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E-ALERT | Food & Drug

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2009 END-OF-YEAR SUMMARY OF DDMAC AND APLB ENFORCEMENT ACTIVITY

This client alert reviews the warning and untitled letters issued in 2009 by the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the Center for Drug Evaluation and Research (CDER) and by the Advertising and Promotional Labeling Branch (APLB) of the Center for Biologics Evaluation and Research (CBER).

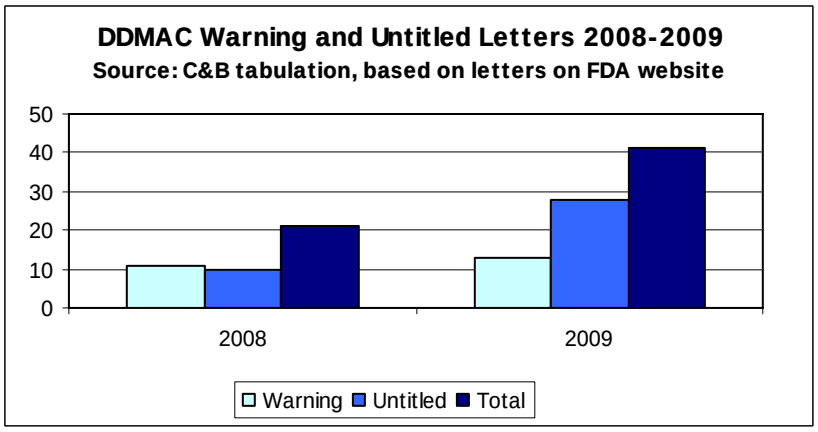
We examined the 41 warning and untitled letters issued by DDMAC in 2009, as well as the 7 warning and untitled letters issued by APLB during this time period. We tabulated the most frequent allegations cited, leaving out allegations included in only a few letters.

Our discussion of the warning and untitled letters focuses only on DDMAC's or APLB's allegations and not on the promotional materials in question or the recipient's response to DDMAC or APLB.

DDMAC

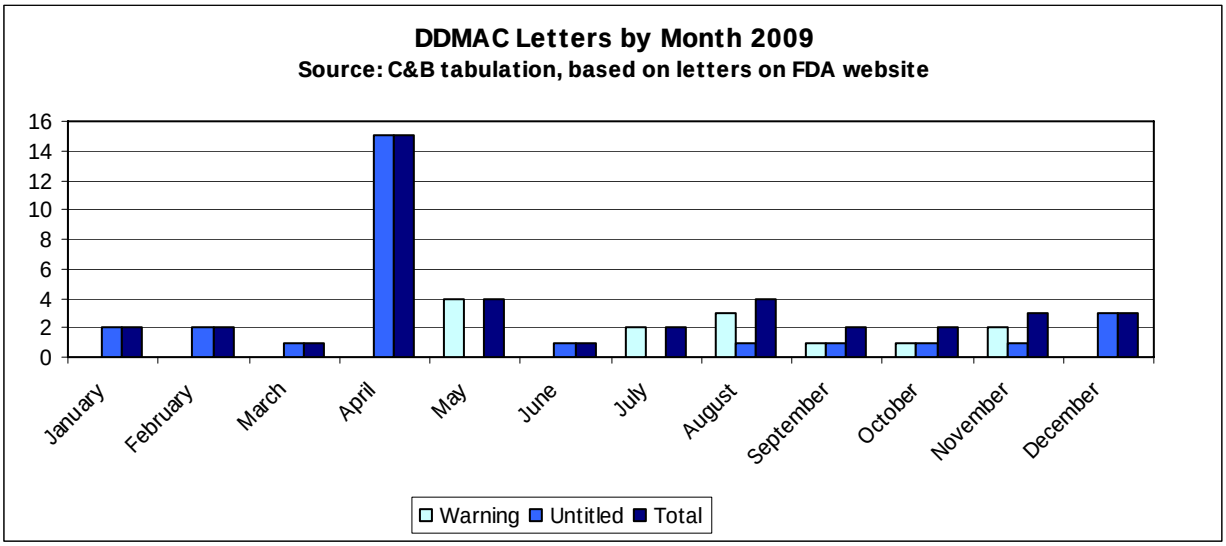
I. ENFORCEMENT ACTIVITY COMPARED TO 2008

DDMAC issued almost twice as many letters in 2009 as it did in 2008 (41 letters versus 21 letters). Of all the letters issued in 2009, 32% were warning letters (compared to 52% in 2008). Although this represented a decrease in the proportion of warning letters issued relative to total letters, we note that more than twice as many warning letters were issued in the second half of 2009 as in the first half (9 letters versus 4 letters). This may signal the start of a potential upward trend.

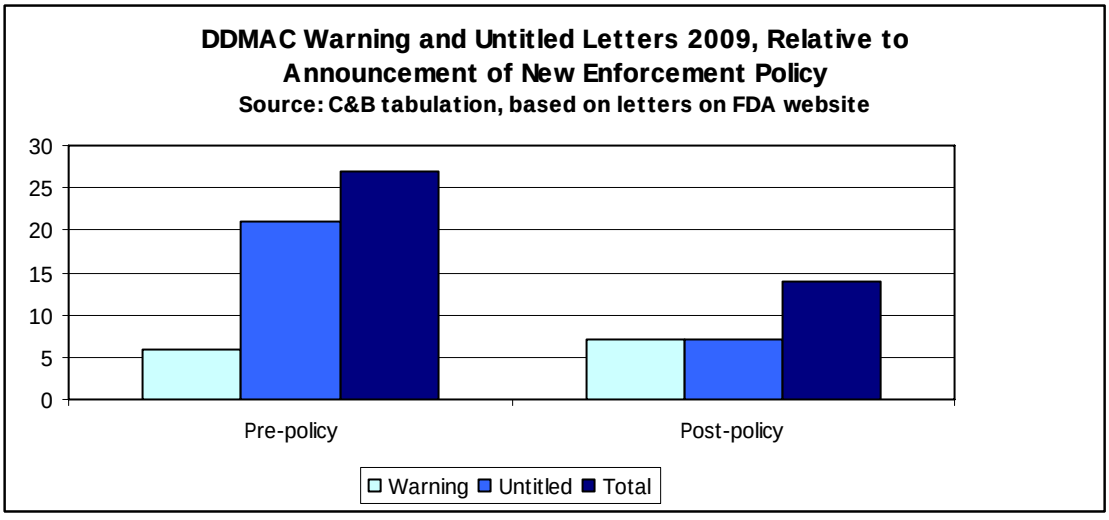


Although the total number of letters issued in 2009 was higher than the 2008 total, this increase was heavily influenced by the fact that DDMAC issued 14 untitled letters on the same day, April 2, 2009. The letters targeted companies' use of branded sponsored links, an issue discussed further in Section II.B. This single day's activity accounted for over one-third of the entire year's enforcement letters. Excluding the 14 sponsored link letters from the annual total, the number of

letters issued each month remained fairly consistent throughout the year, averaging 2.25 letters per month.



On May 18, 2009, the new Commissioner of Food and Drugs, Margaret Hamburg, began her tenure. Hamburg has pledged to improve the effectiveness and timeliness of FDA's enforcement system. In a press release issued in August, she announced that FDA would streamline the warning letter process by limiting review of warning letters by the Office of Chief Counsel to only those that present significant legal issues.[1] Although no increase in total letters issued or warning letters issued after the announcement was apparent, it may take some time for this stronger enforcement posture to produce visible effects.



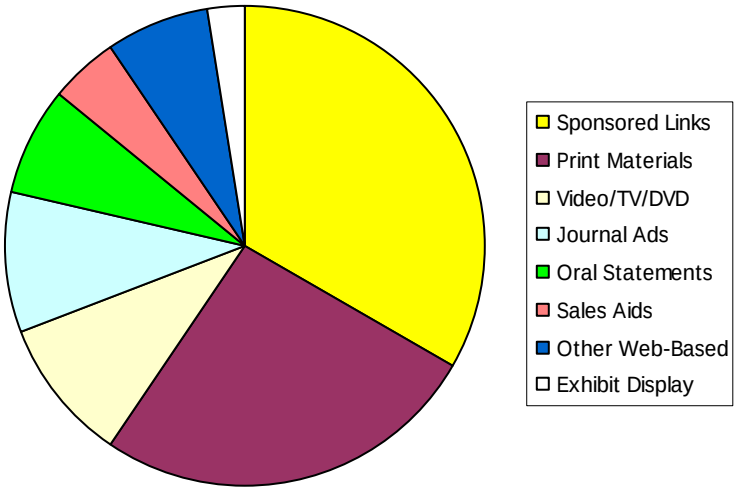
[1] *See* FDA Commissioner Sets Out Vision on Enforcement to Support Public Health (Aug. 6, 2009), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm176119.htm.

II. CONTENT OF WARNING AND UNTITLED LETTERS

A. Promotional Pieces at Issue

DDMAC letters addressed a varied set of promotional media in 2009. These included sponsored links, numerous types of print materials (e.g., dosing card, brochure, mailer, tent card), journal advertisements, oral statements, sales aids, television/video/DVD advertisements, websites, online banners, and an exhibit display. By a significant margin, the highest number of letters addressed sponsored links.

Types of Promotional Pieces 2009
Source: C&B tabulation, based on letters on FDA website



As in previous years, materials intended for healthcare professionals were a significant focus of DDMAC activity. Of the 41 letters issued in 2009, 22 (54%) addressed materials specifically directed at healthcare professionals, such as a professional reprint carrier, holiday promotional post card, dosing sheet, or patient profile card. Four letters (10%) addressed DTC advertising or other patient-directed materials, such as a consumer webcast video. These calculations do not include letters addressing sponsored links, websites, or online banners, however, as these forums are generally accessible to both healthcare professionals and patients.

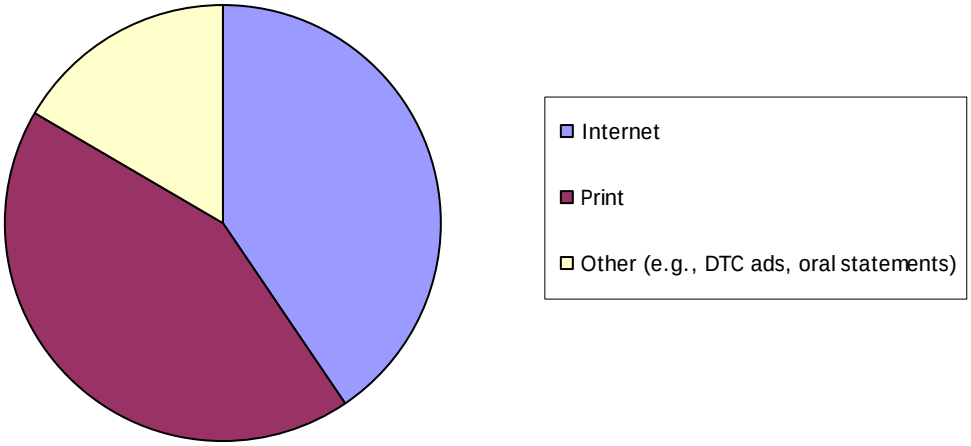
B. Increased Focus on Internet Promotion and New Media

On April 2, 2009, DDMAC issued 14 untitled letters addressing sponsored links on Internet search engines, such as Google. The letters were issued to multiple sponsors and cited multiple products. In each of the letters, DDMAC alleged that the sponsored links made representations about product efficacy without communicating any risk information. In a number of cases, DDMAC was particularly concerned because the products at issue had black box warnings. In all but one of these letters, DDMAC alleged that the statements of indication in the sponsored links were incomplete and misleading, suggesting that the drugs were useful in a broader range of conditions or patients than had been demonstrated by substantial evidence or substantial clinical experience. Finally, in each of

the letters, DDMAC alleged that the sponsored links failed to present the full established name of the drug being promoted, as required by regulation.

Adding the 14 sponsored link letters to 3 other letters addressing web-based promotion (online banners, consumer webcast video, and websites), a total of 17[2] (41%) of the 41 letters issued by DDMAC in 2009 addressed Internet promotional activity. This represents a significant increase over 2008, when 24% of DDMAC letters addressed company or product websites and new media.

Types of Promotional Pieces 2009
Source: C&B tabulation, based on letters on FDA website



In November 2009, FDA held a two-day public meeting on Internet promotion at which it solicited public input regarding FDA regulation of Internet and new media promotion.[3] This field encompasses a host of new promotional activities and emerging technologies ranging from sponsored links and websites to new social media such as chat rooms, blogs, Twitter, and services such as Google Sidewiki. To date, DDMAC has issued letters pertaining to websites, YouTube, banner advertisements, and sponsored links – all of which bear substantial similarities to the print and broadcast promotional materials addressed by existing regulations and FDA guidance. It is not yet clear how FDA will handle new social media, although it is apparent that the agency understands the utility of these platforms in promotional activity. We could begin to see additional DDMAC activity on this front.

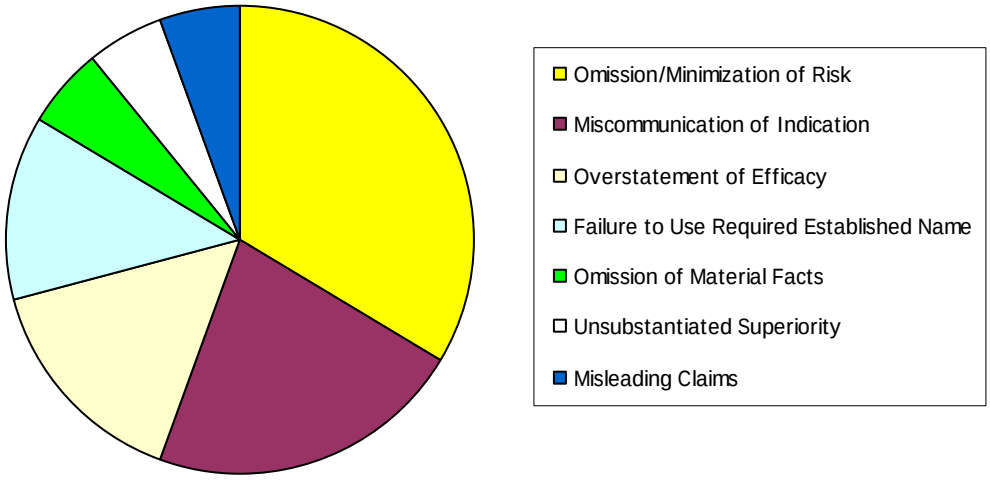
C. DDMAC's Allegations

In 2009, DDMAC focused most on (1) omission or minimization of risk information; (2) broadening, omission, or misleading communication of indication; (3) overstatement of efficacy; and (4) failure to use required established name. The heavy focus on failure to use required established name was due to the 14 sponsored link letters issued on the same day in April.

[2] In addition to these 17 letters addressing Internet issues, one letter addressed a DVD that was also available on the Internet.

[3] *See* Public Hearing on Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools, *available at* http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm184250.htm. FDA will be accepting comments on Internet and new media promotional issues until February 28, 2010.

DDMAC Letters by Allegation 2009
Source: C&B tabulation, based on letters on FDA website



1. Omission or Minimization of Risk Information

By far, the most common DDMAC allegation was omission or minimization of risk information. Of the 41 letters issued by DDMAC in 2009, 37 (90%) included an allegation of failure to adequately disclose risk (whether through omission, minimization, or misleading presentation of risk information).

In a May warning letter, DDMAC alleged that a consumer webcast video failed to convey any risks specific to the product in the testimonial portion of the video, which encompassed the first six minutes of the video's seven-minute running time. The testimonial portion prominently presented efficacy claims about the product, but the only specific risk information presented was relegated to the end of the video and was presented in a telescript format, with rapidly scrolling text in small font and no accompanying audio presentation. The disclosure of risk information also allegedly omitted certain contraindications of the product and minimized some of the serious risks associated with use of the drug by failing to communicate that those risks existed when the drug was taken by patients also taking alcohol, anesthetic agents, narcotics, or phenothiazines.

In a July warning letter, DDMAC alleged that a promotional postcard made various efficacy claims but entirely omitted risk information for the drug, including the warnings, precautions, and common adverse events associated with the drug. The statement, "For Full Prescribing Information, visit [website]," written in small type at the bottom of the card did not mitigate the misleading omission of risk information.

2. Broadening, Omission, or Misleading Communication of Indication

Of the 41 DDMAC letters issued in 2009, 24 (59%) contained allegations that various claims broadened, omitted, or otherwise miscommunicated the indication of drugs.

In a November warning letter, DDMAC alleged that a brochure spoke in broad terms about the product's use in the treatment of hyperphosphatemia and thereby implied that it was appropriate for

use in all patients who suffer from this condition. Even though one page of the brochure referred to the fact that patients should go to all their dialysis appointments, this reference alone was insufficient to communicate that the drug was approved only to treat patients with end stage renal disease. The back cover of the brochure included the statement that the product was "indicated to reduce serum phosphate in patients with end stage renal disease" in small type at the bottom of the page, but DDMAC found this inconspicuous presentation insufficient to mitigate the misleading impression communicated by the totality of the other presentations in the brochure that the drug was appropriate for any patient with hyperphosphatemia.

3. Overstatement of Efficacy

Of the 41 DDMAC letters issued in 2009, 17 (41%) alleged that sponsors had made claims that overstated the efficacy of drugs.

In an August warning letter, a visual aid depicted a ladybug walking through a dollop of the drug product and emerging with an 85% reduction in its spots. DDMAC alleged that this misleadingly suggested that patients could achieve the complete disappearance of a large majority of melasma spots upon treatment with the product, despite the lack of substantial evidence or substantial clinical experience to support this implication.

4. Failure to Use Required Established Name

For each of the 14 sponsored link letters issued on April 2, DDMAC alleged that the sponsors had failed to present the full established name of the drug being promoted despite the requirement to do so at 21 C.F.R. §§ 201.10(g)(1) and 202.1(b)(1). This allegation did not appear in any other letters issued in 2009.

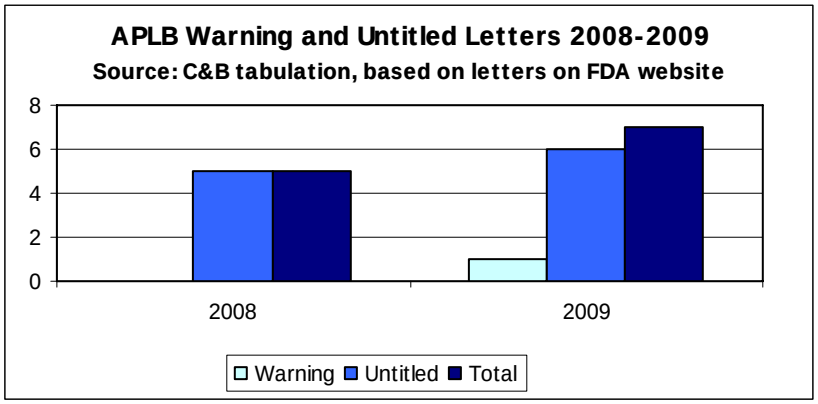
5. Other Allegations

Other, less common allegations that appeared in DDMAC letters in 2009 included unsubstantiated superiority claims, misleading claims, inappropriate reminder labeling, failure to provide adequate directions for use, use of outdated or unapproved labeling, promotion for an unapproved new use, and false or misleading statements.

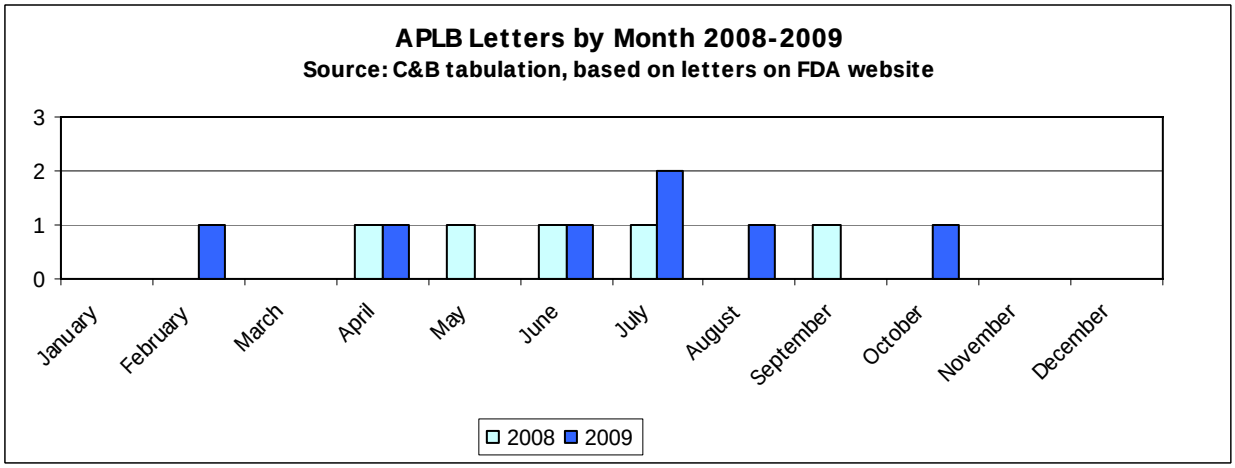
APLB

I. ENFORCEMENT ACTIVITY COMPARED TO 2008

APLB issued approximately the same number of letters in 2009 as it did in 2008 (seven letters[4] versus five letters). The proportion of warning letters to untitled letters remained consistent across both years, with the vast majority of APLB letters being untitled.



The frequency at which letters were issued over the course of the year was comparable across the two years, with letters tending to cluster in the months of April to September, and fewer letters being issued at the beginning or end of the year.



[4] Two letters that were posted on the APLB website and summarized in the monthly C&B e-alerts are no longer available on the website. We have included them in this analysis. These letters are the TISSEEL Warning Letter (Apr. 14, 2009) (now available on the Warning Letters site, at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm162558.htm), and the Sanitoets HIV Test Kit Untitled Letter (Aug. 26, 2009) (now available on the BIMO/Team Biologics/Internet Surveillance/Other site, at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/ucm091547.htm).

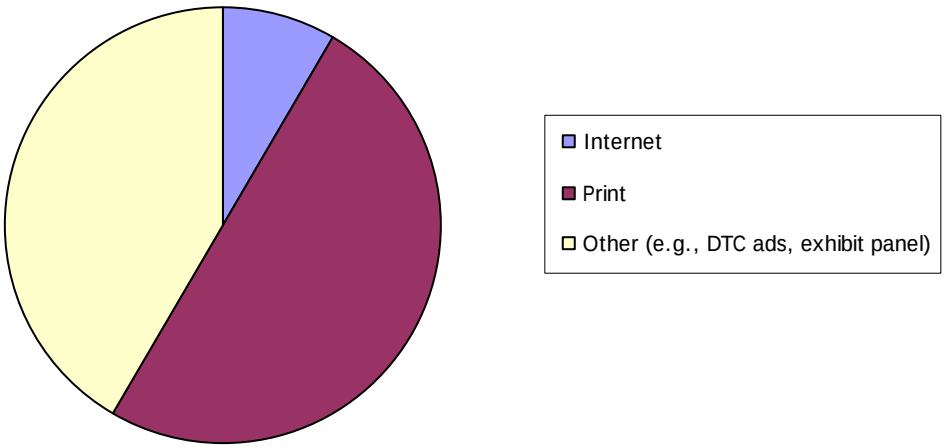
II. CONTENT OF WARNING AND UNTITLED LETTERS

A. Promotional Pieces at Issue

APLB targeted a wider range of promotional materials in 2009 than it did in 2008 (12 types versus 5 types). In 2009, APLB letters targeted DTC advertisements, a presentation, a brochure, a sell sheet, a bag drop (i.e., printed material intended to be dropped into the bags of attendees at medical or scientific conferences), branded panels, an abridged sales aid, a slim jim sales aid, an exhibit panel, a company website, patient biopsy letters, and a sales aid. By comparison, in 2008, APLB letters addressed claims in a press release, a consumer brochure, a consumer website, a flashcard, a clinical email, and a sell sheet. The majority of letters issued across the two years (83%) targeted materials intended for healthcare professionals.

Of the 12 types of promotional pieces addressed in APLB letters issued in 2009, only 1 (8%) addressed an Internet-based form of media – a company website. Based on the general increase in FDA's focus on Internet and new media promotional materials, however, it is possible that APLB's interest in this area could increase as well.

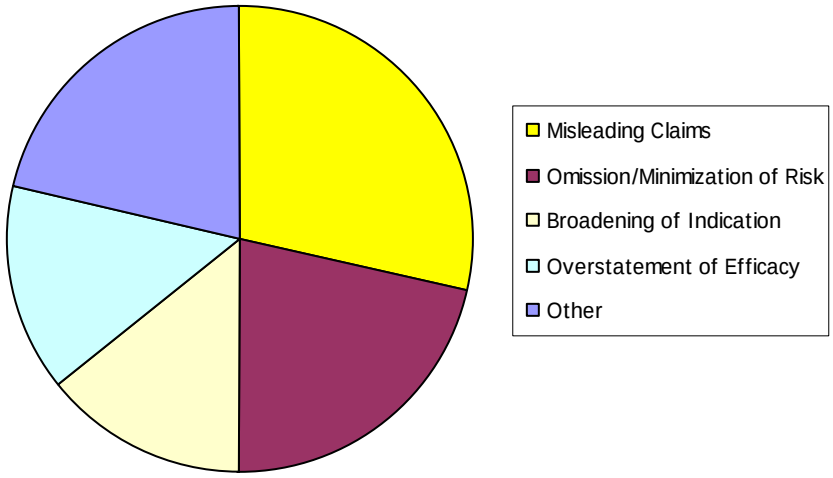
Types of Promotional Pieces 2009
Source: C&B tabulation, based on letters on FDA website



B. APLB's Allegations

In 2009, APLB focused most on misleading claims and omission or minimization of risk information, followed by broadening of indication and overstatement of efficacy.

APLB Letters by Allegation 2009
Source: C&B tabulation, based on letters on FDA website



1. Misleading Claims

Allegations of misleading claims appeared the most frequently in APLB letters issued in 2009. This was comparable to APLB's focus on this area in 2008, when 60% of the letters issued addressed misleading claims. Of the seven letters issued in 2009, four (57%) included an allegation that the promotional piece contained a misleading statement (whether comparative or pertaining to safety or efficacy).

In a June untitled letter, a bag drop presented a claim that the product provided results without anabolic-steroid-like adverse reactions. No comparative studies between the product and anabolic steroids were described in the package insert, and therefore APLB alleged that such a comparative claim was misleading.

In a July untitled letter, APLB alleged that an exhibit panel for a product contained numerous misleading safety claims under the subheading, "Proven tolerability across all indications." For example, one claim misleadingly implied that the incidence of serious adverse events per infusion of the drug was lower than it was with placebo, but the data came from one small study that was not designed to examine safety. By emphasizing the small incidence rate of serious adverse events per infusion, the claim minimized the fact that serious adverse reactions were associated with the drug, including the case of pulmonary embolism reported in a clinical study subject described in the package insert.

2. Omission/Minimization of Risk

Three (43%) of the seven letters issued by APLB in 2009 included an allegation of failure to adequately disclose risk (whether through omission, minimization, or misleading presentation of risk information).

In a February untitled letter, certain DTC advertisements contained "back to school" graphics suggesting that the product was indicated for pediatric populations. APLB found this representation

troubling in light of the fact that the product was contraindicated in children and adolescents who are receiving concomitant aspirin therapy, but the advertisements did not contain any information regarding side effects or contraindications.

3. Other Allegations

Other allegations that appeared in one letter each were failure to include side effects, omission of material facts, and promotion of an unapproved product.

Conclusion

The number of letters issued by DDMAC in 2009 was almost double the number issued in the previous year, and an increase in the number of warning letters issued could be observed in the second half of the year. DDMAC continued to focus on promotional materials directed at healthcare professionals and on the omission and minimization of risk information in promotional pieces. It also appeared to take a heightened interest in Internet and new media promotional activities.

The number of letters issued by APLB in 2009 remained approximately equal to the number issued in the previous year. In 2009, APLB targeted a wider variety of promotional materials than it had in 2008. Consistent with its enforcement activity in 2008, APLB continued to focus on materials directed at healthcare professionals, and the most common allegation in its letters was misleading claims.

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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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