DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

TRANSMITTED VIA FACSIMILE

DEC 18 1998

Gregory M. Torre, Ph.D., J.D.
Senior Director, Drug Regulatory Affairs
Sanofi Pharmaceuticals, Inc.
90 Park Avenue
New York, NY 10016

RE: **NDA 20-839**
Plavix (clopidogrel bisulfate) tablets
MACMIS ID # 7053

Dear Dr. Torre:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of promotional materials for Plavix (clopidogrel bisulfate) tablets disseminated by Sanofi Pharmaceuticals, Inc. (Sanofi), that violate the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Reference is made to brochure (69-981691, B1-A027), journal advertisement (69-981651, B1-K010) and "Mechanism of Action" video (11/98), submitted under cover of Form FDA 2253. DDMAC has reviewed these materials and has determined that they contain promotional claims that are false or misleading, and lacking in fair balance.

Unsubstantiated superiority claims

- In these materials, Sanofi presents claims and representations that state or imply that Plavix is superior to aspirin in patients with documented atherosclerosis, based on the results of CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events), the single pivotal trial that was the basis for the approval of Plavix. For example, in the brochure, Sanofi claims that Plavix is "the only antiplatelet therapy proven vs aspirin to help prevent MI and stroke in patients with documented atherosclerosis" and that "significant overall risk reduction was seen with Plavix vs aspirin." Further, in the journal ad and brochure, Sanofi presents a graphic that depicts aspirin reducing the risk of outcome events by 25% versus control, and Plavix reducing the risk of outcome events by 8.7% versus aspirin. This presentation suggests that Plavix is both superior to aspirin by 8.7%, and superior to control by 33.7%. Although the above claims and representations imply that Plavix has superior efficacy over aspirin, the CAPRIE trial does not provide substantial evidence to support this implication. Therefore, claims that suggest that Plavix has been "proven" to be more effective than aspirin are misleading because they are not based on substantial evidence.

In the brochure and the journal ad, Sanofi presents the disclaimer that "[a]lthough the statistical significance favoring Plavix over aspirin was marginal (P=0.045), and represents the result of a single trial that has not been replicated, the comparator drug, aspirin, is itself effective (vs placebo) in reducing cardiovascular events in patients with recent myocardial infarction or stroke. Thus the difference between Plavix and placebo, although not measured directly, is substantial." This disclaimer is inadequate to correct the misleading promotional messages made by presentation of the claims and graphics described above. In addition, in the journal ad, the disclaimer is presented at the bottom of the page, as a footnote, and not prominently presented with the claim. This presentation is misleading because it minimizes the importance of the balancing information.

- In the video, Sanofi utilizes mechanism of action claims to suggest superior efficacy of Plavix over aspirin. For example, Sanofi states the following:

  > Aspirin reduces the release of thromboxane by stimulated platelets. This, in turn, can result in a reduction of platelets attracted to the growing thrombus. Nevertheless, aspirin only provides for a partial blockade of the platelet aggregation mechanism. Interestingly, there exists a more specific way to intervene in this mechanism...[a description of the mechanism of action of Plavix follows].
  >
  > We now have available to us a potent and specific antiplatelet agent with a mechanism of action different from aspirin. Proven in CAPRIE to be more effective than aspirin...

  The above statements state or imply that the clinical effect of Plavix is superior to aspirin due to its mechanism of action. Although inhibition of platelet aggregation can occur through different mechanisms, Plavix's mechanism of action has not been shown to provide a superior clinical effect. Therefore, claims that state or imply superior efficacy for Plavix over aspirin, based on mechanism of action, are misleading because they are not supported by substantial evidence.

<u>Overstatement of efficacy</u>

- In the brochure and journal advertisement, Sanofi presents the overall risk reduction for Plavix versus aspirin as 8.7% (P=0.045). DDMAC has reviewed this presentation and has determined that it is misleading because it lacks context necessary to interpret and balance the claim. The CAPRIE trial demonstrated the overall risk reduction of a combined outcome cluster of events (i.e., MI, ischemic stroke, or other vascular death) to be 8.7%, based on an incidence of outcome events of 9.78% in patients taking Plavix versus 10.64% in patients taking aspirin. Sanofi's presentation of an overall risk reduction of 8.7% favoring Plavix, without presenting the actual incidence of outcome events for Plavix and aspirin, implies a

greater efficacy for Plavix than demonstrated by substantial evidence. DDMAC notes that in an advisory letter, dated December 11, 1997, we stated that presentation of this claim should closely resemble the information in the approved product labeling (PI) for Plavix (i.e., "The overall risk reduction (9.78% vs. 10.64%) was 8.7%, P=0.045"), and should be accompanied by the disclaimer from the labeling concerning the marginal statistical significance of this single trial. In DDMAC's December 19, 1997 advisory letter, we stated that we would not object to use of the claim "Overall risk reduction - 8.7% - Plavix versus aspirin" with presentation of the disclaimer. However, this claim was presented in conjunction with a table that displayed the incidence rates (%) for the outcome events, thereby providing adequate context for interpretation of the claim. Therefore, when presented without context concerning the incidence of outcome events for Plavix versus aspirin, this claim is misleading because it implies a greater efficacy for Plavix than demonstrated by substantial evidence.

- In the brochure, Sanofi presents claims and a graph depicting a 19.2% relative risk reduction for Plavix versus aspirin for an individual component (i.e., MI) of the combined outcome cluster (i.e., MI, ischemic stroke, or other vascular death). However, MI was the individual component that resulted in the most favorable relative risk reduction for Plavix versus aspirin. Therefore, this selective presentation of the most favorable outcome is misleading because it overstates the efficacy of Plavix. In addition, the event rate for MI for aspirin (3.6%) presented in the brochure is inconsistent with the event rate for MI for aspirin (3.47%) stated in the PI.

Lacking in fair balance

- Promotional materials are lacking in fair balance, or otherwise misleading, if they fail to present information relating to the contraindications, warnings, precautions, and side effects associated with the use of a drug in a manner reasonably comparable with the presentation of information relating to the effectiveness of the drug. The PI for Plavix describes contraindications, precautions and adverse reactions associated with the use of Plavix, including the risk of hemorrhagic events. However, Sanofi fails to present **any** risk information in the "Mechanism of Action" video. Sanofi's failure to present risk information in promotional materials is misleading and lacking in fair balance, and also raises significant patient safety concerns. DDMAC notes that this is the second occurrence of Sanofi's dissemination of promotional materials for Plavix without provision of any risk information.

- Promotional materials are misleading and lacking in fair balance if they contain a representation or suggestion, that a drug is safer, has less incidence of, or less serious side effects than has been demonstrated by substantial evidence. In the brochure, Sanofi selectively presents individual adverse event rates that minimize the actual occurrence of these events. For example, with respect to gastrointestinal (GI)-related adverse events, Sanofi presents the claim "low incidence of..." and presents the following adverse event rates

for Plavix: GI ulcers (0.7%), abdominal pain (5.6%), gastritis (0.8%), dyspepsia (5.2%), and diarrhea (4.5%). However, the PI for Plavix states that overall, the incidence of GI events in patients receiving Plavix was 27.1%. In the absence of such contextual information, the claim, "low incidence," in conjunction with the selective presentation of individual GI-related adverse events is misleading because it implies that Plavix is safer and more tolerable than demonstrated by substantial evidence.

- Promotional materials are misleading if they contain a drug comparison that implies that a drug is safer than another drug when it has not been demonstrated to be safer by substantial evidence. The PI for Plavix states that the overall tolerability of Plavix was similar to that of aspirin, with approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. In addition, clinically important adverse events, including rash and skin disorders, occurred at a higher incidence with Plavix (15.8%) than with aspirin (13.1%). However, presentation of risk information in this brochure clearly implies that Plavix is superior to aspirin with respect to safety and tolerability because Sanofi selectively presents and emphasizes the adverse events that occurred with a higher frequency in the patients receiving aspirin than in the patients receiving Plavix. For example, in this brochure, six of the seven selected adverse events occurring at higher incidences with aspirin than with Plavix are prominently presented with separate headers. However, four selected adverse events occurring at higher incidences with Plavix are presented less prominently and are grouped together under a single header. In addition, Sanofi's presentation of adverse events, in general, emphasizes GI-related adverse events, which overall were higher with the use of aspirin, and minimizes rash and skin disorder-related adverse events, which overall were higher with the use of Plavix. This selective presentation and emphasis of adverse events occurring more frequently with aspirin than with Plavix is misleading because it minimizes the occurrence and seriousness of the risks associated with Plavix therapy, and implies that Plavix is superior to aspirin with respect to tolerability, which has not been demonstrated by substantial evidence.

Sanofi should immediately cease distribution of these promotional materials, and all other promotional materials for Plavix that contain the same or similar claims or presentations. Sanofi should submit a written response to DDMAC, on or before January 6, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, Sanofi should include the date on which these and other similarly violative materials were discontinued.

Sanofi should direct its response to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Sanofi that only written communications are considered official.

In all future correspondence regarding the issues raised in this letter, please refer to MACMIS ID #7053 in addition to the NDA number.

Sincerely,

Janet Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications