

The Evolving US 510(k) Review Process

For many medical devices, the submission of a United States premarket notification, a 510(k), is no longer a routine process with a relatively predictable outcome. It can often be difficult, time consuming and costly to achieve. This article discusses US FDA's initiatives for improving the 510(k) process and factors to consider when planning the submission of a 510(k).

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Strategic priorities

The United States (US) Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) has been criticised by US lawmakers and others for not being sufficiently strict in some of its 510(k) clearance practices. It has also been criticised by industry for sometimes being overly strict and inconsistent. FDA itself has identified a series of challenges related to the 510(k) review process. As a result, it commissioned the US Institute of Medicine¹ (IOM) to conduct an independent review of the 510(k) programme and, if necessary, recommend administrative, regulatory and/or statutory changes. However, the IOM study is not expected to conclude until March 2011, thus CDRH established an internal 510(k) Working Group to recommend possible actions that it could take in the short term to strengthen the programme and identify longer term objectives.

In addition to actions related to the IOM study and 510(k) Working Group, on 20 January 2010 CDRH launched an ambitious programme for improving how CDRH fulfills its regulatory mission. The programme is outlined in the "CDRH FY 2010 Strategic Priorities" document² and an important component concerns the improvement of the 510(k) review process. The document specifies not only broad strategies, but time-bound goals associated with each strategy, together with specific actions CDRH states it will take to meet those goals.

Four CDRH priority areas are identified:

- Priority 1: Fully Implement a Total Product Life Cycle Approach
- Priority 2: Enhance Communication and Transparency
- Priority 3: Strengthen Our Workforce and Workplace



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■ Priority 4: Proactively Facilitate Innovation and Address Unmet Public Health Needs.

Many of the goals described are scheduled to be achieved in fiscal year 2010. For goals that will take more time to accomplish, the document describes supporting actions for 2010. For example, by 30 September 2010 the document states that CDRH will begin



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to implement the recommendations of a 510(k) Working Group. This is an aggressive deadline for a strategic programme issued in January 2010, and it is advised that readers with an interest in the 510(k) process should review this document and keep up-to-date with FDA progress towards achieving this objective. The goals, action items and deadlines not related to the 510(k) review process should also be of considerable interest to those companies marketing devices in the US.

One of the first action items listed in the Strategic Priorities document is that by 28 February 2010 CDRH will have collected input from external constituencies through a public docket and a public meeting. Indeed, a widely publicised public meeting was held on 18 February 2010, titled, “Strengthening the Center for Devices and Radiological Health’s 510(k) Review Process.” Information on the meeting,³ including links to an archived video recording of the event are available on the FDA’s website.

A Federal Register notice explained that the purpose of the meeting was to discuss FDA concerns and receive comments from interested parties on four general topics: Issues Related to the Predicate Device, Issues Related to New Technologies and Scientific Evidence, Issues Related to Practices CDRH has Adopted in Response to a High Volume of 510(k) Submissions, and Issues Related to Postmarket Surveillance and New Information about

Marketed Devices. The notice also provides details on each of these issues and asks a series of related questions.

For example, with regard to problems associated with trying to distinguish between “intended use” and “indications for use” FDA requested comments from interested persons on

- their understanding of an “indication for use” compared with an “intended use”
- what criteria, if any, FDA should use to determine whether or not to consider a different “indication for use” to also be a different “intended use”
- examples of different “indications for use” they believe should or should not be considered different “intended uses” and explain their reasoning
- the advantages and disadvantages of distinguishing between the terms “indication for use” and “intended use” during the review process, or
- the advantages and disadvantages of combining these concepts into one term.

Reviewing these issues and the specific related questions that FDA asked provides some reassurance to anyone who has experience of submitting 510(k)s that at least some challenges encountered during the 510(k) submission and review processes are also shared by FDA.



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→ Increasing submission challenges

While FDA is involved in an effort to improve the 510(k) process, some medical device manufacturers are experiencing increasing difficulties in obtaining 510(k) clearance in a timely fashion. Excluding problems with the quality of the submission or failure to follow FDA advice in FDA guidance documents, some delays in the 510(k) review process occur because although an FDA guidance document has been followed, the document does not fully reflect FDA's current views of the data and information that are needed for submission.

In other cases, FDA has determined that additional information is needed, because of the availability of data gained during the postmarket phase for similar devices from adverse event reports or recalls. At times, FDA appears to believe that some of those problems could have been prevented if they had evaluated additional data and information during the review of the earlier submissions, hence additional data are now being requested for subsequent devices.

As many readers will know, the legal basis for the clearance for marketing of a device through the 510(k) process is the establishment of "substantial equivalence" to one or more "predicate devices" that are already legally on the US market. Even when satisfactory predicate devices have been identified, the FDA reviewer may conduct an extremely detailed technical examination and evaluation of the design and performance features of a device. This is not always easy to understand when it appears to extend beyond a comparison with a predicate device. In some cases, it seems to almost involve the establishment of device safety and effectiveness, which under current US law is required only for high risk devices subject to the premarket approval regulations (21 CFR 814).

Avoiding problems and delays

Manufacturers can avoid 510(k) process problems and delays in a number of ways. Most importantly, the regulatory requirements for the 510(k) process must be understood and followed. The CDRH website and databases provide information on the regulatory classification and coding of the product and should be used to their fullest capability. General guidance on 510(k) submissions should be identified and where applicable, followed. A thorough search of any applicable guidance documents and FDA recognised standards should be performed. With regard to FDA recognised standards, it is critical to check on the CDRH website whether or not the entire standard is recognised or only certain clauses. Predicate devices need to be identified.

If an identified predicate device is on the market outside the US, but not in the US, it is not relevant to the 510(k) process. The predicate device must be on the US market and should be in the FDA 510(k) database. If the 510(k) submission covers the device and accessories, it is important to ensure that the accessories are also on the market in the US, either exempt from the 510(k) process or cleared for the same intended use that is being requested in the new 510(k). Otherwise, data and information to support the

safety and effectiveness of the accessories will also be needed as well as those for the device.

It is becoming increasingly necessary before developing a 510(k) to ask FDA whether or not there are any special concerns related to the submission that are not included in FDA guidance documents, or that cannot be identified by examining information on the predicate device.

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In addition to the precautions mentioned above, an analysis of the challenges that FDA has raised during the 510(k) public meeting regarding the 510(k) process can indicate areas that should be addressed carefully in any submission. For example, FDA stated that in some 510(k)s, submitters often do not choose the most appropriate predicate device and/or do not provide sufficient information about the predicate device to allow a reasonable evaluation of substantial equivalence. Thus, every effort should be made to identify the appropriate predicate device, which may require research beyond the FDA database to gain a better understanding of devices being considered as potential predicates. For more complex devices, efforts may need to be made to obtain more detailed information on the predicate device such as conducting an Internet search to obtain a user manual. Some manufacturers purchase the predicate device; however, this is not practical for many manufacturers or types of device.

If there is a choice between the use of older or newer predicate devices, it is advisable to use the newer devices, given the statement by FDA that old medical devices may have subpar performance compared with current technology. Be prepared to justify the use of more than one predicate device in a convincing manner, based on a regulatory rationale. When clinical studies are needed to support 510(k) submissions, it is strongly recommended that the study protocol be submitted for review by FDA beforehand, even if the study is not to be conducted in the US or is considered a non-significant risk study. The purpose of this is to ensure that FDA will accept the study data in support of the 510(k).

Reading between the lines

The 510(k) process is based on a system that was in part established to allow medical devices marketed before 1976, the year that the Medical Devices Amendments were enacted, to remain on the US market. That is, these products were not subjected to evaluation under the newly enacted medical device regulations, but were "grandfathered." The entire 510(k) process is based on comparing medical devices that need to be cleared for market to a predicate

device, that is, a device that was legally marketed prior to 28 May 1976, a device that has been reclassified from Class III to Classes II or I, or a device that has been found to be substantially equivalent through the 510(k) premarket notification process. Some of the most challenging problems identified by FDA are related to the need to conduct a formal comparison to demonstrate that the medical device to be placed on the US market is substantially equivalent to the predicate device.

Could the current 510(k) debate lead FDA to conclude that another regulatory model may be more effective or more consistent in its application such as the European CE-marking or Global Harmonisation Task Force (GHTF) models? Is this already under consideration? After all, it has been reported that FDA is considering adopting international quality management standard ISO 13485 in place of its own Quality System Regulation, if certain requirements of the standard are revised.

Most of the comments received by FDA for its 510(k) public meeting were supportive of the 510(k) system; criticisms concentrated on the implementation of the 510(k) regulations and not on the principle of substantial equivalence. However, FDA is not limited to improving the 510(k) process. It is an active member of the GHTF and cognisant of other regulatory models such as the European system, which provides an interesting alternative to the 510(k) process. Under the European Medical Device Directives, comparisons of preclinical and clinical data of the device to be placed on the market and equivalent devices often play an important role in establishing that the subject device meets applicable Essential Requirements; however, this process often lacks the rigid constraints that characterise the 510(k) review process.

Prudent medical device manufacturers will closely monitor FDA medical device regulatory and policy initiatives as they evolve, because these may have an important effect on the overall regulation of medical devices in the US and, in particular, gaining market clearance via the 510(k) process. 

References

1. Information on Institute of Medicine can be found at www.iom.edu/About-IOM.aspx
2. CDRH FY 2010 Strategic Priorities, www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHVisionandMission/ucm197647.htm
3. Public Meeting: Strengthening the Center for Devices and Radiological Health's 510(k) Review Process, February 18, 2010, www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm193327.htm#fr

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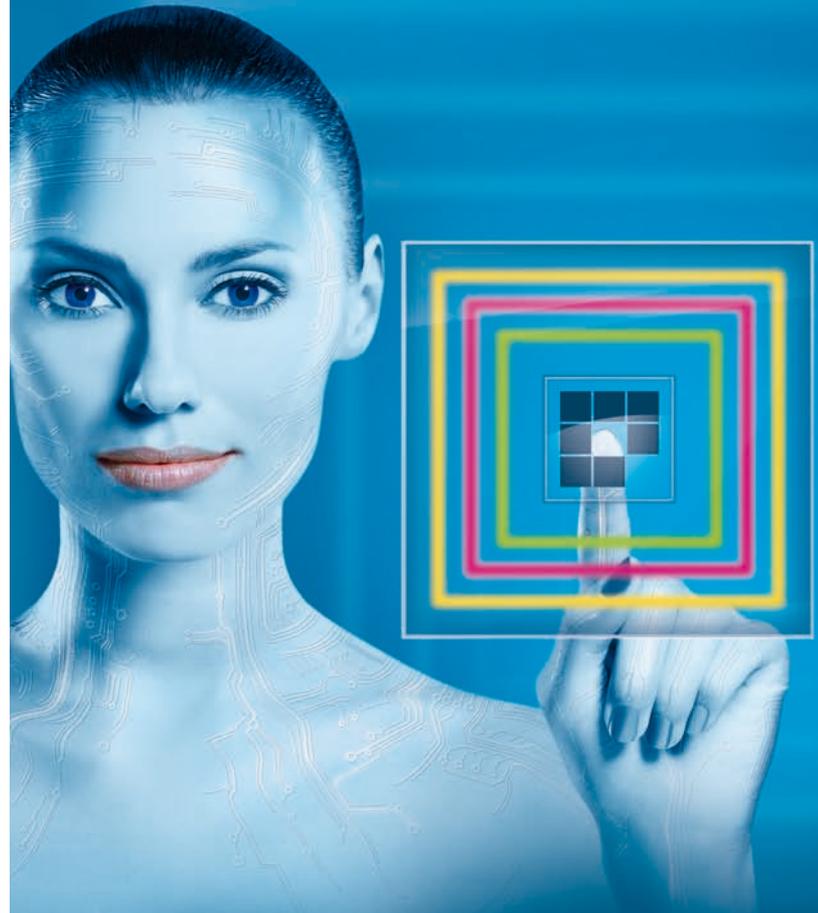
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