DuVal Client Alert

Passing on Tribal Knowledge of FDA Law

The 7th Client Alert in Our Series on 510(k)s

"My creation: It's pronounced 'Fronkensteen"

Halloween 2017

What is the quantum and quality of information needed for your 510(k)?

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;"
- 5th—"Addressing Technological Characteristics in Your 510(k): Finding the Similarities Between Apples and Oranges;" and
- 6th—When Does Your Device Raise Different Questions of Safety and Effectiveness?

Find these prior Client Alerts at our website www.duvalfdalaw.com

In this Client Alert, we discuss the FDA's ever-growing data requirements as the price to be paid to obtain clearance of a 510(k). We arm you with potential responses to FDA so that you can remain on the 510(k) path.

Executive Summary

"My creation: It's pronounced 'Fronkensteen"

When Dr. Frankenstein undertook the creation of his subject it was a well-intentioned misadventure. His attempt to create something beautiful and extraordinary ended up being something hideous and unmanageable which sought to kill others. Dr. Frankenstein had made something reprehensible and dangerous to mankind. While FDA's attempts to create a package of data that will protect the American public is laudable and well-intentioned, their involvement often results in data requests involving over-sized parts and pieces, unnecessary to the creation of the being (data set) to ensure it is safe and functionally works. FDA's requirements are substantially delaying and many times killing innovations beneficial to patients. ***No matter what the quality and quantity of the data submitted by a 510(k), many reviewers seem to believe it is never correct, sufficient or adequate. Many FDA reviewers consistently ask for data that are scientifically interesting, but not required, to make an SE determination.***

By waving the banner of patient safety, it seems as if FDA believes it is inoculated from concerns regarding the loss of jobs, intellectual property and investment in medical devices—matters seemingly too pedestrian for FDA to consider. No matter how much pressure is put upon FDA by Congress, patient advocacy groups and the press, many reviewers seem calloused or indifferent to the impact that their decisions have on the American patient and economy. But this is not an either/or proposition; we can protect patients, speed innovations to market and create U.S. jobs within the

same regulatory system. We simply need to adjust the balance of risks with the benefits and ensure we are extending the benefits of new innovations to patients who need them and to the creation of jobs and support of medical device investment.

In addition to the three areas FDA has to derail a product from the 510(k) path, i.e. arguing it has a different intended use, different technological characteristics and/or raises different questions of safety and effectiveness, FDA can ask for a crushing amount of data. Even if you've passed the definitional hurdles, you can become stuck responding to FDA's requests for data. ***Your job is to advocate why your proposed data set is relevant to and sufficient for establishing substantial equivalence and dissuade FDA from turning your 510(k) into a Frankenstein monster. This Client Alert attempts to encourage you to know when and how to push back on the Agency on non-clinical and clinical data requirements.***

Some Overarching Thoughts

Re-embracing the 510(k) program for what it was intended to be. ***The problem is that FDA often tries to be an architect of regulatory perfection by requiring so much information upfront that it is crushing the balanced ecosystem upon which medical device innovation is built.*** In its quest to protect, FDA often regulates to the rare exception, the rare product problem (e.g., metal-on-metal hip implants, infusion pumps, etc.), meaning in its risk averseness it over-regulates the vast majority of other devices by trying to discover rare problems upfront in the clearance process. The 510(k) program 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, fast, or 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 requires much more data than is really necessary to clear a device. The waste in the system is obvious and unnecessary. FDA re-invents-the-wheel in data requests by ever-increasing and adding to the information it needs to be submitted for device after device. In particular, FDA makes boilerplate requests for clinical data where animal or bench data, or even small confirmatory trials (prospective, non-randomized, or retrospective) would suffice. FDA seriously delays or even kills device clearances by requesting too much data.

FDA personnel are inappropriately risk-averse and request data that are often far beyond that needed to establish SE. In doing so, FDA is ignoring Least

Burdensome requirements as originally enacted in the Food and Drug Administration Act (FDAMA) of 1997. FDA has adopted an almost overbearing approach to the review of performance, animal and human clinical data. Data requests essentially attempt to narrow risk to near zero when that degree of risk is not scientifically, technically or practically possible with any medical device, whether it be under the 510(k) or the much higher PMA standard. FDA's limited tolerance for risk is unreasonable and unlike what is required throughout the rest of the world.

It is difficult to second-guess FDA when they wave the banner of patient safety when making requests for information. Politically speaking, even if a company legitimately complains that FDA is requesting too much data and is not being Least Burdensome, FDA positions itself as the last line of defense for protecting patients. But more and more, data requirements come at the price of suppressing innovation. FDA's two fold mission is just not protecting patients; it is also speeding innovations that are beneficial to patients.

What You Can Do About This Trend

The Importance of Pushing Back Using Least Burdensome Requirements

You are still entitled to argue that the Agency's request for data is not Least Burdensome, despite the Agency's dismissive attitude toward this statutory requirement. We typically pushback on the Agency with Least Burdensome arguments as a foundation for our more detailed arguments. As is well known, Least Burdensome principles came into being during a similar time of political tumult in which industry felt FDA was continuing to mindlessly escalate data requirements simply because it felt it could. We must first note that when our firm discusses Least Burdensome, we do not refer to them as "principles" or "concepts." These are "requirements" because they are a creature of the statute. We confer the authority on them that they are due. This does not allow FDA to sigh or roll their eyes when the words Least Burdensome are uttered by a sponsor in an FDA/sponsor meeting.

It is Congress' attempt, at an overarching level, to direct the Agency to work very hard to minimize the requirements imposed upon a medical device manufacturer. ***It is supposed to be a counter to the natural institutional inclination of a government bureaucracy to continue to require more, when less will do.*** This is especially true for 510(k) devices where the starting point is substantial equivalence or sameness.

Congress took two cracks at Least Burdensome legislation and FDA seems to forget that fact. The first was when it enacted FDAMA in 1997 which included the first Least Burdensome provisions which require FDA to do the following:

> "Whenever the Secretary requests information to demonstrate that devices…are substantially equivalent, ***the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such requests, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly."***

Section 513(l)(1)(D) (emphasis in bold, italics and underlining added).

FDA then added its own interpretation of Least Burdensome in guidance as a "successful means of addressing a premarket issue that involves the most appropriate investment of time, effort and resources on the part of industry and FDA." See "*The Least Burdensome Provisions of the FDA Modernization Act of 1997; Concept and Principles; Final Guidance for FDA and Industry*" (October 4, 2002). But Congress did not have in mind "the most appropriate investment of time, effort and resources." Congress meant what it said, the "minimum necessary." To clarify the statute further and to address continuing concerns that the Agency had not paid enough attention to Least Burdensome requirements, Congress at the request of industry, enacted additional clarifying provisions under the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. FDASIA amended Section 513(i)(1)(D), (21 U.S.C. 360c(i)(1)(D), by adding definition to the word "necessary" in the statute to mean the following:

> (iii) For purposes of clause (ii), ***the term "necessary" means the minimum required information that would support a determination*** by the Secretary that an application provides reasonable assurance of the effectiveness of the device.
>
> (iv) Nothing in this subparagraph shall alter the criteria for evaluating an application for premarket approval of a device.

(Emphasis in bold, italics and underlining added).

So the statute now requires the "minimum required" instead of the "most appropriate" amount of information. The recent amendment was added for a reason and that is because FDA had, in the view of industry, continued to ignore and pay lip service to Least Burdensome requirements and despite protestations over the last eight years or so, has requested whatever amount and type of information FDA wants. This additional legislation puts a renewed spotlight on an issue that is very

important to medical device manufacturers. The problem is FDA knows it has an advantage in applying Least Burdensome requirements because it is hard for Congress to second-guess the Agency in its medical and scientific decision making. This amendment requires the Agency to honestly and actively police its own operations (and interpretations).

A note on clinical data requirements from FDA's guidance

As shown above, Least Burdensome guidance sets the stage when it comes to data requirements by engaging in several "presumptions" if you will that flow from the statute and the available guidance. The ***first presumption*** is the "minimum necessary" presumption. This is drawn directly from the statute. The ***second presumption*** is found in FDA's 2002 guidance, which the Agency has said remains consistent with its current thinking, is that clinical trials are **not** required for most 510(k)s. The 2002 guidance states as follows:

> ***Clinical data is not required for most 510(k)s. Consequently, the Agency should clearly document the issue that warrants a request for such data. In deciding how clinical data should be obtained, FDA and Industry should consider alternatives to randomized, controlled clinical trials***, as discussed above for PMAs, when potential bias associated for alternative controls can be addressed. Alternatives such as reliance on valid non-U.S. data, use of meta analyses, and trial designs employing non-concurrent controls such as historical controls (e.g. literature, patient records), OPC and patients as their own control should be considered to determine if they may be appropriately used.

See, *The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry*," (October 2002) (emphasis in bold, italics and underlining added). In practice today, this second presumption is at best an aspiration for the Agency but clearly fails in translation at the level of the staff reviewers whose default position is to require a clinical trial.

The FDA should not make requests for clinical data that are unnecessarily duplicative or where there are simpler means for obtaining them. In another part of FDA's Least Burdensome guidance, FDA acknowledges that there are times when it should be unnecessary to require data to be repeated. There should be some recognition that the past informs the future. FDA's guidance, "*Evidence Models for the Least Burdensome Means to Market* (September 1999)," in a quote drawn from Appendix 2 entitled "Reduction of Clinical Data—Examples," states the following:

> During the middle to late 1980's, data from bench testing and from clinical studies were needed to support substantial equivalence decisions for these

devices. ***As the familiarity with these devices increased, the reliance on clinical data for the substantial equivalence decision decreased***. There appeared to be a good correlation between the results of the various bench tests on the expandable metal stents and the clinical results observed in patient use for the specific Indication for Use of the palliative treatment of malignant biliary obstruction. This trend was observed in the first 10 submissions, and has continued to the present, with more than 40 cleared 510(k) submissions for expandable metal biliary stents. ***Currently, data from clinical studies are not required unless concerns regarding safety and effectiveness are raised by bench testing results that are significantly different from that observed for the predicate device***.

This example underscores the kind of common sense application of scientific principles which should be made by FDA. When a body of existing experience exists and industry tests have been developed that have been shown to be reliable, FDA should correspondingly need less clinical data and that clinical data need not be as rigorous as for a de novo or PMA.

Our firm has had great experience negotiating with FDA

Sometimes review staff must be told by upper management that the amount of data provided is adequate. We once had a reviewer and branch chief ask for a prospective 350 patient trial, only to have management on appeal agree to accept a completed European study of 32 patients, in addition to another 17 patients whose results had come in by the time discussions with FDA were completed. In another case, we had a review team request a 300 patient trial but we were able to negotiate a 92 patient retrospective chart review from three sites in Europe. In yet another case, we convinced the Director of the Office of Device Evaluation that a division's request for a trial of 150 patients was inappropriate given a minor modification to a device cleared two years earlier. The device was cleared without the additional clinical data.

How does a sponsor know when clinical trials will be required?

The short answer is you don't. But you can do some background checking to find out. ***The most difficult situation is when you search and find the predicates did not provide clinical data for clearance but you know the overall trend is for FDA to ask for such data***. In those situations the sponsor can choose to file its 510(k) without clinical data, but there is no guarantee that the FDA will not make a request for such data later. In these cases the sponsor is presumptive about its position that no clinical trials are required, and avoids conducting a trial, and instead conducts appropriate animal and bench data, and then submits to the Agency for clearance.

The problem with that strategy is if the FDA disagrees entirely with the quantum and quality of the data submitted, the sponsor may get a deficiency letter from FDA stating the need for clinical data. If the request is not overturned on appeal to upper management, a trial will be required and time will have been lost. The FDA will then make a request for Pre-Submission meeting (also known as a Q-Sub) so the parties can discuss what the clinical trial may look like. This is when FDA jumps on your development team and loves to dictate the particulars of the trial protocol—inclusion/ exclusion criteria, randomization, length of follow-up, and statistical analyses, etc.

When devices in the predicate family have conducted clinical trials, the sponsor can attempt to glean what its clinical trial might look like by reading the 510(k) summary on file with the Agency and "clinicaltrials.gov." Even then, however, FDA is constantly evolving its thinking and may want more or different data than what has been published in the past. So you are back to some degree of guess work.

Ultimately you are faced with the same choice, i.e. being presumptive in your position about what will be (should be) required and simply doing your trial and submitting it (and then holding your breath), or requesting a Pre-Submission meeting to dialogue about what FDA expects.

So the alternatives are either to do a clinical trial and hope that the study design and results are acceptable to FDA once the 510(k) is filed and reviewed, or the sponsor can proactively request a Pre-Submission meeting to ask upfront for FDA's input into a proposed clinical trial design. Any of these strategies have associated timelines which must be thought through as part of the regulatory strategy.

Clearly FDA is enamored with the Pre-Sub process and it has grown from being a once-in-awhile program for more difficult-to-pigeon-hole devices, to virtually being an expectation for most devices introducing any degree of novelty. Indeed, a Pre-Sub is very helpful in certain cases. We have a Client Alert on this topic on our website which is entitled "*The Pre-Sub Meeting and Gilligan's Island: When a Three Hour Tour Can Turn Into a Shipwreck*." In other cases, Pre-Subs have allowed FDA to play a much more intrusive and consultative role. FDA has become fond of requesting the data it finds interesting instead of determining whether the data actually provided by a sponsor are the data necessary to make a substantial equivalence determination according to the Least Burdensome requirements.

A note on non-clinical data requirements from FDA's guidance

Moving from the baseline expectation that the Agency shall engage in Least Burdensome requirements demanding only the minimum necessary information, we consider this standard in the context of non-clinical requirements. As is known, a 510(k) requires data of all kinds. Sponsors often hope to provide no clinical data, if truly not necessary to establish substantial equivalence, or the minimum necessary amount of clinical data, if required. But quite often the battle ground often includes a debate over the amount of other data (animal, bench, biocompatibility, sterilization, etc.) required for a submission. There are all sorts of demands for information the Agency may make with any given submission and it is important for the sponsor to know the contours of the law, regulations and FDA's own guidance so the manufacturer can push back if necessary. We share a few of the more common requests here.

Frequently FDA will request data that will meet a futuristic industry standard (e.g., ANSI, AAMI or ISO, etc.) or guidance document that is still in draft form and has not yet been finalized. FDA has a particular penchant for requiring a sponsor to meet a future, yet-to-be adopted standard, **after** the sponsor has already conducted testing under the current (soon-to-be old) standard, even when the current standard is the version "recognized" by FDA. Sponsors must push back on these attempts, and not acquiesce to and encourage such behavior. FDA frequently backs down as these requests are premature and inappropriate, but if they can get away with it they will try. We know, however, that the practicality is that sometimes it is easier, less costly and faster to simply accommodate these requests.

Not infrequently FDA will ask for more animal data after clinical data have been provided. This seems ridiculous to most. For example, a company may have done a small animal study or no animal study at all, but they have developed European clinical data. FDA veterinarians, operating within their own silo, can and often do ask for more animal data. Normally, the point of animal data is to avoid unnecessary human experimentation. Animal data is always a surrogate for human data. But if human testing has already been developed, there is little justification for going backwards and requesting more animal data. Leave it to the U.S. FDA to entertain such backward thinking. Sponsors should push back on such duplicative, unnecessary, and at times unethical requests (i.e. sacrificing more animals than necessary).

FDA may also make requests for data that are not even relevant to a substantial equivalence determination. FDA's own Least Burdensome guidance encourages a sponsor to push back and point it out to the Agency. The FDA in applying Least Burdensome requirements has provided industry with guidance for developing and responding to deficiencies cited by FDA. It encourages industry to push back when

FDA attempts to require information that is not related to the SE decision. FDA states the following in directing the sponsor's response to FDA:

> ***If the sponsor believes that the request is not relevant to the regulatory decision being made, the sponsor should explain why***. If a legally marketed predicate is available to support this argument, the sponsor should also reference the 510(k) predicate.
>
> Finally, in formulating its response, the sponsor may consider suggesting alternate approaches to optimize the time, effort and cost of reaching resolution for the issue within the law and regulations. This could include alternative types of bench testing, proposing non-clinical testing in lieu of clinical testing, the use of standards, etc. ***It should be noted, however, that whatever approach is taken to address the issue, only information relevant to the decision should be provided***. (Emphasis added).

See "*Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA; Final Guidance for Industry and FDA Staff*," (November 2, 2000) at page 5. [This guidance has been finalized without this precise quote, but the underlying import remains. See, "*Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions*" (September 29, 2017).]

Another portion of FDA's guidance document is even more specific about the attempted application of matters/issues irrelevant to a SE decision. The guidance also discusses the inappropriate use of extraneous statutes or regulations in making a SE determination such as submitting testing to demonstrate compliance with OSHA standards or even QSR requirements. FDA's guidance states:

> ***FDA should avoid using the premarket review to ensure compliance with FDA statutes or regulations unrelated to the regulatory decision (e.g. Radiation Control for Health and Safety Act (RCHSA))***. Similarly, verifying compliance with laws and regulations administered by other federal agencies (e.g. Occupational Safety and Health Administration (OSHA)) should not generally be part of the substantial equivalence or approval decision.
>
> ...
>
> ***FDA reviewers should avoid focusing their efforts on ensuring compliance with FDA statutes or regulations unrelated to premarket decisions***. For example, consider the Quality Systems regulation. GMP issues should not affect substantial equivalence determinations in accordance with the new

provisions of FDAMA. Under section 513(f)(5) of the act, FDA may not withhold a 510(k) determination because of a failure to comply with any provision of the act unrelated to a SE decision, including a finding that the facility in which the device is manufactured is not in compliance with GMPs (other than a finding that there is substantial likelihood that the failure to comply will potentially present a serious risk to human health).

See "*The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles: Final Guidance for FDA and Industry*," (October 4, 2002) at pages 6 and 20.

The Agency is also supposed to allow signing declarations of conformity to certain kinds of testing rather than submitting the test results themselves. The idea is reduce the burden on both sides of supplying and reviewing too much data. In FDA's guidance, "*The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry*" (October 4, 2002), FDA explicitly states the following in Hyperlink #6 (emphasis in bold and italics added):

> **Hyperlink #6**
>
> FDA has recognized over 600 voluntary consensus standards. (For a searchable database of standards, see CDRH's Standards Program.) Some of these standards relate to individual products while others address crosscutting issues such as electrical safety, sterilization, and biocompatibility. For example, CDRH has recognized 28 voluntary consensus standards that address numerous aspects of wheelchair performance. While most wheelchairs are Class II devices, many of these standards are applicable to the Class III stair climbing wheelchairs. Other device-specific standards include the ISO standards for heart valves and vascular grafts and the NCCLS standards that apply to most in vitro diagnostic devices. Cross-cutting standards, such as the IEC electrical safety and ISO sterilization standards, apply to numerous device types reviewed by the Center. ***Declarations of conformity to standards that identify test methods can reduce the detail needed in PMA submissions and eliminate FDA review of test procedures. Use of those standards that have performance criteria can further reduce data reporting requirements in the application and save review time.***

The bottom line is keep FDA honest in its requests for information; keep your eyes fixed on what is required to establish the substantial equivalence, and try to ensure it is the Least Burdensome, i.e. the minimum necessary amount of information.

Some encouraging developments—Real World Evidence

FDA recently has published a guidance document which should be encouraging to industry in that it promotes the use of real world evidence using real world data to be considered in a submission. See "*Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*," (August 31, 2017). The idea behind this new guidance is to clarify how FDA will evaluate real-world data (RWD) to determine whether they are sufficient for generating the types of real-world evidence (RWE) that can be used in FDA regulatory decision-making for medical devices.

The use of RWE should allow the use of retrospectively collected data to replace prospective randomized controlled trials or at least make reduce the size and longevity of clinical trials. We have had some very encouraging discussions with FDA on this front and we consider it well aligned with Least Burdensome requirements. FDA's primary concern is that the collection of data is prospectively designed to eliminate bias and produce the most reliable, consistent and interpretable data possible. The jury is still out on this topic, but this is the one of the most encouraging initiatives the Agency has in the works. It has the potential to dramatically reduce the burden of large clinical trials (especially randomized and with long follow-up) on manufacturers.

Some encouraging developments—Data Exclusivity

In the PMA world, FDA actually has statutory authority to approve a new PMA device that is essentially the same as the previously approved products, by relying on data from the previously approved product. FDA has published a guidance document which allows data already developed within a given device segment to be employed by a sponsor seeking approval. See "*Guidance on Section 216 of the Food and Drug Modernization Act of 1997*" (August 9, 2000). We call these generic or "Paper" PMAs. That concept is essentially in line with Least Burdensome requirements and it is being applied to well-known, well-characterized Class III devices. If this kind of thinking makes sense for PMA devices, it should make even more sense for 510(k) devices where we are attempting to establish sameness and recognize the vast amount of information that is the background for any predicate. In other words, the 510(k) program lends itself more readily to this kind of thinking and analysis than the PMA program, yet FDA continues to make the 510(k) program more and more complex, unnecessarily so. ***The Agency should re-calibrate its 510(k) data expectations in light of the Section 216 of FDAMA and what the Agency has done and is doing with "generic" PMAs.***

Conclusion

FDA's mindset must be on whether the data set submitted supports the proposition for which it is offered, i.e. does it demonstrate the device is as safe and effective as the predicate? This is done by knowing the underlying predicate family already enjoys the regulatory presumption that the predicates are safe, effective and have clinical utility. FDA sometimes focuses on how big and powerful and extensive the (Frankenstein) data set can be, without regard to the more limited standard before it. If FDA wants to, it can fashion solutions that will expedite innovations to the market without harming patients or the medical device ecosystem that brings them to market. Our idea is to embolden you to challenge the Agency and to equip you with some arguments to be made to FDA. This will prepare you for a better outcome than simply having FDA dictate the clinical and non-clinical data needed to establish substantial equivalence.

CALL ON US FOR ASSISTANCE WITH YOUR REGULATORY NEEDS

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 Global Fortune 500 to small ups that market and manufacture medical devices, pharmaceuticals, biologics, nutritional supplements and foods. 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. 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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