FDA INSIGHTS

Medical Device Labeling

Regulatory terminology associated with device labeling.

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The device labeling provides the reader with specific information regarding when and how a device can be used consistently with the FDA approval through the Premarket Approval (PMA) process. Information on the PMA process can be found in the April 2004 issue of *Endovascular Today*.

A major focus of the PMA review process includes finalizing the device labeling based on the information obtained during the evaluation of the device. Because there is no specific definition of "off-label" in the Federal Food, Drug and Cosmetic Act (the Act) or the Code of Federal Regulations (CFR), an understanding of the meaning of "on-label" illustrates the relevance of device labeling. This article provides definitions for the regulatory terminology associated with device labeling.

MEDICAL DEVICE LAW AND REGULATIONS

The Federal Food, Drug and Cosmetic Act (the Act) is the law that is applicable to medical device regulation. This law is interpreted in the Federal Register. The Code of Federal Regulations (CFR) is a codification of the general and permanent rules published in the Federal Register. Both the Act and the CFR are necessary references to define the relevant terms regarding device labeling.

Label and Labeling

The term *label* is defined in the Act as, "a display of written, printed, or graphic matter upon the immediate container of any article . . .," that is, the package labels. The Act defines labeling as, "all labels and other written, printed, or graphic matter:

(1) upon any article or any of its containers or wrappers [eg, package labels]; or

(2) accompanying such article at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce."

The term *accompanying* is further described in the Act to include more than just the materials shipped with the device and may include posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, and fillers. As such, the device package labels, instructions for use, technical manuals, and materials posted on the Web are all part of the labeling. The general labeling requirements for medical devices are published in 21 CFR Part 801.

INSTRUCTIONS FOR USE

When the FDA approves a device for marketing through the PMA process, the approval is for specific use(s) of the device. This specific use is the basis for the product labeling (sometimes called the *instructions for use*, or IFU), that is, the labeling reflects the indication for use and describes how the device can be optimally used. Some of the key elements of the instructions for use include the following: device description, indications for use, contraindications, warnings and precautions, anticipated adverse event information, summary of clinical studies (if applicable), patient selection and treatment recommendations, storage and handling information, and directions for use.

INDICATIONS FOR USE

The indications for use provide a general description of the disease or condition that the device will diagnose, treat, prevent, cure, or mitigate as well as a description of the patient population for which the device is intended. As an example, for an endovascular graft, the indications for use would state the type and location of lesions that are indicated for treatment, such as aneurysm of the thoracic aorta. The indications would also describe the patient anatomy that would allow for use of the device,

such as aortic diameter ranges, lengths of required non-aneurysmal aorta proximal and distal to the aneurysm, and necessary access vessel characteristics. It may include limitations on the aortic angulation or other specific lesion characteristics that are considered acceptable when using the device.

INTENDED USES

The term *indications for use* is often used interchangeably with *intended uses*. Intended uses, however, has a different meaning than indications for use, as described in 21 CRF 801.4:

> The words *intended uses* or words of similar import in 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally responsible for the labeling of devices . . . intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.

Intended uses is a broader term, encompassing the labeling and promotion of the device. Therefore, the requirements for the instructions for use, including the designation of indications for use, ensure that the labeling appropriately reflects what the device is being sold to do, that is, the intended uses.

DEVICE USE

Devices may be used in accordance with their labeling, or physicians may decide that the best treatment option for their patient is to use a device outside of the approved labeling. Physicians may legally use an approved medical device to treat a patient for an unapproved use because this is considered practice of medicine. The FDA regulates interstate commerce of medical devices and not the practice of medicine. The Act specifically states that "nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."

As noted previously, the instructions for use reflect the data evaluated to support marketing of the device. When the device is not used in accordance with this labeling, these data may be less relevant, depending on how the use deviates from what is described in the instructions for use. Regardless, the rigor of FDA review has not been applied to the use of the device outside of the approved labeling.

PRESENTATIONS REGARDING INNOVATIVE DEVICE USES

Disclosure policy and presenter attestation forms specifically request that the presenter indicate if off-label use is to be discussed. The disclosure provides the appropriate context for the audience. Interpretation of the information presented should include an understanding that the rigor of FDA regulation has not been applied to the device for that use. This is particularly important when presenters describe personal modifications of devices that then have new intended uses. Data are generally not available and have certainly not been reviewed by the FDA to demonstrate the safety and effectiveness of the device for the new intended use. Consideration of the need for a clinical investigation of the modified device and additional assessment prior to application of the technique would be prudent.

Care should be taken when discussing investigational devices, as well as off-label use of devices, to avoid promotion of devices that have not yet been cleared or approved by the FDA. For investigational devices, conclusions regarding study results may be premature prior to the completion of the evaluation of the device.

FDA EFFORTS TO OPTIMIZE DEVICE LABELS

The FDA is trying to work with medical device companies and clinicians to better communicate the intended uses of devices and to find reasonable options for obtaining appropriate labeling for devices. As an example, marketing clearance letters for non-vascular stents specifically state that these devices are not approved for use in the vascular system. The instructions for use for these stents also include language to warn that data are not available to support vascular use. Not only has the FDA required that the labeling accurately reflect the non-vascular indications, the FDA has asked that the stent manufacturers directly communicate with physicians to discourage vascular use of non-vascular stents and to notify them of adverse events associated with the off-label use of non-vascular stents. In addition, the FDA regularly meets with clinicians and medical device companies to discuss possible study designs and data requirements for evaluating vascular indications in an effort to positively influence the use of devices on-label.

The goal of these efforts is not to interfere with the practice of medicine, but rather, to provide physicians with information based on relevant evaluations for the devices uses. This information should help physicians to identify and provide the optimal treatment options for their patients. ■

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