DuVal Client Alert

Passing on Tribal Knowledge of FDA Law

The 4th Client Alert in Our Series on 510(k)s

Clearing Your Indications for Use:

Staying Under the Umbrella of Intended Use

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 that garners the clearance they seek. 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" **Click here**;

- 2nd—"Seven Quick Tips for Successful 510(k) Submissions--do you need our help with your next submission?" **Click here**; and
- 3rd—"Choosing the Proper Predicate Device(s): Comparing Apples to Oranges" **Click here**.

In this Client Alert, we share our tribal knowledge for identifying the indications for use that fall under the umbrella of the intended use for your chosen predicate device, thus keeping you on the pathway for clearance. Later in our series, we will share insights from our negotiations with the Agency on such matters as whether a device has the same technological characteristics or 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

Beware that FDA frequently interprets the definition of "general versus specific intended use" so narrowly that FDA often considers new indications for a 510(k) device to be a new intended use. This is in contravention of the specific intent of the Congress. When making a 510(k) submission, the FDA will often "play" with the definitions to define a sponsor's subject device in a manner that takes it off the 510(k) path. That is why it is critical for the sponsor to thoroughly understand the 510(k) substantial equivalence definition criterion, as well as FDA's guidance documents so the sponsor can make arguments that ensure each definitional criterion is met. Otherwise the subject device is headed for the de novo or PMA path, and more time and expense.

The very first definitional criterion that must be satisfied is whether the subject device has the same "intended use" as the predicate device. FDA today often takes advantage of this seminal criterion to issue a Not Substantially Equivalent (NSE) determination, concluding that the subject device does not have the same intended use as the predicate device. FDA will often conclude that specific indications do not fall under the general intended use statement or that the general intended use statement is simply broader than or different from the predicate. FDA will also argue that a company cannot create an amalgam of intended use statements from multiple predicates when you can. But FDA's own guidance documents allow for variances in labeling.

FDA's guidance documents do a fair job of setting forth the flexibility with which the 510(k) program is to be interpreted, i.e. to allow for variations in labeling to allow for

broader application of the device. The problem is that without specific indications, a device with a general intended use statement is seemingly cleared for everything (relatively speaking), but can be used for nothing.

The first element of substantial equivalence requires the new device to have the same intended use as the predicate device. The ***intended use*** is the general purpose of the device or what the device does. But having an intended use often does not tell a medical professional specifically where the device may be used and in what patient population. ***Indications for use*** are subsidiary to and fall under the umbrella of the general intended use statement. For years industry went without these terms being defined. FDA has now defined the indications for use as labeling that discusses the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population.

To stay on the 510(k) path, it is critical to persuade FDA that your chosen indications for use fall under the umbrella of your chosen intended use statement. If they do not, the subject device will be found NSE.

In this Client Alert, we distill a couple FDA guidance documents: "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]"[1] ("510(k) Guidance") and "General/Specific Intended Use"[2] ("General/Specific Use Guidance"). We first examine the definitions of intended use and indications for use from FDA guidance. We then show examples of when FDA found indications for use to fall under the intended use and were found substantially equivalent and some example where they were found not substantially equivalent to the predicate devices. Lastly, we provide some tips for crafting an indication for use that keeps you under the umbrella of the cleared use for your chosen predicate device.

Parsing Out Where FDA Stands

Defining Intended Use and Indications for Use.

A new device cannot be substantially equivalent to a predicate device unless it has the same intended use. The definitions for intended use and indications for use have frequently been a confusing point for industry. When we teach industry on what are "indications" in relationship to a general "intended use" statement cleared by FDA,

[1] FDA, "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" (issued July 28, 2014).
[2] FDA, "General/Specific Intended Use" (issued November 4, 1998).

we use the analogy of an umbrella. The intended use describes the overall purpose of the device, and is the umbrella under which you find the distinct indications for use. Indications fall under the protective reach of the umbrella and are deemed on-label. Some indications fall outside of the protective reach of the umbrella, exposed to the elements, and are deemed off-label. ***Without specifically stated indications, the device could often be used for everything and yet nothing***. Ironically, FDA seems to find it perfectly acceptable if a company promotes a device in some impractical, overly broad, general way in which that device can be used without getting specific. The idea is that a generally cleared device has to be used somewhere and specific indication statements can tell physicians where.

In the 510(k) Guidance, FDA defines ***intended use*** as "the general purpose of the device or its function, and encompass the indications for use."[3] The Guidance also describes ***indications for use*** as "the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended."[4] In short, the intended use is meant to be the umbrella claim stating an overall purpose for the device, and the indications are a collection of specific uses to which this device may be used.

For many medical devices, the indication for use and intended use are the same because they have a combined general intended use/indication for use that does "not specify a disease, condition, or population (or an anatomical site from which a disease state or population may be inferred)."[5] The 510(k) Guidance describes these types of indications for use as "tool type" indications, as opposed to ***specific indications*** for use with treatment indications. The Guidance offers examples of devices with "tool type" indications, such as scalpels for cutting tissues, and imaging devices for taking images of the body. The Guidance also points out that devices with general (not specific) indications for use can nonetheless serve as predicates for devices with a specific indication for use. For example, a scalpel that is indicated for removing certain types of cancerous cells (identifying a disease, condition, or population) has a specific indication for use. Not all changes in indications for use between the new device and the predicate device will result in a new intended use.

The following section, **When a New Indication for Use Constitutes a New Intended Use**, distills FDA's guidance for assessing whether such changes between indications create a new intended use.

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[3] The regulatory definition for "intended use" for medical devices can be found at 21 C.F.R. 801.4.
[4] The regulatory definition of "indications for use" for medical devices can be found at 21 C.F.R. 801
[5] See "510(k) Guidance" at page 16.

When a New Indications for Use Constitutes a New Intended Use.

A new device can have a new indication for use that fits within the predicate device's cleared intended use. The key determinant is whether the new indications for use do not raise different questions of safety and effectives in comparison to the predicate device. FDA's General/Specific Use Guidance is especially helpful in deciding when a proposed labeling change falls under the current general intended use statement for its device. In this guidance, FDA lists the two levels of analyses – "Levels of Specificity" and "Decision-Making" – for determining whether a claim being sought fits within the general intended use statement, or if such a claim changes the intended use. We discuss the "Levels of Specificity" and "Decision Making Criteria" below.

Let's start with the criteria for ***levels of specificity*** for ***therapeutic*** devices[6]:

Levels of Specificity.

1. Identification of function (e.g., cut);
2. Identification of tissue type (e.g., soft tissues);
3. Identification of an organ system (e.g., GI tract) or Identification of a specific organ (e.g. liver);
4. Identification of a particular disease entity (e.g., resection of hepatic metastases) or target population; or
5. Identification of an effect on clinical outcome (e.g., use of medical device improves the rate of durable complete remissions with chemotherapy)

An example of this is a device that ablates soft tissue. When a claim is made for ablating cardiac tissue, the level of specificity has moved from Level 1 to Level 2 making it possible FDA could argue that the intended use has changed. If this device were then claimed to treat atrial fibrillation, the level of specificity has moved from Level 1 to Level 4 making it likely FDA could argue that the intended use has changed. Generally when a new device's indications of use is more specific than the predicate device's indications for use, both devices share the same intended use if no new questions of safety or effectiveness are raised.

For making that determination, FDA moves from the ***levels of specificity*** to its ***decision-making criteria*** to determine if a new device has changed the intended use. The criteria that follow, in connection with the levels of specificity above, are the guidance for FDA's decision-making process for determining whether a new device's indications for use constitutes a new intended use (leading to NSE). Per the General/Specific Use Guidance:

[6] See the General/Specific Intended Guidance for Levels of Specificity for diagnostic medical devices.

"[t]he list of criteria should not be considered to be all-inclusive. Nor should the list be viewed as a scale which can be used to calculate a particular outcome. Rather, these criteria should be seen as important contributing factors, which, when used appropriately, can help the agency consistently arrive at reasonable regulatory decisions that relate to the safety and effectiveness of medical devices."

Decision-Making Criteria.

1. ***Risk***- Does a specific use introduce new risks not normally associated with the general use of the device?
2. ***Public Health Impact***- Does a specific use impact public health to a significantly greater degree than the general use of the device? Differences in public health impact can result from changes in target population. These changes may have quantitative dimensions, but routinely will also affect safety and effectiveness because of major qualitative differences in how the device is to be used (e.g. diagnosis vs. screening, cutting soft tissue vs. treating breast cancer).
3. ***Knowledge base***- Is there a body of evidence available to the agency regarding a proposed specific use that reflects existing understanding by the medical community that the more specific use is a subset of the general use, rather than a new intended use? That evidence can be derived from such sources as the medical literature and practice guidelines.
4. ***Endpoints***- To what degree can the performance or clinical endpoints (e.g., ability to ablate tissue; prevention of STDs) used to evaluate the general use be applied to the specific use?
5. ***Tool or treatment?***- To what degree is the device used by the physician intended to perform a task (e.g., a scalpel) as opposed to "being" the treatment (e.g., extra corporeal shock wave lithotripter)?
6. ***Adjunctive therapy***- To what degree does another product not routinely needed for the general use need to be used in conjunction with the device to achieve the specific use safely and effectively?
7. ***Design changes***- To what extent does a modification to a medical device to facilitate the specific use render it less applicable to the other aspects of the general use?

Use these factors to justifying why your new indications for use for your device falls under the umbrella of your predicate device's intended use.

The following examples, quoted from the General/Specific Use Guidance, illustrate FDA's assessment within the 510(k) framework when it comes to new devices with

new specific indications for use. These illustrations are useful for understanding how you can use the framework to assess and justify your position (see also Tip Five below).

Examples of specific indications for uses that ordinarily fall within a general use.[7]

Example 2 **IgG Assay for H. pylori**

General indication for use: identify known or suspected peptic ulcer patients with H. pylori
Specific indication for use: identify known or suspected pediatric peptic ulcer patients with H. Pylori
Determination: SE
Major criteria:

- Risks: There is no evidence that the risk profile for the specific indication for use will be substantially different from that of the general indication for use.
- Knowledge base: A significant body of knowledge is available regarding the use of this test in different age groups.

Example Explanation: This example highlights an indications for use that specifies a narrow target population within a broader population.

Example 4 **Diagnostic Ultrasound**

General indication for use: Evaluation of soft tissue
Specific indication for use: Discrimination of small soft tissue parts (e.g., tendons, nerves)
Determination: SE
Major criteria:

- Risk: The specific indication for use adds no significant risk to the general indication for use.
- Level of specificity: The specific indication for use is simply a statement of the types of anatomical detail that can be evaluated with improved ultrasound technology. It would, therefore, constitute a minimum change in levels of specificity, as defined above.

Example Explanation: This example highlights an indications for use that specifies a particular anatomic site or tissue type that does not imply diagnosis or therapy of a specific disease entity.

[7] See "General/Specific Use Guidance" at pages 7-10.

Example 7 **Percutaneous vascular catheters**

General indication for use: Provide access to vasculature for diagnosis/therapy

Specific indication for use: Provide access to neurovasculature for diagnosis/therapy

Determination: SE

Major criteria:

- Risks: The safety and effectiveness of the device are related to size, shape, flexibility, and biocompatibility for both sets of indications.
- Knowledge base: There is extensive clinical data on the use of these types of catheters in the neurovasculature as well as other vasculature.

Example Explanation: This example highlights an indications for use that specifies a sub-specialty of a particular clinical discipline where the types of treatments or procedures are similar. This example also highlights an indications for use for which a considerable body of knowledge or experience exists to demonstrate that the specific use falls within accepted parameters for the general use of the device, as defined by the clinical community.

Examples of specific indications for use that ordinarily fall outside a general use.[8]

Example 3 **Diagnostic Ultrasound**

General indication for use: Evaluation of soft tissue

Specific indication for use: Aid in differentiation of benign from malignant breast lesions

Determination: NSE

Major criteria:

- Risk: The risk of false negative studies leading to postponement of breast biopsy is far greater than the risk of false negatives in general ultrasound studies.
- Public health impact- Because breast cancer is a leading cause of morbidity and mortality in US women, any change in the management paradigm for suspicious lesions may have a profound impact on public health.
- Level of specificity: The change from a general use (evaluating soft tissue) to a specific recommendation to biopsy or not to biopsy is a

[8] See "General/Specific Use Guidance" at pages 8-9.

significant change. The new indication for use established a use that is qualitatively different from other indications for ultrasound.

Example Explanation: This example highlights an indications for use that provides a new type of diagnostic information or therapeutic option that significantly impacts patient management.

Example 6 **Radiofrequency devices in urology**

General indication for use: Ablation of soft tissue in urology
Specific indication for use: Treatment of prostate cancer
Determination: NSE
Major criteria:

- Endpoints: The clinical endpoint for this indication for use is the patient's health status during management of prostate cancer as opposed to ablation of urological tissue.
- Risk: The manner in which this device is being used for this indication for use is a significant change in the standard of care for treatment of localized prostate cancer. This change creates risks not associated with the general indication for use.
- Public health impact: Because prostate cancer is a common and lethal cancer in men, a device cleared for treatment of that disease would have a significant public health impact.

Example Explanation: This example highlights a specific indications for use that presumes a specific clinical outcome, especially when that outcome could influence patient management outside standard practice.

Some Tips for your 510(k) Submission

Tip One: Ensure the device claim is substantiated and remains a "tool" claim and not a "treatment" claim.

If this applies to your device, understand that FDA understandably clears devices with a general umbrella claim that it can be used for a general intended use such as a device for soft tissue ablation. FDA often reviews devices that are "tools" for general use, versus "treatments" per se. When, for example, a manufacturer decides to claim a device cleared for soft tissue ablation can be used in cardiac ablation that is simply a specific anatomic location in which the "tool" may be used and still be within the general intended use. Cardiac tissue is soft tissue and if a physician were to be so inclined to ablate cardiac tissue with this device, nothing should prevent that from

happening because FDA deems it an off-label use. When a claim is made that the same device can be used to treat atrial fibrillation, FDA is concerned that the claim for safe and efficacious use is unsubstantiated. FDA under its guidance calls these "therapeutic" or "treatment" claims. So an ablation device can be used to ablate cardiac tissue but cannot be claimed for use in treating atrial fibrillation.

The same is true of a device cleared for surgical aspiration device being used for liposuction. The general intended use statement for aspiration does not contemplate use for liposuction. In this case, the "tool" becomes the "treatment." Similarly, think of a device used to safely remove salt and water from fluid-overloaded patients, similar to a dialysis machine. How does a manufacturer sell that device if they cannot describe the type of patients who might benefit from this use? If the manufacturer claims this device treats congestive heart failure, FDA might justifiably argue the tool has become the treatment. But if the manufacturer simply claims the device removes fluid from fluid-overloaded patients who present themselves with such etiologies such as severe burns, renal failure, congestive heart failure, among other maladies, the tool remains a tool. But the labeling now describes the types of patients who may benefit from this tool.

So make a tool claim and state a number of types of patients, conditions and/or anatomical locations for which the device may be used. Focusing on one type of patient, condition or anatomical location actually creates more issues for the company than to make a broader, more all-encompassing, less specific claim.

Tip Two: Be strategic about your intended use statement—use the 510(k) as an advocacy document.

Address these issues in advance in your 510(k) submission, don't leave them to chance. Position your device to meet the published guidance language and craft the submission to fit within them. Even quote portions of these guidance documents to demonstrate your familiarity with them and attempt to fit within them. It demonstrates respect for FDA's guidance and your attempt to follow them closely in making your submission. More importantly, it shows sophistication and an implied willingness to push/advocate your position. For example, use the "Levels of Specificity" and "Decision Making Criteria" in the General/Specific Use guidance to make your case. There must be a balance between having too much argumentation upfront in a 510(k) submission because it will look like you are defending your position well before you need to. Conversely, without any positioning upfront, you may be subject to a reviewer who a) is not knowledgeable about the guidance criteria, b) will

take a position that fits their personal belief system (i.e. risk averseness and FDA's view is always right), and c) doesn't know your level of sophistication upfront.

Also you can use an amalgam of 510(k) statements to construct your intended use statement. Be careful not to be too creative in constructing your intended use statement or you will create problems for yourself with the Agency.

Tip Three: Make sure you understand the contours of the law, regulations and guidance.

That is the key to drafting your 510(k) and interfacing with the Agency. You need to be able to properly articulate and advance/defend your position and make rebuttals to the Agency staff. Without knowledge of the law, regulations and guidance, you are at the mercy of FDA's unfettered discretion and unarticulated positions. And if you need to appeal the decision of a reviewer or Branch Chief, know that at the level of the Division Director, Office Director or Deputy Director for Science and Policy, they do know their stuff—so you had better know it too.

Tip Four: When you market your general intended use strategize about how that can be done with management and marketing.

When a company obtains a general clearance for its device and knows there will be specific, uses to which it may be put—uses that may be potentially controversial with FDA—it must dialogue and strategize internally how the device will be marketed or it will unfairly expose the sales and marketing organizations to FDA enforcement should they be too aggressive in their promotional efforts. This could draw FDA's attention in the form of a warning letter or worse. It behooves management, with marketing and sales, to strategize about how this device can be marketed.

Tip Five: Argue your position using the General/Specific Use Guidance if you encounter a dispute with the chosen indications for use in your 510(k).

Use FDA's framework and words to show why your device's indications for use appropriately fits under the umbrella of the predicate device's intended use. When companies make submissions, they should not concede their position to FDA. Oftentimes the review staff and a Branch Chief may not agree with the company, but management above them (Division Directors and Office Directors) will. The key to getting the review staff and a Branch Chief to agree with your original position on

general versus specific intended use is to construct the argument carefully so it is logical and compelling, and demonstrates to lower level staff that the company actually knows what it is talking about. The first step in constructing this argument is to address and show to FDA that each element of the Decision-Making Criteria and Levels of Specificity (cited above), as they apply to your device, demonstrate the same intended use. And then, leverage what FDA says in guidance to re-iterate the overarching principle of flexibility for the 510(k) program. "[D]ifferences in indications for use, such as the population for which a device is intended or the disease a device is intended to treat do not necessarily result in a new intended use."[9] The 510(k) program is meant to accommodate differences – even differences in indications for use which nevertheless fall under the same intended use.

Need Assistance with Your 510(k)?

Do you need help crafting or understanding the implications of the indications for use for your 510(k)? Have you encountered a dispute with the indications for use used in your 510(k)? Our firm routinely engages with clients regarding medical device submissions and appeals, 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@duvafdalaw.com or by phone at (612) 338-7170.

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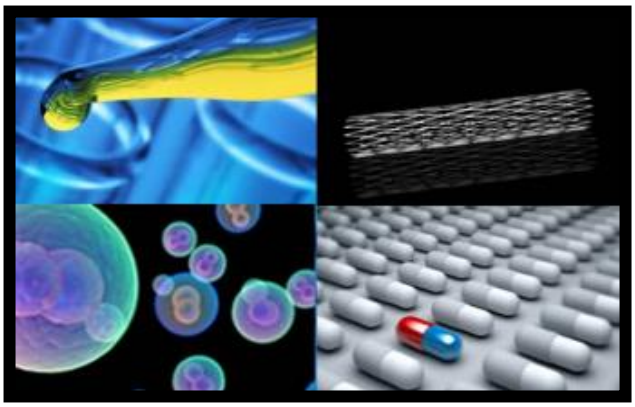

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[9] See "510(k) Guidance" at page 7.

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