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E-ALERT | Food & Drug

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2013 END-OF-YEAR SUMMARY OF FDA PROMOTIONAL ENFORCEMENT ACTIVITY

This alert reviews the warning and untitled letters issued in 2013 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 23 warning and untitled letters issued by OPDP, three warning and untitled letters issued by OCBQ, and nine warning and untitled letters regarding promotional activities issued by OC. We tabulated the most frequently cited allegations, leaving out allegations included in only a few letters.

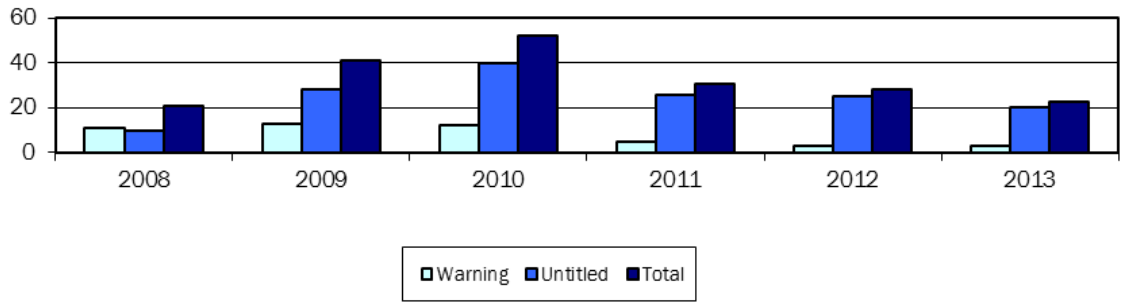
This alert merely summarizes the allegations contained in FDA's letters. It does not contain any analysis, opinions, characterizations, or conclusions by or of Covington & Burling LLP. As a result, the information presented herein does not necessarily reflect the views of Covington & Burling LLP or any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

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

I. ENFORCEMENT ACTIVITY

In 2013, OPDP issued 23 advertising and promotion enforcement letters, fewer than last year's 28 letters. This represents a three-year decline, reversing a trend of increased enforcement action between the years of 2008 and 2010, which peaked in 2010 with 52 enforcement letters.

OPDP Warning and Untitled Letters (2008-2013)
Source: C&B tabulation, based on letters on FDA website

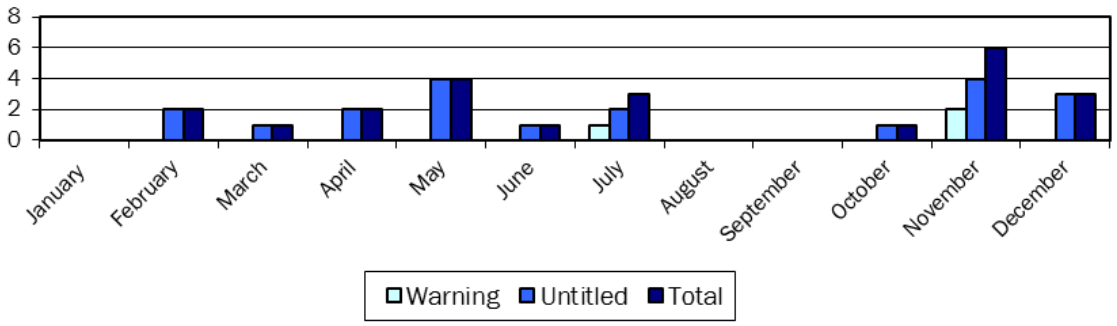


In 2013, FDA's enforcement activity may have been affected by the automatic spending cuts imposed between March 1, 2013 and year end by the Budget Control Act of 2011 and the Government shutdown between October 1, 2013 and October 16, 2013.

In keeping with its tendency over the last several years, OPDP primarily issued untitled letters (as opposed to warning letters) in 2013. Of the 23 letters OPDP issued in 2013, 87% were untitled letters and 13% were warning letters.[1] The average number of allegations in each letter was approximately 2.5 (counted by the number of headings in each letter). In 2011 and 2012, the average number of allegations per letter was 2.3.

There was no discernible trend in the timing of OPDP's enforcement letters. OPDP issued six letters in November (the most in any single month) and none in each of August and September (the only two months without letters). By contrast, in 2012, the number of letters peaked in June (six letters) and dipped in December (zero letters).

OPDP Letters Issued by Month (2013)
Source: C&B tabulation, based on letters on FDA website



A. Bad Ad Program

As we previously reported, OPDP stepped up efforts to involve Health Care Providers ("HCPs") in its Bad Ad Program, which is designed to encourage the reporting of potentially false or misleading drug advertising and promotional materials. In October 2013, OPDP updated its e-learning course and a series of educational case studies to educate HCPs. OPDP continued to offer continuing medical education credits ("CMEs") for HCPs taking its e-learning course. Since the inception of the program in May 2010, OPDP has cited the Bad Ad Program for bringing forth allegedly violative conduct leading to at least eight enforcement actions. In 2013, none of OPDP's enforcement letters credited the Bad Ad Program for bringing forth allegedly violative conduct, though it is still possible that reports under the Bad Ad Program may have resulted in enforcement actions.

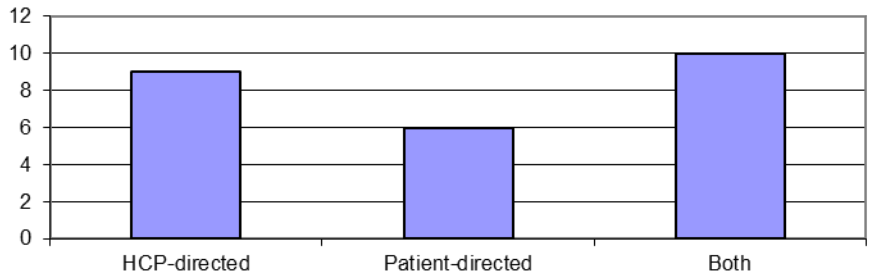
[1] In 2008, 48% of OPDP's enforcement letters were untitled letters; in 2009, 68% were untitled letters; in 2010, 77% were untitled letters; in 2011, 84% were untitled letters; and in 2012, 89% were untitled letters.

II. CONTENT OF ENFORCEMENT LETTERS

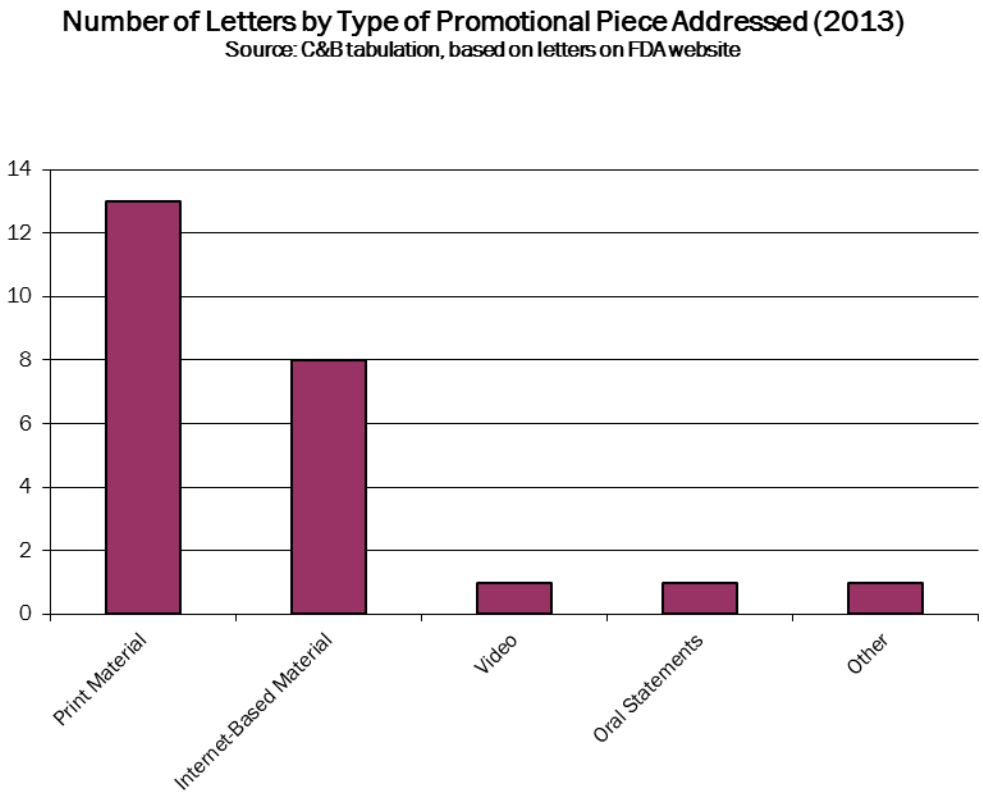
A. Promotional Pieces at Issue

In a departure from past practice, OPDP focused largely on materials directed at both HCPs and patients or widespread audiences rather than materials directed solely at HCPs. Materials focused solely on HCPs have historically comprised the most significant portion of materials addressed in enforcement letters. Materials that were directed toward both HCPs and patients (e.g., general use websites with no distinguishable audience) made up 43% of promotional materials discussed in the letters. By contrast, in 2012, materials directed toward both audiences were addressed in only 29% of enforcement letters, which itself was a noticeable increase from 2011, when only 10% of the letters addressed materials directed toward both audiences. The discussion of materials directed solely at HCPs fell to 39% from 74% and 57% in 2011 and 2012, respectively. The discussion of materials directed solely to patients remained steady, with 26% of OPDP's letters in 2013 addressing patient-directed materials, consistent with the ratios in 2011 and 2012, when 20% and 25% of OPDP's letters addressed these types of materials, respectively.

Number of Letters by Audience (2013)
Source: C&B tabulation, based on letters on FDA website

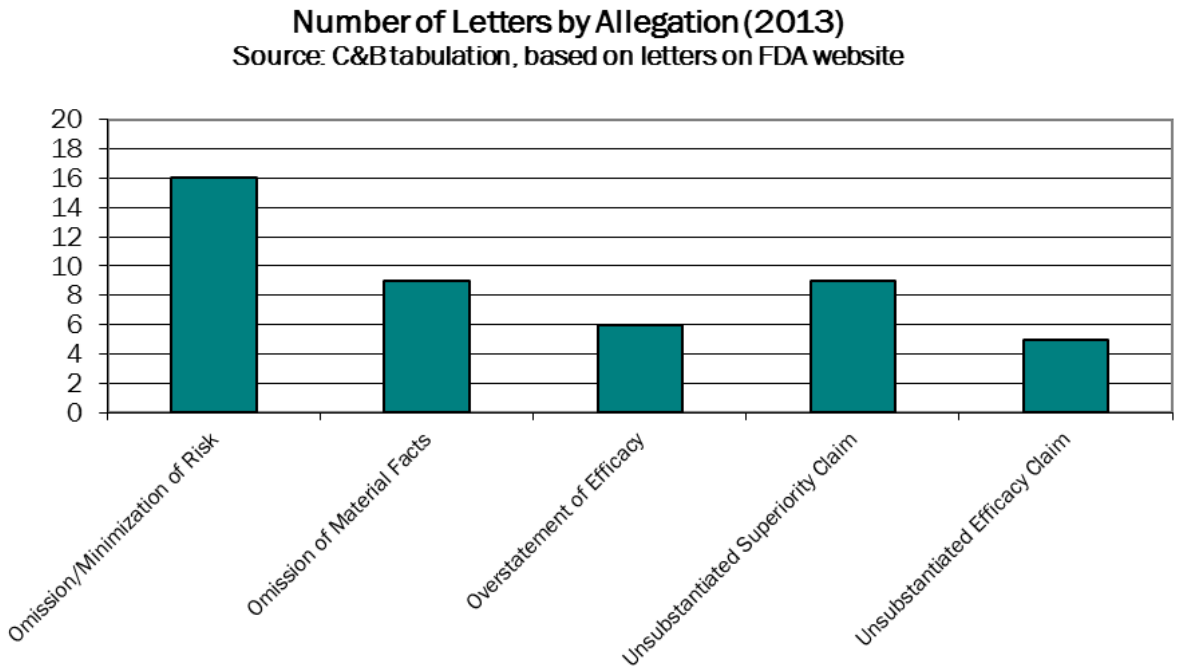


In 2013, OPDP's letters addressed a wide range of promotional pieces, including print materials (e.g., journal advertisements, sales aids, and brochures), Internet-based materials (e.g., websites, web presentations, and banner ads), videos, and oral statements. As in past years, print materials were the most frequently cited medium (54%). By comparison, in 2012, print materials were the subject of 43% of letters, and in 2011, 58% of letters. The ratio of enforcement letters that cited Internet-based materials (33%) was consistent with prior years, 39% in 2012 and 26% in 2011.



B. OPDP's Allegations

OPDP's letters contained allegations similar to those in prior years. OPDP's letters focused primarily on the following allegations: (1) omission and/or minimization of risk information, (2) unsubstantiated claims, (3) unsubstantiated superiority claims (a subcategory within unsubstantiated claims), (4) overstatement of efficacy, and (5) omission of materials facts. These areas of focus were also the most cited allegations in 2012 and 2011, with the exception of omission of material facts.



1. Omission and/or Minimization of Risk Information

Sixteen of the 23 letters (57%) issued by OPDP in 2013 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 one June 2013 untitled letter, OPDP stated that a print advertisement displayed efficacy claims in large, bold, and colorful graphics, while risk information was displayed in adjacent pages in smaller font, and less colorful schematics. OPDP also contended that a reference to the complete prescribing information included with the advertisement did not mitigate the allegedly misleading presentation.

2. Omission of Material Facts

Nine letters (39%) 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 one July 2013 letter, promotional materials indicated that median time to progression of a disease was increased with the use of the drug compared to users of another treatment. OPDP alleged that these claims should have included a disclosure that differences in time to progression were statistically insignificant in clinical trials.

3. Unsubstantiated Superiority Claims

Nine letters (39%) addressed unsubstantiated superiority claims. When FDA alleges that a promotional piece contains unsubstantiated superiority claims, FDA tends to focus on claims that suggest that the subject drug is superior to other treatment options when this has not been demonstrated. For example, in a November 2013 untitled letter, OPDP stated that a lyophilized

drug's webpage suggested that it was superior to other formulations of the drug because it could be reconstituted more quickly. OPDP contended that claims regarding the drug's "improved ease of reconstitution" in the context of operating teams' ability to administer the drug in a crisis situation were unsubstantiated superiority claims because there was no evidence that faster reconstitution times correlated with an overall improvement in the management of crises.

4. Overstatement of Efficacy

Six letters (26%) alleged that the promotional piece(s) overstated the efficacy of the drug. These types of allegations typically encompass outcome guarantees, survival or long-term outcome claims, and suggestions or statements that a drug is more efficacious than demonstrated. For example, in a July 2013 untitled letter, OPDP cited a claim on the physician information section of a webpage stating that patients showed improvement in weeks two through four of treatment in a clinical study. According to OPDP, although patients were evaluated at week two in the pivotal study, the study's primary endpoints were "complete cure" at weeks four and six and measurements between weeks two and four were not prespecified endpoints for use in support of efficacy claims. OPDP thus contended that the claim that patients "showed improvement" in weeks two through four was not supported by substantial evidence and constituted an overstatement of efficacy.

5. Unsubstantiated Efficacy Claims

Five letters (22%) addressed unsubstantiated efficacy 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 (similar to "overstatement of efficacy" claims). For example, in a November 2013 untitled letter, OPDP stated that claims in a direct mailer regarding improved reduction in blood pressure in "challenging patients" were unsubstantiated efficacy claims. OPDP contended that the studies cited in support of the claims described the results of an open-label, uncontrolled trial, which lacked placebo control or blinding, and thus did not support the claims. OPDP further alleged that the referenced study excluded some "challenging patients" such as those with severe hypertension.

6. Other Allegations

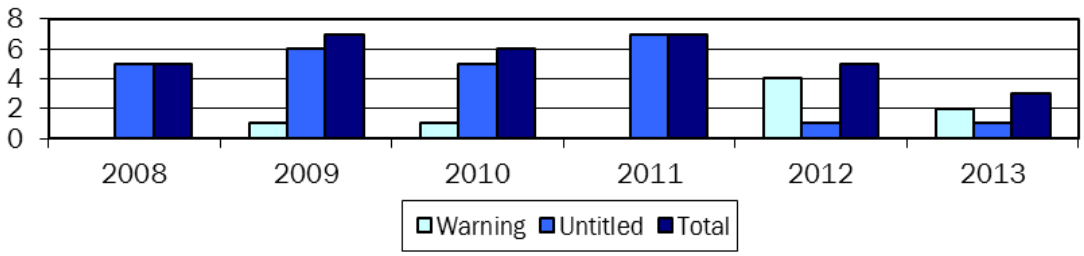
Less common allegations in OPDP's 2013 letters included broadening of indication, unsubstantiated claims, lack of adequate directions for use, inadequate communication of indication, misleading efficacy claim, unsubstantiated mechanism of action, and promotion of an investigational drug.

OFFICE OF COMPLIANCE AND BIOLOGICS QUALITY (OCBQ)

I. ENFORCEMENT ACTIVITY

OCBQ issued few letters (three letters total) compared to past years. Between 2008 and 2012, OCBQ issued between five and seven letters each year. In 2013, OCBQ issued two warning letters one untitled letter. This proportion of warning letters to untitled letters is consistent with 2012 (when 80% of letters issued by OCBQ were warning letters), but prior to that year, the proportion of warning letters was much smaller—only 8% of OCBQ's letters in 2008-2011 were warning letters.

OCBQ Warning and Untitled Letters 2008-2013
Source: C&B tabulation, based on letters on FDA website



II. CONTENT OF ENFORCEMENT LETTERS

A. Promotional Pieces at Issue

Over the last several years, there had been a decline (by nearly 50% since 2009) in the range of promotional materials cited by OCBQ in its enforcement letters. This trend ended in 2013. Although OCBQ's letters focused primarily on Internet-based materials, OCBQ's letters also addressed patient and professional brochures, and about a dozen other categories of materials, including sales aids, reference manuals, press releases, patient and professional e-mails, and patient forms.

OCBQ's enforcement letters also addressed materials intended for both patient and HCP audiences. One letter cited a patient brochure and a professional brochure for the same product; two letters referenced websites accessible by both consumers and HCPs; and one letter referenced myriad materials that may have been accessible by both patients and HCPs (such as press releases).

B. OCBQ's Allegations

OCBQ's 2013 enforcement letters contained allegations under two different subheadings:[2] promotion of unapproved uses and omission of risk information.

1. Promotion of Unapproved Uses

Two of the three letters issued by OCBQ in 2013 contained allegations of promotion of unapproved uses. For example, in an April 2013 untitled letter, OCBQ alleged that statements on a website, a tri-fold patient brochure, and a professional brochure provided evidence that an Autologous Platelet-rich Plasma (A-PRP) system was being marketed for cosmetic uses. OCBQ cited statements such as "strengthen your aesthetic treatment outcomes [using the system]" and "average duration of a full-face treatment is 30-40."

2. Omission of Risk Information

One of the letters contained allegations of omission of risk information. For example, in a May 2013 warning letter, OCBQ alleged that numerous promotional materials failed to provide any risk information associated with an epicutaneous patch test.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH) OFFICE OF COMPLIANCE

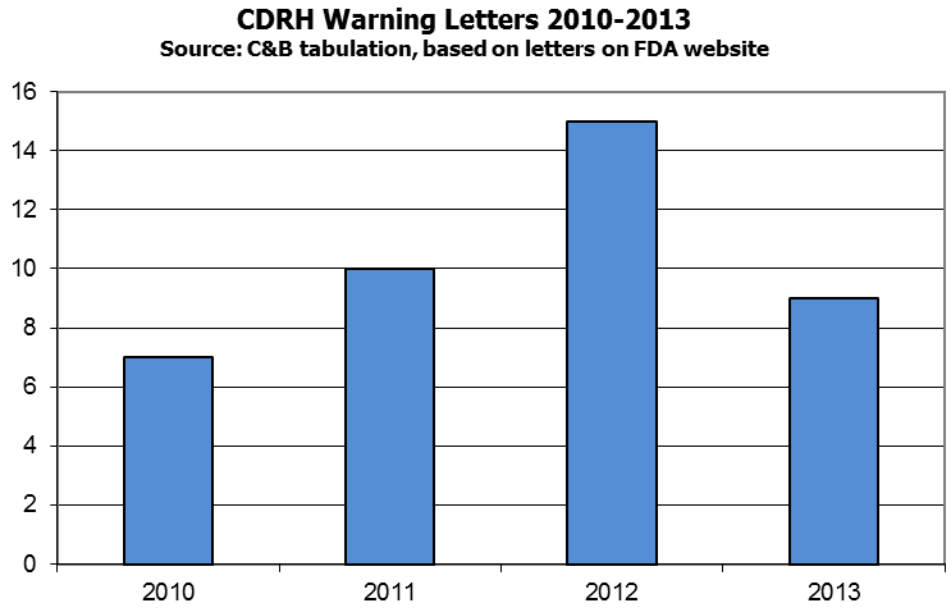
I. ENFORCEMENT ACTIVITY

In 2013, CDRH's Office of Compliance (OC) issued nine letters relating to the promotion of approved or cleared medical devices, a decrease from 2012 (15 letters), but consistent with the number of letters issued in 2010 and 2011 (seven and 11, respectively). Eight of these nine letters were warning letters.[3] The only untitled letter was issued in February 2013 to an unknown number of distributors of decorative contact lenses, notifying the distributors of "safety concerns associated with the sale, marketing, and distribution of decorative or cosmetic contact lenses" and requesting that distributors "review. . . websites, product labels, and labeling, and promotional materials to ensure that the claims . . . do not adulterate or misbrand" these products."[4]

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

[3] Five of these eight letters concerned unapproved devices that FDA alleged were no longer subject to a premarket notification exemption due to promotional statements.

[4] 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. Since the start of the initiative, FDA has posted only this decorative contact lens letter on the website. Although the letter was issued to an unknown number of distributors of contact lenses, for the purposes of this alert, these letters—which raise identical general allegations—are counted as one letter.



II. CONTENT OF ENFORCEMENT LETTERS

A. Promotional Pieces at Issue

While OC focused primarily on websites (discussed in 80% of letters), OC also addressed other promotional vehicles, including catalogs, Twitter posts, television commercials, and billboards. This is consistent with OC's practice in 2012, when OC cited a broad range of promotional pieces, including billboards, brochures, and a radio spot.

B. OC's Allegations

OC's warning letters focused on allegations that manufacturers' promotional activities established intended uses that were inconsistent with cleared or approved uses for their devices. The letters can be broken down into two general categories: (1) letters alleging that claims for devices established new intended uses, and (2) letters alleging that claims for "specific" intended uses were inconsistent with the general indications for which the device was cleared.

1. Claims Outside Cleared or Approved Use

The largest group of letters issued by OC contended that manufacturers statements established off-label intended uses for the devices. For example, a warning letter issued in March 2013 involved a therapeutic massager, which is exempt from premarket notification if it is used to relieve minor muscle aches and pains. However, OC contended that the operation manual for the device suggested new intended uses, including stimulating the lymphatic system and reducing congestion, boosting the immune system, and reducing breast cysts. OC thus alleged that the device was adulterated and misbranded.

Similarly, in an April 2013 warning letter, OC alleged that a device being marketed for a use that was inconsistent with the clearance for the device. The device was registered and listed as exempt as a manual surgical instrument intended to automate hair transplantation under 21 C.F.R. § 878.4800.

According to OC, the device was being marketed to treat the first stages of male and female diffuse hair loss and for thickening of the glabrous skin and eyebrow repair, which OC alleged exceeded the limitation of § 878.4800.

2. General v. Specific Uses for Cleared Devices

In addition to the foregoing letters, in several letters FDA alleged that devices promoted for specific uses -- such as specific aspects of the anatomy or specific diseases -- were inconsistent with the general clearances for such devices. For example, in a March 2013 warning letter, OC alleged that five products, all of which were registered and listed as exempt surgical instruments for general use under 21 C.F.R. § 878.4800, were adulterated and misbranded. Specifically, OC reviewed a company's website and asserted the intended uses listed (which included uses regarding "stem cell proliferation" and "regenerat[ing] and repair[ing] the skin") were not within the scope of the exemption for surgical instruments for general use, because legally-marketed devices under that exemption consisted of either manual or motorized dermabraders indicated for general dermabrasion, scare revision, acne scar revision, and tattoo removal.

Similarly, in July 2013, OC issued a warning letter regarding a device that was cleared as substantially equivalent to previously approved powered inflatable tube massagers under the Section 510(k) clearance process. According to OC, the user manual for the device made claims regarding the prevention of limb paralysis, limb convulsion, rheumatoid arthritis, and management of limbs in pregnant women. OC stated that these claims were new indications that were not consistent with recognized uses for other legally marketed power inflatable tube massagers (to relieve minor muscle aches and pains and to increase circulation), and thus required approval of a premarket approval application (PMA).

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food & Drug Practice Group:

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