Recent Untitled Letters for Off-Label Promotion

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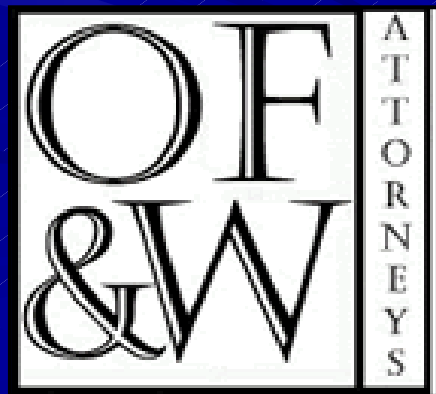

Untitled Letters

- Untitled Letters address off-label promotion violations that are less serious than those addressed in Warning Letters.
- FDA usually requests that a company take specific action to bring the company into compliance within a certain amount of time, usually 30 working days.
- May also serve as a basis for additional regulatory action by the agency.

Off-Label Promotion

- Claims regarding uses of a medical device that have not been reviewed or cleared via a premarket notification (510(k)) or a premarket approval application (PMA).
- Misbrands devices under 21 U.S.C. § 352(o).
- Adulterates devices under 21 U.S.C. § 351(f)(1)(B).

Off-Label Promotion Leading to Untitled Letters

- Promotion outside cleared indications.
- Website promotion.
- Manufacturer-funded educational activities.
- General v. specific claims.

Promotion Outside of Cleared Indications for Use

- Modifies the intended use(s) of the device.
- Requires submission and prior clearance/ approval of a new 510(k)/PMA.

Johnson & Johnson
April 2004

- Product: Band-Aid Scar Healing Gentle Adhesive
- Clearance: 510(k) for the management of both old and new hypertrophic and keloid scars. It can also be used as a prophylactic therapy on closed wounds which may prevent hypertrophic or keloid scarring.
- FDA's Concern: Current labeling includes word "healing" and "implies that the device promotes wound closure, which involves the restoration of diseased parts, thereby curing the wound." This major modification requires a new premarket submission.

A Personal Solution
April 2004

- Product: PelvicFlexer Exercise Device
- Clearance: 510(k) “to assist women in performing Kegel Exercises which may help control stress urinary incontinence.”
- FDA’s Concern: Company’s website promote the device for other uses including: reducing the need for corrective surgery, promoting perineal healing after childbirth, treating constipation and sexual dysfunction, and reducing menstrual cramps and pelvic pain. These uses are beyond the scope of the device’s clearance.
- Company needs new premarket submission for these uses.

Anurex
May 2004

- Product: Anurex
- Clearance: 510(k) for “prompt temporary relief from hemorrhoidal pain and itching, to reduce bleeding and promote healing of the inflamed tissues, and to help avoid painful surgery.”
- FDA’s Concern: Website claims Anurex is effective for “lesions, hematomas, thrombosis, anal fissures, and fistulas, as well as irritation due to prostatistis, irritable colon, and HIV” and for conditions such as “papillitis, post-surgical fibrous stenosis” and others. These uses are beyond the scope of the device’s clearance.
- Company needs new premarket submission for these uses.

KaVo America
March 2005

- Product: DIAGNOdent Laser Fluorescence Caries Detection Device
- Clearance: 510(k) as an aid in the diagnosis of caries.
- FDA's Concern: KaVo's submission did not support absolute caries detection but print advertisement is currently marketing device for complete caries detection, claiming that it provides "accurate, reliable caries detection" and that the device is "the new standard of care in caries detection."
- FDA directs KaVo to cease marketing for absolute caries detection.
- Example of how the scope of 510(k) clearance affects post-clearance promotional parameters.

Power Products
October 2004

- Product: Sleep Right Adjustable Night Guard
- Clearance: 510(k) for prescription use for (1) protection against teeth grinding, bruxism and jaw clenching, (2) short-term pain relief from muscle spasm due to occlusal interference and (3) prevention of chronic tension and temporal mandibular syndrome caused by chronic jaw clenching.
- FDA's Concern: Website promotes Sleep Right for non-prescription use and for headache reduction – both are not cleared uses so a new premarket submission is necessary.

Website Promotion

- Company: United Pacific Company, January 2003.
- Facts: Firm's website included international product indications that were not cleared or approved in the United States.
- FDA's Concern: International claims, not cleared or approved in the US, may become associated with the domestic version of the product, constituting off-label promotion. Company may not promote a device in the U.S. for uses not approved in the U.S. Any such discussion should be placed under a separate foreign/international icon.

FDA's View

- Where firms sell devices outside of the United States, the firm's website should have separate sections where one is dedicated to international customers (under a separate international icon) and the other provides information meant for domestic customers.
- Bifurcation of website should occur at the first page a visitor will visit so it is immediately apparent that there are separate international and domestic versions.

Manufacturer-Funded Educational Activities

- Where a manufacturer sponsors a publication or an educational event, FDA will hold the manufacturer responsible for the claims contained therein.

Pharmacia
April 2003

- Product: Tecnis Foldable Intraocular Lens
- Approval: PMA for primary implantation for the visual correction of aphakia in persons 60 years old or older in whom a cataractous lens has been removed by phacoemulsification.
- Facts: Manufacturer provides a grant to clinicians who provide articles regarding their experience with the product. These articles are published in *Review of Ophthalmology.*

Pharmacia
April 2003

- FDA's Concern:
  - Several articles discuss the Tecnis lens for indications not identified in the relevant PMA.
  - Articles contained superiority claims of the Tecnis lens compared to other marketed lenses.
  - Manufacturer was told to submit a PMA supplement for review and approval prior to making these claims.

General v. Specific Claims

- A change in a device's indication for use from general to specific (e.g., a change that results in an indication for use that is narrower than the approved or cleared general use).
- A more specific indication can modify the device's intended use and may require submission and prior clearance/ approval of a new 510(k)/PMA.

Syneron Medical Ltd
May 2003

- Products:
  - Auro DS for non invasive hair removal.
  - Auro SR for treatment of superficial benign vascular pigmented lesions.
- Clearance: 510(k).
- FDA's Concerns:
  - The Company is promoting the device for claims that are not included in the product's general clearance for the treatment of superficial and benign pigmented lesions.

Syneron Medical Ltd
May 2003

- Examples:
  - Company's Return on Investment Analysis states that lasers can be used to treat telangiectasia, rosacea, and non-ablative skin rejuvenation of the neck, face and hands
  - Product brochure shows pictorial representations for pre- and post-treatment results from telangiectasia, rosacea, skin renewal and age spots.
    - Telangiectasia and rosacea are specific types of benign vascular lesions.
    - Age spots are specific types of pigmented lesions.

Syneron Medical Ltd
May 2003

- FDA's Rationale:
  - Telangiectasia is associated with small blood vessels on the nose. Inappropriate use could result in scarring of the face. Removal of blood vessels in the leg requires more energy and exposure time.
  - Rosacea treatment also can result in scarring.
  - Need skill to remove age spots on the neck without scarring.
  - The device's current clearance did not contemplate these increased risk factors.
  - Company needs new premarket submission for these uses.

4-D Neuroimaging February 2003

- Product: 4-D Neuroimaging Vectorview Magneto Encephalograph Systems
- Clearance: 510(k) for use in diagnostic procedures requiring the measurement and display of extracranial magnetic fields and electrical activity in the brain.
  - General clearance to display information that can be used to diagnose conditions by trained clinicians.

4-D Neuroimaging February 2003

- FDA's Concern: Device is being promoted for uncleared specific indications:
  - Treatment of epilepsy: Language on company's web site implies that device detects and evaluates epileptogenic brain activity.
    - "[The device] provid[es] information about the location and sources of magnetic fields produced by epileptogenic brain activity which may be useful in evaluating candidates for surgical treatment of the epilepsy."
    - CDRH stated more appropriate wording is: "displaying extracranial magnetic fields and information about the electrical activity in the brain which can be diagnosed by a trained clinician."

4-D Neuroimaging February 2003

- Other Uncleared Specific Indications: Company's website includes promotion for other "potential applications" all of which have not been evaluated or cleared by the agency.
  - E.g., functional assessment of closed-head trauma, schizophrenia, problems of the heart, brain, and spine, etc.
- Discussion of Investigational Use of Device: Website also links to information regarding investigational use of device in more specific applications.

4-D Neuroimaging (again!) March 2003

- Product: Same.
- Clearance: Same.
- FDA's Concern: Same.
  - Under "What's new" and "Recent Items" links on the company's website, there was a discussion regarding the results of clinical investigations concerning the use of the device for uncleared indications.
  - Information concerns the same uncleared indications and potential applications noted in previous communication. It would be more appropriate to place this information under an "Investor Relations" link.

Johnson & Johnson January 2003

- Product: UltraCision Scalpel
- Clearance: 510(k) for "soft tissue incisions when minimal bleeding and thermal injury is desired."
- FDA's Concern: Device is being promoted for the specific use of radial artery harvesting.
  - After much discussion, FDA permitted the company to include radial harvesting in the labeling as an example of how the product may be used but insisted that radial artery harvesting not be included as an indication for use.

How to Respond to FDA

- Introductory Call
- Written Response

Introductory Call

- Introduce yourself.
- Gather additional information from the agency.
- Commit to a written response.
- Discuss timeframe if necessary.
- Establish a relationship.

Written Response

- Depending on the circumstances, opening remarks to give an overview of your company, its products, and regulatory history to provide context for reviewing officials.
- A statement of the company's commitment to follow the law.
- Other relevant comments.

Addressing FDA Observations (Micro)

- Individually address each specific observation/ example raised by FDA.
- Quote the FDA observation and follow it with your company's response.
- Explain:
  - If appropriate, what the questioned statement was intended to convey about the product;
  - What are you doing to correct the problem.

Addressing FDA Observations (Macro)

- After you have specifically addressed FDA's specific issues, explain any broader prospective or retrospective actions you plan to address any other promotional issues that could cause the same concern.
  - Retrospective items can be searches to determine how such problems arose in the past.
  - Prospective items are, generally, those that prevent identified or similar problems from occurring in the future.

Macro v. Micro

- Generally, want to provide both a macro and a micro explanation for each observation.
- At times it may be advantageous to omit one or the other.
  - If a specific “micro” observation is indefensible, emphasize the “macro.”
  - If a “macro” response could indicate a broader problem, you may wish to emphasize the “micro.”
  - Fact dependent.

Tone

- Remain professional.
- Adversarial tone is not appropriate.
- Clearly state the company's position.
- If you do not agree with an observation, state it up front (e.g. "we do not agree with this observation") and why.

Tone

- If you do agree with an observation and circumstances warrant, explain why the company did what it did and then tell FDA how the company will respond.
- Remain responsive to FDA and respectful of its concerns.
- Remember that your response can be publicly available through FOIA.

Timing

- Submit responses as soon as possible.
- Generally, within two weeks but always within any timeframe indicated by FDA.

Before Submitting a Response

- Put the document through a legal and technical review by in-house and/or outside experts.
  - Ensures there will not be unforeseen regulatory consequences.
  - Ensures that the company is addressing the right issue in the proper manner.

Other Considerations

- Be realistic - ensure you do not over-commit and set your company up for future problems by setting unrealistic goals you will not be able to meet.
- Whenever possible:
  - provide dates for actions to be taken;
  - avoid making admissions;
  - take corrective actions prior to submitting response;
  - provide supportive documentation (but no more than necessary);
  - explain any time lags in corrective/preventive action if appropriate.
- BUT – use care, do not sacrifice quality or practicality for expediency.

Other Considerations

- Never lie or try to mislead FDA.
  - May trigger criminal liability under 18 U.S.C. § 1001.
- May want to hire an attorney or expert consultant to:
  - conduct an audit;
  - evaluate FDA's observations;
  - provide input;
  - Advise company on a continuing basis.
- If an attorney or consultant is engaged, mention the participation wherever appropriate in your response.

Other Considerations

- Designate any trade secret or confidential information to set the stage for appropriate redaction of trade secrets or other confidential information.
- Involve the company's advertising and promotion people to address the matter at hand and to prevent reoccurrences.

After the Response

- Provide updates (if appropriate).
- Keep your commitments.
  - But if forced into a position where you cannot, explain to FDA your need to make a change.
- Follow up with a request to meet with the agency to discuss its concerns, if appropriate.

Questions?