



So where does this leave us with understanding our responsibilities regarding clinical data requirements for 510(k) submissions? Shortly after the release of the IOM's report, the FDA issued a statement (July 29, 2011) indicating they would not be eliminating the 510(k) program as was recommended. So while changes are certain, the timing and extent of them are not. As of January 2011, the FDA requires clinical data in approximately 10% of all 510(k) submissions (Rosecrans, 2011). Heather Rosecrans, the Director of the 510(k) Staff in the Center for Devices and Radiological Health for the FDA, explained in an overview of the 510(k) process presented in January 2011 that clinical data is required when there is an "Important difference with the predicate device, e.g., new indication for use or new technology."

Considerations if clinical data is needed to support a 510(k) submission

While more clarity is forthcoming regarding the clinical data requirements for 510(k) submissions, it is important to know what the requirements are in the event that a clinical study is needed. Rosecrans explained that when clinical data is required, the requirements for conducting the study are the same as those for conducting an Investigational Device Exemption study as outlined in 21 CFR 812 (2011).

Knowing the regulations to be followed and the responsibilities for sponsors outlined within those regulations will be important in developing a strategy for compliance. Ensuring that the clinical study team has an understanding of the regulations will be important throughout the clinical study process. Upfront training on the regulations for all involved will set the stage for a well-controlled, compliant clinical study. The end result will be a clinical study in which patients are protected and the resulting data being provided to the FDA to support the 510(k) submission has integrity.

Sponsor Responsibilities

21 CFR 812 outlines general and specific responsibilities of sponsors and serves as a guide for general conduct of clinical studies. Requirements regarding the contents of the investigational plan, the report of prior investigations, labeling, and other requirements are described in detail in Part 812 and fall outside the scope of this whitepaper. Specific responsibilities of sponsors are described in 21 CFR 812.40, which include selecting qualified investigators, providing investigators with necessary information, ensuring proper monitoring, and ensuring that IRB approvals are obtained prior to enrolling human subjects. In addition, responsibilities regarding record keeping are contained in 21 CFR 812.140 and 21 CFR 812.145. All of these responsibilities boil down to protection of human subjects, and are presented in more detail as follows.

Selecting Qualified Investigators

It seems logical that if a diabetic device is being researched, a psychiatrist would not be considered to be an investigator. 21 CFR 812.43 specifies that an investigator should be selected based on their training and experience and should be qualified to operate as an investigator in the clinical study. Therefore, investigators involved in the clinical study should have relevant experience. To document this, sponsors may collect their curriculum vitaes, medical licenses, or other evidence of the investigator's background which demonstrates experience in the area being studied. In addition, the sponsor should collect a signed agreement from the investigator stating his or her intent to comply with the appropriate regulations. Minimal agreement contents are summarized in *Table 1*.

Table 1

Contents of agreement as required in 21 CFR 812.43
1. Curriculum vitae
2. Statement of relevant experience (where applicable) including dates, location, extent, and type of experience
3. If the investigator has been involved in research that was terminated, and an explanation of the circumstances that led to that termination
4. A statement of the investigator's commitment to: • Conduct the investigation in accordance with the agreement, investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA; • Supervise all testing of the device involving human subjects; and • Ensure that the requirements for obtaining informed consent are met.

Additional items to consider building into an agreement may include expectations with regard to communication, meeting attendance, data form submission timelines, essential document submission, and financial compensation, among others.

Informing Investigators

Sponsors are required to provide investigators with copies of the protocol and any other information, including previous experience with the device that would be necessary for him or her to conduct the study (21 CFR 812.45). Sponsors should document how this information was disseminated and the dates on which the investigators were given the information. Changes to the protocol or modifications to the device should be communicated throughout the study, and documentation of such should be maintained.

In device studies, the influence of physician technique may be very high, depending on the type and complexity of the device being studied. Carefully and safely deploying an endovascular graft, for instance, relies on expert knowledge of planning and sizing of the graft, along with advanced training on how to deploy the device into the correct position. Trouble shooting in the event of a deployment problem would also be critical. For this reason, ensuring that investigators have adequate information to conduct the study may require much more than just providing them with a protocol. A decision regarding the extent of training that should be required for the study should be made at the start. This may include hands-on training with another physician or engineer, it may require presence of a proctor during a certain number of cases, or other methods suitable for that particular device.

Ensuring Proper Monitoring

The purpose of monitoring is to protect patients by ensuring data integrity and compliance with applicable regulations. In order to ensure that the study is properly monitored, the sponsor must first select qualified monitors. 21 CFR 812.43 (d) indicates that monitors must be qualified by training and experience to monitor the study. This means that the monitors have clinical experience or have received training in the area being studied and that they have been trained or have operated as a monitor. Documentation of the monitor's qualifications should be maintained by the sponsor to demonstrate compliance with this requirement.

The level of monitoring oversight that is implemented during the study may be based on the risk associated with the device, including both the risk to patients and the risk to the company. If this is a complex device or if the device is critical to the sponsor's pipeline, it may be prudent for the sponsor to take a more conservative approach to monitoring, sending monitors to the sites more often to review subject records and regulatory documentation. If it is not a complex device or is less critical to the sponsor's pipeline, perhaps the monitoring plan includes more remote review of data and fewer on-site visits. Either way, a monitoring plan should be implemented prior to the study, and monitoring procedures that are based in the aforementioned regulations should be developed and followed.

Monitoring may be done remotely or on-site and can be done by internal staff or by a third party (i.e., independent monitors or through a contract research organization). Again, the decision regarding which method of monitoring to use may largely be based on a risk assessment of the study in question. In addition, resourcing internally may dictate that an outside firm be used if the sponsor intends to take a conservative approach to monitoring. Regardless, areas to examine through the monitoring process include: the informed consent process, eligibility, protocol compliance, source data verification, and regulatory compliance, among others.

Ensuring IRB Approval

As described in 21 CFR 56.102 (23) (g), the main purpose of IRB review "is to assure the protection of the rights and welfare of the human subjects." Whether using a central IRB or a local IRB, IRB approval is needed prior to beginning any clinical study activity, as required in 21 CFR 812.42. While it is the investigator's responsibility to seek approval from the IRB, it is the sponsor's responsibility to ensure that approval has been obtained.

Generally speaking, most IRBs require specific paperwork be completed with the initial submission, outlining such items as protocol, consent form to be used, consenting practices to be employed, eligibility criteria, staff who will be working on the study, procedural and follow-up requirements, populations that will be included in the study, and other important items. While some sites complete this paperwork without assistance from the sponsor, the sponsor's involvement in this process can help reduce the time to approval. Specifically as it relates to the informed consent document, the sponsor's approval of the document prior to IRB approval would be beneficial. Should additional changes be required to the consent form after IRB approval, the study may be delayed until such a time as the IRB meets again. In some cases, this could be monthly, bi-monthly, or quarterly.

Consideration should be given to implementing procedures at the sponsor level whereby devices are not shipped until such approval is received. Documentation of the approval should be maintained both in the site's files and the sponsor's files.

Maintaining Adequate Records

The FDA has requirements for record keeping for both investigative sites and sponsors. The sponsors will not only be responsible for ensuring that their files are current and complete, but they will also be responsible, through monitoring or other methods, of ensuring that the investigator is keeping records as required in 21 CFR 812.140. Helping the site by setting up a study binder complete with sections for each required type of documentation would be beneficial in assisting the sites with compliance. In turn, many sponsors maintain mirror files, requesting that sites copy them on all pertinent study documentation. While the approach may be different, the regulatory requirements remain the same. Documentation that is specified as a sponsor requirement to maintain is described in *Table 2*.

Table 2

Record requirements for sponsors – 21 CFR 812.40 and 21 CFR 812.50
1. All correspondence with another investigator, IRB, monitor, or FDA,
2. Required reports • Unanticipated adverse device effects • Withdrawal of IRB approval • Current investigator list • Progress reports • Recall and device disposition • Final report • Records related to use of device without obtaining informed consent
3. Device accountability records
4. Signed investigator agreements
5. Records concerning adverse device effects

Conclusion

Running a clinical study could be a monstrous undertaking for a company who historically has not had to produce clinical data for their 510(k) submissions, and this whitepaper has only begun to touch the surface. Many device companies have no infrastructure to support the running of a clinical trial and opt to outsource the responsibility to a contract research organization. Other companies take on the responsibility internally because their financial resources may be limited. With the uncertainty that is currently looming over the requirements for submitting clinical data for 510(k) submissions, companies should consider developing a working knowledge of what it takes to run a clinical study. Understanding the regulatory framework within which they need to operate, choosing competent investigators, providing training both to their internal staff and their investigative sites, implementing a level of oversight that is appropriate for the device being studied, and maintaining all the pertinent documentation will, at the end of the day, allow companies to feel confident in the clinical data that is supporting their 510(k) submission.

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Sandra Maddock, CEO and President

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