



FDA raises the bar: the effects of changes in the 510(k) programme



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The US FDA's 510(k) programme is going through a period of significant change. Glenn Neuman, director of scientific affairs at New World Regulatory Solutions, examines the implications for device manufacturers of this "period of unpredictability" at the agency

There has been a lot of speculation about the actions the FDA

may take concerning the current premarket notification – or 510(k) – programme. FDA Commissioner Margaret Hamburg called for changes in the way it operates, which could include more clinical studies. Alberto Gutierrez, director of the Office of In Vitro Diagnostics Evaluation and Safety (OIVD),

said that companies can expect more aggressive diagnostics regulation, while the FDA's device centre director, Jeffrey Shuren, refuted claims that the agency would make drastic changes to the 510(k) process, opting instead for improvements, including better transparency and a "Total Life Cycle" approach. The prestigious Institute of Medicine (IOM) is conducting an in-depth review of the programme and its report, along with a hefty \$1.3m invoice, is due one year from now. In order to implement more immediate action, the FDA will roll out its

own short-term solutions as early as this September.

Whether we call it "raising the bar" or "strengthening the process" isn't important. What is important is that change is coming, and we need to know what that means for device manufacturers. Medtech executives of all stripes are expecting more stringent reviews; glucose meters have already been singled out (www.clinica.co.uk, 19 January 2010). But change is not just coming – it is already here. And it's not only the FDA that is upping the ante. An amendment to

the EU's Medical Devices Directive (MDD) 93/42/EEC, which came into effect on 21 March 2010, requires that every medical device sold in Europe, regardless of its classification, has a clinical evaluation report in its technical file. There is a global consensus that a deeper review of medical device safety and effectiveness is needed.

As originally intended by Congress in 1976, the 510(k) route to market has served us well over the years. It provided the FDA with a means to apply scientific standards for safety and efficacy while the public benefited from an innovative and competitive medical device market. But in practice, the repeated application of "substantial equivalence" to a predicate device can accumulate large differences (a phenomenon known as "predicate creep"), which, along with advances in technology that outpace regulatory science, has undermined the 34-year-old programme. The weaknesses become apparent through post-market experience, and surprisingly, the FDA lacks the authority to rescind 510(k) approval once it has been granted.

Regulatory climate cycles

Since 1976, it was the FDA's responsibility to interpret "substantial equivalence". In 1990, however, Congress enacted the Safe Medical Device Act, which defined substantial equivalence to be consistent with the FDA's administration of the 510(k) programme. This sequence of events, where law is enacted, administered, and then further refined, demonstrates the interplay of intent, action and results necessary to optimise and modernise regulations. Manufacturers see the same dynamics in their design control activities or when modernising their quality systems: say it, do it, fix it. With organisations as big and complex as Congress and the FDA, the scenario plays out for many years, resulting in long periods of sub-optimal conditions where weaknesses have been identified but not yet fixed. During these periods, the regulatory process becomes unpredictable.

Industry veterans will tell you that these periods of unpredictability appear in cycles and are characterised by longer review times. Entrepreneurs will tell you that this unpredictability can be devastating. We appear to be in the midst of an unpredictable regulatory cycle now. The phrase "the FDA is a moving target these days" has become a mantra among device manufacturers. There are stories of protracted 510(k) review times, currently running to nine months and more. This is the period of uncertainty that precedes formal policy changes – it

means that the FDA has already tightened its reviews, and is struggling internally to find the appropriate review requirements. The regulatory climate is as cyclical as the four seasons, and at the present the FDA is in the heart of a deep, hard winter. The Center for Devices and Radiological Health (CDRH) wants to make the 510(k) process more predictable, and one of the first steps in accomplishing that is to break from what CDRH acknowledges as some questionable past decisions.

Good creep/bad creep

Before making formal policy changes, the FDA seeks input from stakeholders and the public. The agency invited public input on how to strengthen the existing process in a meeting held on February 18. Given the diverse nature of the products the FDA regulates, one of the biggest challenges it faces is balancing flexibility and consistency. We would all do well to spend a day walking in the agency's shoes. On the public side, most opined that the 510(k) programme was working well, while some thought it needed a complete overhaul. Several people suggested that a risk-based approach should be used for 510(k) reviews. The de novo 510(k) was seen to be in greatest need of strengthening.

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Manufacturers did not take well to the implication that they would pick the worst predicate for comparison. Predicate creep, they say, is a good thing, because each new product is an improvement over the last one.

Bad predicate creep can occur not only from multiple substantial equivalence comparisons to predicate devices, but also from a series of small changes made to a cleared device, which in total raise new questions of safety and efficacy. Manufacturers are responsible for controlling their creep through design control (21CFR 820.30), risk management, (ISO 14971) and using the "510(k) decision tree" to determine if and when a new 510(k) is required (510(k) Memorandum K97-1). A decision not to file a 510(k) must be

documented internally, but the FDA can always disagree with that decision.

The Steris SS1 Processor, used to chemically sterilise instruments such as endoscopes, provides a recent example of the negative impact a manufacturer can face when the FDA disagrees with their decision not to file. The FDA viewed the cumulative changes in the Steris SS1 from 1988 to 2008 to be significant, and issued a warning letter to the manufacturer in May of 2008. Steris disagreed, but by December 2009 through to February 2010, the FDA had issued notices declaring that the Steris SS1 device had not been reviewed for safety and effectiveness, that devices labelled for disinfection with the Steris SS1 should be considered misbranded, and that within six months healthcare facilities should find alternative means to disinfect their reusable surgical equipment. Everyone jumped on the bandwagon (except Steris). The FDA notices were followed by warnings from the ECRI Institute, an alert on the Medscape website and numerous news articles.

Then, after listening to the concerns of healthcare practitioners, on 22 February, the FDA extended the recommended timeframe for replacing the Steris SS1 to 18 months, because the burden of changing sterilisation methods in the shorter time period could pose a greater risk to patients than using the "unapproved" system.

But a surprise came on 24 February, when, in a remarkable and unexplained turnaround, the FDA issued e-mails reversing their recommendations, saying "Dear Colleagues...please disregard the previous posting...it was premature." Maybe the creep wasn't so bad, but the damage was already done.

The Steris story exemplifies four important points:

- The FDA has significant concerns over predicate creep and will take any action allowed by law;
- The FDA is struggling internally to find balance in its 510(k) review policies;
- The FDA listens to public opinion when issues of risk to public health are raised; and
- The FDA is in its unpredictable cycle, which detrimentally affected Steris' future profits.

Tougher review is nothing new

Since 1976, the increase in 510(k) requirements has paralleled the growth of the medical device industry. Industry veterans who remember their first 510(k)s chuckle about how it was "back in the old days." What was once a few

pages may now be a few hundred, and what once cost a few hundred dollars may now cost a few hundred thousand. A quick review of the literature will uncover lead stories between 1985 and the present where the FDA was criticised for insufficient reviews. True to the dynamics of regulatory cycles, Congress attempted to keep up by enacting the FDA Modernization Act in 1997 and the Medical Device User Fee Modernization Act in 2002. But technology will always outpace law-making, and the FDA must find ways to bridge the gap. The agency now faces more submissions (approximately 3,500 per year) and conducts more complex reviews requiring multidisciplinary teams, yet their budget has not grown proportionally; the law still requires and industry still expects the job to be done within the original 90 days.

Universal impact

Raising the bar on 510(k) submissions will impact everybody involved. If the FDA has the right tools and resources (see Margaret Hamburg's February 24 speech at NIH, www.fda.gov/NewsEvents/Speeches/ucm201687.htm), their job should eventually get easier. But with the learning curve the agency faces, greater short-term pressures are likely.

From the perspective of medtech firms, if more studies are required, the time and costs of preparing a 510(k) submission will increase, and their pipelines will narrow. Review times will be prolonged. Smaller companies will fail if the requirements exceed their financial resources.

For the public, healthcare costs will increase, and a narrower pipeline from the medical device sector will reduce the number of device improvements and new innovations.

Baby steps

We all might be better served if more stringent requirements are introduced in incremental steps. The FDA's administration of CLIA Waivers under their new 2008 guidance is a good example of how a giant step can effectively shut down a programme. For the first 20 years of CLIA, waivers were granted via the "old rule" established by the CDC. The old rule required that 60 lay people test patient samples and get a 95% concurrence with a professional's result when using the same test. The 95% lower confidence interval (LCI), which is the number FDA statisticians swear by, is 86.3%. The studies could be conducted within a week at three sites, at a total inflation-adjusted submission cost of about \$30,000.

The FDA's January 2008 CLIA Waiver guidance calls for 240 (for qualitative tests) or 360 (for quantitative tests) prospective patient samples to be run, with 95% agreement to a recognised reference method. The 95% LCI for a 240 sample study is 91.5%. While some banked samples are allowed per the guidance, they are discouraged by reviewers, who suggest that additional patients should be tested in order to get the number of reactive samples needed. The cost increase parallels the sample increase – about four times more, virtually overnight.

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The advantage of the 2008 CLIA Waiver guidance is that there are clear performance targets that must be met, and intended operators, who will perform better than lay people, are used. The bad news for industry and the public is the clearance track record since the guidance was published. In 2008, there were 11 CLIA Waiver applications to the OIVD, only six of which were cleared. In 2009, there were six applications, and only one was cleared. This means that the "old rule" devices, with an 86.3% statistical confidence, are dominating the market, and only a few scoring 91.5% are available. Perhaps an intermediate goal of 88.9% would be a more effective way to bring improvements to the waived test market.

A similar situation could occur with 510(k)s, where the public's only option is to be tested with the predicate devices that the FDA is now saying aren't good enough to be used as reference methods. Unless we can ensure the same performance standards for all devices, old and new, more stringent clearance policies can actually put public health at risk.

Policy pitfalls

A good analogy is the car industry. I could still be driving my 1956 Chevy (if only I had it), and as an antique car it would be exempt from current emission standards. But the difference is, if Chevrolet were

making that same model today, it would not be exempt from today's standards. And while devices are grandfathered by regulation, quality systems are not. Device manufacturers who met ISO 13485:1996 still had to meet ISO 13486:2003 to keep their certification. Yet manufacturers of grandfathered medical devices continue to manufacture them today, but without proof that they meet current standards. To be effective, the FDA needs the statutory authority to determine whether old technology meets current standards.

Travel plans

Anyone planning a trip on "Route 510(k)" would be well-advised to get a weather report and a traffic update before embarking. The forecast is lots of wind and localised storms. Currently there are slippery conditions on the less travelled back roads, while most of the well-travelled main roads remain clear.

The main roads represent those devices with which the FDA is familiar and which do not (yet) require clinical data and do not raise new questions about safety and efficacy. The FDA's 510(k) database shows 14 devices were submitted and cleared within the first two months of 2010. These fast track submissions include orthopaedic screws, surgical clips and mesh, balloon catheters, blood pressure monitors and ultrasound devices, and their short review times help to improve the agency's average review time and meet their goals. The back roads represent devices that require clinical data, which represent about 10% of all 510(k)s, but virtually 100% of IVDs. Travel time on the back roads has increased to well over the 90 days specified for traditional 510(k)s. But traffic on the main roads will also be impeded if clinical data becomes a requirement.

At the end of the road, we can expect the medical device industry to persevere. The history of the 510(k) programme is like the stock market – there are ups and downs, winners and losers, but over time the market tends to improve. And the device industry will also survive and thrive in the seasons to come, because it is essential to the public health.

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