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E-ALERT | Food & Drug

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2012 END-OF-YEAR SUMMARY OF FDA PROMOTIONAL ENFORCEMENT ACTIVITY

This client alert reviews the warning and untitled letters issued in 2012 by the Office of Prescription Drug Promotion (OPDP) of the Center for Drug Evaluation and Research (CDER), the Office of Compliance and Biologics Quality (OCBQ) of the Center for Biologics Evaluation and Research (CBER), and the Office of Compliance (OC) of the Center for Devices and Radiological Health (CDRH).

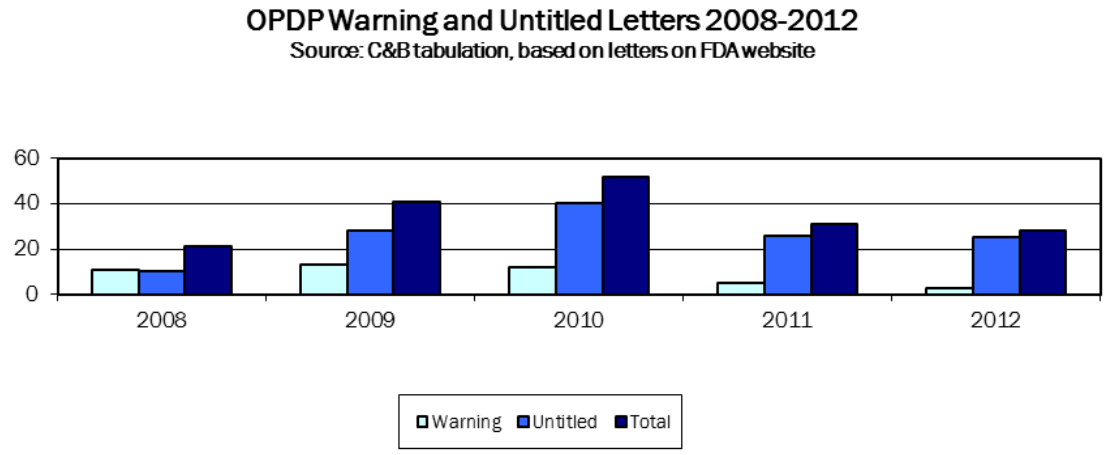
We examined the 28 warning and untitled letters issued by OPDP, the 4 warning and 1 untitled letters issued by OCBQ, and the 15 warning letters regarding promotional activities for approved or cleared devices issued by OC. We tabulated the most frequently cited allegations, leaving out allegations included in only a few letters.

This alert merely summarizes the allegations contained in FDA's letters. It does not contain any analysis, opinions, characterizations, or conclusions by or of Covington & Burling LLP. As a result, the information presented herein does not necessarily reflect the views of Covington & Burling LLP or any of its clients.

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

ENFORCEMENT ACTIVITY

In 2012, OPDP issued a similar number of enforcement letters as it did in 2011 (28 letters versus 31 letters). This represents a two-year decline, reversing a trend of increased enforcement action between 2008 and 2010, which peaked in 2010 with 52 enforcement letters.

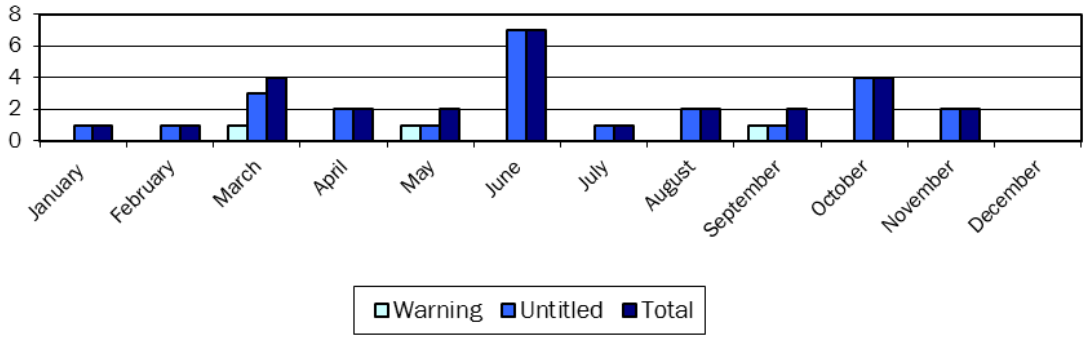


In keeping with OPDP's tendency over the last several years of increased reliance on untitled letters, of the 28 letters issued by OPDP in 2012, 89% were untitled letters and 11% were warning letters.[1] As in 2011, the average number of allegations in each letter was approximately 2.3 (counted by the number of headings in each letter). In 2010, the average number of allegations per letter was 3.2.

OPDP also continued to rely on FDA's "Bad Ad" Program, which the Agency launched in May 2010.[2] The Bad Ad Program is designed to encourage healthcare providers to report false or misleading drug advertising and promotional materials to FDA. To further promote awareness and encourage reporting, in the second year of the program (2011–2012) FDA developed (1) a web-based continuing education program; (2) case studies of misleading prescription drug promotion; and (3) a Bad Ad journal advertisement for placement in widely circulated healthcare professional journals.[3] Since the beginning of the program, OPDP has received hundreds of complaints of potentially untruthful or misleading promotion. In one case, OPDP reported receiving a record 33 complaints on a single advertisement. In 2012, OPDP issued at least three letters as a result of promotional materials reported through the Bad Ad program.[4] This is fewer than OPDP issued in 2011, when at least five letters were issued as a result of such reports.

Throughout 2012, the number of letters issued by OPDP varied each month. June was the month with the most number of letters issued (six letters), and December was the month with the least number of letters issued (zero letters). The number of letters also peaked once in the spring (March, four letters) and once in the fall (October, four letters). Other than few enforcement letters being issued in the early months of the calendar year, and June being an active month for enforcement letters, there is no discernible trend in the timing of OPDP's enforcement letters over the last two years.

OPDP Letters Issued by Month (2012)
Source: C&B tabulation, based on letters on FDA website



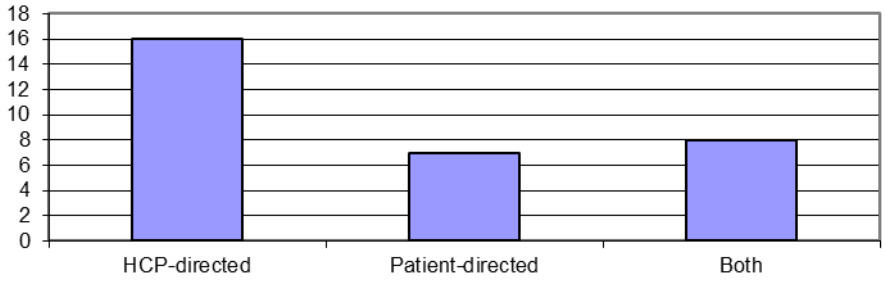
[1] In 2008, 48% of OPDP's enforcement letters were untitled letters. In 2009, 68% were untitled letters; in 2010, 77% were untitled letters; and in 2011, 84% were untitled letters.
[2] *See* FDA, Press Release, "Bad Ad Program" to Help Health Care Providers Detect, Report Misleading Drug Ads (May 11, 2010), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm211611.htm.
[3] FDA, Bad Ad Program: 2011-2012 Year End Report, *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm258719.htm.
[4] In three instances in 2012, FDA specifically identified the Bad Ad Program as being responsible for bringing the subject promotional piece to the Agency's attention. It is unclear whether other enforcement letters were issued by FDA as a result of the Bad Ad Program.

CONTENT OF ENFORCEMENT LETTERS

Promotional Pieces at Issue

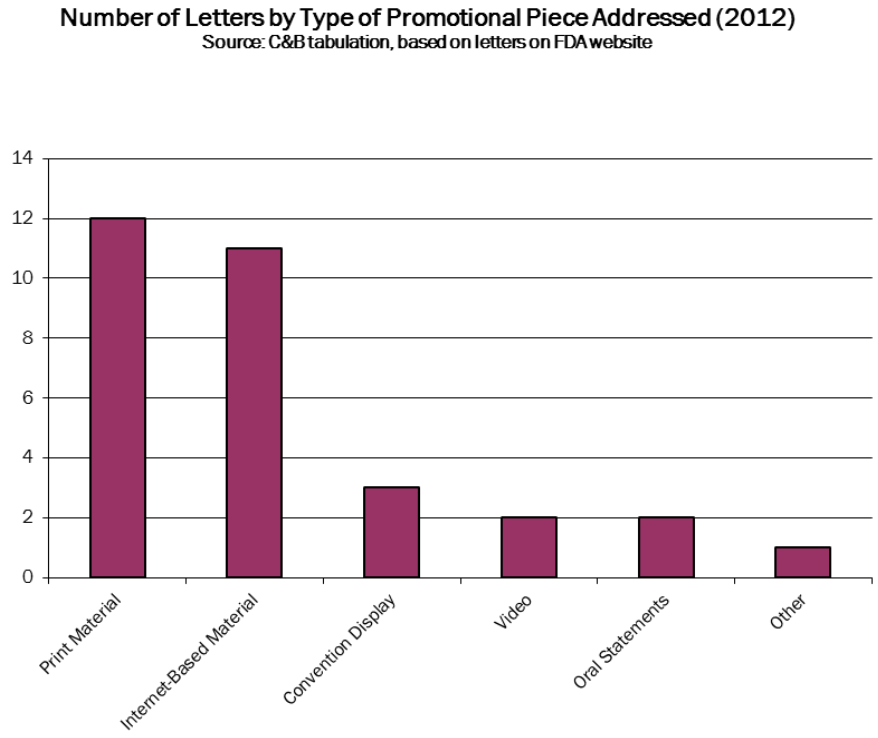
In keeping with past years, a significant portion of OPDP's enforcement letters addressed materials directed toward healthcare professionals. In 2012, 57% of OPDP's letters focused on promotional pieces—such as sales aids and healthcare professional websites and journals—specifically directed at healthcare professionals. This is less than in 2011, when 74% of OPDP's letters addressed these types of materials, but roughly the same as 2010, when 54% of the Agency's letters addressed healthcare professional materials. In contrast, 25% of OPDP's letters in 2012 addressed patient-directed materials—a slight increase from 20% in 2011. Materials that were directed toward both healthcare professionals and patients (e.g., general use websites with no distinguishable audience) were addressed in 29% of OPDP's letters in 2012.[5] This is a noticeable increase from 2011, when only 10% of the letters addressed materials directed toward both audiences.

Number of Letters by Audience (2012)
Source: C&B tabulation, based on letters on FDA website



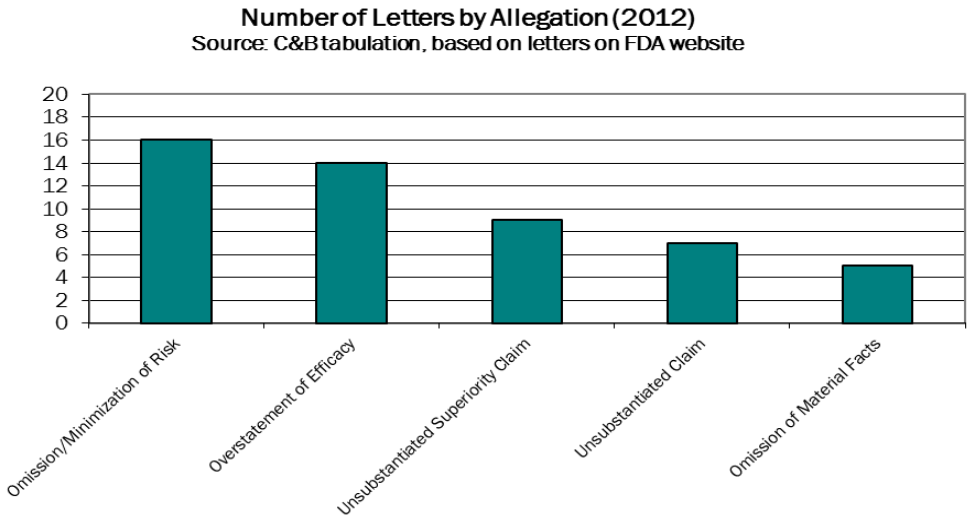
In 2012, OPDP's letters addressed a wide range of promotional pieces, including print materials (e.g., journal advertisements, sales aids, and brochures); Internet-based materials (e.g., websites, web videos, and podcasts); videos; convention displays; oral statements by sales representatives; and a professional telephone script. As in past years, print materials were the most frequently cited medium (43%). This is significantly less, however, than in 2011 when 58% of enforcement letters cited print materials. Notably, the number of enforcement letters that cited Internet-based materials increased in 2012 (39%) from 2011 (26%). Moreover, the margin of difference between the number of letters that cited print materials versus Internet-based materials in 2012 was minimal, possibly reflecting the increasing popularity of websites as vehicles for drug promotion.

[5] These percentages do not add up to 100% because several letters discussed multiple types of promotional pieces (e.g., a general use website and an exhibit at a professional meeting).



OPDP's Allegations

With one exception, OPDP's 2012 letters contained allegations that are similar to those in letters from previous years. In 2012, OPDP's letters focused in large part on the following allegations: (1) omission and/or minimization of risk information, (2) overstatement of efficacy, (3) unsubstantiated superiority claims, (4) unsubstantiated claims (a broader category than unsubstantiated superiority claims), and (5) omission of materials facts. These areas of focus were also the most cited allegations in 2011 and 2010, with the exception of omission of material facts.



1. Omission and/or Minimization of Risk Information

Sixteen letters (57%) issued by OPDP in 2012 contained allegations that the promotional piece(s) omitted and/or minimized the risks of the drug. Such allegations typically focus on promotional pieces that, according to OPDP, omit all risk information, include risk information but omit a particularly important aspect, or include risk information but present it in a way that minimizes its importance. For example, in an April 2012 untitled letter, OPDP stated that a telephone script that included efficacy claims regarding a drug omitted all risk information associated with the use of the drug. Although the script included instructions "indicating that if an adverse event 'is mentioned' the sales representative should 'follow the appropriate procedures,'" OPDP explained this was insufficient to mitigate the telephone script's misleading presentation.

2. Overstatement of Efficacy

Fourteen letters (50%) alleged that the promotional piece(s) overstated the efficacy of the drug. These types of allegations by OPDP typically encompass outcome guarantees, survival or long-term outcome claims, and suggestions or statements that a drug is more efficacious than has been demonstrated. For example, in a September 2012 untitled letter regarding a direct-to-consumer brochure, OPDP stated that the brochure misleadingly implied that the drug would improve specific individual systems in patients with treatment-resistant schizophrenia. As OPDP explained, the drug's clinical trials evaluated composite scale scores, a demonstrated effect on which "does not demonstrate an effect on an individual component of these scales." OPDP stated that the brochure's claims with respect to individual unmeasured symptoms were overstated and unsubstantiated.

3. Unsubstantiated Superiority Claims

Nine letters (32%) issued by OPDP in 2012 addressed unsubstantiated superiority claims. When FDA alleges that a promotional piece contains unsubstantiated superiority claims, the focus is often on claims that state or suggest that the subject drug is superior to other treatment options when this has not been demonstrated. For example, in an October 2012 untitled letter, OPDP pointed to claims in a pitch letter and press release that misleadingly implied that the drug was superior to other animal-derived surfactants for reducing the mortality associated with Respiratory Distress Syndrome. The claims at issue referenced a retrospective, observational, cohort study that did not include a pre-specified efficacy analysis comparing the three surfactant products. According to OPDP, this study design was inadequate to support the promotional materials' comparative effectiveness claims.

4. Unsubstantiated Claims

Seven letters (22%) addressed unsubstantiated claims. These types of claims encompass statements, explicit or implied, that tout the subject drug for results or outcomes, which have not been sufficiently demonstrated. In a March 2012 untitled letter, for example, OPDP cited a claim on a website that suggested patients who used the drug experienced an improvement in satisfaction with their self-appearance. OPDP stated that this claim was misleading and unsubstantiated because the study referenced in support of the claim had failed to demonstrate any significant difference between treatment groups in the relevant self-appearance domains.

5. Omission of Material Facts

Five OPDP letters (18%) addressed promotional materials that omitted material facts. These types of allegations focus on promotional materials that fail to include important information, such as the

intended patient population, dosing parameters, or misstated outcomes. For example, in a May 2012 untitled letter, OPDP described a branded story about an individual diagnosed with hepatitis C who had not responded to other treatment. Once treated with the promoted drug, however, the individual claimed he had "cleared the virus." OPDP stated that claims such as this one misleadingly implied that the drug (as part of a combination therapy) removed hepatitis C virus from the body, even though patients with undetectable levels may still have replication-competent virus.

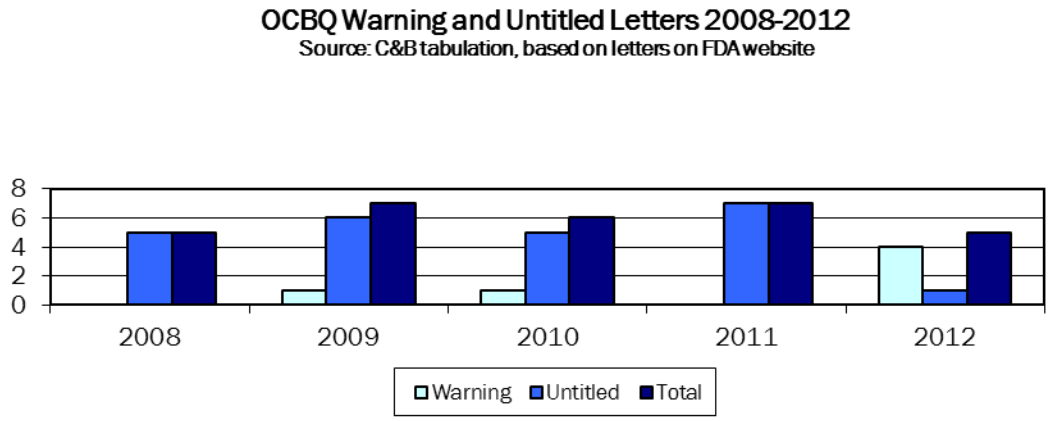
6. Other Allegations

Less common allegations in OPDP's 2012 letters included broadening of indication, misleading efficacy claims, promotion of an investigational drug, and promotion of unapproved use. Even rarer allegations included inadequate presentation of an established name and failure to fulfill "adequate provision" requirement.

OFFICE OF COMPLIANCE AND BIOLOGICS QUALITY (OCBQ)

ENFORCEMENT ACTIVITY

In 2012, OCBQ issued five enforcement letters—one untitled letter and four warning letters. This is consistent with the number of enforcement letters issued by OCBQ each year over the last several years.[6] Four out of five of OCBQ's enforcement letters were warning letters, however, which represents a significant increase in the proportion of warning letters to untitled letters as compared to previous years. Of the enforcement letters issued by OCBQ from 2008 to 2011, 8% were untitled letters. By contrast, 80% of the enforcement letters issued by OCBQ in 2012 were warning letters. Two of the warning letters issued in 2012 addressed products that were not the subject of an approved biologics license application (BLA), nor for which an investigational new drug (IND) application was in effect.



[6] Between 2008 and 2011, OCBQ issued 25 enforcement letters—five letters in 2008, seven letters in 2009, six letters in 2010, and seven letters in 2011.

CONTENT OF ENFORCEMENT LETTERS

Promotional Pieces at Issue

Over the last several years, there has been a decline in the range of promotional materials cited by OCBQ in its enforcement letters. For example, in 2009 OCBQ cited 12 different types of promotional materials. By 2011, the variety of promotional materials had been reduced by half. This trend continued in 2012, with OCBQ's enforcement letters focusing on Internet-based promotions (a YouTube video and a website), journal advertisements, communications with physicians, and a brochure.

In 2012, OCBQ's enforcement letters focused on promotional pieces that targeted either healthcare professionals or did not have a readily distinguishable intended audience. Two of the five letters cited promotional communications with physicians and journal advertisements, while the other three cited websites accessible by both consumers and healthcare professionals and a brochure that lacked a clear indication of the intended audience. OCBQ's 2012 letters did not address any patient-specific promotional pieces.

OCBQ's Allegations

OCBQ's 2012 enforcement letters contained allegations under three different subheadings—[7] (1) promotion of unapproved uses, (2) omission of risk information, and (3) failure to submit post-marketing reports at the time of dissemination.

1. Promotion of Unapproved Uses

Three letters (60%) issued by OCBQ in 2012 contained allegations of promotion of unapproved uses. For example, a September 2012 warning letter contained allegations that a firm promoted its unapproved adipose derived mesenchymal stem cell (AdMSC) product and process to physicians by encouraging the physicians to enroll patients in the firm's clinical trials. Specifically, OPDP pointed to the firm's protocols, which hypothesized that patients enrolled in the clinical trials could clinically benefit from the AdMSC product. Without a BLA or IND in effect, OCBQ stated that the firm was promoting unapproved uses for its AdMSC product.

2. Omission of Risk Information

Two of the letters (40%) contained allegations of omission of risk information. An April 2012 untitled letter, for example, addressed a brochure promoting a mite extract product. According to OCBQ, the brochure did not include any risk information and was disseminated without the product's prescribing information. OCBQ explained that this omission was misleading because it suggested there were no safety risks associated with the product, when this was not the case.

3. Failure to Submit Post-Marketing Reports at the Time of Dissemination

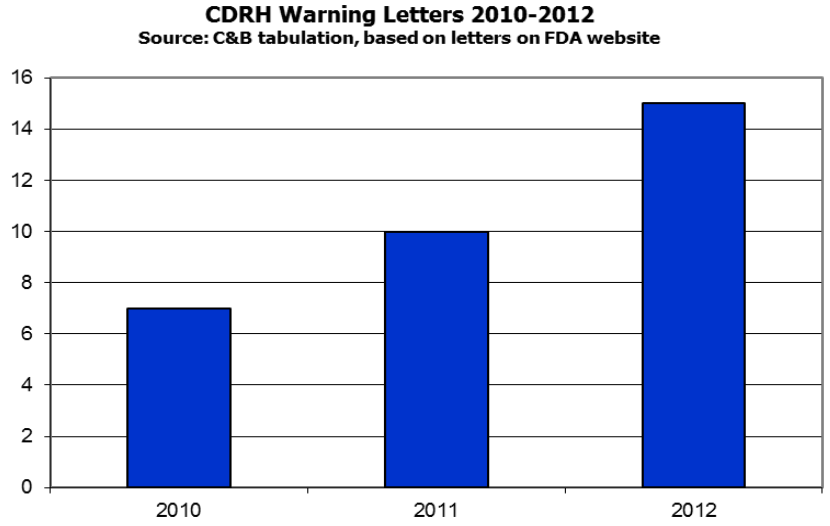
In an April 2012 warning letter, OCBQ alleged that a firm failed to submit a copy of the journal advertisements at issue at the time of the advertisements' initial dissemination. This failure violated 21 C.F.R. 601.12(f)(4).

[7] Not all letters issued by OCBQ explicitly used these subheadings, but the allegations in the enforcement letters fit within these categories.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

ENFORCEMENT ACTIVITY

In 2012, CDRH's Office of Compliance (OC) issued 15 warning letters[8] relating to the promotion of approved or cleared medical devices,[9] an increase from 2011 (10 letters) and more than double the number of letters issued in 2010 (7 letters). In December 2012, OC issued five letters to various eye care providers, warning the providers "to stop the misleading advertising and promotion of refractive lasers used in eye surgery procedures such as LASIK."[10] For purposes of this alert, these letters—which raise the same allegations and all cite Internet-based promotional pieces—are counted as a single letter ("the LASIK letter").



As in 2011, OC sent some enforcement letters to entities other than the manufacturer of the device being promoted. In 2012, OC sent three (20%) such letters, including the LASIK letter. For example, OC issued a letter in June 2012 to a surgical center that engaged in misleading promotion of the LapBand gastric banding procedure via television commercials and billboards.

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[8] CDRH has historically not posted untitled letters that it issues on FDA's website. As part of FDA's Transparency Initiative, CDRH committed to posting its advertising and promotion Untitled Letters from October 1, 2011 forward. According to FDA's website, CDRH did not issue any of these letters in 2012. *See* FDA, Medical Devices, Letters to Industry, *available at* http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm111104.htm.

[9] This number does not include letters addressing promotional activity for devices that were not cleared or approved for any use. In our October 2012 monthly alert, we included two warning letters that addressed unapproved devices because the letters raised issues that we believed would be of interest to our clients.

[10] FDA, Press Release, FDA Warns Against Improper Advertising, Promotion of Lasers Intended for LASIK Corrective Eye Surgery (Dec. 18, 2012), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm332713.htm.

CONTENT OF ENFORCEMENT LETTERS

Promotional Pieces at Issue

While the vast majority of promotional pieces at issue in OC's letters were websites (80%), other promotional vehicles addressed by OC in 2012 included catalogs, Twitter posts, television commercials, and billboards. This diversification is consistent with OC's practice in 2011, where the Agency cited a broad range of promotional pieces, including billboards, brochures, and a radio spot.

OC's Allegations

In 2012, OC's warning letters contained these three types of allegations: (1) claims outside cleared use/promotion of unapproved use, (2) omission/minimization of risk information, and (3) omission of material facts.

1. Claims Outside Cleared Use/Promotion of Unapproved Use

Twelve letters issued by OC included allegations of claims outside cleared or approved use (80%). For example, a warning letter issued in July 2012 addressed a device that had been cleared for certain indications in dermatology and podiatry, such as the coagulation and hemostatis of benign vascular lesions, the treatment of benign cutaneous lesions and benign pigmented lesions, and the treatment of wrinkles. According to OC, claims on a website that promoted the device for skin rejuvenation were outside the device's cleared indications and rendered the product misbranded and adulterated.

Similarly, a warning letter issued in October 2012 addressed devices that had been cleared for "symptomatic relief and management of chronic intractable pain, and adjunctive treatment in the management of post-surgical and post-traumatic pain." OC explained that claims on the company's website misbranded and adulterated the devices because they promoted the devices for "treating or allowing someone to overcome herpes."

2. Omission/Minimization of Risk Information

Three letters (20%) issued by OC included allegations of omission/minimization of risk information. A November 2012 warning letter, for example, addressed a website's promotion of the LapBand gastric banding procedure. OC stated that the website significantly understated the device's risks, in that it failed to mention the risk of death or serious injury. OC also pointed to a video on the website that discussed LapBand's indications, contraindications, warnings, and adverse events. According to OC, the video minimized the risks associated with LapBand because the presentation was in tiny, blurry print, and appeared only briefly.

3. Omission of Material Facts

Two letters (13%) issued by OC in 2012 included allegations of omission of material facts. For example, in the December 2012 LASIK letter, OC stated that the companies' websites were misleading because, while they promoted the benefits of the LASIK devices, they omitted material facts concerning possible consequences that could result from use of the devices, such as dry eye syndrome, the need for eye glasses or contact lenses after surgery, and vision loss. Although some websites did mention certain risks associated with the devices, OC stated that the websites failed to disclose the severity of the symptoms and their long-term persistence.

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