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April 25, 2008

CONFIDENTIAL TREATMENT REQUESTED

DELIVERED BY HAND

The Honorable John D. Dingell
Chairman
United States House of Representatives
Committee on Energy and Commerce
Washington, DC 20515-6115

The Honorable Bart Stupak
Chairman
United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
Washington, DC 20515-6115

Re: Requests to Schering-Plough Corporation and Merck & Co., Inc.

Dear Chairman Dingell and Chairman Stupak:

This letter constitutes the initial response on behalf of Schering-Plough Corporation ("Schering-Plough"), Merck & Co., Inc. ("Merck"), and Merck/Schering-Plough Pharmaceuticals (collectively, "M/SP Pharmaceuticals") to your request letter of April 11, 2008 for certain information related to the ENHANCE clinical trial (the "Request").

M/SP Pharmaceuticals continues to work diligently to gather the documents and information sought in the Request and your prior request letters, and will continue to produce information and documents on a rolling basis in accordance with our discussions and agreement with the Committee.

As before, we request that the Committee treat this letter and any subsequent information provided in response to the Request as confidential and that the Committee provide us with notice and an opportunity to object prior to making any portion of our response public.

For ease of reference, we are reprinting below the specific requests from your letter of April 11, 2008 followed by our responses.

1. **Why were the minutes of the ad hoc Expert Panel meeting created after the fact, and after the participants were told that there would be no minutes or transcript of the meeting (attachment pages 1-17)?**

In order to encourage candid discussion among the panelists, the companies did not originally intend to prepare formal meeting minutes. However, Stanley Petrauskas of Schering-Plough took contemporaneous notes during the discussion. On November 19, 2007, M/SP Pharmaceuticals issued a press release reporting the Panel's recommendation that the primary endpoint be focused to the common carotid artery. (It should be noted that while M/SP Pharmaceuticals carefully considered the advice of the Panel, in the end, the companies decided not to change the primary endpoint. The results reported in the January 2008 press release and at the annual meeting of the American College of Cardiology were presented using the pre-specified endpoints and in accordance with the study protocol and statistical analysis plan.) On November 20, 2007, the Food and Drug Administration ("FDA") requested information regarding the Expert Panel. In response to this request, Schering-Plough informed the FDA that it would produce a package of information, including minutes of the Expert Panel meeting. A first draft of the minutes was completed on December 7, 2007, before M/SP Pharmaceuticals received the Committee's December 11, 2007 letter. A draft was initially circulated to Panel members on December 19, 2007. The Panel members then provided comments on this and subsequent drafts, and the minutes were revised in response to those comments. When the minutes were finalized on January 21, 2008, all members of the Panel indicated to the companies that they accepted them as accurate and consistent with their recollections of the meeting.

2. **For what purpose is the Expert Panel meeting summary (attachment pages 18-24) now being used?**

The meeting minutes were submitted to the FDA on January 22, 2008, and have been provided to other governmental authorities upon request.

3. **Why was Dr. Kastelein not informed about the specifics related to the Expert Panel meeting? (attachment Page 52.)**

The decision to convene the Expert Panel was made based on discussions with Dr. Kastelein, and Dr. Kastelein provided suggestions for experts to include on the Panel. For example, on August 20, 2007, representatives of Schering-Plough and Merck met with Dr. Kastelein to review the ENHANCE data, including the number of biologically implausible and missing values observed in those data. At that meeting, Dr. Kastelein agreed to the formation of an expert panel for the purpose of obtaining definitive advice on how best to address these problems and suggested several individuals to serve on the

panel. Subsequently, Dr. Kastelein was updated on the companies' progress in assembling the Expert Panel. At his request, Dr. Kastelein did not serve on the Panel itself or attend the meeting on November 16, 2007 to ensure the Panel's independence and to facilitate candid discussion among the panelists. After the meeting, Enrico Veltri of Schering-Plough conveyed the Panel's recommendations to Dr. Kastelein. Dr. Kastelein was thus involved in the planning of the Expert Panel and otherwise kept informed about the Panel and its recommendations.

4. **Why was Dr. Kastelein's signature not required for any of the study protocol amendments?**

In accordance with good clinical practice and Schering-Plough's internal standard operating procedures, the ENHANCE study protocol specifies that any amendments to the protocol must have the agreement of the principal investigator(s) and that such agreement must be documented in writing. Under FDA regulations and International Conference on Harmonisation ("ICH") guidelines, the principal investigator is the person directly responsible for the conduct of the clinical trial and patient care at a trial site. *See* 21 C.F.R. § 312.3(b); ICH Good Clinical Practice: Consolidated Guidance (ICH E6) (Section 1.34, at 5) (adopted by the FDA). Dr. Kastelein was the overall lead coordinator of the ENHANCE study and not a principal investigator under the governing regulatory definitions, and thus did not sign specific study protocol amendments. M/SP Pharmaceuticals periodically consulted with Dr. Kastelein throughout the ENHANCE trial, especially regarding significant changes to the study such as those affecting patient treatment or outcome measures. In addition, Dr. Kastelein's colleague, Mieke Trip, was the principal investigator at study site 01, located at the Academic Medical Center (AMC) of the University of Amsterdam, and provided a signature acknowledgement for each of the protocol amendments applicable to that site.

5. **What was the purpose of hiring an independent consultant to review ENHANCE data, and why did Merck/Schering-Plough not proceed with data analysis after Dr. Bots's independent consultation report indicated that the ENHANCE data were, in his own words, "fine"? (attachment pages 53-65.)**

6. **Why did Merck/Schering-Plough convene an Expert Panel in light of an already completed independent consultant's report to assess the quality of the ENHANCE data?**

The companies retained Dr. Bots as an independent consultant on issues relating to the measurement of carotid artery intima media thickness ("IMT") in the ENHANCE trial. These issues included whether the protocol for reading sonographic images was followed during the reading process and how to address "outliers" (i.e., large differences in IMT measurements between visits, including visits only one week apart) and "missing" data (i.e., IMT measurements that were missing because the sonographic

images were not taken properly and the images were disqualified by the readers, or because the image did not exist in the database for some other reason). Although Dr. Bots's January 26, 2007 report stated that the ENHANCE data were no worse than published data from other IMT trials, it also pointed out that "[t]he number of missing data points is most likely somewhat higher [than] what has been reported earlier" and noted that sonographer error could not be cured by selecting another image from clips or videotapes because "in ENHANCE this is not available." Dr. Bots's report stated that "the SP/MSD team would like to [do] their utmost to potentially further reduce the measurement variability in the data, given the restriction [on] the availability of the imaging information." Notwithstanding his personal opinion that the data were "fine," Dr. Bots identified several ways to address these issues. Schering-Plough scientists made a good faith scientific judgment to apply certain of Dr. Bots's recommendations and to pursue additional steps to improve the quality of the dataset. Ultimately, however, they concluded that the problems of variability and missing data points remained. As noted in response to Question 3, after discussions with Dr. Kastelein, the companies decided to convene an expert panel in an effort to obtain definitive advice on the best way to address these problems. As a member of the Expert Panel, Dr. Bots himself accepted that a change in the ENHANCE primary endpoint would be an appropriate way to address the data quality issues presented. Other members of the Expert Panel were more troubled by the data quality issues than Dr. Bots.

7. Did the Expert Panel review Dr. Bots's report from January 2007?

Dr. Bots was a member of the Expert Panel, and as a result the Panel had the full benefit of his views. Dr. Bots's January 26, 2007 report was not among the background materials provided to the panelists in advance of the meeting.

8. Who created the slides and graphs for presentation to the Expert Panel? (attachment pages 25-51.)

The slides and graphs presented to the Expert Panel were created by clinical personnel and biostatisticians working on the ENHANCE study, including Schering-Plough Vice Presidents of Clinical Research John Strony and Enrico Veltri, Director of Statistics Ramachandran Suresh, and Associate Director of Statistics Bo Yang.

9. Why is there no mention of the 2005 data "routine data quality reviews" in the ENHANCE Study Protocol?

Blinded data quality reviews, such as those performed by Schering-Plough statisticians with respect to the ENHANCE data, are performed as part of a sponsor's basic obligations under general principles of good clinical practice, or GCP. The elements of GCP are established by FDA regulations and by detailed guidelines issued by the ICH, which have been adopted by the FDA. The ICH Guideline for Good Clinical Practice (ICH E6) states that "[q]uality control should be applied to each stage of data

handling to ensure that all data are reliable and have been processed correctly" (Section 5.1.3, at 24). The ICH Guideline for Statistical Principles for Clinical Trials (ICH E9) further explains that "[c]areful monitoring can ensure that difficulties are noticed early and their occurrence or recurrence minimized. . . . [T]he checks involved in trial monitoring may include . . . the acceptability of data being accrued, . . . the appropriateness of the design assumptions, . . . and so on . . . ." (Section 4.1, at 23). The review and cleaning of blinded data play an important role in a sponsor's compliance with these guidelines. ICH E9 specifically contemplates a blind review "cover[ing], for example, decisions concerning . . . the checking of possible transformations and definitions of outliers . . ." (Section 7.1, at 37) and states that "only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded" (Section 2.3.1, at 11). These and other basic GCP concepts need not be set forth expressly in the study protocol.

10. Why did Merck/Schering-Plough generate the Statistical Analysis Plan after completion of the study in spring 2006?

The protocol for a clinical trial describes the statistical procedures to be used in analyzing the study data. It is the general and common practice to prepare and finalize a more detailed statistical analysis plan at a later date. The key is that the statistical analysis plan be finalized before data are unblinded. This practice is consistent with ICH Guidelines. ICH E9 states that "[t]he statistical analysis plan . . . may be written as a separate document to be completed after finalizing the protocol. . . . The plan should be reviewed and possibly updated as a result of the blind review of the data . . . and should be finalized before breaking the blind" (Section 5.1, at 27). The methods for addressing missing values and outliers are among those aspects of the statistical analysis plan that may benefit from being updated as a result of the blind review (*see* ICH E9, Section 5.3, at 31). In accordance with these accepted principles, the statistical section of the protocol for the ENHANCE study stated that "[p]rior to the database lock, a detailed Data Analysis Plan will be completed and placed on file. The Data Analysis Plan will contain a more comprehensive explanation of the methodology used in the statistical analyses. The Data Analysis Plan will also contain the ground rules and data handling conventions used to perform the analyses" (Section 8.7). The final ENHANCE Statistical Data Analysis Plan was submitted to the FDA prior to database lock, in accordance with the commitment made in the protocol.

11. Who decided that company statisticians would review data in 2005, prior to completion of the study?

As explained in response to Question 9, Schering-Plough statisticians' blinded review of the ENHANCE data was a routine quality control procedure performed in accordance with requirements of good clinical practice.

12. Did the Food and Drug Administration's (FDA) Division of Drug Marketing, Advertisement, and Communications contact Merck/Schering-Plough prior to their January 23, 2008, letter (attachment pages 66-70) to inform you of their decision that Vytorin television advertisements were misleading? If so, who from FDA contacted Merck/Schering-Plough?

The January 23, 2008 letter is, by its own terms, a "change of opinion" letter. In July 2004, M/SP Pharmaceuticals submitted its Vytorin television advertising campaign to DDMAC for comments. Prior to the January 23, 2008 letter, M/SP Pharmaceuticals had received no request from DDMAC that M/SP Pharmaceuticals include in its television advertisements the language related to clinical outcomes. M/SP Pharmaceuticals believes that at all times its advertisements were appropriate and consistent with comments provided by DDMAC.

13. Did Merck/Schering-Plough suspend their television advertisements on January 22, 2008, due to FDA/DDMAC's determination or for another reason?

M/SP Pharmaceuticals' decision to suspend television advertising was voluntary and made during the week of January 14, 2008, prior to DDMAC's change of opinion letter.

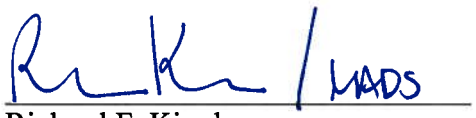
14. Does Merck/Schering-Plough plan to reinstate the Vytorin "Food & Family" television ads in the near future?

M/SP Pharmaceuticals does not have plans to resume television advertising for Vytorin in the near future. M/SP Pharmaceuticals submitted a revised television advertisement to DDMAC on February 13, 2008, but has not yet decided whether it will resume television advertising following DDMAC review of the submitted advertisement.

* * *

Please feel free to contact us if you have any questions regarding this response.

Sincerely,

By: 

Richard F. Kingham
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