FDA Regulatory Letters and Pharmaceutical Industry Promotional Review Practice

Chang, E[1], Noormohamed, S[2], and Nadal J[2]
1: Bayer HealthCare Pharmaceuticals / Rutgers University Post-Doctoral Fellow, Wayne, NJ USA
2: Bayer HealthCare Pharmaceuticals, Wayne, NJ USA

Background

FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) regulates the promotional activities of pharmaceutical manufacturers in the United States.[1] DDMAC responds to violative promotions by issuing regulatory letters to the offending manufacturer(s). Untitled letters demand cessation of the promotional activity, while Warning letters additionally specify other mandatory, corrective actions. Failure of companies to comply with these directives can result in product seizure, civil monetary penalties, and/or other enforcement actions.

To avoid DDMAC enforcement, manufacturers have implemented procedures by which promotional materials, prior to release, are examined and edited cross-functionally, by regulatory, legal, medical, marketing and other professionals. DDMAC Untitled and Warning Letters are likely an important influence on these promotional review (PR) practices. Industry promotion reviewers may interpret these letters as indicators of DDMAC positions, and/or as guidance for promotion content. The nature and extent of the influence of DDMAC letters on promotion review practice, to our knowledge, has not been examined in the published literature.

Objectives

- To characterize the relationship between DDMAC letters and promotional review practitioners in the pharmaceutical industry.
- To evaluate the content of DDMAC Untitled and Warning Letters for patterns of enforcement with regard to violation types, drug categories, and types of promotional materials.

Methodology

- A web-based, anonymous survey consisting of 27 questions investigating the impact of DDMAC letters on promotional review was disseminated to approximately 120 representatives at 36 pharmaceutical and biopharmaceutical companies. The survey was designed to quantify the impact of DDMAC letters on promotional review decisions, versus other influences, and assess for perceptions of DDMAC enforcement activities, with regard to scrutiny of particular violation types, drug classes, and promotional material types.
- DDMAC regulatory letters from years 1997-2009, made available online by the FDA, were accessed and analyzed.
  - Information recorded included cited violation types, types of promotional materials referenced, and category of drug product associated with the violative promotional activities mentioned in the letters (as per tier-1 Facts and Comparisons categorization).

Results

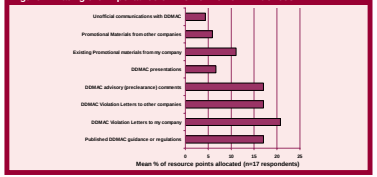
Table 1. Survey Respondent Demographics

	n (% of respondents)
Company Function*	
Marketing	3 (9.7)
Medical Affairs	10 (32.3)
Medical Communications	8 (25.81)
Regulatory Affairs	10 (32.3)
Graduate Degrees Held*	
JD	1 (3.2)
MBA	3 (9.7)
MS	2 (6.5)
PharmD	27 (87.1)
Years of Promotional Review Experience**	
0-1	2 (6.7)
1-2	11 (36.7)
2-3	5 (16.7)
3-5	3 (10)
5-10	6 (20)
10-20	3 (10)

*n=31 respondents **n=30 respondents

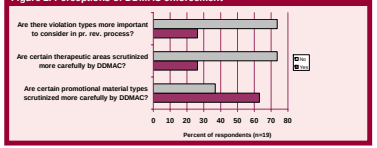
Selected Survey Results

Figure 1. Rating the Importance of Promo. Review Influences†



• Respondents rated DDMAC Warning and Untitled Letters as important as, or more important than, other influences on promotional review

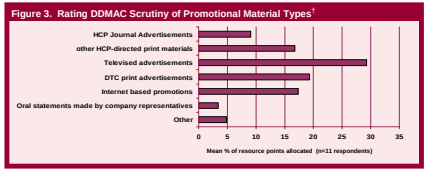
Figure 2. Perceptions of DDMAC enforcement



• Most respondents (74%) did not feel that specific violation types were more important to consider in the PR process, or that certain drug categories were more carefully scrutinized by DDMAC.

• Most respondents (63%) felt that certain promotional material types were more carefully scrutinized by DDMAC

Figure 3. Rating DDMAC Scrutiny of Promotional Material Types†

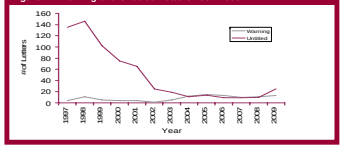


• Respondents rated televised and DTC print advertisements as more closely scrutinized by DDMAC than other categories of promotional material/activity.

†Respondents were asked to rate the following categories by allocating resource points to each category from a fixed point total.

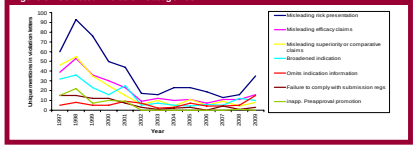
Selected Letter Analysis Results

Figure 4. Warning and Untitled Letters 1997-2009



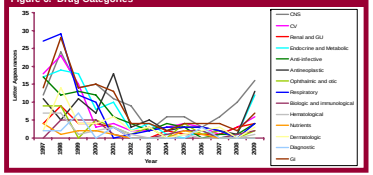
• Decline in overall volume of letters 1998-2004, and increase in yearly Warning letter issue 2002-2005, agrees with previous observations.[2]

Figure 5. Selected Violation Categories



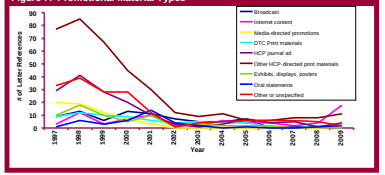
• Of the operational violation categories used in this study, misleading risk presentation was consistently the most cited each year.

Figure 6. Drug Categories



• CNS, endocrine/metabolic, and antineoplastic drugs together appear to most recently (2007-9) be associated with greatest, and most rapidly increasing, share of violations (55% of all drug categories mentioned in 2009).

Figure 7. Promotional Material Types



• Internet-based content was mentioned in an increasing number of violation letters in the time period considered: median 3.3% of letters annually (range 2%-5%) 1997-2000; median 17% (range 9-46%) 2005-2009.

Discussion

- Others have discussed likely importance of DDMAC letters in instructing marketing efforts[2]; survey respondents in our study overall confirmed, quantitatively, that letters were as important as, or more important than, other influences in the promotional review process.
- Some respondents felt certain types of DDMAC-enforced violations were more important to consider than others, or that certain drug categories were more closely scrutinized by DDMAC. Most felt that certain promotional activities were more closely scrutinized than others.
  - Indicates many promotional reviewers feel DDMAC does not uniformly regulate all promotional activities. Given the finite resources and relatively small staff of DDMAC, not likely the agency is able to detect and pursue all violative promotions.[1]
- Overall decrease in quantity of regulatory letters from 1997-2004, and a relatively stable quantity 2004-2008 (though a significant increase in Untitled letters was issued in 2009), despite yearly DDMAC submission increases from 1997-2009.[1,4]
  - May reflect increased industry compliance or changes in DDMAC resources, staff, direction. Reduced letter output after 2002 has been attributed to policy change lengthening process for letter release by DDMAC.[5] Further study is needed to evaluate these and other potential factors.
- Misleading risk presentations, manifest as lack of fair balance, or minimization of safety concerns by other means, was consistently the most cited violation category each year.
  - This agrees with stated priorities of DDMAC representatives.[3]

Limitations

- Survey questions were not validated.
- Survey respondents were a small, heterogeneous cohort.
  - Difficult to generalize survey findings to all pr. review professionals, or the industry as a whole.
- Survey respondents indicated (data not shown) that important factors affecting promotional review, such as company policies on pr. review and CIA and other agreements with government agencies were not uniform across the respondents' companies.
  - These factors may have confounded perspectives on review influences such as advisory/preclearance comments.
- Letter analysis was limited to publicly available violation letters.
- Letter analysis results are limited to the operational definitions used in the study to categorize information from the violation letters.

Conclusions

- Survey respondents on average rated DDMAC violation letters at least as important as other categories of influences on pr .review practice.
  - DDMAC violation letters to respondents' companies were rated as most important, with a mean of 20.7% of resource points allocated to this category.
- While most respondents (74%) did not feel certain violation types were more important to consider in promotional review, or that certain drug categories were more carefully scrutinized by DDMAC, many (63%) did feel certain promotional material types were more closely reviewed.
  - DTC materials were rated as most scrutinized (print, mean of 19% of resource points allocated; televised ads, 29%).
  - While DTC print and broadcast promotions were a relatively small percentage of promotional activities mentioned in DDMAC violation letters (2% in 2009, 13% 1997-2009), this is not necessarily an indicator of DDMAC surveillance or enforcement activity with these material types.
- Misleading risk presentation has consistently been the most cited violation category 1997-2009 (35% of violations cited in 2009, 30% of violations cited overall 1997-2009).
- Internet-related promotions were most mentioned promotional activity in 2009 (46% of all activities mentioned), share trending upwards since 2007.
- CNS, metabolic/endocrine, antineoplastics together were greatest share of drug categories mentioned in 2009 (55%).

References

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