Guidance for Industry

General/Specific Intended Use

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Preface

Public Comment:

Comments and suggestions may be submitted at any time for Agency consideration to CAPT. Daniel Schultz, M.D., Center for Devices and Radiological Health (HFZ-470), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact CAPT. Daniel Schultz, M.D. at 301-594-5072.

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Guidance for Industry on General/Specific Intended Use

Introduction

This guidance[1] document identifies the general principles that will be considered by the Food and Drug Administration (FDA) in determining when a specific indication for use is reasonably included within a general indication for use of a medical device[2] for purposes of determining substantial equivalence under Section 513(f) or Section 520(l) of the Federal Food, Drug and Cosmetic Act (the Act). This guidance is issued in accordance with new Section 513(i)(1)(F) of the Act, which was added by Section 206 of the Food and Drug Administration Modernization Act of 1997 (FDAMA).

There are a number of reasons medical device manufacturers may seek to add a specific indication for use to a general use of a legally marketed predicate device. In some cases, technology may drive a manufacturer's decision to request the addition of a specific indication for use; "minor" technological changes to a device may make it more applicable to one specific indication for use and less applicable to other uses. Alternatively, a new competing device may enter the market with a specific claim resulting in a potential loss of market share for the device without that claim. Sometimes the identification of a specific intended use is the result of the evolution of medical practice once a device is marketed. When the medical community adopts a specific indication for use as routine practice, manufacturers and physicians want that specific indication for use to appear on the labeling for both liability and reimbursement purposes.

Purpose

The purpose of this document is to help medical device manufacturers understand the principles used by FDA to determine whether the addition of a specific indication for use to a medical device cleared for marketing with a general indication for use could trigger the need for a PMA. The guidance is intended to help manufacturers answer the following questions: Under what circumstances is a device with a new, specific indication for use likely to be found

[1] This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] Please note that the addition of a specific use to a device may result in a product that is considered a combination product or otherwise requires input from other FDA Centers as presented in the intercenter agreements effective October 31, 1991. In such cases, regulatory issues not addressed in this document may apply.

to be substantially equivalent to a device legally marketed for a general indication for use? Conversely, when does a specific indication for use become a new intended use that requires submission of a PMA to establish the safety and effectiveness of the device?[3]

This guidance does not offer a bright line rule to answer these questions. The agency believes it could not formulate such a rule without compromising the ability of FDA reviewers to factor in the important public health and regulatory considerations that are essential to making appropriate classification determinations. Thus, the purpose of this guidance is to describe that decision-making process and its basis in the law and in agency practice.

Nor does this guidance construct a new or separate SE/NSE decision-making process. That process is addressed in other agency guidance (see Blue Book Memorandum #K86-3, "510(k) Substantial Equivalence Decision-Making Process"). Instead, this document provides guidance to sponsors by describing the criteria that FDA considers in deciding whether the addition of a specific indication for use alters the intended use of a product that is already marketed with a general indication for use, requiring approval of a PMA.

Item #4 of the 510(k) flowchart (K86-3), which FDA reviewers have used for years in 510(k) evaluations, asks "Do the differences [in indications] alter the intended therapeutic/diagnostic effect" and directs FDA reviewers to "consider impact on safety and effectiveness ." This general/specific guidance, therefore, does not add a new level of scrutiny to the review process; rather, it articulates the factors which are currently used by FDA in assessing the impact of a change from general to specific use on safety and effectiveness.

Definitions

For the purpose of this guidance, the definitions for "**general to specific**" and "**level of specificity**" listed below are used.

General to Specific

A change from a **general to a specific indication for use** is defined as: Any proposed increase in the level of specificity of the indication for use of a medical device. A change in a device's indication for use from general to specific usually results in an indication for use that is narrower than the approved or cleared general use. Such a change or additional indication generally will narrow the indication for use with respect to function, target population, organ or organ system, tissue type, disease entity, or analyte.

[3] A second related issue is, when would a specific intended use that falls within a general use not require a submission of any kind, i.e. be considered a use already cleared under a current 510(k)? This question will *not* be directly addressed in this document. Guidance in making that determination is available in the ODE guidance document entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device."

Levels of Specificity

The level of specificity is defined as: a qualitative ranking of the proposed indications for use of a medical device. Levels of specificity for diagnostic and therapeutic devices in order of increasing specificity from general to specific can be categorized as follows:

Levels of Specificity for <u>diagnostic</u> medical devices:

1. Identification or measurement of a physical parameter (e.g., image, heart rate) or biochemical parameter (e.g., analyte)
2. Identification of a new or specific target population (e.g., women, children of a certain age range) or anatomical location (e.g., MR of the brain)
3. Identification of the clinical use of the measurement (e.g., diagnosis, screening)
4. Identification of or implication of an effect on the clinical outcome (e.g., screening mammography reduces breast cancer mortality)

Levels of Specificity for <u>therapeutic</u> (including preventive) medical devices:

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
5. Identification of an effect on clinical outcome (e.g., use of medical device improves the rate of durable complete remissions with chemotherapy)

<u>Regulatory Background</u>

For products not requiring a Premarket Approval that are not exempt from premarket notification (510(k)), a 510(k) submission is required whenever a medical device is introduced into commercial distribution in the United States (21 CFR 807.81). In addition, a 510(k) is required when a legally marketed device is to be significantly modified in design, components, method of manufacture, or intended use (21 CFR 807.81(a)(3)). In either situation, review of the 510(k) submission is how the agency's experts determine whether the device is substantially equivalent (SE) to the predicate device to which it is being compared.

The 510(k) review process requires the agency to determine the proper classification for a medical device. Devices that are determined to be substantially equivalent to legally marketed devices that are not Class III devices subject to premarket approval, are placed in the same regulatory class as the predicate and may go to market upon receiving clearance from FDA. Devices determined to be substantially equivalent to a Class III device subject to premarket approval requirements, as well as devices determined to be not substantially equivalent (NSE) to a predicate device, are placed in Class III. Unless reclassified into Class I or Class II, these

devices cannot go to market without an approved PMA or a completed product development protocol. Under new 513(f)(2) of the act, sponsors of devices declared NSE may seek FDA evaluation of their devices' automatic Class III designation.

FDA has issued guidance documents that describe the process by which substantial equivalence decisions are rendered. Guidance about the Agency's 510(k) decision making process is contained in Blue Book memorandum #K86-3 (http://www.fda.gov/cdrh/k863.html). Guidance about Agency decisions with respect to the requirement for 510(k) clearance when modifications are made to legally marketed devices are contained in Blue Book memorandum #K97-1 (http://www.fda.gov/cdrh/ode/510kmod.pdf or 510kmod.html). While these guidance documents provide information relevant to FDA's decision-making processes with respect to general/specific use, Congress indicated through FDAMA § 206 that FDA should provide additional guidance on the approach that the agency takes when evaluating whether a new indication for use, which appears to fall within the scope of the intended use of a legally marketed predicate device, is a new intended use that would require a PMA.

Blue Book memorandum #K86-3 further states that the Center assesses any differences in indications for use in terms of the safety and effectiveness questions those differences may raise. This guidance also indicates that some modifications in indications will be considered a new use, "even though the intended effect of the new device is very similar to that of the predicate device." The Blue Book memorandum notes that slight modifications in indications for use can significantly change the intended use of the predicate device.

It should also be noted that the agency has received previous Congressional guidance which bears directly on the issue of substantial equivalence in the Report of the Committee on Interstate and Foreign Commerce on the Medical Device Amendments of 1976 (Senate Report):

> *The committee believes that the term, substantial equivalence, should be construed narrowly where necessary to assure the safety and effectiveness of a device but not narrowly where differences between a new device and a marketed device do not relate to safety and effectiveness.*

FDAMA

The Senate committee report which preceded the final FDAMA bill stated that "this clarification [with respect to general/specific use] is important because FDA has not established a consistent pattern upon which persons who submit premarket notifications may rely." (S. Rept. 105-43, at 48 (1997)). Two specific examples may help us to understand the need to address the general/specific use issue.

The first example, cited in the same 1997 Senate report, relates to a substantial equivalence determination made for condoms, using the general indication for use of prevention of

sexually transmitted disease as a predicate for condoms labeled to prevent the transmission of HIV. This was a situation where an overriding potential public health benefit, an established safety profile, and an identical mechanism of action were weighed against concerns regarding the level of available effectiveness data in deciding that 510(k) was the appropriate regulatory pathway for this indication for use. The Senate report concluded that, "[T]his determination made *perfect public health sense*, despite the fact that the general use labeling pre-dated the 'Medical Device Amendments of 1976' and HIV was unknown at that time." (S. Rept. 105-43, at 48**).**

A second example, cited in Blue Book Memorandum #K86-3, relates to powered suction-aspiration devices, which were initially cleared to remove tissue and fluid from the body during surgery. New versions of these devices were presented to the agency to be cleared for use in "suction lipectomy" for body contouring. In this instance, FDA determined that this was a new intended use requiring submission of a PMA. Key factors that led the agency to this decision included:

1. The aspiration process performed by the device became the surgical outcome for which the device was intended to be used, rather than the device being intended to aid the physician in performing surgery. This surgical outcome, which would affect large numbers of "well" patients desiring enhanced body image, had never been validated through controlled clinical trials.
2. The removal of large quantities of body fat raised questions of safety and effectiveness not posed by the labeling of pre-Amendments aspirators, e.g., possible metabolic changes, and permanent bagging of the skin resulting when the fat removed from the area exceed the ability of the skin to contract.

These major differences in risk, benefit, and clinical endpoints led FDA to conclude that submission of a PMA was necessary to establish whether there was reasonable assurance that the device was safe and effective for this intended use.

Decision-Making Criteria

The criteria that follow are provided as guidance on the Agency's decision-making process for determining substantial equivalence or non-equivalence for general/specific uses. The 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. These criteria should be evaluated in connection with the Levels of Specificity[4] described earlier in this document.

[4] Please refer to Levels of Specificity section under Definitions.

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?

Specific uses that ordinarily fall within a general use for the purpose of determining that the device with the specific indication for use is substantially equivalent to the general use device include:

- Those indications for use that specify a sub-specialty of a particular clinical discipline where the types of treatments or procedures are similar (see below, example 7);
- Those indications for use that specify a particular anatomic site or tissue type that does not imply diagnosis or therapy of a specific disease entity (see below, example 4);
- Those indications for use that specify a narrow target population within a broader population (see below, example 2); and,
- Those 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 (see below, example 7).

Specific indications for use that ordinarily fall outside a general use for the purpose of determining substantial equivalence include:

- Those indications for use that involve the diagnosis, therapy, or prevention of a particular disease entity or entities, especially where such entity carries clinical implications not normally associated with other general uses of the device (see below, examples 1, 5, 8);

- Those specific indications for use that presume a specific clinical outcome, especially when that outcome could influence patient management outside standard practice (see below, example 6);
- Those indications for use that provide a new type of diagnostic information or therapeutic option that significantly impacts patient management (see below, example 3).

Examples

The following are examples of Agency determinations with respect to 510(k) submissions made for purposes of establishing the substantial equivalence of a new device labeled with the specific indication for use to the legally marketed device labeled for the general use. The Agency believes these examples will help illustrate its consideration and application of the criteria and levels of specificity described above in this memorandum.

Diagnostic Devices

In vitro diagnostics

1. Factor VII Assay
    - General indication for use-Quantitative measurement of Factor VII in patients with known or suspected Factor VII deficiency (identifying or assessing a group of people with a rare genetic disorder)
    - Specific indication for use- Factor VII assay as a predictive marker for stroke (using the same test on a significant number of asymptomatic adults at risk for stroke)
    - Determination: **NSE**
    - Major criteria:
        - Risks- The specific use may initiate, based upon current practice guidelines, additional invasive diagnostic studies and/or treatment modalities for a population at risk for severe neurological impairment or death.
        - Public health impact- A device intended to predict stroke has a far greater public health impact than a device intended to identify a Factor VII deficiency both in terms of the individual and the public at large.
        - Knowledge base- The new indication for use is not well-described in the published literature, and clinical information from other sources are not available.

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.

In vivo diagnostics

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

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.

Therapeutic Devices

5. Cryosurgery in gynecology
    - General indication for use- Ablation of tissue in gynecology
    - Specific indication for use- Endometrial ablation (with ultrasound guidance)
    - Determination: **NSE**
    - Major criteria:

- Risk: The risks related to ablation of the entire endometrial lining as well as a portion of the myometrium under ultrasound guidance are far greater than ablating isolated lesions of the cervix and other, more circumscribed, gynecologic abnormalities.
- Public health impact: Women with abnormal uterine bleeding constitute a large group, estimated in the hundreds of thousands. Currently, these women are treated with surgical procedures performed under direct visualization. The potential public health impact of a device intended to treat large groups of women with significantly different technology and without direct visualization is considerable.
- Knowledge base: As opposed to other gynecologic applications of cryosurgery, which are widely reported in current published literature, the scant supporting literature for this indication for use dates back 2-3 decades and reports preliminary investigations or is anecdotal in nature.
- Endpoints: The endpoints for most cryosurgical procedures are physical destruction of a defined lesion as opposed to a functional reduction in the level of menstrual bleeding. Therefore measurements used to assess safety and effectiveness for this particular indication are entirely different from the measurements used to assess other cryosurgical indications.

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.

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.

8. Excimer Laser
   - General indication for use- Cut, coagulate soft tissue
   - Specific indication for use- Photorefractive keratectomy (PRK) for myopia
   - Determination: **NSE**
   - Major criteria:
     - Risk: The risk of visual impairment associated with this specific indication for use is not associated with generalized tissue ablation.
     - Public health impact: Because myopia is a very common condition affecting millions of people, including children and adolescents; and severe visual impairment is such a profound disability, the public health impact of a device cleared for such use is significant.
     - Endpoints: The endpoint of visual acuity is unique to this indication for use. Methods used to assess other laser applications do not apply.

9. CO_2 Laser
   - General indication for use-Skin resurfacing
   - Specific indication for use- Wrinkle removal
   - Determination: **SE**
   - Major criteria:
     - Level of specificity: The specific indication for use is very similar to the general indication for use.
     - Endpoints: Endpoints are very similar, that is restoring the skin to its original condition.

It should be noted that the vast majority of submissions for 510(k)s for specific indications for use are cleared as substantially equivalent to a legally marketed predicate for the general use. Some of these submissions require clinical data before clearance. The list of examples cited above include some of the relatively few cases that have not been found substantially equivalent in order to illustrate a spectrum of situations where FDA may make a NSE determination.

Conclusion

Determinations of substantial equivalence related to specific versus general indications are often difficult and complex. There are multiple factors that influence those determinations. Those factors vary from device to device and also may change over time with respect to a particular device. This document attempts to elucidate some of those factors in an effort to assist manufacturers in their research and development efforts. Manufacturers may obtain further guidance by communicating directly with the relevant ODE division either through submission of a 510(k) or prior to making a submission.