DuVal Client Alert

Passing on Tribal Knowledge of FDA Law

510(k) Series
Epidsode 6

"IT'S ELEMENTRY MY DEAR WATSON"

QUESTIONS OF SAFETY AND EFFECTIVENESS?

THE 6TH CLIENT ALERT IN OUR SERIES ON 510(k)s

We arm you with potential responses to FDA so that you can remain on the 510(k) path

When Does Your Device Raise Different Questions of Safety and Effectiveness?

This is the next Client Alert in our series on drafting and filing strategies for 510(k)s. The strategies we share in this series are borne out of our experience in counseling clients on how to ensure their 510(k) is an advocacy document, not just an evidentiary document, which garners the clearance they seek. A 510(k) submission is an advocacy document **with** evidence. Here are the previous Client Alerts in this 510(k) series:

1st "Dotting the I's and Crossing the T's: Withstanding the 510(k) Acceptance Review;"
2nd "Seven Quick Tips for Successful 510(k) Submissions--do you need our help with your next submission?"
3rd "Choosing the Proper Predicate Device(s): Comparing Apples to Oranges;"
4th "Clearing Your Indications for Use: Staying Under the Umbrella of Intended Use;" and
5th "Addressing Technological Characteristics in Your 510(k): Finding the Similarities Between Apples and Oranges."

You can find additional episodes of this series at: duvalfdalaw.com

In this Client Alert, we alert you to arguments FDA often makes to suggest your device raises different questions of safety and effectiveness and does not belong on the 510(k) path. We arm you with potential responses to FDA so that you can remain on the 510(k) path. In a future Client Alert and the final in this 510(k) series we will also discuss the quantum and quality of data that should be submitted for clearance and where to push back on the Agency.

EXECUTIVE SUMMARY

"It's elementary my dear Watson."

When Sherlock Holmes uttered those famous words to his assistant and sidekick, Dr. Watson, it underscored how he had unlocked the mystery of an intractable case and was ready to share it with him. But Sherlock's skills were applied to cases of first impression and difficult, murky facts. He unlocked those mysteries through inductive and deductive reasoning. ***He made difficult things elementary.***

FDA often does just the opposite. It makes simple things difficult. We don't need a Sherlock Holmes in FDA's interpretation of the 510(k) program. It was designed to be the plow horse of the American medical device pre-market system because it operates on what is already known and knowable, i.e. precedent. It may not be sexy, or fast, high science, like the PMA program, but it has served the American public well. FDA, possibly out of boredom or a desire to grow its regulatory fiefdom, has made the 510(k) program something it was not intended it to be—high science and making the known, mysterious. FDA frequently contorts its definitional and scientific analysis to find a device somehow has different technological characteristics and raises new questions of safety and effectiveness. FDA often uses this analysis to bounce a device off the 510(k) path and on to either the de novo or PMA path.

FDA has three strikes at derailing a product from the 510(k) path: arguing it has a different intended use, different technological characteristics and/or raises different questions of safety and effectiveness. If a sponsor is unsuccessful establishing it has the same intended use, it cannot remain on the 510(k) path. But if you've passed the definitional hurdle on same intended use and even if FDA has decided you have different technological characteristics, you may be able to save your 510(k) application by convincing them your device does not raise different questions of safety and

effectiveness. But doing so is never an easy task with today's FDA. Your job is to advocate why your device raises the **same** questions of safety and effectiveness. And sometimes the evidence is as plain as the smoking pipe in front of your face.

ANALYSIS

The 510(k) pathway was designed to allow innovation

The 510(k) pathway is designed to be sufficiently flexible to accommodate technological innovation and yet allow for the subject device to be substantially equivalent to a predicate device(s). As such, 510(k) devices are allowed, even expected, to have some differences from the predicate, even though they must be "substantially" equivalent. Over time the 510(k) process accommodates significant changes over the predicates devices that may even go back decades even though each incremental change vis-a-vis a given predicate may not be nearly so great. As FDA has said in its 2014 510(k) guidance document on substantial equivalence determinations:

> *A new device does not need to be identical to the predicate device for it to be found substantially equivalent to the predicate device. In FDA's experience, it is rare for a new device to be identical to a predicate device.* Given the diversity of technologies evaluated under this review standard, *this guidance adopts a flexible approach* to determining "substantial equivalence" to accommodate evolving technology while maintaining predictability and consistency to promote confidence among device developers, practitioners, and patients.
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> *Devices reviewed under the 510(k) program commonly have different technological characteristics from their predicate device*(s); however, FDA rarely makes a finding of NSE at Decision Point 4.

*The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]," dated July 28, 2014 (hereinafter the "**New 510(k) Guidance**")* (emphasis in bold and italics added).

Yet the Agency often does not celebrate technological innovation, even though it should. FDA almost appears to fear it because it will make their workload harder and/or it may make the 510(k) program too permissive in its analytical (definitional) boundaries. It's almost as if FDA works against the 510(k) program instead of with it.

FDA's own guidance documents recognize that incremental changes, even advantages, to products occur as technology improves and new ideas are brought to bear upon pre-existing product ideas. Sometimes the predicate landscape demonstrates the progression or evolution that the devices in the predicate family have made. FDA has pejoratively called this "predicate creep." But predicate creep is a good thing, not a bad thing. It means technology is progressing and naturally evolving; which is what the 510(k) program was designed to foster.

Here are three overall concerns we see with FDA's application of the whether a device "raises different questions of safety and effectiveness:" 1) FDA often finds differences without articulating why; 2) FDA elevates theory (and sometimes conjecture) over scientific data and that ignores the hierarchy of the evidence/proof; 3) FDA makes arguments there are different questions of safety and effectiveness inappropriately citing literature, or arguing why the sponsor's device increases risk. We explore below how to use logic and FDA's own arguments against them to demonstrate there are not different questions of safety and effectiveness.

The Revised (and We Believe Incorrect) Standard Under FDA's New 510(k) Guidance

Let's start with FDA's guidance on this topic. FDA has taken a markedly different approach in its new guidance on how to analyze when a subject device raises different questions of safety and effectiveness from a predicate. FDA's new approach differs greatly from FDA's old guidance and we believe it is not faithful to the statute or regulations. We address both below.

The New 510(k) Guidance uses an expansive interpretation of the information required to file a 510(k). The new guidance engages in a three step process for determining whether a device has the same technological characteristics and raises new questions of safety and effectiveness. Suffice it to say, this new approach is very granular and will afford FDA many more opportunities to find a device is different and raises new questions of safety and effectiveness. This is just another change to the 510(k) program that will make it easier for FDA to push a device off the 510(k) path.

Step One involves the ***identification of technological characteristics*** of the new and predicate device. **Step Two** involves the ***identification of differences*** in technological characteristics between the new and predicate device. **Step Three** involves ***a determination of whether the differences in technological characteristics raise new questions of safety and effectiveness***. We addressed Steps One and Two in our fifth Client Alert in this 510(k) Series entitled "*Addressing Technological Characteristics in Your 510(k): Finding the Similarities Between Apples and Oranges.*"

Step Three of FDA's 510(k) guidance is the one we want to focus on here. It involves a determination of whether the differences in technological characteristics raise new questions of safety and effectiveness. Under Step Three, FDA must determine whether a "different question of safety and

effectiveness" is a question raised by the technological characteristics of the new device that was not applicable in the 510(k) for the predicate and poses an important safety or effectiveness concern for the new device. In the New 510(k) Guidance a "different question of safety or effectiveness" is a question raised by the technological characteristics of the new device that was not applicable to the predicate device, and poses a significant safety or effectiveness concern for the new device. The Guidance states as follows:

> *3. Step 3 – Determination of Whether the Differences in Technological Characteristics Raise Different Questions of Safety and Effectiveness*
> If FDA determines that there are differences in the technological characteristics of the new device and the predicate device, FDA will review and evaluate all relevant information bearing on any such differences in technological characteristics to determine whether they raise different questions of safety and effectiveness for the new device as compared to the predicate device (Decision Point 4 on the Flowchart). ***A "different question of safety or effectiveness" is a question raised by the technological characteristics of the new device that was not applicable to the predicate device and poses a significant safety or effectiveness concern for the new device.***

This appears to be a wholly new standard for the 510(k) program. The new standard is very difficult to achieve because in most cases the question of safety and effectiveness frequently was not considered in the review of the predicate but may not necessarily be new to FDA. Again, the 510(k) program is designed to be sufficiently flexible to accommodate new technological innovation. If every minor permutation in a subject device stymies FDA, the program will be lost to technical readings and will not be innovation-friendly.

The guidance goes on to provide three examples, but it only provides examples where the subject device raises different questions of safety and effectiveness from the predicate device. FDA, predictably, does not

provide examples where the subject device, having different technological characteristics, does not raise different questions of safety and effectiveness. So the FDA's guidance is of limited utility and leaves an opportunity for sponsors to make their case. We have done so many times with FDA.

Something as simple as the biocompatibility of a material, used in the subject device but not found in the predicate device, but which is very well-characterized and well-known to the Agency, could preclude a SE determination under this new standard. For example, we note how the biocompatibility of nitinol, commonly used for stents and used for the first time in an orthopedic application, might conceivably raise different questions of safety and effectiveness. We encountered that situation once where FDA review staff initially said the subject device had different technological characteristics and raised different questions of safety and effectiveness. Both conclusions were overturned by FDA management on appeal. The issue of whether nitinol caused any different biocompatibility issues in the bone versus the blood stream was answered in favor of the sponsor and the device was cleared. But one can see the kind of analytical discretion reviewers have (and take) to go a different, more exclusionary, direction.

The other problem is how FDA chooses to define "different." Different can be viewed restrictively in the eyes of an uncreative, black and white, reviewer. Frequently, a sponsor's device may use a novel approach to an old problem using old technology, but is similar in overall approach to the approach by which the predicate family addressed the issue. Take for example, the difference between a "t-plate" used in fixating bone fragments in distal radius wrist fractures and the next generation intermedullary nail. The intermedullary nail is pounded into the intermedullary space. When it was cleared it constituted a novel approach over the existing t-plate approach (i.e. in which the wrist is splayed open and the t-plate affixed), but was still within the overall approach of the

predicate family (i.e. the intermedullary nail is pounded into the intermedullary space, but still affixes bone fragments). Certainly, the FDA today could find "different" questions of safety and effectiveness to disallow clearance of the intermedullary nail for use in wrist fractures, even though intermedullary nails are commonplace in general orthopedic surgeries, but FDA found them SE. Again, it is doubtful whether today's FDA would make the same SE determination.

Finally, the approach advocated in Step Three seems to avoid or even contradict the commonsense approach taken in K86-3, i.e., is the change "consequential?" In older FDA guidance, the K86-3 Blue Book Memo which, sadly, has been decommissioned, FDA stated that in determining whether a device has new technological characteristics, FDA should focus on changes that are "consequential" and require them (and only them) to be addressed:

> In taking this approach, ***the Center focuses on the technological differences that are medically and scientifically significant and avoids the difficulties that would arise from a mechanistic application of rigid formal criteria*** to the wide variety of substantial equivalence questions posed by new devices proposed for marketing under a 510(k). Substantial equivalence determinations of necessity ***require the Center to exercise reasonable scientific judgment***.

See 510(k) K86-3 Blue Book Memo at 7.

K86-3 was much more commonsensical and pragmatic drawing upon FDA's vast repository of institutional knowledge and finding similarities where they can be found. Frankly, today's reviewers can be mechanistic. Using K86-3, i.e. determining the "consequentiality" of the change, is more SE friendly and directed reviewers to focus on the "exercise reasonable scientific judgment." The emphasis was on proceeding to a clearance if there were accepted scientific methods for evaluating the questions of safety and effectiveness and the data submitted substantiated the subject device had

not diminished safety and effectiveness in comparison to the predicate. This analysis and emphasis enabled to the 510(k) program to accommodate technological innovation without prematurely and inappropriately relegating a device to the de novo path.

Looking deeper into the criteria set forth in CDRH's Blue Book Memorandum, we must look at any given product and the Blue Book questions holistically and ask "Are the changes really 'consequential?'" As FDA has (in the past) stated:

> Thus, from a scientific perspective, to determine which technological changes are "consequential," the Center considers whether:
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> - The new device ***poses the same type of questions about safety and effectiveness*** as a predicate device;
> - There are ***accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected*** as a result of the use of the new technological characteristics; and
> - There are ***data to demonstrate that new technological characteristics have not diminished safety or effectiveness***.

See 510(k) K86-3 Blue Book Memo at 7 (emphasis added).

This approach looks for the same "type" of question and has a more charitable view of differences if there are accepted scientific methods to evaluate safety and effectiveness and data to demonstrate the new technological characteristics have not diminished safety of effectiveness. This third requirement is notable because it does not at all comport with the narrative and flow chart found in the New 510(k) Guidance. The New 510(k) Guidance does not allow FDA to look at the sponsor's data to answer the question of whether a device raises different questions of safety of effectiveness. But K86-3 did. That is a travesty because often FDA's concerns could be allayed, and the 510(k) path salvaged, if FDA simply looked at the data provided in support of the sponsor's argument.

We juxtapose this approach with FDA's new granular approach that requires a deep dive into every conceivable difference between the subject and

predicate device. It also deliberately divorces itself from looking at whether there are accepted scientific methods to evaluate safety and effectiveness and data to demonstrate the new technological characteristics have not diminished safety of effectiveness. ***Many inquiries today turn into a scientific experiment and answers to Additional Information questions in a review get turned into a mini-Ph.D. dissertation, all to satisfy the insatiable scientific curiosity of impractical reviewers. Reviewers often ask for what they want, not what they need.*** Least Burdensome requirements are lost in all of this. This approach lends itself much more readily to a finding of different technological characteristics that raise different questions of safety and effectiveness.

It is unfortunate that today's FDA did not embrace the good, common sense and pragmatic aspects of K86-3 in its New 510(k) Guidance. It almost seems like the new FDA is trying so hard to show itself to be more sophisticated and competent than previous FDA administrations that simple decisions have been made very complex. ***Today FDA typically starts with a presumption that a device is different and raises different questions of safety and effectiveness, eliminating the collaborative aspect, flexibility and practicality of the 510(k) program.*** This predisposition to find differences versus similarities runs counter to the underlying premise for the 510(k) program. The new standard also contradicts the approach taken in K86-3, i.e. to consider whether the change is "consequential," and focuses on ***the mere presence of a change***—which all 510(k)s have—and ***not the essence of a change***.

Three overall concerns with FDA's interpretive approach and how to challenge them

A. FDA often finds differences without articulating why

FDA reviewers often have an unarticulated concern or belief that a device raises a new question(s) of safety and effectiveness and use it as a basis to deny clearance. If FDA could simply say, with respect to any device, that "we think this device raises different questions of safety and effectiveness than the predicate(s) because it has different technological characteristics and is ineligible for the 510(k) path," what would ever stand in FDA's way from saying that for any device it did not want cleared as a 510(k) device? How do companies practically refute an unarticulated, unsupported statement?

It is a dangerous regulatory precedent to allow FDA review staff and management to stray outside of the framework of the 510(k) program. When review staff or their management do not articulate, with any degree of specificity that the device raises different questions of safety and effectiveness, that is what they are doing. When review staff or their management have a "gut impression," "belief," or "concern," call it what you want, that the device has differences that they "feel" raise new questions of safety and effectiveness, those are not concrete reasons to which industry can respond.

The check on FDA's unbridled discretion, its bare conclusion, is the standard that Congress has provided, i.e. whether the device actually raises different questions of safety and effectiveness. This is to be guided by the flexibility with which the 510(k) was designed. The older guidance documents provided industry and FDA with some analytical tools to address and interpret that problem. If FDA is simply allowed to raise unarticulated concerns and use that to derail products from the 510(k) program, then the

510(k), as a whole, is in trouble. Your job is to convince the FDA why the devices raise the same questions of safety and effectiveness.

B. FDA elevates theory over scientific data and that ignores the hierarchy of the evidence/proof

Another important and related point to be considered here as part of the ensuring the integrity of the 510(k) program and FDA's decision-making is the hierarchy of the competing evidence. In many cases the review division brings theory, conjecture or a gut impression to compete in the hierarchy of evidence against hard scientific/ medical data submitted by the manufacturer. One can understand if FDA elevates its own theory above that of a company's theory, giving more credibility to FDA's position due to FDA's experience across many devices. But how can theory, even if it is authored by FDA, be elevated over hard evidence, i.e. performance and clinical data? Again, how does industry compete with and respond to the review staff's theory, conjecture or a gut impression? This is when industry is completely at the mercy of a fair and impartial decision maker in FDA management. Industry can only hope that FDA management can be sympathetic to the review staff's concerns and intuition, but at the end of the day will be data-driven. FDA should not allow a general ephemeral concern or theory to trump hard scientific and medical data.

FDA also should not avert their eyes from data in the file to answer these questions as the New 510(k) Guidance unwisely does, which wastes the time of everyone involved. The New 510(k) Guidance permits this practice while K86-3 allowed just the opposite. If there were data in the sponsor's file to answer whether there are different questions of safety and effectiveness, it was reviewed. To do otherwise, undermines the very purpose of the 510(k) and means FDA is using an Agency-created technicality to avoid earning its user fees.

C. FDA often inappropriately cites literature or increased risk to support their position

Often in deficiency letters FDA will cite literature and public reports of adverse events to support their position that the subject device requires additional data, clinical or otherwise, to ensure its safety and effectiveness. But, applying logic, it is that very citation to literature and/or public reports which makes the case that the questions being raised are not new because the literature to which FDA cites is evidence of that fact. We have more than once turned Branch or Divisional management around to our side by simply pointing out this fact. ***Our point is simply that what is being pointed out by FDA is evidence that all the issues are known possible issues and therefore do not raise "a different question of safety and effectiveness" under the 510(k) program.*** In the event staff does not mention the literature, it is your duty to do so and point out that the questions being raised are not new or different.

Similarly, sometimes the Agency in a deficiency letter will make reference to the fact your device may "increase" risk. Again, applying simple logic, our response to that has frequently been something like this: "The FDA's very point suggests the risks are not new, because the reference is to '**increased**' risk. This implies the presence of a baseline risk which is being increased." In other words, this is not a **new** risk, it is an **existing** risk being increased, and thus is not "a ***different*** question of safety and effectiveness" under the 510(k) program.

Finally, FDA staff frequently fails to review FDA's own guidance documents when it draws the superficial conclusion that a sponsor's device raises different questions of safety and effectiveness. Often FDA's own guidance can be cited against them to demonstrate that the guidance contemplates those very issues.

Conclusion

It is amazing how collaborative FDA used to be finding many device iterations involving new technological approaches that could be embraced under the 510(k) pathway. Today's FDA has more of a "shut down" mentality when reviewing submissions. They often spend much of their time trying to conjure up countervailing arguments why a device does not belong on the 510(k) pathway. That includes making the argument that it raises different questions of safety and effectiveness. Rather than being open-minded about the possibility, FDA reviewers often expend intellectual capital trying to defeat the sponsor's argument. Fortunately, more experienced and collaborative FDA management will listen to strong arguments and intervene or overturn the review staff.

When the sponsor uses creativity and solid logic in making the argument that their device does not raise different questions of safety and effectiveness, finding similarities—in the words of Sherlock Holmes—is "elementary."

DuVal & Associates
Drug, Device and Food Law

DuVal & Associates is a boutique law firm located in Minneapolis, Minnesota that specializes in FDA regulations for products at all stages of the product life cycle. Our clientele includes companies that market and manufacture medical devices, pharmaceuticals, biologics, nutritional supplements and foods. Our clients range in size from Global Fortune 500 companies to small start-ups. As one of the only dedicated FDA regulatory law firms in the United States, our mission and absolute focus is providing our clients appropriately aggressive, yet compliant, guidance on any FDA related matter. We pride ourselves not only on our collective legal and business acumen, but also on being responsive to our client's needs and efficient with their resources. DuVal & Associates understands the corporate interaction between departments like regulatory affairs, marketing, sales, legal, quality, and clinical, etc. As former industry managers in the drug and device spaces, we have been in your shoes. Our firm has extensive experience with government bodies. We understand what it takes to develop and commercialize a product and bring it successfully to the market and manage its life cycle. Impractical or bad advice can result in delays or not allow for optimal results; while practical, timely advice can help companies succeed.

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