HEALTH DECISIONS
Agile Clinical Development

The 510(k) Process in a Period of Change:

A Practical Look into the Future of Medical Device Development

WHITE PAPER

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The entire medical device community seems to agree that FDA's 510(k) process for clearance of Class II devices must change. The question is how. Conflicting opinions have come from two groups within FDA's Center for Devices and Radiological Health (CDRH)[1,2], an authoritative Institute of Medicine committee[3], an industry survey[4], and a device-industry association.[5] The debate creates much uncertainty for companies seeking clearance of a device in the next few months that it is important to review the elements of the current 510(k) process, the debate, and then to identify a strategy for seeking clearance.

The 510(k) Process Today

Unlike the PMA process for approval of high-risk devices, the 510(k) process generally does not require clinical studies to demonstrate the safety and effectiveness of a new device. Instead, the 510(k) process requires demonstrating the "substantial equivalence" of a new device to a "predicate" device that is already on the market. Thus, the 510(k) process resembles FDA's Abbreviated New Drug Application (ANDA) process for generic drugs. Because studies have already been conducted to establish the safety and effectiveness of the chemical entity prior to approval of the brand name drug, the manufacturer of a generic has to demonstrate equivalence, not repeat animal and clinical studies of the compound. The 510(k) process presumes that a predicate device, like the brand-name drug previously approved by FDA, is safe and effective. However, there is no requirement that the maker of the predicate device ever submitted information establishing its safety and effectiveness. This difference between the 510(k) process and ANDA underlies the debate concerning the future of 510(k).

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Factors Driving Change

Industry Frustration

In May 2011, the Institute for Health Technology Studies (IHTS) issued a report based primarily on a survey of more than 300 people who have used the 510(k) process.[6] The report identifies numerous and substantial problems, including:

- The 510(k) process is very slow compared to processes in the EU and most other regions.
- Regulatory requirements loom large in decisions to invest in a new device, and yet there is much uncertainty about what is required.
- Only 24% of respondents found FDA's 510(k) submission requirements very clear or certain.
- No less than 85% of respondents perceived substantive changes in the 510(k) review process in the last three years.
- The list of perceived changes in FDA's requirements included key issues such as clinical endpoints, duration of studies, sample size and post-hoc statistical analysis.
- More than 70% of respondents perceived differences between FDA's guidance documents and the way FDA reviewed their submission.
- Almost 90% of those who perceived a difference between the guidance document and the actual review indicated that FDA asked for information beyond the required guidance.
- Frustrations were greatest for small companies. For them, the 510(k) process is almost twice as long as for big companies, a staggering 330 days.

Safety Concerns Based on Device Recalls

Device recalls added to the drive for 510(k) reform, but with an emphasis on increased rigor rather than faster review. A June 2011 Government Accountability Office report stated that from 2005 through 2009, firms initiated 3,510 medical device recalls, on average more than 700 per year, noting that FDA classified nearly 83 percent of the recalled devices as presenting only a remote probability of serious adverse health consequences.[7] However, a February 2011 article in the Archives of Internal Medicine reported that of 113 recalls categorized as possibly causing serious health problems or death, 71% were cleared through the 510(k) process.[8] This article bolstered opposition to the industry's appeals to speed up the 510(k) process.

The IOM Committee vs. the Industry and FDA

The IOM committee issued its report, "Medical Devices and the Public's Health: FDA 510(k) Clearance Process at 35 Years," on July 29, 2011.[9] When FDA requested the report, the agency's 510(k) Working Group had defined the aims of the 510(k) program as:

1. To assure, through a quality review process, that marketed devices, subject to general and applicable special controls, provide a reasonable assurance of safety and effectiveness;

2. To foster innovation. While the IOM committee said these aims were laudable, it "…found that the 510(k) program lacks the statutory basis to make it a reliable premarket screen for safety and effectiveness of Class II medical devices." The committee also said the 510(k) process "cannot be transformed into a premarket evaluation of safety and effectiveness as long as the standard for clearance is of substantial equivalence to any previously cleared device." Seeing no point in trying to fix the 510(k) process, the committee offered this sweeping recommendation:

> The Food and Drug Administration should obtain adequate information to inform the design of a new medical-device regulatory framework for Class II devices so that the current 510(k) process, in which the standard for clearance is substantial equivalence to previously cleared devices, can be replaced with an integrated premarket and postmarket regulatory framework that effectively provides a reasonable assurance of safety and effectiveness throughout the device life cycle.

The Industry Responds Loud & Clear

An industry vocal about problems with the 510(k) process came out swinging in its defense. AdvaMed stated, "The report's conclusions do not deserve serious consideration from the Congress or the Administration" and ". . . numerous academic studies have shown the process is overwhelmingly safe and that the IOM committee found no evidence to the contrary." From the industry's perspective, the IOM committee's recommendation to scrap the 510(k) process threatened to decrease predictability and transparency.

FDA Response: Measured but Unmistakable

CDRH Director Jeffrey Shuren, M.D. greeted the IOM committee's report by denying that the 510(k) process should be eliminated.[10] "The 510(k) program has helped support a robust medical device industry in the U.S. and has helped bring lower-risk devices to market for the patients who need them," Shuren said. FDA commissioner Margaret Hamburg denied that the IOM committee's report represents policy.

In short, the IOM committee considered the 510(k) process flawed based on its definition in law and called for new legislation. On the other hand, the IOM committee said it was not suggesting that "all, many, or even any" medical devices cleared through 510(k) are unsafe or ineffective.

Changes You Can Count on: Better Guidance, Greater Data Requirements

While much remains unsettled, some changes are clear. FDA will:

- Streamline its review process for "innovative, low-risk" products
- Publish guidance to clarify when clinical data should be submitted to increase predictability and transparency
- Require a brief description of scientific information known to manufacturers regarding the safety and effectiveness of select higher-risk devices on a case-by-case basis through device-specific guidance
- Improve decision making through a network of external experts to help FDA understand new device technology
- Establish a public database of important device information, including summaries of the basis of FDA's decisions to clear specific devices[11]

Rigorously executed, these changes will greatly improve predictability and transparency.

Addressing Evolving Regulations and Requirements

All signs indicate that FDA will require increased data with 510(k) submissions, whether from post-market surveillance, clinical studies or both. FDA has promised to clarify data requirements by late October 2011.[12] With data requirements increasing, the race to market and the ability to continue marketing conditionally approved devices will increasingly hinge on collecting greater amounts of data and preparing FDA submissions rapidly and accurately. Maximizing efficiency in every aspect of clinical trials will be more important than ever, and the same data handling and reporting capabilities required for clinical studies will be equally valuable in post-marketing studies.

NOTE: Health Decisions will provide an update to this white paper following the FDA's October announcement about additional data requirements for the 510(k) clearance process.

Selecting a Strategic Clinical Development Partner

Health Decisions. a global CRO, offers unmatched capabilities to ensure that device companies achieve timely clearance of their products under the 510(k) process during a period of change and uncertainty.

Conducting Clinical Studies More Efficiently

Unlike conventional trial management, Health Decisions' Agile Clinical Development approach scales seamlessly with higher data requirements and cuts clinical trial timelines by 25% through a three-pronged approach that combines Adaptive Design and Adaptive Operations, enabled by our proprietary HD360° Clinical Management System. HD360° combines flexible data capture and powerful data management with advanced reporting, collaboration and sophisticated business intelligence, enabling every member of a study team to work faster and more efficiently to meet development goals. These are the capabilities required to meet the growing data requirements facing device developers in a period of uncertainty.

Bringing the Right Tools to Post-Market Surveillance

As the demand for post-market data increases, device manufacturers should be aware that different means of collecting such data can have marked effects on cost and quality. WebEDC is certainly one valuable data-collection tool, but is not always the best choice for collecting post-market data. Optical Mark Read (OMR) allows inexpensive paper input with rapid and accurate automated conversion of data to electronic form for rapid processing and analysis. It is important to choose a partner for post-market studies that offers a choice of data collection methods. Health Decisions offers webEDC, OMR and SmartPen (for situations where time is at a premium), allowing you to choose the tool that best meets your needs.

Regulatory Expertise

Health Decisions has the regulatory expertise needed in a time of change as well as practical judgment about the types of evidence that are acceptable to FDA for surgical, therapeutic or diagnostic devices, including IVDs, for both the 510(k) clearance process and PMAs.

About Health Decisions

Health Decisions is the leading contract research organization (CRO) in Adaptive Clinical Trials committed to shortening development timelines and maximizing pipeline value for medical device, pharmaceutical and biotech companies. Through Agile Clinical Development—a strategic three-pronged approach that combines adaptive design, adaptive operations and proprietary technology — Health Decisions delivers real-time performance metrics that enable sponsors to make the most of competitive market opportunities. Health Decisions is headquartered in Durham, NC, with over twenty years of experience helping sponsors exceed development goals in Phase I-IV clinical trials across all major therapeutic areas.

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1 CDRH Preliminary Internal Evaluations, Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM220783.pdf

2 CDRH Preliminary Internal Evaluations, Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations

3 Medical Devices and the Public's Health: FDA 510(k) Clearance Process at 35 Years. Committee on the Public Health Effectiveness of FDA 510(k) ClearanceProcess; Institute of Medicine of the National Academies. National Academies Press. July 29, 2011.
http://www.iom.edu/Reports/2011/Medical-Devices-and-the-Publics-Health-The-FDA-510k-Clearance-Process-at-35-Years.aspx

4 A Comprehensive Analysis of FDA 510(k) Process: Industry Practice and Implications for Reform. Institute for Health Technology Studies. May 24, 2011.
Available from: http://www.510k.net/resources/110719+NorthwesternU+NPC+510$28k$29+webcast+slides+FINAL__AMENDED.pdf

5 Ubl, SJ. AdvaMed Statement on IOM 510(K) Report. Advanced Medical Technology Association. July 29, 2011. http://www.advamed.org/MemberPortal/About/NewsRoom/NewsReleases/PR-IOM72911.htm

6 A Comprehensive Analysis of FDA 510(k) Process: Industry Practice and Implications for Reform. Institute for Health Technology Studies. May 24, 2011. Available from:
http://www.510k.net/resources/110719+NorthwesternU+NPC+510$28k$29+webcast+slides+FINAL__AMENDED.pdf

7 United States Government Accountability Office. "Medical Devices: FDA Should Enhance Its Oversight of Recalls."GAO-11-468. June 2011.

8 Zuckerman DM, Brown P, Nissen SE. Medical device recalls and FDA approval process. Archives of Internal Medicine. February 14, 2011.

9 Medical Devices and the Public's Health: FDA 510(k) Clearance Process at 35 Years. Committee on the Public Health Effectiveness of FDA 510(k) ClearanceProcess; Institute of Medicine of the National Academies. National Academies Press. July 29, 2011.
http://www.iom.edu/Reports/2011/Medical-Devices-and-the-Publics-Health-The-FDA-510k-Clearance-Process-at-35-Years.aspx

10 FDA to seek public comment on IOM recommendations; Agency continues to improve device review process. FDA. July 29, 2011.
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm265908.htm

11 FDA to improve most common review path for medical devices. Press release. January 19, 2011.
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm240418.htm; 510(k) and science report recommendations: Summary and overview of comments and next steps.
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM239449.pdf

12 Edney A. FDA will rule on new class of moderate-risk devices by October.
http://www.bloomberg.com/news/2011-08-04/fda-will-rule-on-new-class-of-moderate-risk-devices-by-october.html?cmpid=yhoo