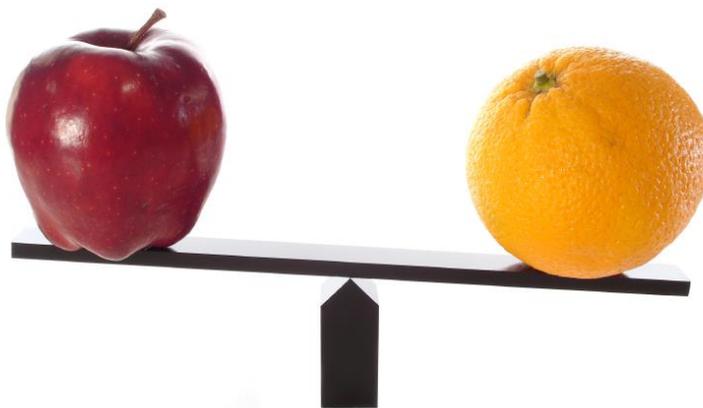


DuVAL CLIENT ALERT

Passing on Tribal Knowledge of FDA Law

The 3rd Client Alert in Our Series on 510(k)s



Choosing the Proper Predicate Device(s): *Comparing Apples to Oranges*

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 born out of our experience in counseling clients on how to ensure their 510(k) is an advocacy document that garners the clearance they seek. Our first Client Alert in the series described how to withstand FDA's Refuse to Accept (RTA) review. In this Client Alert, we share our tribal knowledge for choosing and advocating your choice of a predicate device. Later in our series, we will share insights from our negotiations with the Agency on such matters as whether a device 1) has the same intended use, 2) has the same technological characteristics, or 3) raises different questions of safety and effectiveness in comparison to the predicate device. We share what not to do when depicting your device in a submission and how to persuade FDA to your position. We also discuss the

quantum and quality of data that should be submitted for clearance and where to push back on the Agency.

EXECUTIVE SUMMARY

One of the key choices for staying on the premarket notification (“510(k)”) pathway is choosing the right predicate device(s). In 2011, FDA conducted a review of its “Not Substantially Equivalent” (“NSE”) determinations from 2005-2010 and found that lack of a “suitable predicate” was one of the top four reasons for NSE determinations.¹ As you know, a 510(k) needs to demonstrate that the new device to be marketed is “substantially equivalent” to a legally marketed device (“predicate device”). To be declared “substantially equivalent,” the new device must have (1) the same intended use as the predicate device, and (2) the same technological characteristics as the predicate device or (b) have different technological characteristics but show that the differences do not raise different questions of safety and effectiveness from the predicate device. Choosing the right predicate device is one of the (if not **the**) most important components in a 510(k) strategy; choosing incorrectly can mean that more time, effort and resources are needed to clear your device, and moreover, it can put your clearance at risk. And sponsors need to know upfront that FDA does not always agree with a chosen predicate or may suggest that the sponsor must have only one predicate and is not entitled to multiple predicates. Additionally, the review staff may or may not understand or embrace the appropriate role for “reference devices.” We explain these to you in this **Client Alert**.

Choosing Your Predicate Device(s)

Know the framework for selecting a predicate device.

Nearly any legally marketed device can serve as a predicate device. Per 21 CFR 807.92(a)(3), a predicate device can be one which was legally marketed before the enactment of the Medical Device Amendments of 1976, was reclassified from III to II or I, or was previously cleared through the 510(k) process. There are a few key things to note about this. First, this means that a predicate device cannot be a device that was approved as a Premarket Approval (PMA). Second, a predicate device can be a

¹ FDA, “Initial Results of 510(k) Audit - Analysis of Not Substantially Equivalent (NSE) Determinations” (June 15, 2011) at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM447401.pdf>.

device that has been cleared, but is no longer marketed (or never marketed). Although a predicate device can be an older cleared device that is no longer sold, we advise clients to use caution when using such older devices. Please see below in the section entitled “**Be Wary of Older Devices.**”

Be strategic about differences in technology.

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 own words, “it is rare for a new device to be identical to a predicate device.”² The 510(k) standard provides 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.”³

Although the basic requirements for 510(k) content apply to all 510(k)s, the type of data and information necessary to establish substantial equivalence varies by the type of device and the differences between the new device and the predicate device.

Stay tuned for the Client Alert on [Technological Differences in Your 510\(k\)](#) which will be featured later on in this series of Client Alerts on 510(k)s.

Identify a primary predicate device if multiple predicate devices are used.

FDA recommends that submissions identify the *primary predicate* when more than one predicate device is cited in a 510(k). The primary predicate will be the predicate device with the most similar intended use and technological characteristics as the new device. This helps FDA hone in on one predicate for analytical purposes, but does not preclude the use of multiple predicates when the sponsor is attempting to expand the intended use statement (or indications), provided, however, the core intended use remains the same. Frankly we are not entirely sure why FDA really wants a company to select a primary predicate when it accepts multiple predicates. But there are areas where FDA seems to acknowledge multiple predicates but then proceeds down an analytical path that focuses in only on the primary predicate (we believe inappropriately so). For example, FDA sometimes argues that the subject device must not raise different questions of safety and effectiveness in comparison to

² See “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]: Guidance for Industry and Food and Drug Administration Staff” at page 6.

³ Id.

the primary predicate, when, indeed, the sponsor must demonstrate the subject device must not raise different questions of safety and effectiveness in comparison to the multiple predicates chosen. Stated another way, there may be instances in which a subject device “raises a different question of safety and effectiveness” in comparison to the predicate device, but the subject device may not raise a different question of safety and effectiveness when considering a second or third (multiple) predicate. So, in effect, the FDA takes away what it appears to give. By focusing in on the only the primary predicate, the FDA can use analysis like this to bounce the subject device off the 510(k) path even though these are not different questions of safety and effectiveness when considering the other (multiple) predicates. This kind of analytical misinterpretation of the 510(k) program undermines the very idea that multiple predicates are permissible and can accommodate technological innovation.

Do not use split predicates.

The FDA guidance, “[The 510\(k\) Program: Evaluating Substantial Equivalence in Premarket Notifications \[510\(k\)\]](#)”⁴ (“[510\(k\) Guidance](#)”), indicates that the 510(k) regulatory standard does not permit the use of *split predicates*. A split predicate is where one predicate device is used to demonstrate with the same intended use and another predicate device is used to demonstrate the same technological characteristics. When multiple predicates are cited, *each identified predicate device must have the same intended use*. Technological differences are allowed but only if they achieve the same intended use. Also, a primary predicate device should generally be identified to facilitate the FDA review of a 510(k) with multiple predicate devices.

As stated above FDA will allow for differences in technological characteristics as long as the intended use is the same. We agree with the Agency on this call: if both the intended use and technological characteristics are different, it would be an inappropriate stretch to allow such a device to proceed down the 510(k) path.

Use multiple predicates, if it makes sense.

A 510(k) may identify multiple predicate devices. Multiple predicates can be used when the submitter wants to combine features from multiple predicate devices

⁴ FDA, “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]: Guidance for Industry and Food and Drug Administration Staff” (July 28, 2014), <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf>.

without altering the (1) intended use and/or (2) risk profile relative to the predicate devices. Multiple predicates can also be used to create an amalgamated intended use statement that bears language from two different predicates as long as they are consistent with the overall intended use of the device. The guidance even allows a sponsor to combine two disparate technologies for the convenience of the user as long as it does not alter the risk profile relative to each device (see the FDA example below).

The [510\(k\) Guidance](#) indicates that “FDA encourages manufacturers to identify a single predicate device to simplify and facilitate the decision-making process.” However, the 510(k) process does allow for multiple predicate devices if your 510(k) strategy can meet the criteria for using multiple predicates in the guidance. When identifying multiple predicate devices, the predicate devices and new device must have the same intended use, and the predicate devices, when combined, should not raise new risk factors that alter the safety profile of the new device so that a substantial equivalence comparison cannot be made.

The [510\(k\) Guidance](#) provides several examples where multiple predicates are used effectively. For example, Multiple Predicates Example 5 shows how features from multiple predicate devices can be combined for convenience, *even where such added features fall under a different classification regulation*.

Multiple Predicates Example 5:

A manufacturer submits a 510(k) for a urinary catheter with a thermometer. The thermometer/temperature-measuring feature is not affecting the intended use or risks of using the catheter (assuming it is integrated appropriately), nor is the catheter affecting the performance or risk profile of the thermometer. **The temperature-measuring feature is a convenience component that is added to the catheter, with the intended use of the device still being that of the catheter to pass fluids to or from the urinary tract, so it is appropriate to have a legally marketed catheter serving as the primary predicate.**⁵ (Emphasis added.)

Use of multiple predicates may require new performance testing. Nevertheless, multiple predicates can be used so long as it does not alter the intended use of the new device or risk profile relative to the predicate devices.

Be aware that FDA review staff may fight this criterion and tell a sponsor it they cannot have multiple predicates or they cannot combine multiple

⁵ See “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]: Guidance for Industry and Food and Drug Administration Staff” at page 13.

predicates with different functionality (or different classifications). This is inappropriate. We have many times pushed back and convinced FDA that our clients' combination of technologies is an appropriate combination of technologies and we have overcome review staff objections. This has allowed our client to proceed down the 510(k) path. FDA will also sometimes argue that an amalgam of intended use or indications statements from devices having essentially the same intended use statement is inappropriate. We often fight and win those arguments as well. It is important to anticipate and consider making those arguments preemptively in a 510(k) submission or in your Pre-Submission documents. It can be a more difficult argument to make after a reviewer has staked out a contrary opinion because institutional inertia often sets in with the reviewer and the first level of management, i.e. the Branch Chief.

Use reference devices to address differences in technological characteristics where FDA has seen the same issues of safety and/or effectiveness before.

FDA has vast institutional knowledge to draw upon in reviewing devices from every therapeutic segment. It makes sense for FDA to draw profitably from this experience in reviewing new technologies. Even when a device has different technological characteristics, because it has employed a new material or a new approach to resolving an issue in a different therapeutic context, that new material or approach may not be entirely new to FDA. For example the use of nitinol in stents in the peripheral and coronary vasculature has become ubiquitous. When nitinol was used as an orthopedic implant for distal radius fractures (in the wrist), it had never been used in that manner before. There was not a predicate device that had used nitinol in an orthopedic implant. FDA borrowed from its existing knowledge of nitinol in stents to clear its use in an orthopedic implant. FDA found the technological characteristics were the same and the nitinol device did not raise different questions of safety and effectiveness, e.g. biocompatibility, tensile strength, etc. The reference devices help the FDA get there analytically. Even with this new use being acceptable under the framework of the 510(k) program, FDA still rightfully asked for data to ensure the device was substantially equivalent in performance to its chosen predicates.

Essentially, a reference device allows FDA to use its experience with other devices. Reference devices do not serve as predicate devices because of differences in intended use and/or technological characteristics, but they are meaningful nonetheless because they have technological similarities to the new device. Citing

reference devices in the 510(k) can bridge the gap in differences between a subject and predicate device.

Be wary of older devices.

Almost all 510(k) submissions claim substantial equivalence to a medical device that has been recently cleared under the 510(k) process. There are good reasons for that. The FDA seems to have a general disdain for the data that has been developed (or more aptly put, has not been developed) for predicate families. FDA believes older devices do not have adequate data supporting their original clearance. Rightly or wrongly, new 510(k) submitters are being asked for data to bridge that data gap. FDA in the last seven years or so has been asking new 510(k) applicants to provide data on 510(k)s where none was previously required. FDA asks for new and better data when it can to update the dossier, if you will, for these predicate families.

In addition, there can be a general lack of information available about an older predicate device. There is always the option of obtaining a redacted copy of the predicate device's 510(k) submission through a Freedom of Information Act (FOIA) request, but that is not always ideal. It takes months - and sometimes up to a couple of years - for a 510(k) to be requested via FOIA, and sometimes so little information was required or so much information has been redacted from the cleared 510(k) that there is very little meaningful information to be gleaned.

Finally, it is also likely that the older devices are no longer on the market, thus making it difficult (if not impossible) to have a predicate device available to test. This is important for a 510(k) where predicate device data may be needed to support the acceptance criteria used for the performance testing on the new device. In addition, for devices that are no longer on the market, it is sometimes important to understand why that device is no longer on the market. Was there a safety, manufacturing, or some other type of issue? If that is the case, then these types of issues ideally would be addressed upfront in a 510(k) submission before FDA points it out to the applicant in an Additional Information (AI) letter .

Advocating for Your Predicate Device(s)

From an overarching perspective, there are several things to keep in mind if and when you need to advocate for your chosen predicate device(s). ***First***, the 510(k) process engages in a ***regulatory presumption*** that each applicant should not be required to reprove over and over again what is already known about the underlying safety and effectiveness of the predicate device(s), its material properties, biocompatibility,

mechanical performance, its application and value to the medical community, etc. The regulatory presumption acknowledges that the underlying predicate device has been deemed safe and effective for its labeled intended use and has clinical utility. The regulatory presumption also acknowledges that the predicate family has demonstrated the underlying safety and effectiveness of the technological approach and the applicant need not reprove what is known or knowable.

The applicant need only demonstrate it has not diminished safety and effectiveness **in comparison** to the predicate. In this manner, the 510(k) program is sufficiently flexible to accommodate incremental technological changes in technology. What this means is that if you choose a predicate device with the same or a similar technological approach as the subject device (assuming that both have the same intended use), then your 510(k) should not require extensive data to demonstrate safety and effectiveness in an absolute sense, as with a PMA. With a 510(k) device, the safety and effectiveness of the underlying technological approach has been established. The sponsor must simply show its device is at least as safe and effective as the predicate. The sponsor simply demonstrates the subject device's "sameness" to the predicate.

Second, today's FDA Administration sometimes treats incremental technological innovation, i.e. differences between the new subject device and the predicate device, as if they do not belong on the 510(k) pathway. The irony is that the 510(k) program is designed to be sufficiently flexible to accommodate technological innovation. The substantial equivalence standard anticipates, even expects, that there may be differences between the new device and the predicate(s). When there are differences, you must simply demonstrate that those differences do not raise different questions of safety and effectiveness. Technological differences are an expected part of the 510(k) program, so be confident in defending your chosen predicate if you can demonstrate that it fits in the 510(k) pathway.

Third, it is your job to tell your story, to convey why your device has a predicate. This is the art of advocacy. Don't treat your submission like it is simply an evidentiary document where the data need to be cut and pasted into a format provided in an FDA guidance document. The 510(k) is an advocacy document and you need to anticipate where your submission may get derailed if you don't think through your arguments.

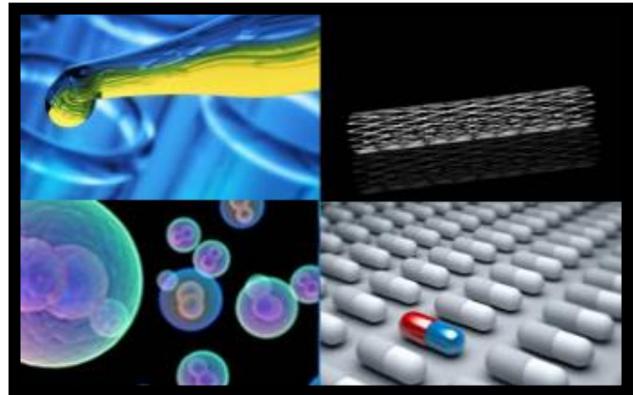
Need Assistance with Your 510(k)?

Do you need help identifying the best predicate device(s) or advocating to FDA about the appropriateness of your chosen predicate device(s)? Our firm routinely engages with clients regarding medical device submissions, including advising on

regulatory strategy, counseling on regulatory and FDA matters, and providing general assistance with 510(k) submissions and Pre-Submissions. Watch for the next **Client Alert** in our series on 510(k) submissions. If you have any questions or would like more information about how we can help you with your 510(k), please contact us at duval@duvalfdalaw.com or by phone at (612) 338-7170.

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