Summary of DDMAC Enforcement Correspondence
September 2006

In September 2006, FDA’s Division of Drug Marketing, Advertising and Communications (DDMAC) posted three warning letters on its website. The letters addressed the issues below. This summary describes only DDMAC’s allegations. It does not reflect the recipient’s response or analysis by Covington & Burling.

**Broadening of Indication**

Two promotional pieces for Rythmol® SR (propafenone HCl) Extended-Release Capsules contained numerous representations that promote the use of Rythmol® SR to treat the broad population of patients with “atrial fibrillation” or “AFib.” But according to the Indications and Usage section of the package insert, Rythmol® SR is indicated for patients without structural heart disease. Its use in patients with permanent atrial fibrillation or patients exclusively with atrial flutter or PSVT has not been evaluated. By failing to identify the limitations to the drug’s indication, the claims in the promotional pieces incorrectly implied that the product is useful for all patients with atrial fibrillation. (Reliant, 9/14/2006)

**Overstatement of Efficacy**

A sample-request letter for VoSpire ER® (albuterol sulfate) Extended-Release Tablets included the claim, “Compliance is enhanced by convenient twice daily oral administration.” While twice-daily dosing may be more convenient than taking a drug four to six times per day, this claim incorrectly implies that characteristics of VoSpire ER® and its dosage and administration cause patients to improve their compliance with the treatment regime. No references were cited to support this claim; nor is FDA aware of any evidence supporting enhanced compliance rates for patients on VoSpire ER® therapy as compared to those on any other treatment. (DAVA, 9/21/2006)

**Unsubstantiated Superiority Claims**

A professional journal advertisement for Prograf (tacrolimus capsules and injection) contained the following two claims: “STABLE RENAL FUNCTION” and “FAVORABLE CARDIOVASCULAR PROFILE.” These claims falsely suggested that Prograf is associated with fewer abnormalities of renal function, blood pressure, and lipids than cyclosporine. The reference cited to support these claims does not constitute substantial evidence or substantial clinical experience because the relevant endpoints, serum creatinine and the use of antihypertensive and antihyperlipidemia medications, were not primary efficacy endpoints in the study. Instead, these endpoints were reported as part of post hoc analyses of safety and adverse event data collection and were therefore insufficient to support the superiority claims in the advertisement.

In addition, the Prograf advertisement contained two headlines, “PRO-GRAFTED FOR LONG TERM SUCCESS” and “SUPERIOR REJECTION PREVENTION,” that when read together conflict with language in the approved labeling. Together these headlines incorrectly suggest that Prograf is better or more effective than cyclosporine in preventing organ rejection at one year and long term after
renal transplantation. Prograf, however, was not superior to cyclosporine on overall one-year patient and graft survival, the primary endpoints of the study cited in the advertisement as support for these claims. The study did show a statistically significant difference between Prograf and cyclosporine with regard to biopsy-confirmed acute rejection at one year, but the Clinical Studies section of the package insert concludes that, as a result of the nature of the study design, comparisons of differences in such secondary endpoints could not be made reliably and therefore could not support a conclusion of superiority. (Astellas Pharma, 8/31/2006)

Omission/Minimization of Risk Information

A professional journal advertisement for Prograf (tacrolimus capsules and injection) included the claims “STABLE RENAL FUNCTION” and “FAVORABLE CARDIOVASCULAR PROFILE.” But the product’s package insert states that hypertension is a common adverse event of Prograf therapy and includes precautions for other cardiovascular events, such as myocardial hypertrophy. The package insert also contains warnings regarding the potential for nephrotoxicity with Prograf therapy. As a result, the advertisement minimized the cardiovascular and renal risks associated with Prograf. The advertisement did include risk information, but it presented the risk information in the bottom half of the piece using typography that was difficult to read. In contrast, the advertisement presented the effectiveness claims using large, bold headers with a significant amount of surrounding white space. Thus, the presentation of the risk information was insufficient to overcome the misleading suggestion that Prograf is safer than has been demonstrated. (Astellas Pharma, 8/31/2006)

Two promotional pieces for Rythmol® SR (propafenone HCl) Extended-Release Capsules made numerous representations about the dosing of Rythmol® SR and its use for atrial fibrillation, but failed to provide any information about the risks of the product. The fact that each piece referenced the “full Prescribing Information, including Boxed Warning” was insufficient to provide appropriate qualification or pertinent information for the claims made in the promotional pieces. (Reliant, 9/14/2006)

Omission of Material Facts

A sample-request letter for VoSpire ER® (albuterol sulfate) Extended-Release Tablets contained claims related to both the drug itself and to its use for the treatment of asthma, but failed to present any risk information, including the most serious and frequently occurring risks associated with the drug. (DAVA, 9/21/2006)

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This information is not intended as legal advice, which may often turn on specific facts. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein.

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