



U.S. MEDICAL DEVICE CLEARANCE: NAVIGATING THE FDA 510(k) PREMARKET APPROVAL PROCESS FOR MEDICAL DEVICES





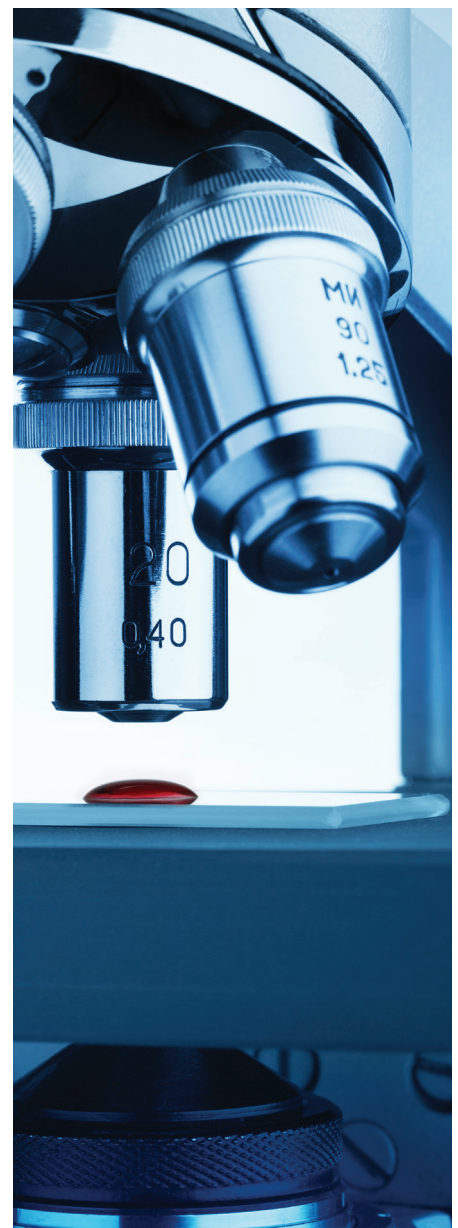
U.S. Medical Device Clearance: Navigating the FDA 510(k) Premarket Approval Process for Medical Devices

Speed to market represents an important competitive advantage for medical device manufacturers, and can be a key factor in the total lifetime profitability of a new medical device. Successful manufacturers have robust internal programs and processes that streamline new product development activities. Such systems can reduce the risk of roadblocks and setbacks that can delay the introduction of new products into the marketplace.

With annual estimated expenditures of more than \$127 billion and an average annual per capita expenditure of \$399,¹ the U.S. is the largest market for medical devices in the world. However, the U.S. regulatory approval process for medical devices is complex and not always well understood by manufacturers, especially for new entrants to the U.S. market. Even for manufacturers well versed in the U.S. regulatory scheme, existing regulations are often subject to interpretation, and new and revised laws can introduce new regulatory hurdles. These factors can result in significant challenges when it comes to marketing medical devices in the U.S.

The Food and Drug Administration (FDA) is the federal agency responsible for the regulatory oversight of medical devices in the U.S. Most medical device premarket reviews conducted by the FDA fall under its 510(k) Premarket Notification program. In recent years, the FDA has instituted a number of changes to its application and review process to facilitate the prompt assessment of device applications. But, for many manufacturers, the breadth and complexity of the application process still results in the submission of incomplete or inaccurate 510(k) applications. Such problems can lead to delays in the review and clearance process, and the potential loss of market opportunity.

This UL white paper discusses the challenges encountered by medical device manufacturers seeking market clearance under the FDA's 510(k) program. The paper begins with an overview of the FDA's various programs for the review of new or significantly modified medical devices, and a description of the information requirements for a 510(k) submission. The white paper then summarizes the most common problems experienced by device manufacturers during the application preparation and agency review process. The paper concludes by offering specific strategies that manufacturers can employ to improve the completeness and accuracy of their 510(k) submissions and to increase the likelihood of a timely review and clearance.





An Overview of FDA Review of Medical Devices

Virtually all medical devices sold or marketed in the U.S. must meet mandatory regulations administered by the FDA in order to protect the health and safety of patients and healthcare providers alike. Medical devices classified as posing a significant risk of illness or injury, or which are not “substantially equivalent” to other devices previously cleared by the FDA, are subject to the agency’s rigorous premarket approval (PMA) process. Among other requirements, the PMA process requires a device manufacturer to submit clinical data to support claims made in connection with its device.

However, approximately 80 percent of all medical devices are covered under the FDA’s 510(k) premarket notification program. Under the 510(k) program, the FDA does not actually “approve” medical devices. Instead, it “clears” them for sale in the market, implying a less rigorous review than that required under the PMA program. However, the 510(k) review program still requires device manufacturers to submit extensive documentation supporting the substantial equivalence of their devices to other legally marketed medical devices previously cleared by the FDA (referred to as “predicate devices”).

Aside from new medical devices, the FDA’s 510(k) requirements are also applicable to previously approved medical devices that have been modified so as to potentially affect their safety or effectiveness. Device modifications potentially requiring the need for a new 510(k) submission include new intended uses of a previously cleared device, or changes in a device’s design, material or chemical composition. The FDA has developed distinct submission processes for use in these scenarios, as shown in Table 1

A small number of medical devices are exempt from FDA review. For example, the FDA can grant an investigational device exemption (IDE) that allows a medical device under development to be used in clinical studies for the purposes of collecting data on its safety and effectiveness in support of a PMA application or a 510(k) submission. Typically, however, medical devices used in such studies that pose significant risk to patients used must be pre-approved by the FDA and an institutional review board.

In addition to meeting product approval or clearance requirements, medical device manufacturers and importers must complete an “establishment registration” with the FDA, and pay an establishment registration fee. Establishment

registration information is subject to annual verification. Foreign medical device manufacturers are also required to designate a U.S. agent who can represent a manufacturer in connection with the FDA’s oversight of medical devices.

Finally, for all medical devices that have been approved or that have received market clearance from the FDA, manufacturers must list their devices with the FDA’s public medical device database.

Key Information Requirements of an FDA 510(k) Submission

The 510(k) premarket notification program is primarily intended for medical devices that are “substantially equivalent” to other medical devices that have previously received market clearance from the FDA. In this context, substantial equivalence refers to factors such as a device’s design, construction, use indications, safety performance, effectiveness and any other applicable characteristics. Accordingly, the scope and depth of information provided with a 510(k) submission must be sufficient to allow FDA reviewers to determine whether the subject medical device is substantially equivalent to an identified predicate device.

TYPE	WHEN TO USE	BENEFITS
Special	For modified devices	Processed within 30 days of submission
Abbreviated	When a guidance document exists or when special controls have been established	Test data may not be required
Traditional	In all other cases	Established submission and review process

Table 1: FDA premarket notification clearance alternatives



Here is a brief summary of the specific information required by the FDA in connection with all 510(k) submissions:

- **Device description** — A 510(k) submission must include a description of the medical device, including all models and accessories or components, as well as device performance specifications. In addition, it is advisable to include information on the materials used in all device components that come in direct contact with patients.
- **Substantial equivalence** — The FDA evaluation of 510(k) submissions is based on whether a given medical device is substantially equivalent to a device that has previously received market clearance from the FDA. To facilitate this evaluation, device manufacturers must specifically identify a predicate device (or devices) whose use indications, technological characteristics and performance are comparable to the device being submitted for review. In cases where a medical device and predicate device differ from each other, a manufacturer must submit data or other rationale that clearly demonstrates that the differences do not affect the intended use or raise new or different questions regarding a device's safety and effectiveness.²
- **Sterilization and shelf life** — For all medical devices labeled as sterile, manufacturers must provide verification and validation data on a device's sterilization and shelf life. Specific information should

include the method of sterilization used (that is, dry heat, moist heat, ethylene oxide (EO), or radiation), and a description of the packaging used to maintain sterility of a device.³

- **Biocompatibility** — Manufacturers of medical devices that come either in direct or indirect contact with patients must submit testing data regarding the biocompatibility of any patient-contacting materials. The exception to this requirement is when the identified predicate device uses identical materials produced using the same manufacturing, processing, packaging, and (if applicable) sterilization methods.

- **Software** — 510(k) submissions for medical devices containing or utilizing software must include software documentation, including information on the role of software in causing, controlling and/or mitigating hazards that could result in injury to either a patient or a device operator. The extent of documentation to be provided depends on a manufacturer's estimate of a device's "level of concern," which is the potential severity of injury that could occur as a result of device failures, design flaws or other causes.⁴
- **EMC and electrical safety** — For medical devices incorporating electronic components,





manufacturers should submit test data providing evidence of compliance with applicable electromagnetic compatibility (EMC) and electrical safety standards.

- **Performance testing** — Performance testing data is required to support a manufacturer's claim of substantial equivalence with a predicate device. The extent of performance data required in connection with a 510(k) submission depends on the complexity of the device, as well as its intended use. Performance data can be based on a variety of types of testing, including bench testing, animal testing, clinical studies and clinical trials, but should be conducted on all device sizes and models in a manner consistent with actual use. As an alternative to testing, manufacturers can submit previously published data for a predicate device to demonstrate substantial equivalence.
- **Proposed labeling** — A 510(k) submission must include labeling information, including final draft copies of all proposed labels, labeling, user instructions and service manuals, as well as copies of proposed promotional materials and/or advertising. Manufacturers are also encouraged to submit copies of labeling used in conjunction with an identified predicate device.

Common Challenges for Manufacturers Making 510(k) Submissions

According to its policy, the FDA has 90 days to review 510(k) submissions

received directly from medical device manufacturers. However, that time limit can be extended in cases in which FDA reviewers determine that a submission is incomplete, or that additional information from a manufacturer is required. FDA data indicates that the agency requests additional data in connection with approximately 75 percent of all 510(k) submissions received.⁵ As a result, the average review time for 510(k) applications received directly from device manufacturers is now more than 145 days, a nearly 50 percent increase in review time over the past decade.⁶

While the reasons for delays in the review of 510(k) submissions are varied, the FDA has identified⁷ a number of common factors that typically result in extended review times, as follows:

1. **Inadequate device description** — Surprisingly, one of the leading factors resulting in 510(k) review delays is the absence of a complete and thorough description of what the medical device actually does. According to FDA data, approximately 50 percent of all 510(k) submissions failed to provide an adequate device description. Without detailed information of a device's intended function, FDA reviewers cannot assess whether the remaining documentation accompanying the submission is sufficient for the purposes of the review.
2. **Failure to identify suitable predicate devices** — The success of the 510(k) review process is dependent on a manufacturer identifying similar medical devices that have

previously been cleared by the FDA. Predicate devices must be carefully selected so that their key characteristics are comparable to those of the device being submitted for review. Nearly 40 percent of 510(k) submissions failed to identify a suitable predicate device.

3. **Missing or inadequate performance testing** — Performance testing is required for all 510(k) submissions, yet more than half of all 510(k) submissions fail to provide performance test data, or submit performance test data that was inconclusive. Without performance testing, FDA reviewers cannot evaluate whether a medical device is as safe and effective as the predicate device.
4. **Missing or inadequate clinical data** — In addition to performance test data, the FDA also requires the submission of clinical data for some device types to support specific clinical claims of equivalence with a predicate device. At least one in 10 510(k) submissions failed to include required clinical data. In some cases, the need for clinical data is not apparent during preparation of the 510(k) submission.
5. **Missing or inadequate biocompatibility information** — Nearly one-third of 510(k) submissions received by the FDA provided inadequate information regarding device biocompatibility, or failed to provide any biocompatibility data at all.



6. Failure to follow device-specific standards and current FDA guidance

— Regulatory requirements are almost as unique and distinct as the countries that enforce them. Even if a device is approved in another region, the FDA may require more or less data or submission information in a different format. The FDA frequently issues general and device-specific guidance documents to aid manufacturers in understanding its requirements. Nonetheless, approximately 40 percent of 510(k) submissions fail to reflect current FDA requirements or guidance.

In addition to these common factors, omitting any required information or documentation, regardless of the reason, will almost always result in a request for additional information from FDA reviewers, thereby extending the review process. The FDA also provides comprehensive and detailed instructions for preparing a complete 510(k) filing. Even seemingly inconsequential deviations from these instructions, such as failing to follow pagination requirements or the FDA's eCopy guidelines, can provide a sufficient basis to reject a 510(k) submission after initial screening, delaying the advancement to the substantive review phase.

Strategies for Facilitating 510(k) Device Review

The scope and complexity of information required by the 510(k) review process means that manufacturers seeking market clearance for new medical

devices must develop a comprehensive compliance strategy to avoid unnecessary delays and setbacks in the submission and review process. At a minimum, such a strategy should include the following elements:

- **Develop an in-depth understanding of the 510(k) program and process** — The FDA has developed one of the most comprehensive medical device regulatory programs in the world, along with an extensive catalog of guidance documents on the application of its regulations for the review and clearance of medical devices. Manufacturers who develop an in-depth understanding of the FDA's requirements and processes as they apply to specific medical devices can avoid many of the errors or omissions illustrated earlier in this paper.
- **Stay current** — Today's medical device industry is characterized by continuous innovation. In this dynamic environment, the FDA is continually reviewing its regulations and practices, and modifying existing requirements or developing new ones to remain current with the latest product developments. Therefore, staying abreast of the FDA's proposed rulemakings and other actions can provide device manufacturers with advanced notice of regulatory changes that could affect their products.
- **Formulate a 510(k) action plan as early as possible** — The most effective way to achieve 510(k)

clearance with minimal surprises and setbacks is to integrate regulatory compliance planning into the new product planning process. This integrated approach saves time, since requisite testing can be coordinated with product development activities, and provides greater flexibility in addressing design changes required by regulatory considerations.

- **Dedicate internal resources for the duration** — Because of the complexity of the regulatory review process, device manufacturers should consider appointing specific individuals within the organization with responsibility for overseeing and addressing regulatory compliance issues for the duration of the project. Doing so will reduce the risk of gaps in vital communications and understandings that can result in delays in the device review and clearance process.
- **Engage a knowledgeable advisor** — There is no substitute for experience. A knowledgeable advisor or consultant with extensive medical device expertise and first-hand experience dealing with 510(k) submissions can quickly determine the requirements applicable to specific medical devices, streamline the 510(k) documentation process and anticipate most, if not all, of the challenges encountered by manufacturers that choose to navigate the process alone.



Conclusion

The U.S. market for medical devices is the world's largest and potentially the most lucrative for medical device manufacturers. But device manufacturers first have to navigate the complexities and the details of the FDA's 510(k) review process. Whether due to lack of knowledge or oversight, most manufacturers typically encounter one or more setbacks in their efforts to obtain prompt clearance from the FDA, resulting in costly delays in bringing new products to market. However, device manufacturers can reduce the likelihood of these delays by becoming more knowledgeable about the FDA's requirements, staying current with the constantly changing regulatory landscape, and working with an experienced advisor or consultant in the preparation of a 510(k) submission.

Over the past decade, UL has worked with medical device manufacturers on more than 700 510(k) submissions through the FDA's Accredited Persons program. This extensive experience with the FDA medical device clearance process and a wide variety of medical devices makes UL a reliable partner for global manufacturers seeking entry into the U.S. market. Please contact Medical.Inquiry@ul.com or visit www.ul.com/medical for more information.



¹"The Medical Device Market: USA," Report by Espicom Business Intelligence, September 2013. Web. 20 December 2013. <http://www.espicom.com/usa-medical-device-market>

²Additional details regarding substantial equivalence documentation for 510(k) submissions is available in "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3)," U.S. Food and Drug Administration, June 30, 1986. Web. 20 December 2013. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm>.

³Additional details regarding required sterilization documentation for 510(k) submissions is available in "Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA," U.S. Food and Drug Administration, August 30, 2001. Web. 20 December 2013. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072783.htm>.

⁴Additional details regarding required software documentation for 510(k) submissions is available in "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," U.S. Food and Drug Administration, May 11, 2005. Web. 20 December 2013. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm>

⁵A detailed timeline of the FDA's communication performance goals in connection with 510(k) applications is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm070201.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery#timeline. Web. 14 January 2014.

⁶"Medical Device Pre-Market Programs: An Overview of FDA Actions," U.S. Food and Drug Administration, November 12, 2011. Web. 20 December 2013. <http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm276272.htm>.

⁷Statistics quoted in this section are derived from "Analysis of Pre-Market Review Times Under the 510(k) Program," U.S. Food and Drug Administration, Center for Devices and Radiological Health, November 9, 2011. Web. 20 December 2013. <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm263385.htm>