Standards for Clearance of 510(k) Premarket Notifications in the US

Janice Hogan and *Gwyn Simmons* discuss whether the Food and Drug Administration has raised the bar.

Over 90% of all medical devices that reach the market in the US are reviewed by the Food and Drug Administration via the 510(k) premarket notification process. This process, which was first implemented in 1976, has recently come under increased scrutiny from both Congress and the media. The fundamental criterion for 510(k) clearance requires the device manufacturer to establish "substantial equivalence" to another device that is already on the market. However, congressional pressure is building to require more comprehensive data to support a finding of substantial equivalence before 510(k) clearance is granted. Because of this recent scrutiny and pressure to reform the 510(k) premarket notification programme, there is concern within the medical device industry that the FDA may change, or has already changed, its standards for clearance of medical devices via the 510(k) premarket notification process. This article provides a brief overview of the current standards regarding the premarket notification process, the pressures to reform, and possible changes that might result.

Pressure is building to better support findings of substantial equivalence for 510(k) clearance

Overview

Under the Federal Food, Drug, and Cosmetic Act, a medical device may be marketed in the US only with the FDA's prior authorisation, absent an exemption. Within the FDA, the Center for Devices and Radiological Health is responsible for the regulatory review of medical devices. Devices are generally classified by the FDA in one of three classes based on the level of risk associated with the device.

Devices that present relatively low risk are generally placed in Class I or Class II and require the manufacturer to seek clearance from the FDA via the 510(k) premarket notification route prior to marketing, unless exempted from this requirement by regulation. A medical device that does not qualify for 510(k) clearance is placed in Class III, which is reserved for devices classified by the FDA as posing the greatest risk (eg life-sustaining, life-supporting or implantable devices, or devices that are not substantially equivalent to a predicate device). A Class III device generally must undergo the premarket approval process, which requires the manufacturer to prove the safety and effectiveness of the device to the FDA's satisfaction.

Typically, medical device manufacturers would prefer to have their devices cleared through the 510(k) premarket notification process because that path is faster and usually less burdensome than the PMA approval process. The FDA generally grants 510(k) clearance when submitted information establishes that a proposed device is "substantially equivalent" in intended use and safety and effectiveness to a "predicate device", which is a legally marketed Class I or Class II device or a "preamendment" (in commercial distribution before 28 May 1976) Class III device for which the FDA has not yet called for a PMA application.

The 510(k) process is usually less burdensome than the PMA process

Establishing equivalence

The FDA has established a detailed analytic framework to guide reviewers in determining whether a new device is substantially equivalent to a legally marketed predicate. According to this framework, the first question that a reviewer should ask in making a substantial equivalence decision is whether the device has the same general intended use as the predicate product(s). If the intended use differs, the analysis stops, and the device is deemed "not substantially equivalent" (NSE) and is thus ineligible for 510(k) clearance. While the new device must have the same general intended use as a predicate to be found substantially equivalent, the new device need not be labelled with exactly the same specific claims as the predicate device. Differences in the indication statements will not render a new device NSE if the differences do not alter the intended diagnostic or therapeutic effect of the device, considering the potential impact on safety and efficacy. Consequently, a new device with the same general intended use as a predicate device may have slightly different indication statements but may still be found substantially equivalent (SE) and cleared via the 510(k) process.

A device must be substantially equivalent to a predicate device to qualify for 510(k) clearance

The next question that must be asked in the substantial equivalence evaluation is whether the new device has the same technological characteristics, such as design, materials and energy sources, as the predicate devices. If the characteristics are the same or are very similar, the new device may be found substantially equivalent. However, if there are new characteristics, the reviewer must

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The FDA must consider whether differences could affect safety or effectiveness

further ask whether they could affect safety or effectiveness, and, if so, whether they raise new types of effectiveness or safety questions. It should be noted that the precise question considered by the FDA is whether the differences could affect safety or effectiveness, not whether they do. If the technological differences could affect safety or effectiveness, the reviewer next considers whether they raise new types of safety or effectiveness questions. If the new technological characteristics raise different types of safety or effectiveness issues from the predicates, the device is NSE. If the new characteristics do not raise any new types of questions of safety or effectiveness, the device may be found SE if accepted scientific methods exist to assess the effects of the new characteristics, and if data are available to demonstrate that the new characteristics do not impact safety or effectiveness.

In some instances, multiple predicate devices may be used to demonstrate substantial equivalence. FDA guidance explicitly authorises use of a combination of predicates to support SE determinations[1]. Thus, it is possible to argue substantial equivalence using one predicate with the same intended use/indications for use as the new device and another predicate with similar technological features. However, "combination predicate" arguments are not always accepted by the agency in cases where there is no predicate device with both the same intended use and similar technological features to the new device. The ability to use combinations of predicates to support 510(k) clearance has provided the primary mechanism to use the 510(k) process to clear many devices with novel combinations of technological features. Thus, any change in the interpretation of this policy to narrow the ability to use combination predicates would have a major impact on the breadth of the 510(k) pathway, potentially shifting more novel products to the more arduous premarket approval route. Although, again, there are no public statistics on the number of 510(k) notices that rely on a combination of different types of predicates, it appears that there may be change on the horizon in this area as well, if not already ongoing.

Data requirements

It is at this point in the 510(k) review process that a determination must be made about the type and amount of data required to support 510(k) clearance. Although the FDA does not provide statistics on the proportion of 510(k) notices that require supporting human clinical or animal testing, this figure has been estimated at only 10%. Thus, the vast majority of 510(k) cleared products reach the market without any supporting human or animal testing. According to the FDA's substantial equivalence paradigm, the criterion for requiring animal or human testing is when "performance data generated by accepted scientific methods are not available". Typically, such data are used to show that the technological features do not raise new questions of effectiveness or safety. For example, if there is an accepted standard method for mechanical testing of an orthopaedic implant, and testing the product according to this standard yields very similar results to another such product already on the market, animal or human testing likely will not be needed. However, if no such standard exists, while mechanical testing may still be required, further evaluation in humans or animals may also be necessary to demonstrate substantial equivalence.

It is estimated that 10% of 510(k) notices require supporting human clinical or animal testing

The type and amount of data that must be included in a 510(k) notice varies depending on the type of product, the intended use, and the extent of new technological features. Each premarket review division of the CDRH's Office of Device Evaluation has discretion to determine the precise clinical data requirements for the 510(k) notices under its purview. If there are any serious safety or effectiveness concerns, the FDA may require 510(k) data similar to those needed to support a PMA filing, or it may simply find the device NSE.

Time frames

The FDA must respond to a 510(k) notice within 90 days of receiving the submission. The agency's response may be to ask additional questions or request further information, rather than to grant clearance. The average FDA review time for traditional 510(k) notices over the last several years was approximately 100 days, and clearance of 510(k) submissions that include clinical data often may take longer than the average submission without clinical data. Therefore, for a 510(k) submission with clinical data, it may take six to 12 months from the date of submission to obtain 510(k) clearance.

Modifications that could affect a cleared device's safety or effectiveness require a new 510(k)

After a device receives 510(k) clearance, any modification that could significantly affect its safety or effectiveness, or that would constitute a major change in the intended use of the device, will require a new 510(k) submission. Although mean FDA review times for 510(k)s have been relatively steady, such statistics do not reflect the time spent on 510(k)s that were ultimately withdrawn unless resubmitted. Thus, if a manufacturer learns after 510(k) submission that the FDA will require animal or human clinical testing to support clearance then, if this information cannot be gathered within six months, the FDA will typically require withdrawal of the 510(k) or find it NSE, requiring resubmission after the necessary data is collected. In the past it was often

possible to keep a 510(k) pending for several years, but this is now less likely due to the advent of user fee-associated review time goals.

De novo review

If a device is found NSE because no predicate exists, it may be downclassified to Class I or II

Even if a device is found NSE because no appropriate predicate exists, under a statutory provision enacted in the Food and Drug Administration Modernization Act of 1997, it may be possible to obtain downclassification to Class II, thereby permitting 510(k) clearance. Section 513(f)(2) of the FDC Act authorises the FDA to downclassify to Class I or II low-risk devices that the agency has classified as Class III because there is no predicate device. This process, which is called *de novo* review, requires the submission of a 510(k) notice and a finding by the FDA that the device is NSE. The company has 30 days after the NSE finding to submit a request for *de novo* review. The request must show that the novel device presents low risk to patients and describe the general and special controls that the manufacturer believes are adequate to provide a reasonable assurance of safety and effectiveness for devices within the general category. The FDA has 60 days to review that request, although the agency can extend that period by requesting additional information, including clinical data, regarding the device. If the FDA grants the request, the device is permitted to enter commercial distribution in the same manner as if the agency had granted 510(k) clearance. In addition, the device can then serve as a potential predicate for all devices within that new classification, thus facilitating subsequent clearance of other devices of the same type. However, this process has been used only 46 times in the approximately ten years since its enactment, across all divisions of the FDA.

Trends in FDA review time

Review of FDA statistics on average 510(k) review time, average number of 510(k) submissions, and average submissions by therapeutic area per year shows little change over the past several years. These trends are illustrated in Figures 1-3 below. However, these statistics do not provide sufficient insight into any changes that may occur in the agency's interpretation of the 510(k) clearance standard.

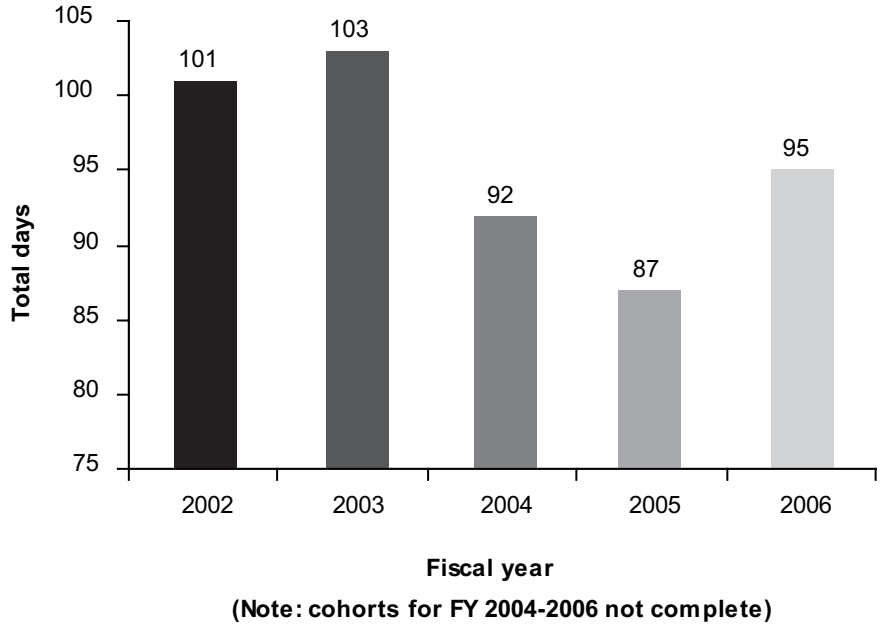
The majority of 510(k) products is very similar to previously cleared predicates

For the vast majority of 510(k)s, the new products presented are very similar to previously cleared predicates, and in many instances there are acceptable standards for testing. Thus, these simpler products weight the average review time statistics heavily toward the current average of 100 days. However, these data are likely not to be representative of the typical review times for more novel or complex products, and it is these important products for which information is lacking. More data are needed on the proportion of 510(k)s that require animal or human clinical testing, as well as the number of submissions that are withdrawn each year, and the number of submissions using combinations of predicates.

Average review time

Over the last several years, the average total review time for 510(k) notices has remained consistent at approximately 100 days. This is illustrated in Figure 1, below.

Figure 1. Average total review time to final decision – as of 31 December 2007

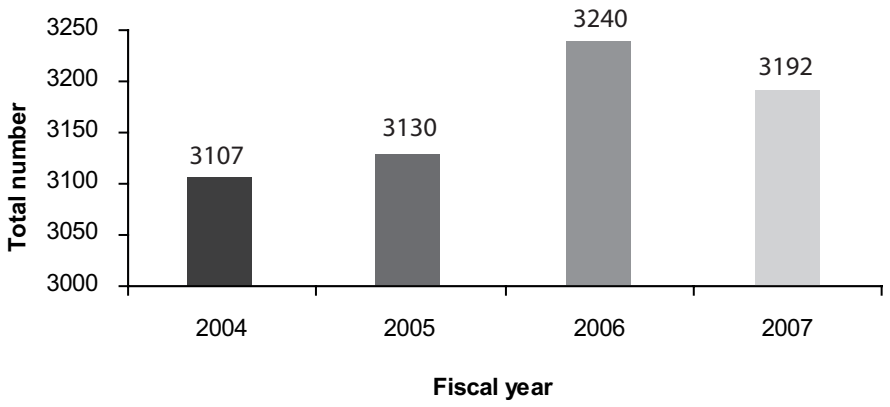


Number of 510(k)s received

Since 2004, the number of 510(k) notices submitted to the ODE has remained relatively constant. However, as shown in Figure 2 below, the number of 510(k) notices submitted has increased slightly.

The number of 510(k) notices submitted has grown slightly since 2004

Figure 2. Number of 510(k)s submitted per year

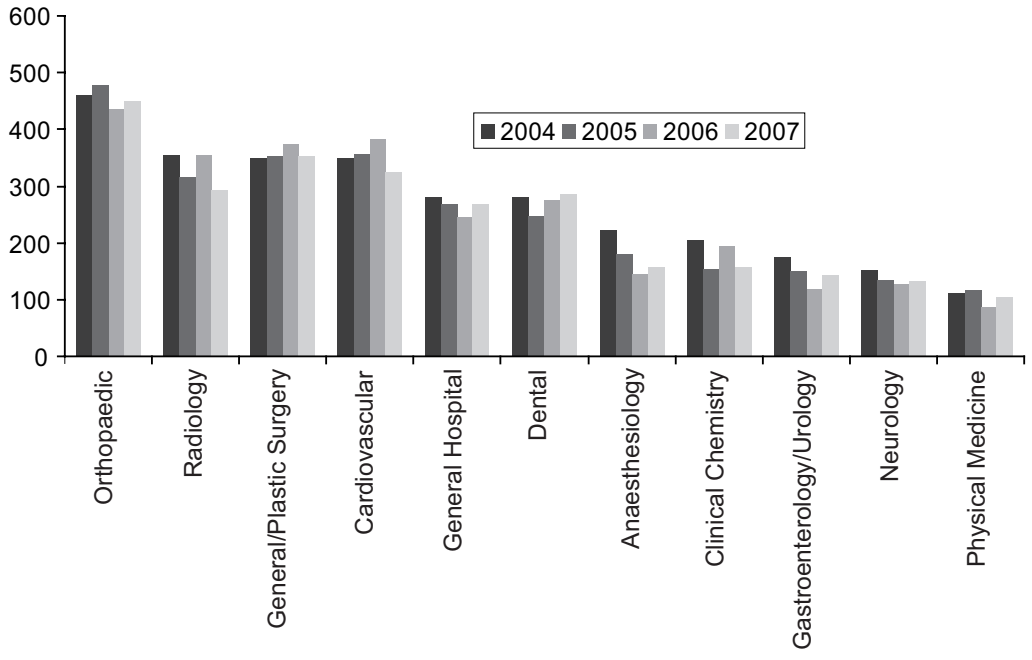


510(k) review by therapeutic area

Of the over 3,000 510(k) notices submitted each year since 2004, the number cleared by each therapeutic area has remained fairly consistent. As illustrated in Figure 3 below, submissions classified as orthopaedic products represent the largest number of 510(k)s cleared in any one therapeutic area, with approximately 100 more 510(k) notices cleared each of the last four years than in any other area.

More devices are cleared as orthopaedic products than any other type

Figure 3. 510(k) clearances in fiscal years 2004-2007 by select therapeutic areas



Current trends in the review and evaluation of 510(k) notices

As a consequence of recent calls for reform of the 510(k) premarket notification programme by Congress and consumer advocacy groups, it appears likely that the FDA will review its substantial equivalence analytical framework. It is likely that this review will include an assessment of the type and amount of data that will be required to support substantial equivalence and the use of

combination predicates to show substantial equivalence. At the present time, there is no pending legislation to change the 510(k) programme, and to date the FDA has not publicly announced a change in policy. Despite this, there is the possibility that the FDA has tightened or will tighten its interpretation of substantial equivalence. This could result in more rigorous reviews of 510(k) notifications, which may make it more challenging in the future to clear novel products via the 510(k) pathway. Two areas of potential change, increased data requirements and the use of combination predicate arguments, are addressed in more detail below.

Submission of more comprehensive data

It has been estimated that over 8,000 new medical devices are marketed in the US each year, and that annually about 3,500 are reviewed and cleared for marketing via the 510(k) process[2]. Only a few dozen products undergo the more rigorous PMA review each year, and the remainder, generally very simple, low-risk devices, are marketed with no requirement for prior FDA clearance. As noted above, only a few hundred devices per year are required to undergo human clinical testing as a prerequisite for 510(k) clearance. These trends have created the perception in some sectors that the 510(k) premarket notification process is not thorough[3,4]. According to critics of the programme, because the 510(k) process rarely requires the submission of clinical data to support the safety or effectiveness of new medical devices, complex medical devices are being marketed without adequate evaluation[5].

Critics say the 510(k) process leads to devices being approved without adequate evaluation…

Congressional pressure is being exerted in the form of potential legislative reforms focused on limiting the use of the 510(k) process and requiring PMA review of the highest-risk devices such as implants[6]. While there is no legislation pending to change the 510(k) programme, the Government Accountability Office is in the process of assessing the 510(k) programme as mandated in the FDA Amendments Act of 2007. Specifically, the GAO was directed to report to Congress by 27 September on the FDA's evaluation of the intended use and technological features of devices cleared via the 510(k) process, focusing on the FDA's consideration of device materials, principles of operation and power sources. The GAO has publicly stated that the report would not be completed by the deadline; however, it would brief Congress on the report's findings by 27 September. No release date for the full report has been announced[7]. Depending on the outcome of this report, it could provide a further impetus for legislative reform.

Consumer advocacy groups have criticised the FDA's 510(k) notification process and called for reforms. In particular, critics argue that companies are using the 510(k) process in order to circumvent the more rigorous PMA process and get complex devices to market without providing comprehensive clinical trial data[8]. Some critics of the 510(k) programme have called for additional testing requirements, including a requirement that manufacturers test each new medical device against the predicate in a randomised clinical trial. Other critics have called for a requirement that all implantable devices go through the PMA process[9].

…and some have called for additional testing requirements

In a speech at a recent industry meeting, CDRH director Daniel Schultz defended and praised the present 510(k) programme even while suggesting that in the future the FDA may require more comprehensive data for certain 510(k) submissions. Specifically, Dr Schultz stated that many of the devices entering the market via the 510(k) process are "really very close to the edge in terms of whether they are 510(k) or PMA". Dr Schultz suggested that, to make certain that the 510(k) programme remains viable and to avert legislative reform that could statutorily increase the standards for clearance, the agency must keep up with technological advances in medical device technology and require the submission of more data to show that the "510(k) process is flexible enough to handle devices that only require minimal information and also products that need more data"[10]. More recently, Dr Schultz has encouraged industry to accept FDA-imposed increases in standards to help minimise the need for legislative reforms. He has emphasised that it is reasonable for the FDA to request more data under the 510(k) paradigm because "more devices that do not precisely match the technology or indication of predicate products were coming before the agency as 510(k) submissions"[11].

In addition, Dr Schultz has indicated that increasing data requirements for more complex devices may increase the amount of time that it will take the FDA to evaluate and clear devices[12].

Increasing data requirements for more complex devices may increase evaluation times

Although the FDA has not made public any formal policy regarding the type and amount of data that may be required in the future, a recent letter written by Dr Schultz sheds some light on what types of data may be expected in support of 510(k) clearance in the future. Responding to criticism of the FDA's approving changes to Medtronic's implantable cardioverter defibrillator, a marketed device, on the basis of bench testing rather than clinical data, Dr Schultz stated that in some cases engineering analyses may be the most appropriate way to address the FDA's concerns, while in other cases clinical data may also be needed. Further, Dr Schultz stated that most clinical trials could not be sufficiently powered to detect small but clinically meaningful differences in performance[13]. Although the device in question was not cleared via the 510(k) process, his

comments are nevertheless useful, particularly regarding the necessity for the submission of clinical trial data. For example, his statements that different types of data are appropriate in different situations may imply that increasing the data requirement standards for 510(k)s might mean more performance testing data, and might not always require the submission of clinical data. Moreover, because it would be unreasonable to expect medical device manufacturers to design clinical trials with sufficient power to detect all potentially clinically significant changes in device performance, clinical data may not always be optimal.

Should the FDA change the standards for 510(k) clearance by increasing performance testing data requirements, requiring clinical data from testing directly against predicates, or requiring PMAs for implantable devices, and the possible corresponding increase in review time, these changes will affect both the agency's resources and the medical device industry. It is likely that the greatest impact will involve those devices with the most complex technology and those that are implantable. For example, it is likely orthopaedic devices will come under increased scrutiny. As noted above, orthopaedic submissions account for the largest number of 510(k) notices in any single therapeutic area, and the FDA clears more in this than in any other therapeutic category. In addition, orthopaedic devices are predominantly implants. Cardiovascular devices are another likely area of increased scrutiny. Changes to the standards for 510(k) submissions may be inevitable, but the time and cost requirements will likely make implementation a challenge to both the medical device industry and the agency.

Changes will impact complex devices and implantables

Acceptance of combination predicate arguments

As mentioned earlier, FDA guidance explicitly permits the use of combination predicates to support substantial equivalence determinations[14]. Accordingly, a new device can be found substantially equivalent if the new device has the same intended use/indications for use as one predicate and has the same technological characteristics as another predicate. Although such arguments are not always accepted by the agency, numerous products have been cleared based on combination predicate arguments. Recently, it appears that the FDA has been less inclined to accept such arguments, and the use of combination predicates to support substantial equivalence is likely to become more difficult.

The FDA appears less inclined to use combination predicates to support substantial equivalence

At the present time, the FDA has not announced publicly a change in policy regarding its acceptance of the combination predicate argument and there is no pending legislation in this regard. However, as noted above, there has been increased pressure on the agency with respect to the 510(k) programme by Congress and consumer advocacy groups. Recently, industry has experienced pushback from the agency with respect to substantial equivalence arguments that are based on a combination of predicates, pushback that has not been experienced previously. Dr Schultz in his speeches seemed to confirm this possible trend. For instance, by stating that the FDA may require more data in submissions where intended use is similar but not quite the same as the predicate and the technology differs from the predicate, Dr Schultz may be signalling that in the future the agency may request data beyond what was required for the predicates[15]. As such, it appears that the FDA is tightening its interpretation of substantial equivalence, which might have an impact on the agency's willingness to accept combination predicate arguments.

During informal discussions with the FDA, the agency has indicated that there has been no change in policy regarding its interpretation of the so-called Mohan Memorandum regarding combination predicate arguments, and that when considering a combination predicate argument, it applies the analytical framework described in the Mohan Memorandum to each potential predicate as part of its substantial equivalence argument. According to the FDA, this has always been its approach. Thus, any perceived pushback from the agency may be the result of its overall increased scrutiny of the 510(k) process and narrowing interpretation of substantial equivalence rather than a specific change in policy regarding its acceptance of combination predicate arguments.

However, it has not formally changed its policy regarding combination predicates

Outlook: the need for greater transparency

Recent congressional pressure and comments by the FDA point to a possible change in standards for clearance of 510(k) notices. Any change in the current standards for review and clearance of medical devices, and the possible corresponding increase in review time, whether implemented by legislative reform or by FDA policy, would have a significant impact on the medical device industry and FDA resources. While the exact impact cannot be determined at this time, it is likely that the greatest impact will be on devices that are the most technologically complex and those that are implanted. Should the FDA change the standards for 510(k) clearance, whether by increasing performance testing data requirements, requiring clinical data from testing directly against predicates, or requiring PMAs for implantable devices, and the possible corresponding increase in review time, in the future it will be more challenging to use the 510(k) process to bring novel medical devices to market.

It is possible that changes in the 510(k) programme will occur via internal FDA policy rather than through any formal rule-making or legislation, and so the changes may not be visible to industry. There is a tremendous need for transparency to ensure that, if the FDA's interpretation of the 510(k) substantial equivalence requirements is modified, industry is aware of this and can plan accordingly. The FDA has discretion to issue a guidance document regarding this topic, but it may be difficult to draft a general guidance document covering these topics that is applicable across all therapeutic areas. Therefore, it may be more helpful for the FDA to publish annual statistics on the proportion of 510(k)s that require clinical data, and to provide more publicly available information about this in the 510(k) database so that manufacturers can better understand the likelihood that clinical testing may be needed prior to submission. In addition, any changes in FDA policies and training of reviewers on the interpretation of 510(k) clearance requirements should be publicly available so that manufacturers can fully understand the agency's approach.

Changes in FDA policy on interpretation of 510(k) requirements should be publicly available

In summary, change to the 510(k) programme is on the horizon if not already occurring, and this change is likely to make the clearance process more challenging for novel and complex devices. Therefore, close observation of trends in FDA review will be increasingly important over the coming months, and tracking of potential legislative initiatives will also be important.

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