

Strategic Planning For US Premarket Approval Submissions

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The United States premarket approval (PMA) process is costly and time-consuming and differs in important ways from the CE-marking process. This article discusses the importance of strategic planning for submission of a PMA and the issues that should be considered, which can lead to a reduction in the time and cost involved.

A Class III device requirement

Under United States (US) regulations, medical devices are classified into Classes I, II and III, based on the level of control that the Food and Drug Administration (FDA) believes is necessary to ensure the safety and effectiveness of the device. Class I includes the lowest risk devices and Class III devices with the greatest risk. Class III devices require a premarket approval (PMA) application to obtain marketing clearance in the US. However, it should be noted that some devices, called Class III preamendment devices, which were on the market before the enactment of the US medical device regulations, may require a Class III 510(k). These types of devices and the requirements of a Class III 510(k) are not discussed in this article.

A PMA application is the most stringent type of device marketing application that FDA requires. The requirements for the content and submission of a PMA are stipulated in US Title 21 Code of Federal Regulations (CFR) Part 814. A PMA application involves many volumes that cover device description and intended use, nonclinical and clinical studies, case report forms, manufacturing methods, labelling, and other information and data. To facilitate the regulatory review process, FDA has developed extensive guidance on the submission of PMA applications and on the type of information and data that should be included for specific types of products (Table I). It is important that companies review all relevant guidance documents at the beginning of the PMA development process to ensure

that FDA expectations are understood. Under the PMA process, FDA conducts a scientific and regulatory review of information and data submitted by the PMA applicant to determine whether or not the PMA contains sufficient valid scientific evidence to ensure that the device is safe and effective for its intended use(s).

Shortening the review time

The PMA regulations specify that FDA has 180 days to review the PMA and make a determination; however, the review time is frequently longer than this. Therefore, it is extremely important that PMA applicants take certain steps, including those discussed in this article, to avoid delays during the PMA review process. Before FDA approves or denies a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting. The purpose of this review is to provide FDA with a recommendation on whether or not FDA should approve the submission. After FDA notifies the PMA applicant of approval or denial of the PMA, FDA publishes a notice on the Internet announcing the data on which the decision is based; this provides interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.

Fees

FDA requires the payment of fees (termed user fees) for reviewing various types of regulatory submissions, includ-



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Table 1: Where to find FDA guidance documents and other information on the requirements of a PMA application.

- All the guidance documents and other information on PMA requirements can be found on the FDA Center for Devices and Radiological Health (CDRH) website: www.fda.gov/cdrh
- Information on user fees for PMAs can be found at www.fda.gov/cdrh/devadvice/pma/userfees.html
- Guidance document, Expedited Review of Premarket Submissions for Devices: www.fda.gov/cdrh/mdufma/guidance/108.pdf
- Draft guidance document, The Review and Inspection of Premarket Approval Application Manufacturing Information and Operations can be downloaded from www.fda.gov/cdrh/comp/guidance/1566.pdf
- Draft guidance document, The Review and Inspection of Premarket Approval Applications under the Bioresearch Monitoring Program can be downloaded from www.fda.gov/cdrh/comp/guidance/1602.pdf

ing PMA applications (see Table I). When reviewing this information, readers should note that nonUS medical device companies that are considered to be small businesses by FDA are not eligible for user fee reductions or waivers unless they file a US tax return. Therefore, the fee that large or small nonUS companies must pay for submitting a PMA application during fiscal year 2006 is US \$259600. FDA will not accept the application unless payment is received on or before the time that the PMA application is submitted.

Selecting the right PMA application

There are several types of PMA application, including, the traditional PMA, a modular PMA, a streamlined PMA and a Product Development Protocol. Before beginning the PMA process companies should decide which type is most appropriate for their product. The two types of PMA applications most frequently submitted to FDA are described below; information on the other types of PMA applications can be obtained from the CDRH website or by contacting FDA.

A traditional PMA. This is submitted in one step, that is, all elements required for a PMA such as scientific and technical information on the device, manufacturing, non-clinical studies, clinical studies and labelling are submitted in one single application. This is the best type of PMA to submit when the device has already undergone clinical testing and has been approved in a country with established medical device regulations.

A modular PMA. This consists of well-defined sections or modules that are submitted separately to FDA as soon as the testing and analysis required for each module is completed. Thus, the PMA application is completed over a defined period of time. This type of PMA submission is recommended for products that are in early stages of clinical study. FDA reviews each module separately as soon as it is received and provides feedback on each module during the review process. The advantage of this approach is the

possibility of a more rapid completion of the review process when the last parts of the PMA are submitted, because much of the review work will have already been done. In addition, because the content and format of each element of a module are established during discussions between FDA and the applicant, the likelihood of important omissions in the application are reduced.

Access to an expedited review

At the beginning of the process of developing a PMA, companies should determine whether or not their products qualify for an expedited review. FDA considers a device appropriate for expedited review if the device is intended to treat or diagnose a life-threatening, irreversibly debilitating disease or condition and addresses an unmet medical need (Table I). This need is demonstrated if

- the device represents a breakthrough technology that provides a clinically meaningful advantage over existing technology
- no approved alternative treatment or means of diagnosis exists
- the device offers significant, clinically meaningful advantages over existing approved alternative treatments
- the availability of the device is in the best interest of the patients.

New draft guidance documents

FDA has recently developed two new guidance documents to add to the numerous ones it already provides on the preparation and submission of PMA applications.

■ “The Review and Inspection of Premarket Approval Application Manufacturing Information and Operations” draft guidance issued on 19 June 2006. This describes the procedure that FDA follows when reviewing the manufacturing section of a PMA, the administrative process and projected timeframes involved with each step of the review, how the inspection of a manufacturing facility fits into the approval process, and FDA expectations. The information on timeframes is particularly useful for strategic planning to ensure that manufacturing operations comply with US regulations. Even though the content of the final guidance document could be different, the current information is useful for companies in the process of developing a PMA.

■ “The Review and Inspection of Premarket Approval Applications under the Bioresearch Monitoring Program,” draft guidance issued on 20 June 2006. This describes the role of CDRH’s Division of Bioresearch Monitoring (DBM), which is responsible for reviewing the clinical and nonclinical laboratory study sections of a PMA. DBM is also responsible for identifying sites related to the conduct of clinical investigations that are to be inspected. The sites that FDA may wish to inspect include the sponsor, monitor, contract research organisation, clinical investigator and laboratory conducting nonclinical studies. Sites are generally selected because of their contribution to the pivotal →

→ study data, compliance history, concerns identified by the FDA review team, adverse effects reported in the PMA, or other considerations. The vast majority of the inspections that DBM directs are of sites related to the conduct of clinical studies in the US under the US Investigational Device Exemption (IDE) regulations found in 21 CFR Part 812. However, FDA also conducts inspections of sites outside the US. Again, although the wording in the final guidance document may be different, the draft text should still be taken into consideration when PMA projects are planned.

The quality of PMA data

The quality, clarity and completeness of the information and data provided in a PMA have a significant effect on the time that it takes FDA to review the PMA. FDA has stated that a PMA application contains administrative elements, but good science and scientific writing is essential to the approval of PMA application. Furthermore, FDA states that if a PMA application lacks elements listed in the administrative checklist, FDA will refuse to file a PMA application and will not proceed with the in-depth review of scientific and clinical data. Problems with the review and approval of a PMA can also result from a PMA application that lacks valid clinical information and scientific analysis on sound scientific reasoning. Companies planning the development of a PMA application should place considerable emphasis on providing FDA with complete, accurate and well-organised applications that contain information that is consistent and includes all required information. In this regard, FDA advises manufacturers to perform a quality control audit of a PMA application before submitting it to FDA to ensure that it is scientifically sound and well organised to facilitate the review.

Location of clinical investigations

The clinical investigation section is one of the most important sections of a PMA application. This section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and other information from the results of clinical investigations. Any investigation conducted under an IDE must be identified as such.

Thus, the activities related to the conduct of clinical studies and analysis of clinical data needed for a PMA represent a significant part of the budget of a PMA application; in part, this is due to the high costs of actually conducting these studies. Therefore, companies sometimes wish to reduce these costs by conducting all or some of the clinical studies needed for a PMA outside the US. It is possible to do this providing the requirements for conducting these studies are met. These requirements are specified in Part 814.15, Research conducted outside

the US, of Title 21 of the US CFR. In addition, early talks should be held with FDA to discuss studies that have already been conducted outside the US, which will be used to support the PMA, or studies that are planned to be conducted outside the US. This will help avoid the need for repeating clinical studies, which in some cases could jeopardise the success of a PMA project.

Strategic planning

The development of a PMA application should begin with careful planning and documentation of the steps and tasks needed for submission to FDA. Some of the more critical issues that should be addressed when a PMA project is initiated include the clinical-study strategy and the type of submission. In addition, it is important to determine and document project roles and responsibilities, project steps and timelines, and the issues to be addressed during early contacts with FDA. Prudent companies will devote considerable time to this phase of the PMA application so that realistic project timelines and budgets can be established and met and costly delays avoided. [mdt](#)

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