FDA INSIGHTS

Premarket Approval and Premarket Notification

Uncovering the mystery of FDA device regulation classifications.

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Part of the mystery of device regulation for some is the mechanism by which a device is allowed to be marketed. The foundation of FDA medical device regulation is the risk-based classification of devices. This classification dictates the level of regulatory oversight for the product type, with devices being assigned to one of three classes. Devices with the most risk, Class III devices, are subject to the highest level of regulatory oversight. While all classes are subject to some basic controls, such as the need to follow appropriate design controls, the higher classes have additional specific requirements, such as premarket notification or premarket approval.

Class II devices, which require marketing clearance, obtain this clearance through the premarket notification process. Class III devices require FDA approval prior to marketing, which is usually accomplished through the premarket approval process. In an effort to unveil the most common routes to market, these processes are briefly described in this article.

PREMARKET NOTIFICATION [510(K)]

A premarket notification application is referred to as a 510(k), so named for the statute in the Food Drug and Cosmetic Act that describes these types of submissions. In a 510(k), the sponsor demonstrates that the device is substantially equivalent to a legally marketed device. This involves comparing aspects of the marketed device and the new device, such as the intended use, device features, and performance, as needed for the type of device.

When a 510(k) is submitted, the file first undergoes a screening review to determine whether it is administratively complete. If the file is determined to be reviewable, the assigned reviewer may conduct the entire substantive review or may seek consulting review help, depending on the complexity of the information provided in the 510(k). For example, if clinical data are presented in the application, a clinician and a statistician may be included on the review team. Alternatively, for devices such as standard polyester vascular grafts in which no clinical data are needed, the lead reviewer could look at the comparison data provided, such as the comparison of the strength, permeability and dimensional testing results, intended use, yarn materials, weave pattern, sterility assurance, etc., as well as the administrative parts of the file and not form a review team. Whether a team review is needed or not, the lead reviewer should try to identify any deficiencies or concerns and communicate them to the sponsor within about 70 days, or preferably less. The FDA's statutory time period for review of 510(k)'s is 90 days. The communication may be by letter, phone, fax, or e-mail. Once the sponsor provides the additional information, the reviewer is expected to complete the review of the additional information in a more timely fashion, if possible. Assuming substantial equivalence has been demonstrated, completion of the review involves summarizing the information submitted and any interactions with the sponsor and writing an "SE letter." Generally, this letter consists of a form letter with a bit of specific information about the device.

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Four to five thousand 510(k)'s are completed in the Center for Devices and Radiological Health (CDRH) each year. These files are anywhere from several pages to several feet thick and involve sign-off at the review-division level. General postmarket requirements apply to devices cleared

under the 510(k) process, such as the need to report adverse device effects to the FDA; however, additional postmarket requirements are rarely imposed.

PREMARKET APPROVAL

The mechanism for obtaining approval is through submission of a premarket approval (PMA) application. The sponsor of a PMA needs to demonstrate that the device is reasonably safe and effective for the intended use(s) through submission of details on the device description and manufacture, results of preclinical and usually clinical studies, biocompatibility, sterilization, packaging and shelf-life of the device, as well as other information as described in the PMA regulation.

> "the PMA process is much more complicated and time consuming than the 510(k) process."

Thirty to fifty original PMAs are completed by the CDRH each year. The size of these files tends to be measured in feet and always involves a team review. A PMA may be submitted in a modular format, where nonclinical information is submitted for review prior to the clinical section. When the clinical section is submitted, the PMA has a 180-day review cycle.

Review of a PMA involves most of the offices within the CDRH. The Office of Device Evaluation or the Office of In Vitro Diagnostic Device Evaluation and Safety has the lead responsibility for the PMA. This involves review responsibilities, communicating with the sponsor of the submission, and coordinating the reviews from the other offices. The Office of Health and Industry Programs is responsible for commenting on the patient labeling. The statistical reviewers are located in the Office of Surveillance and Biometrics. Consulting reviewers, such as engineers and physiologists, are in the Office of Science and Engineering Laboratories, previously named the Office of Science and Technology. Last, but not least, the Office of Compliance includes the Division of Enforcement that reviews the manufacturing section of the PMA and the Division of Bioresearch Monitoring that audits the clinical data to determine the extent to which the appropriate regulations and the clinical protocol have been followed. This Office also has responsibility for incorporating the findings of the FDA field staff who conduct inspections of clinical sites and manufacturers.

Review of the PMA almost always involves requests for additional information and interaction with the sponsor. This may take place during the initial 180 days or, if a major amendment is required to address the FDA concerns, the clock is stopped on the file and restarted once the additional information is received.

After the in-house review of a PMA, an FDA advisory panel review may be required. These independent panels of experts are composed of representatives from clinical practice and academia, with both an industry and a consumer representative. The panel provides recommendations regarding the approvability of the device, conditions of approval and labeling. Additional information on FDA advisory panels can be found in the November/December 2002 issue of *Endovascular Today*.

When a decision has been made to approve a new device, the closeout process begins for the PMA. This involves putting together the necessary documentation, such as the lead reviewer memo and the consulting review memos as well as the necessary clearances from the Office of Compliance. In addition, the final review of the labeling and summary of safety and effectiveness data, the tools FDA has to communicate information to device users and patients, is done at this time. The approval order, which is the letter of approval to market the device, is finalized. This includes the conditions that must be met to be in compliance with FDA requirements; some generic conditions that apply to all PMA-approved devices and other specific conditions of approval for certain devices. These conditions may include a requirement to conduct a postapproval study. Such studies may be intended to provide longer-term safety and effectiveness data, to include the collection of additional information that may be used to modify the labeling, to study learning curve or training issues, or to address some other potential issue specific to the device that was approved.

Finally, a "one pager" is written for the FDA internet and depending on the potential public health significance or public interest regarding the device approved, a press release may be prepared. Sign-off for a PMA application is at the office level, including sign-off by the PMA staff and possibly the Office Director, in addition to the review division.

Clearly, the PMA process is much more complicated and time-consuming than the 510(k) process, and it is rightly so, given the differences in the types of devices that are subject to premarket approval and premarket notification and premarket approval. Additional information on the regulation of medical devices can be found at http://www.fda.gov/cdrh. ■

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