

## FDA Post-Approval Advertising and Labeling Requirements for Devices

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Once a medical device has received US Food and Drug Administration (FDA) approval (for Class 3 devices) or FDA substantial equivalence (SE) determination (for Class 1 or 2 devices), there are still additional FDA labeling, advertising and disclosure requirements that you must follow in order to stay commercially available. If you do not comply with these requirements, an FDA warning letter is a possible result.

Officially, the FDA warning letter documents your firm's non-compliance to federal law. Thus, warning letters are to be taken very seriously when you receive one, and better still, they are to be avoided in the first place. By reviewing the FDA post-approval labeling requirements, as well as the common promotional material errors reported by FDA warning letters, regulatory professionals can help their companies avoid disciplinary actions.

### The Food Drug and Cosmetic Act (FDA law)

According to FDA law, section 201(m): The term "labeling" means all labels and other written, printed or graphic matter:

1. upon any article or any of its containers or wrappers, or
2. accompanying such article.

While the terms "written, printed" are easily understood, it is important to understand that the term "graphic matter" includes drawings, photographs and animation that may well be included in advertising.<sup>5,6</sup> Thus, while the advertisement may not have any textual unapproved uses described, if graphics show such usage, the advertisement is not in compliance. It must also be re-

membered that FDA has stated that the term "accompanying" is interpreted liberally to include more than physical association with the product and extends to posters, pamphlets and brochures, and basically includes all advertising.<sup>11,12</sup>

For purposes of medical device classification, FDA law section 513(A)(2), specifies that FDA is to determine a device's safety and effectiveness with respect to how the device is represented to be used or intended to be used. Additionally, the conditions of use prescribed, recommended or suggested in the labeling, and any probable benefit to health from the use of the device, are weighed by FDA against any probable risk of injury or illness from such use.

Thus, a medical device is defined and classified by FDA using the device's intended use and associated claims balanced by the risk to benefit ratio. The higher the risk, the higher the device classification and the associated regulatory control.

### FDA Class 1, 2 and 3 Devices

Most people looking over their device's FDA SE or approval letter will stop reading once they reach the expected phrase... "(Y)ou may begin commercial distribution of your device." However, if one continues reading, additional conditions of approval are required by the letter. In most cases, usually buried within legalistic text, you will find that your device is restricted by many conditions.

### Prescription Devices

If an FDA approval letter states that, "The sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Fed-

eral Food, Drug and Cosmetic Act under the authority of section 515(d)(1)(B)(ii)," then:

FDA has determined that, under the act [i.e., Investigational Device Exemption (IDE) section 520(e) and commercial distribution section 515(d)(1)(B)(ii)] and regulations (21 CFR 801.105 and 801.109), your device has a potential for a harmful effect, or the method of its use or the collateral measures necessary to its use are not safe for a layperson to use except under the supervision of a practitioner licensed by law to direct the use for such device. Hence, "adequate directions for use" cannot be prepared. Your device will be exempted from being declared misbranded for failing to provide adequate instructions for use [section 502(f)(1)] if all the following conditions are met:

- 21 CFR 810.109 (a)(2)(b): The label of the device bears the statement "Caution: Federal law restricts this device to sale by or on the order of a physician," or alternatively uses the symbol "Rx ONLY."
- 21 CFR 810.109(d): Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the device is to be dispensed, distributed by or on behalf of the manufacturer, packager or distributor of the device that furnishes or purports to furnish information for use of the device, contains adequate information for such use, including indications...under which practitioners licensed by law to employ the device for which it is advertised or represented. This information will not be required on so-called reminder

## Message from GMP Labeling

We hope this newsletter includes information that you can use. Our goal is to periodically publish articles, written by quality professionals, that are timely and informative to the companies in our marketplace. Of course, along the way, we also hope to reinforce our image as a valuable resource to our customers.

Businesses regulated by the FDA and/or are ISO 9000 registered will find GMP Labeling products helpful in maintaining compliance. More than 5000 facilities in the U.S., Canada and Europe use GMP Labeling products on a daily basis.

piece labeling, which calls attention to the name of the device, but does not include indications or other use information.

The only exception to the prescription use requirement is when your advertising states only the device's name and makes no claims or other information; then a disclosure is not required. If the advertising makes any claims or instructions for use, whether textual or graphic in nature, the prescription use statement is required.

In short, if your device is restricted as a prescription device, your advertising and promotional materials (including Web sites) must state either "Rx ONLY" or "Caution: Federal law restricts this device to sale by or on the order of a physician" on all materials.

### Retention of Historical Labeling

An often forgotten device listing regulation requires that manufacturers maintain a historical file containing both the product labeling and advertisements in use on the date of initial FDA establishment registration and device listing, as well as copies of all those promotional pieces, which have been updated or changed after initial listing [21 CFR 807.31(a)(2) and (b)]. Additionally, Quality System Regulation (QSR) 21 CFR 820.184(e) requires a copy of the primary identification label and labeling for each production unit in the device history record.

### Claiming FDA Approval

While everyone who completes the FDA process would like to tell the world that their device is now "FDA Approved," there are certain restrictions that apply. Class 1 or 2 medical devices that successfully complete the 510(k) process are prohibited by 21 CFR 807.97 from making any representation that creates an impression of official FDA approval; such impression would be

considered misleading and constitute misbranding. FDA accepted wording to acknowledge the successful completion of the 510(k) is that the device is "cleared" or received "premarket clearance."<sup>3, 5, 8</sup>

The historical labeling and advertising prohibition in section 301(l) against manufacturers claiming "FDA Approval" for premarket approval (PMA) and investigational device exemption approved devices was lifted in the FDA Modernization Act of 1997, Section 421.

### Additional Requirements for PMA Approved Class 3 Devices

While premarket approval letters state, "FDA approves your application and you may begin commercial distribution of your device," in most cases, you will also find that your device is restricted by several more conditions of approval in addition to the prescription use requirement. Failure to comply with these conditions can result in FDA's withdrawal of premarket approval [21 CFR 814.82(c)] and other regulatory actions.

### Final Printed Labeling

Prior to commercial distribution of your premarket approved device, you must submit to FDA final printed labels of your device. This allows FDA to compare your final instructions for use (IFU) and advertisements to the claims and labeling agreed upon in the final approval order.

### Restricted Device

When the FDA approval letter states: *FDA has also determined that, to ensure safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution and use must not violate sections 502 (q) and (r) of the act...*

FDA has determined that under section 502(r)(2) of the act, your "further restricted" device is misbranded, unless your device is distributed (or offered for sale) with all its advertisements and other descriptive printed matter bearing a "brief statement of the intended uses of the device and all relevant warnings, precautions, side effects and contraindications," as well as any special conditions put on the device by FDA.

The majority of approval letters that contain this further restricted requirement also contain the prescription use restriction as described above. In short, your device is thus restricted as both a "prescription device" and a "further restricted" device requiring both the "prescription statement," as well as a "brief statement" (also known as a "brief summary") on all promotional materials.

### PMA Annual Report Requirements

Specifically for premarket approved devices, manufacturers must submit to FDA an annual report [21 CFR 814.82(a)(9) and (b), 814.84(a)]. FDA can specify in the PMA letter additional annual report required data, such as providing the written promotional materials for the reporting time period. Prior to 1986, annual report submissions were required to include the product's "written promotional materials" as specified in FDA's boilerplate conditions of approval.<sup>2</sup> This requirement was removed with the publication of the final premarket approval regulation in 1986.<sup>1</sup>

While no longer required, many PMA holders continue to routinely submit promotional materials within their annual reports. There are potential benefits to the submissions of promotional materials. For example, in product liability lawsuits, it has been helpful to the manufacturer to demonstrate that FDA has reviewed the product's promotional materials and claims. Another benefit is

keeping FDA informed of the product's marketing direction and providing reassurance to FDA inspectors when they are auditing your facility and reviewing such promotional pieces. Submission of these materials also assists in complying with the device listing requirement for maintaining a promotional materials historical file (i.e., maintained as part of the manufacturer's copy of the PMA Annual Report document).

common labeling errors made by medical device companies that resulted in FDA warning letters:

- A. Labeling and advertising that make additional, unapproved claims or provide false or misleading information for the device. The promotion of unapproved claims is the promotion of an "unapproved device." As devices are defined by their claims and indications, the

by section 502(r) (e.g., artificial heart valve).<sup>9</sup>

- C. Labeling and advertisements that do not bear the required prescription use statement, (e.g., a bone mineral analysis system).<sup>8</sup>
- D. Labeling not maintained in device history record, e.g., electrode cables.<sup>4</sup>
- E. Promoting 510(k) FDA cleared devices as "FDA Approved." While no recent FDA warning letters were found to contain this error, historically, this was a common error.

## FDA Warning Letters and Consequences

There are many consequences for a company that receives an FDA warning letter, as it is the initial step in the criminal prosecution procedure for misbranded and adulterated products. Consequences can include, but are not limited to the following actions:

- All other US Federal agencies are notified of the warning letter so they may take any actions in regard to contracts and other activities.
- No requests for FDA Certificates for Foreign Governments will be approved until the violations stated in the letter have been corrected.
- No other Class 3 devices undergoing the FDA premarket approval process, to which any specified quality system deficiencies are reasonably related, will be approved until corrections are undertaken.
- FDA warning letters are publicly available and will usually end up in the lay press.

Finally, the warning letter recipient has only 15 working days to respond to FDA's issues, providing either corrective actions and/or corrective action plans.

## Avoiding the FDA Warning Letter

While in many cases the marketing department has the largest voice in preparing any product's advertising, every company should have a policy where all advertising, marketing and Web pages are reviewed and approved by the regulatory affairs department prior to distribution. Initiating this type of regulatory review policy has been successfully used in response to FDA warning letters<sup>6</sup>. However, it is always better to avoid re-



Examples of custom labels prepared by GMP Labeling.

## Common Promotional Material Errors

FDA obtains promotional materials from many sources, including complaints from competitive companies, FDA's own Web monitoring or convention attendance, FDA compliance inspections,<sup>10</sup> and reviewing PMA annual reports' submitted promotional materials.<sup>7</sup> Once FDA is aware of non-compliant promotional materials, they can also request copies of all the product's historical labeling and promotional materials,<sup>7</sup> as required under device listing regulations.

Based on FDA's warning letter database (<http://www.fda.gov/foi/warning.htm>) focusing on medical devices with labeling and advertising violations, the following items describe the most

promotion of unapproved claims results in FDA determining that the new claim renders the device adulterated for failure to obtain prior FDA approval for the "unapproved device" via sections 502(o), 515(a) and 515(g). A restricted device is considered misbranded if its advertising is false or misleading in any particular [section 502(q)]. Examples of devices receiving such warning letters include external hemo-stasis patches,<sup>5,6</sup> MRI,<sup>3</sup> deep brain stimulation for tremor control systems<sup>7</sup> and artificial heart valves.<sup>9</sup>

- B. Advertisements for "further restricted" Class 3 devices that do not include the brief statement required

ceiving a warning letter by having a policy in the first place.

## Regulatory Labeling Policy

As discussed above, policies on the regulatory review of promotional materials are to ensure consistency of such materials especially in regard to compliance with FDA requirements, such as including the required prescription use and brief statements, and using only approved product claims or indications. By using the information provided in this article along with the referenced laws and regulations, regulatory affairs, marketing and education departments can work together to develop a policy that ensures compliance to FDA regulations.

### About the author

*David H. Mueller, MS, has been active in medical device regulatory affairs with over 17 years of industry experience, including participation in ISO and AdvaMed Industry committees. He is currently regulatory affairs manager for St. Jude Medical in Minnetonka, Minnesota.*

### Notes

1. Federal Register, July 22, 1986, *Final Rule, Premarket Approval of Medical Devices*, 21 CFR Parts 16 and 814, Docket 79-0009.
2. Food and Drug Administration *PMA (Boilerplate) Conditions of Approval*, 28 March 1984.
3. Food and Drug Administration Warning Letter, 8 August 2002, Phillips Medical System, Andover, MA; Intera MRI.
4. Food and Drug Administration Warning Letter, 11 August 2003, ElectroMold, Louisville, KY; Electrode Cables.
5. Food and Drug Administration Warning Letter, February 12, 2004, Marine Polymer Technologies, Danvers, MA; Syvek Patch.
6. Food and Drug Administration Warning Letter, 11 July 2003; follow up company correspondence of July 21, 2003; FDA reply 19 August 2003; company conclusion August 28, 2003, Scion Cardio-Vascular, Miami, FL; Clo-Sur PAD.
7. Food and Drug Administration Warning Letter 23 March 2000, Medtronic, Minneapolis, MN; Activa Tremor Control System.
8. Food and Drug Administration Warning Letter, 8 May 2003, Image Analysis, Columbia, KY; QCT Bone Mineral Analysis System.
9. Food and Drug Administration Warning Letter, 12 May 1998, Medtronic, Minneapolis, MN; Freestyle Aortic Root Bioprosthesis.
10. Food and Drug Administration Warning Letter, 23 November 1998, Medtronic, Minneapolis, MN; Activa Tremor Control System.
11. US Department of Health and Human Services, Food and Drug Administration, *Device Advice, Labeling Requirements*, 23 April 2003, <http://www.fda.gov/cdrh/devadvice/33.html>
12. US Department of Health and Human Services, Food and Drug Administration, August 1999, *Guidance for Industry and FDA, Regulation of Medical Devices, Background for International Officials*.

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