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REVAMPING THE 510(K) PROCESS

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REVAMPING THE 510(K) PROCESS

How the Implementation of the US FDA's Recent Initiatives to Improve the 510(k) Programme Could Impact Your Business

Imagine your company recently developed an innovative medical device that draws upon well-established medical technologies and combines them in a new way to address a gap in the standard of care. Your laboratory and animal testing demonstrates that your device performs as intended in all respects, and your confirmatory clinical data establishes a very good safety profile for your device - in fact, you believe that your device is actually safer than the standard of care. In accordance with your company's business strategy, you obtained a CE mark to market your device in the European Union. Management has now made it your job to file an application with the US Food and Drug Administration (FDA) and get this product on the US market as quickly as possible.

You submit your 510(k) notice to the FDA. Forty-five days later, you receive a 12-page list of questions about the information provided in, or missing from, your submission. As you review the questions, you are overwhelmed. Why is the FDA questioning whether your device has an appropriate predicate? Why is the Agency saying you need to submit additional clinical data? Doesn't the FDA understand that your product will benefit US patients? As you struggle to understand the critical and burdensome nature of the Agency's requests, rest assured, you are not alone.

FDA scrutiny of medical devices submitted for pre-market review via the 510(k) pathway has increased markedly in recent years. In large part, this increased scrutiny is the result of concerns raised by industry, consumers, third-party payers and healthcare providers, as well as by FDA employees and the US Congress, that the current 510(k) pathway does not function as intended. In response to such scrutiny, the FDA's Center for Devices and Radiological Health (CDRH) commissioned both internal and external evaluations of the 510(k) process[1].

On 19 January 2011, the CDRH released its *510(k) and Science Report Recommendations*, which announced a plan for implementing 25 initiatives to improve the 510(k) programme in 2011[2]. The FDA has touted these initiatives as 'steps to foster medical device innovation and assure the safety and effectiveness of medical technologies used by and on patients in the United States'[3]. While, overall, the planned initiatives are viewed by industry as positive updates to an overburdened pre-market notification pathway, they also create some degree of uncertainty for medical device companies who are nervous about how the 510(k) pathway of 2012 will look.

This article begins with the history and development of the FDA's 510(k) pre-market notification pathway and walks through the recent scrutiny of the 510(k) process, the FDA's recently announced plan of action for improving the 510(k) programme in 2011, and how these initiatives are likely to impact the medical device industry. Finally, this article will provide practical solutions for helping to minimise the likelihood that you will find yourself in the hypothetical situation outlined above.

History of US device regulation

Although food and drugs have been regulated by the US federal government since the enactment of the *Food and Drug Act of 1906*, medical devices were not federally regulated until the *Federal Food, Drug and Cosmetic Act*[4] (FFD&C Act) was enacted in 1938. Devices were originally regulated by the FDA (or its predecessor agency) under the adulteration and misbranding provisions of the Act and were not subject to pre-market clearance or approval before being introduced into US commerce. When the FFD&C Act was enacted, post-market regulation of medical devices was viewed by Congress and the FDA as sufficient to protect public health because most lawfully marketed medical devices with legitimate diagnostic or therapeutic benefits (as opposed to 'quack' devices with no medical benefit) employed fairly simple technologies.

Physicians skilled in using these devices could easily recognise whether the device was performing properly. Thus, the FDA's major concern was to ensure that the labelling for these legitimate devices was truthful, and that the devices were not misbranded.

From 1938 until the 1960s, most of the FDA's activities in the device area were directed toward policing 'quack' devices. It was not until the 1960s that the FDA started to focus on the potential risks posed by new and complicated devices used to diagnose or treat critical medical conditions. By this time, many new devices were so complicated that even skilled physicians were unable to determine whether the devices were performing properly. With the increasing complexity of medical device technology, the FDA's ability to protect patients from defective devices was questioned by Congress, in part because the safety and effectiveness of medical devices did not have to be established before they were marketed. In the FDA's view too, an increasing number of US patients were now exposed to devices that could present a serious health risk if manufactured or used improperly.

Attempting to strike a balance between the need for improved patient protection and the desire to encourage research and innovation involving complicated medical devices, Congress enacted the *Medical Device Amendments of 1976* (Public Law 94-295). This watershed legislation amended the FFD&C Act to create a risk-based approach to the regulation of medical devices depending on the specific questions presented by a device's intended use and technological characteristics. The regulatory framework established three classes of devices (Class I, Class II and Class III) to govern the applicability and extent of pre-market review of medical devices, calling for the FDA to set general controls for some devices and requiring pre-market clearance or approval for others.

What is the 510(k) pathway?

Section 510(k)[5] of the FFD&C Act was enacted as part of the 1976 Amendments, as the primary pathway to market for lower risk medical devices (i.e. Class I and Class II medical devices). This section requires entities proposing to market a medical device for human use in the USA to take the following action at least 90 days before introducing the device into commercial distribution in the USA:

- notify the FDA of the Class in which the device is classified or, if the device is not classified, provide a statement indicating the device is not classified and describing the basis for the company's determination; *and*
- notify the FDA of action taken to comply with the requirements of Sections 514 (performance standards) and 515 (pre-market approval) of the FFD&C Act.

The 510(k) process applies to all Class I and Class II devices intended for introduction into US commerce after 28 May 1976 that are not explicitly exempted from pre-market notification requirements by regulation. [Devices marketed prior to 28 May 1976, the so-called 'pre-amendments devices', are 'grandfathered' provided that the devices are marketed under the same labelling and design and that they were not considered adulterated or misbranded prior to 1976.] Devices for which 510(k) clearance is required may not be marketed or sold in the USA until the applicant receives an 'order' from the FDA finding the device 'substantially equivalent' to one or more legally marketed 'predicate devices'. [A predicate device is a legally marketed Class I or Class II device, or a Class III device for which pre-market approval is not required.]

To secure a finding of substantial equivalence, a device must have the same intended use and substantially similar technological characteristics as one or more predicate devices. If the new device's technology is not substantially similar, the FDA will assess whether the new technology raises new questions of safety or effectiveness as compared to the predicate devices. If so, the device cannot be found substantially equivalent. However, novel or different technological characteristics that do not raise new issues of safety or efficacy will not necessarily preclude a finding of substantial equivalence if the performance of the device is shown to be comparable to that of the predicates via

accepted scientific methods, including human clinical trials.

As the 510(k) process is designed to find a device 'substantially equivalent' to legally-marketed predicate devices, by definition pre-market notification does not determine whether a device is 'safe and effective' for its intended use. With that said, the 510(k) review process in essence has evolved into an initial review of the safety and efficacy of new, lower risk medical devices. In particular, the modern 510(k) process promotes the protection of public health by allowing the CDRH to require a more in-depth review of devices that:

- raise unanswered questions of safety and effectiveness relative to legally-marketed predicates;
- appear to be less safe or effective than legally-marketed predicates; *or*
- have indications for use or technologies that are sufficiently different from those of legally-marketed predicates so that adequate comparisons are not feasible.

When a device is found to be not substantially equivalent (NSE) to legally-marketed predicate devices, the device is automatically classified into Class III. Class III medical devices are regulated through the pre-market approval (PMA) process, which is designed to establish a reasonable assurance of safety and effectiveness for novel or high-risk medical devices. PMA approval typically requires considerably more supporting data (including a uniform requirement for human clinical data) and significantly lengthier review times than 510(k) clearance. While Class III is the default for devices found NSE via the 510(k) pathway, there is an alternative for novel, low-risk devices - *de novo* down-classification. For such devices, sponsors may seek to have the device down-classified from Class III into Class II or Class I, thereby permitting clearance via the 510(k) pathway[6].

Since section 510(k) was first enacted, dramatic changes to the FDA's 510(k) pre-market notification process have taken place. Many of these changes have resulted directly from new legislation amending the FFD&C Act[7], while others were implemented by the FDA in response to industry demands that the pre-market clearance process be more efficient and predictable. The 510(k) pre-market notification pathway is now the most common pathway to market for new medical devices in the USA. In fiscal year 2010, the FDA received 3936 510(k) pre-market notifications, and only 212 original PMA applications, Panel Track PMA Supplements and 180-day PMA Supplements seeking market authorisation for new devices or substantial changes to existing devices[8].

Recent concerns over the 510(k) programme

Although the current 510(k) programme provides the FDA with the flexibility to tailor the pre-market review process to address the specific characteristics of the device under review, over the past few years, industry, consumers, third-party payers and healthcare providers, as well as FDA staff and Congress have questioned whether the 510(k) process functions as initially intended. Consumer advocacy groups have characterised the 510(k) programme as a 'fast track process' or 'loophole', expressing concern that the process allows unproven devices onto the US market without sufficient data to demonstrate their safety and effectiveness. Meanwhile, industry has complained that increased scrutiny by some reviewers at the FDA is hindering medical device development and preventing US patients from receiving innovative treatments in a timely fashion. In particular, sponsors of 510(k) notices have experienced significant delays in obtaining 510(k) clearance due to increasing data requirements, inconsistent application of policies, and a general lack of transparency in the Agency's review process.

Criticism of the 510(k) programme has not been limited to outside observers; even FDA staff have raised concerns about its effectiveness and implementation. In May 2008, a group of nine FDA whistleblowers contacted the FDA Commissioner with allegations that political power was being allowed to trump scientific review at the FDA, and raised concerns regarding the review process for certain devices. The group then contacted Congress in October 2008, alleging that Agency managers 'ordered, intimidated, and coerced FDA experts to modify

their scientific reviews, conclusions and recommendations in violation of the law'[9]. Of particular concern was the review of the ReGen Collagen Scaffold[10]. Following clearance of the ReGen device in December 2008, the *Wall Street Journal* published details of the reviewers' concerns regarding the Collagen Scaffold device in a March 2009 exposé[11]. The summation of these actions prompted both congressional and internal Agency investigations into the clearance of this specific device as well as the 510(k) review programme generally.

The public concerns raised regarding the 510(k) programme have led to increasing public and governmental pressure on the Agency to ensure that devices are appropriately low risk for the 510(k) pathway and that such devices receive a thorough evaluation before clearance. While no formal changes to the 510(k) programme had been implemented in response to these pressures, the following trends have been observed within the Office of Device Evaluation (ODE) and the Division of Radiological Devices:

- Delayed review of pre-investigational device exemption (IDE) submissions, and inconsistency in Agency response to such submissions, including the unwillingness of certain branches to meet with sponsors until the company has reviewed the Agency's written comments.
- Longer review times for 510(k) notices, including many instances in which review times are considerably longer than the statutorily defined 90-day review period.
- Increasing instances where multiple rounds of review are required to respond to the FDA's concerns, particularly for complex medical devices or submissions involving clinical data.
- Increasing requirements for pre-clinical (laboratory and animal) and clinical (human) data. In some situations, significantly increased data requirements have been imposed even for slightly modified versions of previously cleared devices.
- Increasing objections to substantial equivalence arguments, particularly where split predicates or multiple predicates are involved, or where the proposed indications for use are more specific or more general than those of the predicates. The FDA has also resisted the use of certain cleared devices as predicates because they are 'dated' or are in different product codes.
- Increasing data requirements and timelines for *de novo* down-classification.

Evaluating the 510(k) programme

In response to the concerns raised by both industry and consumers and increasing Congressional pressure, in September 2009, the CDRH commissioned both internal and external evaluations of the 510(k) process to evaluate how well the 510(k) programme was meeting its two public health goals of facilitating innovation and assuring that medical devices are safe and effective[2]. The evaluation was to be conducted internally by two newly-established committees: the 510(k) Working Group and the Task Force of the Utilization of Science in Regulatory Decision Making. The Working Group was charged with evaluating how well the 510(k) programme was meeting its two public health goals and suggesting actions that the FDA could take to assure these goals would be met going forward. In parallel, the Task Force was charged with addressing how the CDRH can better incorporate new science into its regulatory decision-making.

In addition to the internal investigations outlined above, the CDRH also requested an independent, outside evaluation of the 510(k) programme by the Institute of Medicine (IOM), which has convened a committee to address the following questions:

- Does the current 510(k) process optimally protect patients and promote innovation in support of public health?
- If not, what legislative, regulatory or administrative changes are recommended to achieve the goals of the 510(k) process[1]?

While the IOM's report was initially expected in March 2011, the current estimate for the report is now the summer of 2011.

The Working Group and Task Force issued preliminary reports in August 2010 outlining 55 recommendations for the 510(k) programme[12-13]. These reports provided a number of suggestions and recommendations aimed at improving the

consistency of Agency decision-making and strengthening the 510(k) programme. The Working Group also confirmed recently observed trends that:

- fewer 510(k) notices are being found substantially equivalent;
- more 510(k) notices are going through multiple rounds of review, indicating an increased number of requests for additional information issued by the Agency; *and*
- the length of the average 510(k) notice has dramatically increased over the years as devices (and regulatory submissions) have become more complex.

Initial industry reaction to the Working Group and Task Force reports was cautious, with serious concerns raised regarding several of the proposals. The public was given the opportunity to comment formally on these reports through three open public dockets, two public meetings and three town hall meetings. In follow-up to comments received on the 55 recommendations in the preliminary report, on 19 January 2011, the CDRH announced a plan for implementing 25 initiatives to improve the 510(k) programme in 2011[2]. The CDRH appears to have carefully considered the community's comments on each of the report's recommendations in deciding which initiatives to implement at this time.

New initiatives and their impact on industry

Of the 25 initiatives proposed by the FDA to implement during 2011, the following eight key initiatives are likely to have the most significant impact on the medical device industry:

Streamlining the *de novo* classification process

The CDRH plans to issue guidance outlining modifications to the *de novo* down-classification process in order to make this process more efficient and decrease the time to market for novel, low-risk devices. Dr Jeffrey Shuren, Director of the CDRH, clarified during the media briefing announcing these 25 new initiatives that the FDA is considering ways to determine whether a device would qualify for down-classification earlier in the clearance process and to streamline further the process by requiring submission of limited information necessary to begin the reclassification process of the device. Dr Shuren noted that modifications to this process are still being discussed, and the public will have the opportunity to comment on any Agency-proposed recommendations before they are implemented. A draft guidance outlining new proposed procedures for *de novo* down-classification is scheduled for release at the end of September 2011.

Currently, the *de novo* classification process can take upwards of a year, while companies work with the Agency to obtain a final regulation down-classifying the device and to reach an agreement on appropriate special controls. With the recent increase in the number of devices being referred to the *de novo* pathway that in the recent past would have been eligible for 510(k) clearance, an increasing number of medical device sponsors will likely continue to be faced with seeking *de novo* down-classification via the process that is currently in place. It is hoped that a more efficient process will allow novel, low-risk devices onto the market sooner, while still providing adequate safety and performance information.

Providing additional guidance on pre-submission communications

The Agency will supplement the existing guidance on pre-IDE meetings to provide additional guidance to enhance the quality of pre-submission interactions between industry and the CDRH. Draft guidance is slated for release on 30 November 2011.

In recent years, the pre-IDE meeting process has become an increasingly popular means for companies to obtain Agency feedback on the regulatory strategy for new devices, even in situations where the company does not intend to submit an IDE application. Given the Agency's recent inconsistent response to meeting requests, this guidance is likely to be welcomed by industry as a means of defining the confines and expectations of the process.

Modifications to 510(k) devices

In June 2011, the Agency intends to issue new

draft guidance to clarify the types of changes to a device that do or do not require the submission of a new 510(k) notice. The guidance is also expected to address which modifications are eligible for submission of a Special 510(k) notice, which typically are cleared significantly faster and require less information than traditional 510(k) notices. Each of these areas remains an ongoing source of uncertainty for industry, despite the FDA's existing guidance on these topics[14-15].

Use of multiple predicates to establish substantial equivalence

The Working Group recommended that the CDRH develop additional guidance on the use of more than one predicate to support a finding of substantial equivalence, which sparked controversy within the medical device community. Industry, healthcare providers and venture capitalists expressed concern that to disallow the use of 'split predicates' would stifle innovation and prevent otherwise appropriate devices from being available to US patients. Meanwhile, patient groups and third-party payers suggested that the use of split predicates and multiple predicates should be disallowed to ensure patient safety. The Agency's announcement of the 25 initiatives clarified that the term 'split predicate' refers to the use of one predicate to support the intended use of a new device and another predicate with a different intended use to support its technological characteristics. The Agency clarified that the use of a true split predicate is inconsistent with the 510(k) regulatory standard, but emphasised that it supports the use of multiple predicates in establishing substantial equivalence. As the term 'split predicate' is used inconsistently by different groups, the FDA will no longer use this term going forward. The Agency intends to issue draft guidance on the 510(k) paradigm in September 2011, which, among other things, will clarify when it is appropriate to use multiple predicates to demonstrate substantial equivalence.

Establish a Center Science Council

The FDA has already established a Council of senior Agency experts to ensure timely and consistent science-based decision-making. The Council will:

- oversee the development of a procedure for responding to new scientific information;
- periodically audit review decisions of 510(k) devices to assess adequacy, accuracy and consistency; *and*
- establish an internal team of clinical trial experts to provide support and advice for the CDRH and prospective IDE applicants.

The charter for this Council was posted on the FDA's website on 31 March 2011, along with a series of frequently asked questions about the Council, its role and its responsibilities[16-17] (*see also* page 45 of this issue). In addition, the FDA has established a web-based form for submitting questions and comments regarding the Council. This form can be accessed at www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm249233.htm. The Council's inaugural meeting was scheduled for April 2011 and the results of its initial 510(k) audit are expected to be posted on the FDA's website on 15 June 2011.

Guidance on clinical data

The CDRH has promised to issue draft guidance in July 2011 aimed at improving the quality and performance of clinical trials. This guidance is intended to clarify when clinical data should be submitted in a pre-market submission.

With Agency requests for clinical data on the rise, this guidance is anticipated to provide much needed predictability for industry. It is estimated that 10-15% of 510(k) notices now include clinical data, and many sponsors are surprised to learn only after submission of their 510(k) notice that clinical data will be required to assess the technological characteristics of the device and support a finding of substantial equivalence. 510(k) sponsors should be aware that the Agency's willingness to accept confirmatory clinical data from small, single-arm studies is decreasing and requests for hypothesis driven, randomised, controlled studies are becoming increasingly common for devices that present differences from the predicates.

Develop a network of external experts

In light of the volume and pace of new scientific

findings, the CDRH intends to develop a network of external experts to provide the Agency with additional scientific expertise. To address public concerns about conflicts of interest by involving members of the medical device community, the Agency will publish a procedure outlining parameters for engaging outside experts by 15 September 2011.

Notice to industry

The CDRH is developing a process for informing industry when the FDA has modified the regulatory expectations for devices based on new scientific evidence. The CDRH intends to develop a procedure regarding the parameters for issuing these letters and post it to the Agency's website by 15 June 2011. Such notices may be useful in notifying industry when additional data requirements will be necessary to support clearance of new versions of existing devices.

Other initiatives

The Agency also intends to implement four recommendations from the initial reports only on a case-by-case basis through new device-specific guidance. Specifically, the Agency will issue guidance related to:

- requiring manufacturers to provide regular, periodic updates of device modifications;
- requiring 510(k) notices to include a list and brief description of all scientific information known or reasonably known to the submitter related to the safety and effectiveness of a new device;
- requiring 510(k) notices to include manufacturing data; *and*
- requiring a pre-clearance inspection to ensure compliance with Good Manufacturing Practices prior to granting 510(k) clearance.

Additionally, the Agency continues to hold public meetings to discuss the implementation of certain planned initiatives, including a meeting held on 7 April 2011 to allow industry and other interested parties to comment on establishing a database of current device labelling and a database that contains photographs and schematics of cleared devices (*see also* page 58 of this issue). The Agency appears to be cognisant of industry's concerns regarding the release of confidential and proprietary information, and thus decided that further consultation between the FDA and the medical device community on this topic was warranted.

The FDA also referred seven of the recommendations from the Working Group and Task Force reports to the IOM for consideration as part of the IOM's independent review of the 510(k) programme. The Agency has stated that it will consider any comments the IOM provides prior to deciding whether to implement these particular recommendations. The seven recommendations referred to the IOM for review are:

- consolidating the terms 'indications for use' and 'intended use';
- whether the Agency should consider off-label use when determining the intended use of a device;
- issuing guidance regarding when a device should no longer be available for use as a predicate;
- issuing a regulation on the CDRH's authority for rescinding 510(k) clearances;
- requiring that manufacturers keep one unit of a device available for FDA evaluation;
- creating a Class IIb category of devices for which clinical information, manufacturing information or post-market evaluation would typically be necessary to support a determination of substantial equivalence; *and*
- requiring post-market surveillance studies as a condition of clearance for certain devices.

The referral of these items to the IOM for further consideration has been viewed by industry as a positive step, as substantial concern was raised regarding the implementation of these items[18]. However, some have questioned whether the IOM is the appropriate body to consider these issues and consumer advocates continue to criticise the Agency for 'yielding' to industry on important issues that impact patient safety[19]. Importantly, advocates and critics of the new initiatives alike should be aware that the Agency may be statutorily limited in its ability to implement some of the proposed reforms.

However, considering the pending report from the IOM and the hotly-debated topic of the 510(k) programme in the media and Congress, further developments to the 510(k) programme may well be on the horizon.

Response and recommendations

At this time, these 25 new initiatives have not yet been implemented and the 510(k) programme is officially unchanged. However, in practice, the observed trends at the CDRH indicate that the 510(k) process has been substantially altered over the past few years via informal and unofficial practices of individual ODE branches, resulting in a 510(k) process that can at times be unpredictable and inconsistent. While the recently-announced initiatives to improve the 510(k) programme have generally been received favourably by industry, there is still very much a 'wait and see' attitude as to whether the proposed new rules and guidance will in fact clarify the 510(k) programme, decrease review times, and instil further transparency into the review process. In particular, there is concern that the increased data requirements will continue to be required, even in instances where there are no safety issues presented, and that such requirements are not in line with the original goals of the 510(k) programme. That being said, the release of these specific planned initiatives is indicative that the FDA has recognised this changing landscape within the Agency and industry's concerns, and is seeking to increase predictability and consistency in the 510(k) programme.

Timely and appropriate implementation of these reform efforts will be critical to creating a transparent and predictable regulatory pathway for medical devices entering the US market. So far, the Agency appears to be on schedule for implementing these initiatives according to the released timeline. The increase in the FDA's funding for this fiscal year should be helpful in dedicating resources appropriately and meeting the scheduled timelines.

In order to facilitate the smoothest process possible in this changing landscape of US medical device regulation, companies hoping to introduce new devices to the US market should:

- **Manage expectations**
  - Recognise that the current uncertainty in the 510(k) pathway means that you should not expect to receive clearance within 90 days of submission, even for relatively straightforward submissions, and adjust timelines for market introduction accordingly.
  - Be prepared to receive at least one request for additional information from the Agency and consider working with a legal or regulatory consultant who can help you to identify the weaknesses in your application early and design an appropriate regulatory strategy to meet your company's business needs.
- **Do your homework**
  - Conduct careful predicate research prior to submitting a 510(k) notice to the FDA to address not only the intended use and technological characteristics of cleared devices, but also the definition of the product codes and regulations for these products.
  - Limit the use of predicate devices to a single predicate that supports both the intended use and technological characteristics of the device, if possible. If additional predicates are needed to support additional features of the device, position them as secondary to the primary predicate.
  - Investigate the level of supporting pre-clinical and clinical data that the FDA has required to support the most recent 510(k) clearances for similar devices.
- **Meet with the FDA early and often**
  - If your device presents differences in indications for use or technological characteristics from other cleared devices, consider meeting with the FDA to discuss the proposed regulatory pathway and plan for evaluating the device.
  - Prior to conducting clinical studies of a new device, discuss the protocol with the FDA in advance. The Agency is more likely to reject data obtained under a protocol it has not reviewed in advance.
  - Use the pre-IDE process to present new devices to the FDA and to confirm

expectations for data requirements to support 510(k) clearance with FDA staff.
  - Attempt to resolve disagreements with the Agency through telephone conferences and meetings, and go up the chain of command within the Agency only when resolution cannot be achieved within the branch.
- **Get help**
  - Engage with industry leaders, medical researchers, regulatory consultants and legal counsel who are well-informed of FDA developments, including the informal policies that may differ among review branches, and who can assist you during the pre-IDE, 510(k) or *de novo* down-classification process.

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