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Advertising and Promotion of Medical Devices

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ABSTRACT: Dr. Portnoy, a former senior clinical reviewer and manager for the FDA's Center for Devices and Radiological Health, provides guidance for determining acceptable practices for the claims, content, and appearance of advertising and promotional materials for medical devices. In the course of doing so, he discusses important regulatory and legal precedents, and provides examples of successful and problematic advertising and promotion strategies including those that resulted in FDA Warning Letters, enforcement activities, and in some cases, monetary and criminal penalties

The United States currently spends approximately \$80 billion annually for medical device products and technologies.¹ Advertising and promotion of medical devices is a significant post-market activity of the regulated industry. Maintaining a competitive marketing strategy and program is increasingly important in today's medical marketplace. Nonetheless, it is also critical to remain in compliance with current U.S. Food and Drug Administration (FDA) statutes and regulations regarding advertising and promotion of medical products.

The purpose of this Article is to provide guidance for determining acceptable practices for the claims, content, and appearance of advertising and promotional materials. To this end, the author discusses important regulatory and legal precedents, and provides examples of successful and problematic advertising

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¹ Press Release, Advanced Medical Technology Association, Advamed Names Stephen J. Ubl As New President (July 14, 2005), at <http://www.advamed.org/publicdocs/PR-280.htm> (last visited Apr. 4, 2006).

and promotion strategies, including those that resulted in FDA Warning Letters, enforcement activities, and in some cases, monetary and criminal penalties.²

I. Warning Letters

Several Warning Letters are referenced in this Article to provide examples of common ways in which manufacturers violate FDA laws and regulations with respect to advertising and promotion of medical devices.³ Warning Letters are sent by the FDA's Office of Compliance to a particular device manufacturer and typically cite a specific instance or related instances in which the manufacturer is not in compliance with the Federal Food, Drug and Cosmetic Act (FFDCA).⁴ Such instances have included noncompliant manufacturing, insufficient quality control practices, mismanagement of clinical trials, and noncompliance in advertising and promotion of the device.⁵ These letters also provide valuable insight into the type of enforcement actions the FDA has at its disposal, including recall, seizure, injunction, administrative detention, fines, and civil and criminal penalties, all of which are designed to elicit compliance with FDA law.⁶

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The Warning Letter usually first identifies the instance of non-compliance, cites the violated federal regulation, then provides a remedy by requesting that the manufacturer take prompt action to correct the violation, and typically closes by stating that failure to promptly correct the violation may result in enforcement action by the FDA.⁷ The manufacturer is also required to notify the FDA in writing within a specific period of time, usually fifteen working days, as to the specific actions taken to correct the stated violations.⁸ While FDA Warning Letters are

² For background information on government regulation of medical devices, see Edward M. Basile et al., *Medical Device Labeling and Advertising: An Overview*, 54 FOOD & DRUG L.J. 519 (1999), available at www.fdpi.org/pubs/Journal%20Online/54_4/art2.pdf (last visited Mar. 25, 2006).

³ See CTR. FOR DRUG EVALUATION & RES., FDA, *Warning Letters and Notice Letters of Violations to Pharmaceutical Companies* [hereinafter FDA, *Warning Letters*], at www.fda.gov/cder/warn/ (last visited Mar. 26, 2006) for a database of warning letters issued by the Division of Drug Marketing, Advertising, and Communications and by Headquarters.

⁴ OFF. OF REGULATORY AFFAIRS, FDA, REGULATORY PROCEDURES MANUAL MARCH 2004 at 4-2 (2005) [hereinafter FDA REGULATORY PROCEDURES MANUAL], available at www.fda.gov/ora/compliance_ref/rpm/ (last visited Mar. 25, 2006).

⁵ See, e.g. FDA, *Warning Letters*, *supra* note 3.

⁶ FDA REGULATORY PROCEDURES MANUAL, *supra* note 4 at 4-2.

⁷ *Id.* at 4-13 to -14.

⁸ *Id.* at 4-13.

sent directly to the manufacturer, they are also made available for public review via the FDA's website.⁹

II. Advertising and Promotion Materials—Consistency with Product Labeling

In general, the regulatory framework governing the advertising and promotion of medical devices is poorly defined. Many other regulated areas (such as securities or tax) are governed by extensive sections of the Code of Federal Regulations, as well as by formal agency documents such as private letter rulings or office of general counsel memos. In contrast, CDRH regulation is based primarily on unwritten policy. Consequently, determining what is acceptable and what is unacceptable can be difficult.

The single most important principle guiding acceptable medical device advertising and promotion is that any material—including such things as print, poster boards at scientific meetings, and video—must be consistent with the final product labeling of the medical device or therapy.¹⁰ Of all the guiding principles, this is the easiest to interpret and the least ambiguous.

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A. Definition of Labeling

According to Premarket Application (PMA) regulation, “A device may not be manufactured, packaged, stored, labeled, distributed, or advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device.”¹¹ “Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA.”¹²

The FFDCCA defines “labeling” as “all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article”¹³ at any time while a device is held for sale after shipment, or delivery for shipment, in interstate commerce.¹⁴

⁹ See FDA, *Warning Letters*, *supra* note 3.

¹⁰ See 21 C.F.R. § 814.80 (2005).

¹¹ *Id.*

¹² *Id.* § 814.82(c).

¹³ 21 U.S.C. § 321(m) (2005).

¹⁴ See *id.* See also *United States v. Sullivan*, 332 U.S. 689, 690 (1948) (further defining labeling).

The FDA interprets the term “accompanying” liberally to mean more than physical association with the product, so that labeling encompasses posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, and the like.¹⁵ “Accompanying” also includes labeling that is brought together with the device after shipment, or delivery for shipment, in interstate commerce.¹⁶ Finally, consistent with this broad definition of labeling, content on manufacturers’ websites also comes under the FDA’s purview.¹⁷

B. Advertising is Considered Labeling

In *United States v. Research Laboratories, Inc.*, the Ninth Circuit stated: “Most, if not all, labeling is advertising. The term ‘labeling’ is defined in the [FFDCA] as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising.”¹⁸ The FDA has tools beyond final product labeling to govern advertising and promotional claims. Specifically, manufacturers must comply with the terms of the written Approval Order for PMA products (typically available on the FDA’s website).¹⁹

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For example, in a Warning Letter to Medtronic dated May 12, 1998, the FDA’s Office of Compliance notified Medtronic that an advertisement in an issue of the *Annals of Thoracic Surgery* made inappropriate representations about Medtronic’s Freestyle Aortic Root Bioprosthesis and that other promotional litera-

¹⁵ The FDA interpretation is based upon *Kordel v United States*, 335 U.S. 345, 347-50 (1948).

¹⁶ See *Sullivan*, 332 U.S. at 696–97 (1948).

¹⁷ See *United States v. Livdahl*, 356 F. Supp. 2d 1289 (S.D. Fla. 2005).

¹⁸ *United States v. Research Laboratories, Inc.*, 126 F.2d 42, 45 (7th Cir. 1942).

¹⁹ CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FDA, *Information on Premarket Approval Applications*, at www.fda.gov/cdrh/pmapage.html (last visited May 10, 2006).

Under the Federal Food, Drug, and Cosmetic Act (the Act) and the FDA regulations, Code of Federal Regulations, Title 21 (the Regulations), a manufacturer or others must submit a PMA for FDA review and approval before marketing certain new Class III devices. The PMA submitter must provide reasonable assurance that the device is safe and effective for its intended use and that it will be manufactured in accordance with current good manufacturing practices. As part of the review process, FDA may present the PMA to an expert advisory panel for its recommendations. After obtaining the panel recommendations, the agency makes a determination to approve the PMA, deny it, or request additional information. When the FDA either approves or denies the PMA, it must publish a notice in the Federal Register to inform the public of the deci-

ture included unsupported clinical performance claims.²⁰ The Warning Letter referenced a separate letter sent to Medtronic in March 1998 advising Medtronic that the labeling being used for the device was different from what had been originally approved. The March letter instructed Medtronic to take corrective action by adding a footnote with bolded typeface stating, “there are no clinical data available to evaluate the long-term impact of the AOA [a-Amino Oleic Acid] treatment.”²¹

The Warning Letter advised Medtronic that promotion and advertising materials must be consistent with the approved labeling as specified in the Approval Order. The FDA noted that the advertisement implied that the treatment is “known to provide long-term durability and improved hemodynamics,”²² a claim clearly inconsistent with the approved labeling. Medtronic is now in compliance with the FDA’s Warning Letter, including the following disclaimer as a footnote on its website for the Freestyle Aortic Root Bioprosthesis: “The AOA treatment has been shown in multiple animal studies to be effective in mitigating leaflet calcification. Its long-term impact in human patients has not been shown.”²³

The general point here is that PMA Approval Orders give the FDA granular control over virtually all aspects of advertising and promotion, even the style of the typeface.

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III. Valid Scientific Evidence

In addition to product labeling, the FDA is able to exert control over advertising and promotional materials through its scientific standards for medical devices. The FDA requires manufacturers to demonstrate the safety and effectiveness of

sion and make available a summary of the safety and effectiveness data upon which the decision is based. This publicly available summary does not include proprietary data or confidential information submitted by the applicant.

CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FDA, *Device Evaluation Information*, at www.fda.gov/cdrh/ode/whatwedo.html#2 (last visited May 10, 2006).

²⁰ Letter from Lillian Gill, Director, Office of Compliance, FDA Center for Devices and Radiological Health to Arthur D. Collins, President and Chief Operating Officer, Medtronic, Inc. (May 12, 1998) [hereinafter Letter from Lillian Gill to Medtronic], available at www.fda.gov/foi/warning_letters/t1762m.pdf (last visited May 10, 2006).

²¹ *Id.* at 1–2.

²² *Id.* at 2

²³ MEDTRONIC, *Freestyle® Aortic Root Bioprosthesis*, at www.medtronic.com/card-surgery/products/free_aoadurab.html (last visited Mar. 26, 2006).

a medical device using “valid scientific evidence.”²⁴ According to the FFDCA, valid scientific evidence is,

[E]vidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.²⁵

In contrast, “[i]solated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.”²⁶

As mentioned, the FDA regulatory regime depends far more on informal policy than promulgated rules. One might speculate that FDA personnel consider the FFDCA definition overly broad as the FDA typically applies a higher standard, based on stricter scientific standards. Such standards, discussed below, indirectly govern the basis of device manufacturers’ advertising and promotional content because the FDA uses them to determine whether a clinical investigation regarding the safety and effectiveness of a medical device is well controlled.

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A. *Types of Evidence*

The key scientific standards that are essential to a well-controlled clinical investigation include:

- The data collection and analysis methods should be prospectively designed, wherever possible including a clear and documented protocol.
- Controlled studies are typically considered more scientifically robust and withstand greater scientific scrutiny as compared to uncontrolled studies (such as single-arm, observational, or so-called clinical registry studies).
- The study should capture and reflect clinically relevant and meaningful endpoints.

²⁴ 21 C.F.R. § 860.7 (c)(1) (2005).

²⁵ *Id.* § 860.7(c)(2).

²⁶ *Id.*

- The study sample size should be statistically justified whenever possible.²⁷

One indicator for what the FDA considers as valid scientific evidence is whether the data and analytical findings are robust enough to support publication in the peer-reviewed scientific or medical literature.²⁸ In general, if the data are acceptable for publication in a reputable journal as a full article and not just an abstract, then the FDA will likely accept the data as valid scientific evidence.

Finally, it is important to note that valid scientific evidence is typically not only collected in the clinical setting, but may also include results from studies conducted in the laboratory, technical testing results (so-called bench data), animal studies, or some combination of these.²⁹

As an example, Johnson & Johnson's subsidiary Biosense Webster was able to provide results from an animal study³⁰ to support a very specific marketing claim of the accuracy of its CARTO XP Electroanatomical Mapping System, which allows electrophysiology cardiologists in the catheterization laboratory to "visualize catheter tip location with sensor accuracies of less than 1 mm."³¹

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B. Unacceptable Retrospective Data Analysis

The FDA does not generally accept retrospective analysis of previously collected data in support of advertising and promotional claims. Manufacturers might be tempted, of course, to perform post hoc statistical analyses on multiparameter data sets, as this is an easy exercise given that virtually all data are now collected and stored in electronic form and readily available for analysis by company scientists, statisticians, clinicians, regulatory affairs associates, upper management, and most importantly, the marketing department.

²⁷ See *id.* § 860.7(f).

²⁸ See CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FDA, *Guidance for Industry - Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review*, at www.fda.gov/cdrh/modact/evidence.html (last visited May 10, 2006).

²⁹ See 21 C.F.R. § 860.7(f).

³⁰ See CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FDA, 510(k) Premarket Notification Database, C. 510(k) Summary, www.fda.gov/cdrh/pdf2/k020863.pdf (last visited May 10, 2006).

³¹ BIOSENSE WEBSTER, JOHNSON & JOHNSON, *Carto XP System: Paving the Way to Unprecedented Accuracy*, at www.jnjgateway.com/home.jhtml?page=viewContent&contentId=09008b988008e25c&loc=USENG (last visited May 10, 2006).

This methodology, known as “data dredging,” not only fails the “good science” test, but also usually raises legitimate statistical issues relating to Type 1 Error (also known as false positives). The convention for demonstrating statistical significance of scientific data is that the calculated p-value (which specifies the probability of a positive study result occurring by chance alone) is set at $p=0.05$, or 5%. One way to interpret the practical implication of the p-value is to consider the following “thought experiment.”

Assume that a medical researcher wants to evaluate whether there is a correlation between the use of a new medical therapy (compared to the standard of care) and a specific favorable outcome such as clinical success (effectiveness) and/or the demonstration of a low incidence of adverse events (safety). It is also important to consider that the researcher may be evaluating other objective results in addition to or in lieu of clinical outcome measures that may be subject to potentially ambiguous interpretation, but are generally accepted as “surrogate endpoints” that may be considered acceptable substitutes for safety and effectiveness outcomes.

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Instead of performing this study just once as is typically the case, let us allow the researcher to repeat the same study twenty times. The p-value ($0.05 = 5\%$) tells us that the researcher likely will observe a favorable study result or clinical outcome for the new therapy (as compared to the standard of care) in at least one of the twenty experiments ($1/20 = 0.05$), but purely by chance alone. This does not mean that there really is no scientifically meaningful correlation between administration of the new therapy and the observed favorable clinical outcome. It is just not *statistically* proven—reflecting the important and inescapable paradigm of Type I Statistical Error.

Continuing the thought experiment, let us now allow the researcher to perform an equivalent evaluation, but this time doing the same experiment only once and simultaneously evaluating twenty independent measures in the hope of identifying at least one with a promising correlation to the pre-defined favorable clinical outcome. Once again, the p-value tells us that of these twenty study parameters, at least one will likely show a positive correlation with the desired clinical outcome based on chance alone.

This is the essence of why retrospective data mining is unacceptable, and prohibited as the basis of support for marketing,

advertising, and promotional materials that reflect the performance of a medical technology or therapy.

In summary, to statistically prove what appears to be a theoretical correlation between a new medical therapy and a favorable clinical outcome, the sponsor needs to perform a prospective investigation with clearly defined study endpoints intended to demonstrate in a statistically rigorous manner the validity of the correlation. Only with such support can a manufacturer make an advertising and promotion claim.

IV. Comparisons to Competitor Products

The FDA's Office of Compliance is very sensitive to manufacturers who compare the performance of their medical technology to a competitor's product. It is not uncommon for a competitor to see a promotional advertisement published in a medical journal and report this to the FDA's Office of Compliance, especially if the competitor believes that the advertisement offers an unfavorable comparison. While the Office of Compliance has limited resources to pursue enforcement activities, the content of numerous Warning Letters suggests that the agency deems this type of infraction important and that it merits further investigation, which often results in enforcement activity.

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An example is a Warning Letter dated August 12, 1999, from the FDA to Thoratec Laboratories Corporation citing "numerous claims that the agency considers objectionable."³² In the Warning Letter, the FDA notes that in a video displayed during the 1999 American Association for Thoracic Surgery Conference, "Thoratec made numerous comparative claims regarding its VAD [ventricular assist device] and the ABIOMED, Inc. BVS-5000®" and that "[t]he claims are misleading."³³ The letter explains that:

The video compares Thoratec's VAD with ABIOMED's BVS-5000 for use as an intermediate to long-term bridge to transplant. The comparison is misleading for several reasons. Bridge-to-

³² Letter from Lillian Gill, Director, Office of Compliance, FDA Center for Devices and Radiological Health to D. Keith Grossman, President and Chief Executive Officer, Thoratec Laboratories Corp. 1 (Aug. 12, 1999) [hereinafter Letter from Lillian Gill to Thoratec], available at www.fda.gov/foi/warning_letters/m2863n.pdf (last visited May 10, 2006).

³³ *Id.*

transplant is not a use for which the ABIOMED device has been approved. Your comparisons imply that ABIOMED has studied the device for that use and has sought and received such a claim, and implies that the Thoratec device is better than the BVS-5000 for such an approved claim.³⁴

V. Direct Comparison Studies

In evaluating comparison claims, the FDA generally applies the same type of scientific principles it uses to assess direct claims. Consequently, a manufacturer seeking to support performance claims relative to a competitor must collect supporting data in a manner consistent with some or all of the following study design principles:

- Comparison claims are supported by appropriate data type (bench vs. clinical).
- Comparison study is prospectively designed.
- Comparison study uses a concurrent control, which is the competitor product.
- Statistical analysis prospectively specifies the intended labeling claim and statistical methodology identifies an appropriate hypothesis to test the comparison.
- Study is adequately powered to statistically demonstrate the labeling claim.³⁵

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In the Thoratec Warning Letter, the FDA provides some guidance as to what might be necessary to support a comparison claim, namely a controlled clinical trial:

Thoratec's video quotes portions of information from two articles appearing in the *Annals of Thoracic Surgery* in 1995 and 1996. However, neither article reflects results from a *controlled clinical trial* conducted by either Thoratec or ABIOMED. Both articles instead reflect European clinical

³⁴ *Id.* at 2.

³⁵ Based on professional experience at the FDA, the author considers these design principles axiomatic for valid direct comparison claims. *See, e.g.* CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FDA, *Statistical Guidance for Clinical Trials of Non-Diagnostic Medical Devices*, at www.fda.gov/cdrh/ode/odeot476.html (last visited May 10, 2006); CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FDA, *Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA; Final Guidance for Industry and FDA Staff*, at <http://www.fda.gov/cdrh/modact/guidance/1195.html> (last visited May 10, 2006).

experience with circulatory support devices. The portions of the articles quoted are taken out of context and provide only the briefest statements of comparison between devices.³⁶

From a clinical trial design perspective, complying with the above criteria can be quite burdensome. As a result, direct comparison studies are rarely performed. Other factors that discourage manufacturers from performing direct comparison studies include the following:

- Demonstration of small changes in clinical performance often requires a prohibitively large sample size (i.e., $N > 1000$).
- Direct comparison studies are typically expensive
- The manufacturer runs the risk that the results of the study may actually favor the performance of the competitor product (although the manufacturer is not obligated to disclose the results of such studies).

When the stakes are high enough, however, a manufacturer may choose to perform a direct comparison study to support future advertising and promotion claims. In 2003, Johnson & Johnson's (J&J) Cordis division launched the REALITY Trial comparing the performance of its CYPHER sirolimus-eluting stent to Boston Scientific's Taxus paclitaxel-eluting stent. In this 1,386 patient randomized and blinded study, J&J set out to statistically demonstrate a 43% reduction in restenosis rate relative to Taxus, a clinically meaningful measure of chronic success. The trial was completed last year with favorable results to J&J. The principle investigator stated, "In this study, the incidence of stent thrombosis was 78% lower with the CYPHER stent than with the Taxus stent."³⁷ With these results, J&J may have the necessary data to support a marketing claim of the superiority of CYPHER when compared directly to the performance of Boston Scientific's Taxus drug-eluting stent, a claim which ultimately could translate into billions of dollars in additional sales of this blockbuster technology.

³⁶ Letter from Lillian Gill to Thoratec, *supra* note 32, at 2 (emphasis added).

³⁷ JOHNSON & JOHNSON, *REALITY Trial Data Suggest Drug-Eluting Stents Differ Significantly in Rate of Blood Clot Formation – Stent Thrombosis*, Mar. 6, 2005, available at www.jnj.com/news/jnj_news/20050306_100405.htm;jsessionid=K1DG3BWQMCXC4CQPCB3WU3QKB2IIWTT1 (last visited May 10, 2006).

VI. Off-Label Use

Off-label use of medical devices is a medical practice with significant implications for advertising and promotion. The FDA's Office of Compliance may aggressively pursue off-label use via the Warning Letter and occasionally with more severe enforcement activities. Off-label use is defined as "an intended use other than that in the proposed labeling."³⁸ It is important to distinguish between off-label use of a medical device that occurs as part of "the practice of medicine" and that which is promoted by a manufacturer either intentionally or unintentionally. The former is allowed; the latter is not.

According to the FDA's Guidance for Institutional Review Boards (IRBs) and Clinical Investigators (1998 Update):

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner *when the intent is the "practice of medicine"* does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.³⁹

This critical concept is often summarized as, "The FDA does not regulate . . . the practice of medicine."⁴⁰ That being said,

³⁸ CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FDA, DETERMINATION OF INTENDED USE FOR 510(K) DEVICES; GUIDANCE FOR CDRH STAFF (UPDATE TO K98-1) (2002), *available at* www.fda.gov/cdrh/ode/guidance/857.pdf (last visited May 10, 2006).

³⁹ OFF. OF THE COMM'R, FDA, "Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices, in INFORMATION SHEETS: GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS 1998 UPDATE, *available at* www.fda.gov/oc/ohrt/irbs/offlabel.html (last visited May 10, 2006) (emphasis in original).

⁴⁰ See, e.g., Letter from Steven M. Niedelman, Acting Director, Office of Compliance, FDA Center for Devices and Radiological Health to Joseph W. Spadafora, D.O., St. Lucy's Outpatient Surgery Center (Jul. 19, 2000) *available at* www.fda.gov/oc/ohrt/irbs/offlabel.html

however, the FDA does regulate the practice of medicine when specifically promoted by the medical device industry, and policing the off-label promotion of medical technology through enforcement activities is an important aspect of the mandate of the FDA's Office of Compliance.

There are several ways in which companies either intentionally or unintentionally promote a medical therapy for an off-label intended use:

- Different Patient Population
- Different Intended Use
- General vs. Specific Intended Use

For an example of the promotion of different patient populations, consider again the Thoratec Warning Letter dated August 12, 1999.⁴¹ The VAD at that time was approved to treat bridge-to-cardiac-transplant heart failure patients.⁴² In the promotional video, however, Thoratec made claims for use of the VAD to treat patients with viral myocarditis, which was not an approved use for the device because it constitutes a different patient population.⁴³ At the conclusion of the Warning Letter, Thoratec was notified to:

[T]ake prompt action to correct these violations. Failure to promptly correct these violations may result in FDA's initiating regulatory action without further notice. These actions include, but are not limited to, seizure, injunction and/or civil money penalties.

Please notify [CDRH's Office of Compliance] in writing, within 15 working days of your receipt of this letter, of the specific steps that you have taken to correct the noted violations.⁴⁴

fda.gov/foi/warning_letters/m3970n.pdf (last visited May 10, 2006); Ctr. for Devices & Radiological Health, *Drug Information, Questions and Answers on Paxil*, available at www.fda.gov/cder/drug/infopage/paroxetine/paxilq&a.htm (last visited May 10, 2006); CTR. FOR DEVICES AND RADIOLOGICAL HEALTH, FDA, *LASIK Eye Surgery: What is LASIK?*, available at www.fda.gov/cdrh/LASIK/what.htm (last visited May 10, 2006).

⁴¹ Letter from Lillian Gill to Thoratec, *supra* note 32.

⁴² *Id.* at 1-2.

⁴³ *Id.* at 1.

⁴⁴ *Id.* at 7.

A Warning Letter dated April 28, 1999, to Cordis Corporation addressed the issue of different intended use.⁴⁵ The FDA cited that the manufacturer published an advertisement in *Endovascular Surgery* regarding its S.M.A.R.T. stent, which, according to the FDA, promoted an implied claim of off-label use for the stent.⁴⁶ At the time, many interventional cardiologists used biliary stents off-label to treat coronary blockages. However, biliary stent manufacturers were not permitted to promote this off-label use. The FDA cleared Cordis' S.M.A.R.T. stent in 1998 with the following indication: "The Cordis Nitinol Stent and Delivery System is intended for palliation of malignant neoplasms in the biliary tree."⁴⁷ The FDA's clearance of this product imposed several limitations and requirements on the labeling and marketing of the stent. The clearance letter advised Cordis that CDRH's Office of Device Evaluation "had determined that there was a reasonable likelihood that this device would be used for an intended use not identified in the proposed labeling and that such use could cause harm"⁴⁸ and directed the company to include the following limitation in the Warnings section of the stent labeling: "The safety and effectiveness of this device for use in the vascular system have not been established."⁴⁹ The Warning Letter stated that:

An ad that appears in the February, 1999 issue of *Endovascular Surgery*, called also on its cover "an Interdisciplinary Journal for Vascular Specialists," advertises Cordis' S.M.A.R.T. stent and refers to it as being from Cordis Endovascular. The ad makes an implied claim for vascular use for the stent because it appears in a journal intended for vascular specialists.⁵⁰

Likewise in this letter, the FDA notified the manufacturer to "take prompt action to correct these violations" with the same warning about possible enforcement consequences with a failure to do so in a timely manner.⁵¹

⁴⁵ Letter from Lillian Gill, Dir., Office of Compliance, FDA Center for Devices and Radiological Health to Bob Coradini, President and Chief Executive Officer, Cordis Corp. (Apr. 28, 1999) [hereinafter Letter from Lillian Gill to Cordis], available at www.fda.gov/foi/warning_letters/m2569n.pdf (last visited May 10, 2006).

⁴⁶ *Id.* at 2.

⁴⁷ *Id.* at 1.

⁴⁸ *Id.*

⁴⁹ *Id.*

⁵⁰ Letter from Lillian Gill to Cordis, *supra* note 45, at 2.

⁵¹ *Id.*

The third and final example involves the important distinction between “general” and “specific” intended use. In a Warning Letter dated May 14, 1998, to RadioTherapeutics Corporation,⁵² the FDA noted that RadioTherapeutics’ radiofrequency (RF) generator was granted marketing clearance with the intended use as “a medium power electrosurgical generator intended for use with separately approved electrodes for the thermal coagulation of soft tissues.”⁵³ The Warning Letter observed, however, that in a press release dated April 30, 1998, RadioTherapeutics Corporation described the device as utilizing radiofrequency energy to ablate or destroy diseased tissue and that it has been used clinically to treat primary and metastatic liver tumors. The Warning Letter quoted the press release: “In clinical trials, the RadioTherapeutics AF Ablation System is demonstrating its potential to address the significant need for an alternative or complementary treatment for liver tumors that cannot be removed surgically.”⁵⁴ This example illustrates that a manufacturer is not permitted to promote a medical technology that has been cleared for a general indication, such as “for coagulation of soft tissue,” to be used in a more specific manner, in this case “for the treatment of liver tumors.”

The letter cited the specific violation of FDA law as follows:

The statements in all of these press releases that the RadioTherapeutics RF Ablation System is effective in treating liver cancers and tumors have changed the intended use of your product. RadioTherapeutics Corporation has not presented to the agency evidence to support these claims. . . . The press releases have misbranded the RF Ablation System within the meaning of section 502(o) because no notice or other information respecting the device was submitted to FDA as required by section 510(k) of the Act and as provided in FDA’s regulations at 21 CFR 807.81(a)(3)(ii), which require the submission of premarket notification for a major change or modification in the intended use of a marketed device.⁵⁵

⁵² Letter from Lillian Gill, Dir., Office of Compliance, FDA Center for Devices and Radiological Health to Robert Behl, Chief Executive Officer, RadioTherapeutics Corp. (May 14, 1998) [hereinafter Letter from Lillian Gill to RadioTherapeutics], available at www.fda.gov/foi/warning_letters/d1783b.pdf (last visited May 10, 2006).

⁵³ *Id.* at 1.

⁵⁴ *Id.*

⁵⁵ *Id.* at 2.

The important point is that in order to gain market clearance of a more specific indication, the manufacturer would likely be required to provide the FDA with clinical performance data demonstrating the safety and effectiveness of the device for the more specific intended use.

VII. Enforcement

As noted in the Warning Letters, the FDA's Office of Compliance typically instructs the manufacturer to take prompt action to correct the stated violations. Failure to promptly correct the violations can result in the FDA initiating enforcement actions, which include but are not limited to seizure, injunction, civil money penalties, and criminal investigations that occasionally result in felony convictions.⁵⁶ This section of the Article briefly summarizes two examples of FDA enforcement actions relating to off-label use of medical technology, and finishes with an example of an enforcement action unrelated to advertising and promotion, but illustrative of the significant enforcement authority that the FDA has at its disposal for egregious violations of federal law.

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In 2000, Laser Vision Centers, Inc., agreed to pay \$1.5 million in civil money penalties for illegal distribution of "Bermuda Cards" which enabled certain VISX excimer lasers to be used for capabilities beyond those approved by the FDA. The manufacturer elected to pay the fine rather than go to court.⁵⁷

Study investigators as well as medical device manufacturers are subject to significant monetary penalties for violating FDA law. In one case, the investigator, an ophthalmologist, agreed to pay \$1.1 million in civil monetary penalties levied by the FDA for violations during a clinical study of LASIK therapy for nearsightedness.⁵⁸ The violations that occurred on at least 175

⁵⁶ See, e.g., *id.* at 3; Letter from Lillian Gill to Cordis, *supra* note 45, at 2; Letter from Lillian Gill to Thoratec, *supra* note 32, at 2; Letter from Carol A. Hepe, District Director, FDA Cincinnati District Office to Dennis Dirksen (Sept. 5, 2003), available at www.fda.gov/foi/warning_letters/g4319d.pdf (last visited May 10, 2006); FDA REGULATORY PROCEDURES MANUAL, *supra* note 4, at 10-5.

⁵⁷ CTR. FOR DEVICES & RADIOLOGICAL HEALTH, FDA, CDRH ANNUAL REPORT FISCAL YEAR 2000 at 11 (2000), available at www.fda.gov/cdrh/annual/fy2000/annualreport-2000.pdf (last visited May 10, 2006).

⁵⁸ Press Release, FDA, Louisiana Ophthalmologist Fined \$1.1 Million by FDA For Clinical Study Violations (Nov. 5, 2003), available at www.fda.gov/bbs/topics/news/2003/new00972.html (last visited May 10, 2006).

occasions involved studies of a laser built by the physician,⁵⁹ and included:

- “Us[ing] an unapproved laser on patients before the study began”;
- “Treat[ing] more subjects than allowed under the study plan that was approved by FDA”;
- “Ignor[ing] parameters of the study by treating near-sightedness beyond the permitted range and by treating astigmatism and both eyes of some patients”;
- “Fail[ing] to submit complete, accurate, and timely reports to FDA about the ongoing study”;
- “Misrepresent[ing] to FDA that [the primary investigator] was using an FDA-approved laser to treat patients when, in fact, the procedures were performed with an unapproved, experimental laser.”⁶⁰

The salient aspects of this FDA enforcement action reveal that “studies of high risk devices such as ophthalmic lasers must be conducted according to an investigational plan reviewed and approved by the FDA and an investigator must obtain [adequate] informed consent from each participant” before treating the subject with the investigational therapy.⁶¹

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The final example represents the largest monetary penalty ever paid to the FDA by a medical device manufacturer and one of the first times such conduct led to felony convictions for failing to report device malfunctions and patient deaths to the FDA. In 2003, Guidant Corporation plead guilty and agreed to pay \$92.4 million for alleged violations regarding Endovascular Technologies (EVT), a wholly owned subsidiary of Guidant, and the Ancure Endograft System, a device used to treat aortic aneurysms.⁶² During clinical trials and during surgeries, doctors reported that they were having difficulty implanting the device and removing part of it in the manner called for by the approved Instructions for Use labeling.⁶³ In some instances, the device

⁵⁹ *Id.*

⁶⁰ *Id.*

⁶¹ *Id.*

⁶² *Guidant Corp. Subsidiary Pleads Guilty, Will Pay \$92 Million in Medical Device Case*, 12 HEALTH L. REP. (BNA) 967 (2003) [hereinafter *Guidant*].

⁶³ Linda Bren, *Company Caught in Coverup of Medical Device Malfunctions*, FDA CONSUMER, Nov.–Dec. 2003, at 42, available at www.fda.gov/fdac/departs/2003/603_irs.html (last visited May 10, 2006).

lodged in the body, requiring surgery to remove the system and correct the aneurysm.⁶⁴ According to a press release from the U.S. Department of Justice, EVT knew about the malfunctions because its sales representatives were “present in the operating room during each surgery” and because “reports of those failures were repeatedly tabulated and distributed to company officials.”⁶⁵ The FDA cited the following alleged violations:

- Guidant failed to report thousands of adverse events including twelve patient deaths;
- EVT admitted it failed to tell the FDA about device malfunctions; and
- EVT admitted that the device, which it claimed to be an alternative to surgery, malfunctioned thirty-three percent of the time it was used during a nineteen-month trial.⁶⁶

This example illustrates that because the FDA rules and regulations regarding reporting device malfunctions, adverse events, and patient deaths may be subject to interpretation under some ambiguous clinical circumstances, it is ultimately in the best interest of the manufacturer to take a prudent and conservative approach to managing the situation. This should include timely contact with the FDA to elicit feedback and guidance regarding proper implementation of patient safety measures and accurate interpretation of FDA reporting requirements.

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VIII. Conclusion

Advertising and promotion of medical devices is a significant post-market activity of the regulated industry. While maintaining a competitive marketing strategy is increasingly important in today’s medical marketplace, it is also critical to remain in compliance with FDA statutes and regulations regarding advertising and promotion of medical products. Disregarding these principles can result in FDA enforcement actions, including receiving a Warning Letter, which is publicly available, or possibly more severe consequences including monetary and occasionally criminal penalties.

⁶⁴ Kurt Eichenwald, *Maker Admits It Hid Problems in Artery Device*, N.Y. TIMES, June 13, 2003, at A1.

⁶⁵ Press Release, U.S. Attorney’s Off. N.D. Cal., U.S. Dep’t of Justice (June 12, 2003), available at www.usdoj.gov/usao/can/press/html/2003_06_12_endovascular.html (last visited May 10, 2006).

⁶⁶ *Guidant*, *supra* note 66, at 967.