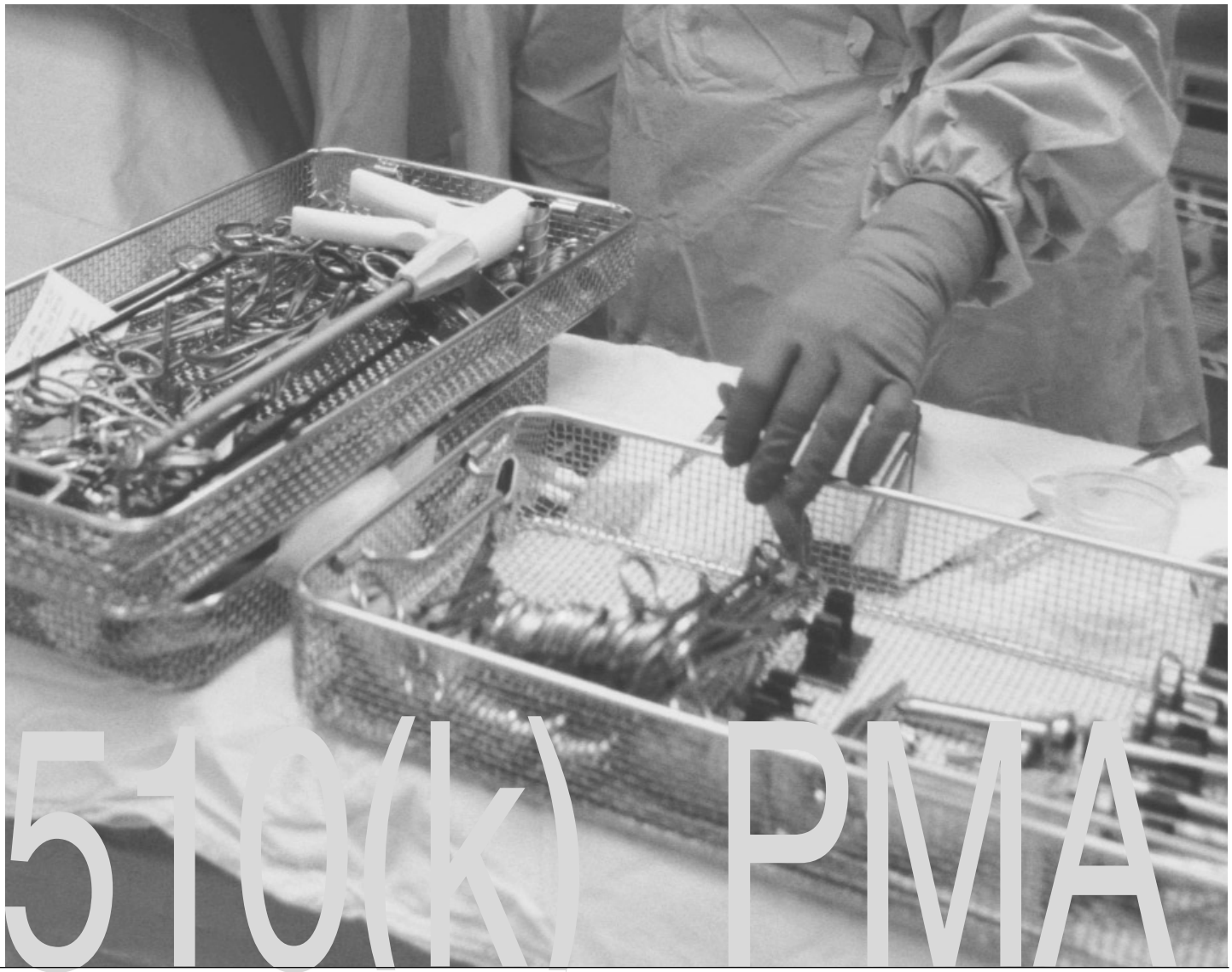
Promoting Devices for Specific Indications Based Upon a General Clearance

BY JEFFREY K. SHAPIRO

Many medical devices receive 510(k) clearance from FDA for general indications but are labeled and promoted for more specific indications. Frequently, FDA asserts that such specific uses are not covered by the original clearance and require separate 510(k) clearance or even premarket application (PMA) approval. For example, if an excimer laser device has general clearance for cutting or coagulating soft tissue, then FDA may treat promotion specifically for photorefractive keratectomy as a new intended use. In many cases, manufacturers are surprised by FDA's position, believing that their labeling and promotional activities were consistent with the original clearance. This article discusses disputes with FDA over the scope of 510(k) clearance and provides advice on how to navigate this difficult area.



Intended Use

The "intended use" of a medical device refers to the objective intent of the persons legally responsible for the device's labeling. Under the Federal Food, Drug and Cosmetic Act, a device generally may be sold only for intended uses for which FDA has granted 510(k) clearance or PMA approval.

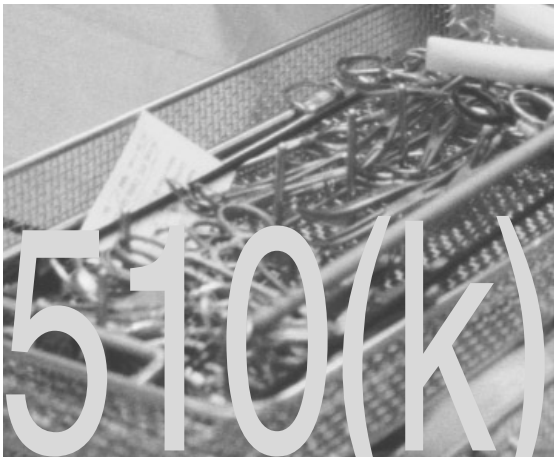
The intended uses may be inferred from the labeling, advertising, promotional material or oral statements surrounding distribution of the device.[1] FDA has long considered user training to be legally equivalent to labeling and promotion as a determinant of intended use.[2] When a device is promoted for a new intended use that is not covered by the existing clearance (or PMA approval), FDA may allege that the product is adulterated or misbranded.[3]

Indications for Use

Since 1996 FDA has required that every 510(k) submission include an "indications for use" statement, which provides key operational detail underpinning FDA's overall legal conclusion as to a device's intended use. FDA's regulations define the term "indications for use" as a "general description of 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] An FDA guidance adds:

"The indications include all the labeled patient uses of the device, for example:

- the condition(s) or disease(s) to be screened, monitored, treated or diagnosed;
- prescription versus over-the-counter use;



- parts of the body or type of tissue applied to or interacted with;
- frequency of use;
- physiological purpose (e.g., removes water from blood, transports blood, etc.); or
- patient population."[5]

The guidance also notes that the "indications for use are normally found in the indications section of the labeling, but indications also may be inferred from other parts of the labeling such as the precautions, warnings or the bibliography sections."[6]

Scope of Clearance

The cleared indications for use statement sets forth the expected uses upon which FDA's clearance decision is based. Any modification to the indications for use is a modification to the labeling. A critical question is whether describing a general indication in more specific terms is, in fact, a modification. In some cases, it might be argued that the more specific indication is implicit in the general clearance and that labeling, promoting or training for it does not in any way modify the cleared indications for use.

Judging from FDA's warning letters, it appears that the agency generally rejects this view. FDA tends to treat the literal language of the cleared indications for use statement as a baseline. A departure (whether in labeling, promotion or training) is liable to be treated as a modification to the indications for use.

Even when a manufacturer makes such a modification, however, a new 510(k) clearance is not necessarily required. As with any labeling change, the manufacturer must assess whether the modified labeling creates a major change or modification in the device's intended use.[7] If it does, then a new 510(k) clearance is required. If it does not, a new clearance is not required.

FDA's *Deciding When to Submit a 510(k) for a Change to an Existing Device* provides guidance in determining whether any device modification, including a labeling change, requires a new 510(k) submission. With respect to the indications for use, FDA states: "changes in the indications for use section of labeling raise more agency concern than any other aspect of labeling. In fact, most changes in this part of the labeling will require the submission of a 510(k)." However, FDA concedes that not every such change will require a new 510(k) submission. For example, FDA states that modifying the indications for use to add a new patient population with similar demographics and risk level may not require a new 510(k) submission.[8] If a company promotes for a more specific use but does not alter the indications section of the labeling, it is even more likely that a new 510(k) submission is not required.

Another FDA guidance, *General/Specific Intended Use*, also may be helpful. This guidance addresses FDA's determination of whether a specific use is substantially equivalent to a general use or whether the specific use requires PMA approval. It does not directly address whether a specific intended use falls within an existing 510(k) clearance.[9] Nonetheless, the guidance provides helpful definitions and decision-making criteria that may help when assessing whether labeling or promoting a device for a more specific indication is likely to be considered a new intended use. For instance, FDA observes that a specific use is less likely to be considered substantially equivalent to a general use if it introduces new risks, dramatically broadens the patient population, leads to a major qualitative difference in device use (e.g., diagnosis versus screening, cutting soft tissue versus treating breast cancer), must be evaluated by a different set of clinical endpoints or requires device modifications that are not necessary for the more general use.[10] This same type of reasoning is likely to be useful in deciding whether promoting a device for a specific use exceeds the scope of a more general clearance.

Problems

FDA's application of the foregoing general principles has not always hit the mark. In one warning letter, FDA addressed a robotic surgical platform cleared "to assist in the accurate control of [certain] endoscopic instruments during ... laparoscopic surgical procedures such as cholecystectomy or Nissen fundoplication." When the device was promoted for radical prostatectomy, FDA alleged that the indication was a new intended use requiring separate clearance.[11] In doing so, FDA ignored the fact that radical prostatectomy is a laparoscopic procedure, which would seem to fall squarely within the scope of clearance. While it is true that only cholecystectomy and Nissen fundoplication were highlighted in the cleared indications, the phrase "such as" clearly seems intended to communicate that these procedures were illustrative and not exhaustive of the scope of clearance, especially because FDA knew the device was intended as a general surgical platform. Yet, the logic of FDA's warning letter seems to require a new 510(k) submission for every possible laparoscopic surgical procedure in which the platform might be used.

Another problem FDA has acknowledged relates to user training. When a surgical device has a general clearance described in terms of function (e.g., coagulation of soft tissue), it is often necessary to train surgeons by reference to specific procedures involving real anatomical locations. Yet, FDA has long held that training for a specific intended use is legally the equivalent of labeling for it. This places companies in a Catch-22 in which they must teach specific procedures to train surgeons for the cleared use but FDA insists that teaching such specific procedures is a change in intended use requiring separate 510(k) clearance or PMA approval.

New FDA Policy

In an apparent attempt to address these

issues, in October 2002, Dan Schultz, director of the Office of Device Evaluation, Center for Devices and Radiological Health (CDRH), indicated in a public forum that FDA is willing, in appropriate cases, to enter into agreements allowing companies to modify their labeling, training and promotional material to include additional procedures not expressly set forth in the indications for use statement—without requiring new 510(k) clearance. These agreements must be reached in advance and must meet at least the following requirements:

- Additional procedures may be included in the device labeling, promotion and training, but not in the "indications for use" portion of the labeling. The latter must conform to the cleared indications for use statement.
- The company must determine that labeling the device for use in the additional procedure is not a modification requiring new 510(k) clearance under FDA's regulations. This determination is especially important if new tools or device modifications are necessary for the additional procedure.
- The company must generate clinical data adequate to support the safety and effectiveness of the additional procedure and maintain the data in company files. Apparently, the company is expected to make the determination as to what data are adequate. FDA may inspect to determine that the company has adequate design control procedures addressing the effect of the labeling change and clinical data on the safety and effectiveness of the new use.

Schultz noted the foregoing agreement is similar to the agreement eventually reached with the manufacturer of the robotic surgical platform during negotiations over the warning letter citing promotion of the device for radical prostatectomy, which was discussed above. The new policy avoids requiring a new 510(k) for every possible surgical procedure. In addition, it helps resolve the conundrum that arises when a general clearance requires discussion of specific procedures in order to train users of the device.

Schultz added the agreement is essentially an attempt to allow sponsors reasonable discretion to determine that an additional procedure falls within the cleared indications for use, which must remain unchanged in the "indications for use" section of the labeling. Schultz indicated that the legal basis for the policy is that changes in the indications for use are more likely to signal a major change in intended use as compared to other parts of the labeling. FDA's scientific expertise, he argues, enables it to exercise discretion in construing whether a labeling change alters the intended use. Thus, for example, FDA has discretion to conclude that the intended use will not be altered if the labeling for a surgical device carries the description of an additional procedure in the instructions for use but the indications for use section of the labeling remains unchanged.

The new policy has not been published in formal written guidance. Preferably, the agency will provide written guidance as soon as possible. Doing so will ensure that industry learns what the requirements are and will aid in evenhanded administration of the policy. Nonetheless, companies apparently need not wait for such guidance if they wish to avail themselves of the type of agreement that Schultz outlined. With or without written guidance, it remains to be seen whether the new policy will successfully resolve some of the difficult issues in this area.

Practical Advice

It pays to be careful when drafting the indications for use statement. CDRH's Office of Compliance is likely to read it literally and any ambiguity is typically construed as restrictively as possible. Ideally, the indications for use statement will set forth a detailed roadmap as to how the device will be labeled and promoted. It is best if the statement lists all possible indications. If that is not possible, illustrative uses should be introduced with the phrase "including but not limited to" rather than "such as." As discussed above, on at least one occasion FDA seems to have interpreted the phrase "such as" as exhaustive rather than illustrative of the cleared indications.

Of course, the strategic trade-off is that greater specificity at the outset of the 510(k) process may lead FDA to require more data in the 510(k) submission. Companies sometimes prefer to accept ambiguity and possible restrictions on their promotional activity in order to reduce the burden of obtaining clearance.

As a practical matter, a disagreement with FDA about the scope of clearance can arise whenever a device's intended use can be described with varying levels of specificity. The best approach to avoid misunderstanding is to consider the issues in advance rather than wait until FDA initiates an enforcement proceeding. With careful thought, the risk of a problem in this area can be significantly reduced.

NOTES:

1. 21 USC 321(m); 21 CFR 801.4; *Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (DC Cir. 1980).
2. Warning Letter to Fukuda Denshi America Corp., FDA, 28 March 1996.
3. 21 USC 331(a), (d), and (k), 351(f), 352(f), 352(o), 355(a).
4. 21 CFR 814.20(b)(3)(i).
5. *Deciding When to Submit a 510(k) for a Change to an Existing Device*, FDA, 10 January 1997; p. 24.
6. *Deciding When to Submit a 510(k) for a Change to an Existing Device*, FDA, 10 January 1997; p. 25.
7. 21 CFR 807.81(a)(3)(ii).
8. *Deciding When to Submit a 510(k) for a Change to an Existing Device*, FDA, 10 January 1997; p. 10.
9. *General/Specific Intended Use*, FDA, 4 November 1998; pgs. 2–3.
10. *General/Specific Intended Use*, FDA, 4 November 1998; p. 6.
11. Warning Letter to Intuitive Surgical Inc., FDA, 12 April 2001.

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