Most medical devices require authorization by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (FDCA) in order to be legally marketed in the United States. Such authorization may be clearance of a premarket notification (510(k) clearance), de novo classification, or approval of a premarket application (PMA). Each of these, in turn, may require varying levels of supporting bench or clinical data, depending upon the type of device and its intended use.

A sound regulatory strategy requires an understanding of the pathway to market and data requirements applicable to a proposed device. There are several ways to obtain advance information from FDA on these issues. Each approach has its strengths and weaknesses. It is worth knowing the ways in which FDA can be approached, the pros and cons of each type of approach, and how to improve communications with FDA in order to gain the best possible understanding of the requirements that will likely pertain to your proposed device. The discussion below will address the available options.

FDA's Website
The Device Center's website (www.fda.gov/cdrh) is a good place to start the research, because it is quick, free and often quite useful. The 510(k) database can be used to search for potential predicate devices. In many cases, there will be a 510(k) summary that can provide information on other predicate devices and the data provided to support clearance. Unfortunately, this information is often presented in fairly general terms. Nonetheless, it can still be helpful. For example, the 510(k) summary will usually provide at least an indication as to whether clinical data were required. In rare cases, FDA also may post its 510(k) decision memo, which will be somewhat more detailed.

If useful predicate devices are identified, it is possible to obtain the underlying 510(k) submission via a Freedom of Information Act request to FDA. Unfortunately, it is unpredictable how long FDA will take to respond and it may take more time than is practical. It is a good idea to check whether FOI Services (a private firm) has already obtained the 510(k) in question (www.foiservices.com), in which case it can be downloaded for a fee.

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FDA’s guidance document database also should be reviewed. In some instances, FDA has published guidance that will reveal the likely pathway (e.g., 510(k) v. PMA) and/or the typical data required to support a 510(k) submission or PMA filing. These documents, when available, usually will provide a detailed map of the path to market.

If a proposed device is in Class III and approval has already been granted to other devices in the same class, FDA’s PMA database may be useful. Every approved device will have a summary of safety and effectiveness (SSE) posted in the database discussing in detail the approved labeling for the device and the preclinical and clinical data submitted to support approval. Even if the proposed device has somewhat different technology or intended use (thus, potentially altering the data requirements), a prior SSE will provide a wealth of information about the road ahead.

Informal Consultation

After making the most of FDA’s website, it may be appropriate to contact FDA officials to obtain more information. A useful approach is to identify officials who would likely review a 510(k) or PMA for the proposed device.

In the Device Center’s Office of Device Evaluation (ODE), there are five divisions, each encompassing a varying number of branches that review specific types of devices. For example, the Division of Reproductive, Abdominal, and Radiological Devices has a Division Director, a Deputy Director and four branch chiefs. If your device were intended for obstetric use (as an example), you might call or e-mail Colin Pollard, currently chief of the Obstetrics/Gynecology Devices Branch, to initiate discussions.

If the device is an in vitro diagnostic, then the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) is the analog of ODE. This office, too, is organized by division. However, instead of searching for a branch chief, you would look for the relevant “Associate Director.” For example, in the Division of Chemistry and Toxicology Devices, the Associate Director for Chemistry is Captain Stephen P. Rhodes, USPHS, has estimated that ODE and OIVD have a combined average of more than 400 meetings per year, not including telephone or e-mail interactions.5

Informal contacts with agency officials will yield information or opinions that are not legally binding upon the agency. Furthermore, when FDA responds to questions, the answers are only as valid as the information provided as the basis for the questions. Thus, it is critical to provide accurate and complete information to your contact at FDA. Despite these limitations, informal contacts with FDA are usually the least expensive and fastest way to elicit a great deal of helpful advice.

PreIDE Program

FDA’s preIDE program is the agency’s basic mechanism for interactive presubmission communications with industry. The current Director of ODE’s Investigational Device Exemption (IDE) Program, Captain Stephen P. Rhodes, USPHS, has estimated that ODE and OIVD have a combined average of more than 400 meetings per year, not including telephone or e-mail interactions.5

The benefit of this extensive outreach effort is to help industry with design testing and development plans that will expedite review and approval. Early interaction also allows FDA personnel to familiarize themselves with the new technologies. Although there is a cost in time and money to both agency and industry, the benefit is generally perceived to exceed the cost.

There are many possible time points in the premarket process where industry may request advice. Prior to proof of concept, it is possible to discuss concepts, testing plan (in broad outline), bench test methodologies, possible regulatory pathways, and potential combination product issues. Typically, FDA considers it premature to discuss these matters in a face-to-face meeting, so telephone and e-mail contact are generally offered.

At the preclinical and clinical phases, FDA encourages preIDE meetings and teleconferences. At the preclinical phase, FDA’s feedback may be sought on bench testing plans, animal study protocols, and feasibility study protocols. In addition, FDA may be willing to provide preliminary feedback on the regulatory pathway and guidance as to whether an IDE approval will be required for any clinical study (i.e., whether the device qualifies as “significant risk” under the IDE regulations).6

At the clinical phase, FDA’s feedback may be sought on the need for further bench/animal studies, the need for a pilot study prior to initiating the pivotal study, proposed study protocols, the regulatory pathway, and proposed indication for use. In addition, FDA may be willing to provide preliminary feedback on issues such as whether the device qualifies for expedited status and the need for an advisory panel meeting.

To obtain a preIDE meeting, a firm must submit a complete pre-meeting package that includes a device description, pre-clinical test plan/results, clinical/statistical test plan, and other
information necessary for FDA to understand the device and the issues for which feedback is sought. It is essential to prepare a list of “focus questions” for which FDA’s feedback is sought. The process of preparing this list of questions will help the firm determine the key outstanding scientific and regulatory issues. The list will also guide FDA’s preparation and may help prevent the meeting from wandering off course.

Some Divisions have their own checklists and guidelines as to what must be in the pre-meeting package, so it is important to inquire. Once the package is submitted to FDA, a project manager is assigned and a meeting will be scheduled. Typically, these meetings are scheduled to occur 4 to 6 weeks after submission. If significant new information becomes available after the package is submitted (e.g., device modifications, changes to study design), it may be necessary to reschedule the meeting. As the meeting approaches, it will be necessary to provide a proposed agenda to FDA and exchange lists of attendees.

The preIDE process is typically focused on study design and testing issues. Yet, it may be the best opportunity to obtain FDA’s feedback on the regulatory pathway to market. This regulatory issue is intimately linked to study design, since studies to support PMA approval are generally more extensive than those supporting 510(k) clearance or de novo classification. Nonetheless, the regulatory issues sometimes are lost in the scientific discussion of study design. Therefore, unless it is clear that a proposed device will require PMA approval, it is a good idea to provide FDA in the preIDE package with a specific analysis of the proposed pathway to market (e.g., proposed predicate devices and substantial equivalence argument) and to include at least one focus question asking for FDA’s feedback on this issue.

FDA’s preIDE program is not iterative. Generally, FDA will grant a single meeting for the same topic. Thus, it is important to think through carefully the timing of the meeting and its objectives. You should view it as “your meeting” in the sense that you are responsible for determining what questions need to be answered, for ensuring that FDA actually answers those questions, and for seeking clarification or elaboration when FDA’s answers do not seem clear or complete. It is important to bring the right team to the meeting with all of the expertise necessary to discuss the focus questions you have developed.

FDA’s advice at a preIDE meeting is not legally binding and may change in light of technological and regulatory evolution. Thus, it is important to maintain contact with FDA on these issues if your development program extends over several years.

Finally, if a binding commitment is needed, FDA by statute offers “determination” and “agreement” meetings. In general, the former is for PMA devices and allows a written request for a determination of the type of valid scientific evidence that will be necessary to demonstrate that the device is effective for its intended use. The latter generally allows a binding agreement between FDA and the sponsor or applicant regarding the parameters of an investigational plan (including a clinical protocol). These two types of meetings are not widely used, but they may be appropriate in some circumstances.

The 510(k) Program
FDA regulates devices under a risk-based scheme, in which devices determined to be substantially equivalent to lawfully marketed Class I and II devices are cleared to market subject to postmarket controls. A 510(k) review is, in essence, a classification proceeding during which FDA determines whether a proposed device is substantially equivalent (SE) or not substantially equivalent (NSE) to a Class I or II device already cleared to market.10

FDA will find a device SE if it has the same intended use and either the same technological characteristics as a predicate device or different technological characteristics that 1) do not raise new types of questions of safety and effectiveness, and 2) data are provided to demonstrate that the proposed device is at least as safe and effective as the predicate. As a practical matter, this review does examine safety and effectiveness to a degree, at least to the extent of determining equivalence to a device already cleared to market. It is not, however, a full review of safety and effectiveness. As a legal matter, FDA’s issuance of a “clearance” letter is actually an order classifying the device into Class I or II based upon substantial equivalence.

If a proposed device is found NSE, it will generally require a PMA approval or de novo classification.11 This may happen if the proposed device does not have a predicate device, presents a new intended use, or has different technological characteristics compared to the predicate device and raises new questions of safety or effectiveness. FDA can make the foregoing determinations without a review of data. In addition, FDA may find a device NSE if the data provided do not demonstrate that the device is at least as safe and effective as the predicate device. In this situation, it may be possible to generate appropriate data to ultimately support clearance of a new 510(k) submission rather than move to the de novo or PMA pathways.

An important implication of the foregoing discussion is that the 510(k) process itself may be an appropriate way to obtain FDA’s ruling on the classification of the device, without the necessity to conduct a study and provide data. If
A 510(k) is submitted and found to be NSE for lack of data, a new 510(k) may be submitted after the appropriate testing has been performed. If the 510(k) is submitted and found to be NSE for the other reasons mentioned above, that is a definitive ruling that the device is in Class III, requiring de novo classification or PMA approval.

A 513(g) Request

An option for obtaining written advice about the classification of a device is a “513(g) request.” It is named for Section 513(g) of the FDCA, which provides:

Within 60 days of the receipt of a written request of any person for information respecting the class in which a device has been classified or the requirements applicable to a device under this Act, [FDA] shall provide such person a written statement of the classification (if any) of such device and the requirements of this Act applicable to the device.

A 513(g) request is fairly simple to prepare. Generally speaking, it should include a cover letter, a complete device description, an “Indications for Use” statement, and either proposed labeling or labeling of a similar device already on the market. A user fee is now required for each 513(g) request. Within 60 days, and sometimes sooner, FDA will provide a written response that is binding unless amended or revoked in writing. The advice in response to a 513(g) request only covers the device as described in the initial request. If the device is modified (or was not accurate in the first place), the 513(g) response may not apply.

A 513(g) request can be used for a wide range of inquiries. These include whether a product is subject to FDA regulation at all, whether it is regulated as a device (versus a cosmetic, biologic or drug), whether it is within an exemption from 510(k) requirements, whether a 510(k) is needed for a modification to the device, and whether a device with a new technology or intended use must undergo a 510(k) or PMA pathway to market.

There has sometimes been uncertainty about whether a particular stand alone software product is subject to medical device regulation. FDA has withdrawn its 1989 draft policy statement, “FDA Policy for the Regulation of Computer Products.” This guidance had never been finalized but had provided operational policy guidance to industry and agency staff for many years. Some agency officials have said that the principles embodied in the draft guidance still apply in most cases. Nonetheless, FDA has no current written guidance on the regulation of stand alone software products. A 513(g) request can be used to elicit formal advice as to whether a particular stand alone software product will be regulated as a medical device and the requirements that will apply.

Request for Designation

A combination product raises the question about which Center will have primary jurisdiction (i.e., Drug, Device or Biologic). A “Request for Designation” (RFD) can be submitted to the OCP seeking a written ruling as to which center will have primary jurisdiction. This process and the requirements for an RFD are set forth in 21 C.F.R. Part 3. The OCP must make its written jurisdictional determination within 60 days of filing. There is no user fee for an RFD.

Final Thoughts

It is critical to obtain information from FDA on the requirements applicable to a proposed device. It will typically require significant time and funding resources to do so. Therefore, when developing a business and regulatory strategy, it is essential to build in this information gathering process. This is particularly true for novel or complex devices, for which it is virtually impossible to successfully conduct a clinical study and prepare an appropriate 510(k) submission or PMA filing without consulting FDA in advance. It is essential to develop a careful strategy for communicating with FDA using the right tools at the right time in the development process. Hopefully, the foregoing discussion will help get you started in formulating a successful strategy that will result in a smooth pathway to market for your device. △

2 The Device Center’s formal name is the Center for Devices and Radiological Health (CDRH). The Drug Center’s formal name is the Center for Drug Evaluation and Research (CDER). The Biologics Center’s formal name is the Center for Biologics Evaluation and Research (CBER).
3 Currently, these are: Stephen Rhodes, CAPT, USPHS, CDRH; Virginia Behr, CDER; and Sheryl Land-Whiteford, PhD, CBER.
4 21 C.F.R. § 10.85(k).
6 21 C.F.R. 812.3(n).
7 FDCA, §513(g)(3)(D).
8 FDCA, §520(g)(7).
9 FDA’s description of these two types of meetings can be found in “Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff.”
10 Substantial equivalence may also be claimed to a pre-amendment device (on the market prior to May 28, 1976), for which PMA applications have not been called. There are also Class I and II devices that are exempt from the 510(k) requirement.
11 In de novo classification under Section 513(f)(2) of the FDCA, FDA essentially creates a new classification for novel low risk devices that lack a predicate device. The process requires an additional 60 days, and usually includes the development of special regulatory controls for the device. Once the classification exists, future devices may seek 510(k) clearance based upon substantial equivalence to the de novo device.
12 An original and one copy of the 513(g) request should be mailed to the 513(g) Coordinator, Office of Device Evaluation, Center for Devices and Radiological Health c/o Document Mail Center (HFZ–401), 9200 Corporate Boulevard, Rockville, Maryland 20850. The current contact person is Lawrence J. (Jake) Romanell, Program Operations Staff, ODE, CDRH.
13 In Fiscal Year 2008, the standard fee is $2,498 and the small business discounted fee is $1,249.
14 See 21 C.F.R. § 10.85(e).
15 For a detailed treatment of combination products, see Fox and Shapiro, “Combination Products: How to Develop the Optimal Strategic Path for Approval” (FDANews 2006) (www.fdanews.com).