ONE HUNDRED TENTH CONGRESS

U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

JOHN D. DINGELL, MICHIGAN
CHAIRMAN

September 2, 2008

Mr. Fred Hassan
Chairman and CEO
Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Mr. Richard T. Clark
Chairman, President, and CEO
Merck & Co., Inc.
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889

Dear Mr. Hassan and Mr. Clark:

Under Rules X and XI of the Rules of the U.S. House of Representatives, the Committee on Energy and Commerce and its Subcommittee on Oversight and Investigations are continuing to investigate the safety and effectiveness of Vytorin, a prescription drug manufactured by Merck and Schering-Plough.

We have received a copy of Sir Richard Peto's consultant report on the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study, which was submitted to the U.S. Food and Drug Administration (FDA). At our July 22, 2008, meeting with your counsel, we were advised that Dr. Peto's report would provide a complete assessment of Vytorin's association with cancer in the SEAS study and provide a full review of available data. After reviewing the five-page report, however, we were somewhat surprised to discover that the report contains little more than the information that was presented at the July 21, 2008, press conference announcing the SEAS results. We are also at a loss to understand why this report was kept by you from our Committee and the public.

We are concerned that an esteemed scientific consultant to Merck and Schering-Plough may have generated a secret report to FDA—a report whose contents may have been misrepresented to our staff as the report itself appears to contain information which is publicly

available. Therefore, we ask that you provide answers to the following questions in writing:

1. Is the attached report the totality of Dr. Peto's submission to FDA?

2. Why was Dr. Peto's consultant study not made publicly available?

3. When did Merck, Schering-Plough, the Merck/Schering-Plough joint venture, or any of their agents, attorneys, or lobbyists first contact Dr. Peto about his consultant report?

4. When was Dr. Peto's report submitted to FDA?

5. Was Dr. Peto's report reviewed or edited prior to its submission to FDA by anyone from Merck, Schering-Plough, the Merck/Schering-Plough joint venture, or any of their agents, attorneys, or lobbyists? Please supply any drafts and all other documents that describe the review or editing of the report.

6. Has Dr. Peto prepared any other analysis of the association (or lack thereof) between Vytorin and cancer for any other regulatory agency or peer-review journal?

7. What role, if any, did Merck, Schering-Plough, the Merck/Schering-Plough joint venture, or any of their agents, attorneys, or lobbyists have in the preparation of the attached Peto report and decision to submit it to FDA?

Finally, we ask that you make Dr. Peto available for a staff interview as soon as possible.

Please deliver copies of your responses to the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, Room 316, Ford House Office Building, no later than two weeks from the date of this letter. After review of your response, we may require additional records and/or staff interviews with company officials.

Thank you for your prompt attention to this matter. If you have any questions related to this request, please contact us or have your staff contact John F. Sopko or Paul Jung of the Committee staff at (202) 226-2424.

Sincerely,

John D. Dingell
Chairman

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

Attachment

cc: The Honorable Joe Barton, Ranking Member
Committee on Energy and Commerce

The Honorable John Shimkus, Ranking Member
Subcommittee on Oversight and Investigations

Independent report on cancer analyses in the SEAS, SHARP and IMPROVE-IT trials

Sir Richard Peto, FRS
Co-director, Clinical Trial Service Unit
& Epidemiological Studies Unit (CTSU)
Professor of Medical Statistics and Epidemiology,
University of Oxford, UK

Summary: The two hypothesis-testing trials (SHARP and IMPROVE-IT) contain about four times as many cancers as the SEAS trial. They do not confirm the hypothesis raised by the SEAS trial that treatment increases the overall risk of developing cancer, and, as there is no increase with time in the relative risk (active vs placebo) suggested by the cancer incidence and mortality from all 3 trials together (or just from the pair of hypothesis-testing trials), the SEAS, SHARP and IMPROVE-IT trials do not provide credible evidence of any adverse effect on cancer.

Background

1. Results from 90,000 patients in 14 statin trials: safety of cholesterol-lowering and safety of statins

Allocation to 5 years of substantial LDL-cholesterol lowering by a statin has no apparent effect on cancer. The Cholesterol Treatment Trialists' collaboration (CTT, Lancet 2005; 366: 1267-78) includes 90,000 patients randomised evenly between statin (which substantially lowers LDL-cholesterol) and control. Based on 5530 patients with cancer onset after randomisation, the statin vs control relative risk was 0.997 (with 95% confidence interval 0.95-1.05; not significant). Of these patients, 2163 died of their cancer during the scheduled follow-up period; the relative risk for cancer death was 1.01 (with 95% confidence interval 0.91-1.12; not significant).

NB: Within this null average, some trials suggested a decrease and some an increase in overall cancer or in particular types of cancer, but no type of cancer was clearly increased or decreased in the aggregated data from all 14 trials. An independent meta-analysis of these results was previously provided to regulatory authorities in Europe by the CTSU.

2. Results from 2,000 patients in SEAS trial of ezetimibe + simvastatin: hypothesis generating

In the final results from the SEAS trial, there appears to be about a 50% increase in total cancer incidence in the group allocated ezetimibe + statin, but this is based on only 67 vs 102 cases, and there is no significant increase in any particular type of cancer (Table 1).

3. Results from 20,000 patients in the combined interim results from the SHARP and IMPROVE-IT trials of ezetimibe + simvastatin: hypothesis testing

Two other large trials of ezetimibe + statin are still in progress, (i) SHARP (ezetimibe + simvastatin vs placebo in 9,000 patients; recruitment completed, but treatment and follow-up continuing) and (ii) IMPROVE-IT (ezetimibe + statin vs placebo + statin in 11,000 patients; recruitment continues towards an eventual target of 18,000 patients). Together, they have already accumulated about four times as many cancers as SEAS (Table 1).

The University of Oxford Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), which has decades of experience in cancer epidemiology, in vascular and other trials, and in collaborative meta-analyses of trials proposed that the hypothesis-generating SEAS results should be tested by reviewing the combined cancer results from SHARP and IMPROVE-IT and reporting on them to the relevant regulatory authorities, independently of the drug manufacturers.

NB: Although CTSU is conducting the SHARP trial, it is doing so independently of the study sponsor, and has a policy of not accepting honoraria or consultancy fees. This report has been initiated, conducted and interpreted independently of any sponsor.

4. Main result: no overall increase in the total number of patients with cancer in the two hypothesis-testing trials

	Active	Control
Hypothesis generator: SEAS	102	67
Hypothesis test: SHARP & IMPROVE-IT	313	326

If treatment really did increase total cancer by 50% then this would have been clearly apparent in the hypothesis testing trials. Instead, there was no evidence of any increase.

Note that if an unexpected hypothesis has been generated by a relatively small study and it is then tested by a larger one, it is not statistically appropriate to consider the combined results from the hypothesis generator and the hypothesis tester (total for 3 trials: 415 active vs 393 control patients with cancer; 2p=0.5). It is the results of the hypothesis tester on its own that provide unbiased evidence.

5. Site-specific findings (Table 1)

In the hypothesis-generating SEAS study, there were no significant increases of particular types of cancer; the largest absolute excesses were of skin cancer (12 active vs 7 control; p=0.36) and prostate cancer (23 vs 14; p=0.18). Table 1 shows the sites in 12 broad groups; finer and finer

subdivision produced smaller and smaller numbers per site, but found no excesses greater than those of skin and prostate. In the pair of hypothesis-testing trials, these patterns were reversed: there was a non-significant reduction in the numbers with skin cancer recorded (74 active vs 89 control) and with prostate cancer recorded (25 vs 36). If active treatment has no real effect on any type of cancer then, with 12 groups, one would expect about half of them to favour active treatment in the hypothesis test, about half to favour control, and for perhaps one or two of these differences to be conventionally significant until correction is made for the multiplicity of new hypotheses being tested. This is exactly what is seen in Table 1: of the 12 results in the hypothesis-testing trials, 7 favour treatment, 5 do not, one of these 12 comparisons is conventionally significant (kidney cancer 25 vs 11; p=0.03) but it ceases to be so when the p-value is multiplied by 12 (Bonferroni correction) to correct for the multiplicity of tests.

6. Cancer incidence without cancer death, cancer death and all cancer (Tables 1 and 2)

In the hypothesis-testing pair of trials, active treatment was associated with non-significantly more cancer deaths (97 active vs 72 control; 2p=0.06) and a non-significant reduction in other cases of cancer (216 active vs 254 control; 2p=0.14), yielding the overall total of 313 active vs 326 control cases of cancer.

7. Time trends in the overall data

If there were a real adverse effect on cancer incidence or cancer mortality then previous experience with the epidemiology of cancer (ie, with other causes of the disease in humans) strongly suggests that the relative risk (active versus control) should grow bigger with time, but it does not, whether the hypothesis-testing trials are considered separately or (as in Figure 1) all 3 trials are considered together.

As the hypothesis generator was the number of cancers in SEAS rather than the time trend in SEAS, it is perhaps appropriate for Figure 1 to be based on all 3 trials. If so, then Figure 1 suggests no time trend with respect to cancer incidence (or mortality). If, instead, the two hypothesis-testing trials had been considered alone there would have been a slight and non-significant trend towards a decrease in the relative risk with the passage of time, again contrary to what would have been expected if active treatment caused cancer.

Notes

Cancer incidence or cancer death: In SEAS and IMPROVE-IT, the incident cancers analysed here include not only those that were reported as SAEs because they occurred while on study treatment (or within 15 days of stopping it) but also those (11 in SEAS; 15 in IMPROVE-IT) that arose after the end of study treatment and caused death from cancer within the follow-up period.

Qualifications: The author of this report has for the past 15 years been professor of medical statistics and epidemiology at the University of Oxford, UK (before which he was University Reader in Cancer Studies), and has been closely involved in cancer epidemiology, in randomised trials and in conducting and interpreting collaborative meta-analyses of trials for several decades. He is co-author of the Oxford Textbook of Medicine chapter on cancer epidemiology, and of a major 1981 report on the causes of cancer in the United States that was commissioned by the US Congressional Office of Technology Assessment and published in the Journal of the National Cancer Institute (Doll R & Peto R, JNCI 1981; 66: 1191-1308)

**Table 1: Any cancer with onset since randomisation between active combination therapy (ezetimibe and simvastatin) and placebo*
(NB. In 2 trials [SEAS & SHARP] control=double placebo,
and in 1 trial [IMPROVE-IT] control=simvastatin + placebo)**

	SEAS (hypothesis generating)				IMPROVE-IT & SHARP (hypothesis testing)			
	Active	Control	p-value (2-sided)	Bonferroni -corrected p-value**	Active	Control	p-value (2-sided)	Bonferroni -corrected p-value**
Number randomised	944	929			10319	10298		
Digestive tract	14 (1.5%)	12 (1.3%)	0.84	NA	57 (0.6%)	61 (0.6%)	0.71	NA
Hepatobiliary/pancreatic	6 (0.6%)	4 (0.4%)	0.75	NA	15 (0.1%)	18 (0.2%)	0.61	NA
Respiratory/intrathoracic	9 (1.0%)	11 (1.2%)	0.66	NA	37 (0.4%)	30 (0.3%)	0.46	NA
Skin	12 (1.3%)	7 (0.8%)	0.36	NA	74 (0.7%)	89 (0.9%)	0.24	NA
Breast	8 (0.8%)	4 (0.4%)	0.39	NA	21 (0.2%)	19 (0.2%)	0.87	NA
Prostate	23 (2.4%)	14 (1.5%)	0.18	NA	25 (0.2%)	36 (0.3%)	0.16	NA
Kidney	2 (0.2%)	2 (0.2%)	1.00	NA	25 (0.2%)	11 (0.1%)	0.03	0.36
Bladder	7 (0.7%)	6 (0.6%)	1.00	NA	19 (0.2%)	20 (0.2%)	0.87	NA
Genital	4 (0.4%)	4 (0.4%)	1.00	NA	6 (0.1%)	5 (0.0%)	1.00	NA
Haematological	8 (0.8%)	6 (0.6%)	0.79	NA	18 (0.2%)	19 (0.2%)	0.87	NA
Other known sites	3 (0.3%)	1 (0.1%)	0.62	NA	13 (0.1%)	12 (0.1%)	1.00	NA
Multiple/unspecified	15 (1.6%)	8 (0.9%)	0.21	NA	28 (0.3%)	19 (0.2%)	0.24	NA
Total: Any cancer	102 (10.8%)	67 (7.2%)	0.01	NA	313 (3.0%)	326 (3.2%)	0.60	NA

Counts are for the number of patients reporting at least one such outcome. Data correct as of 15th July 2008.
* Includes the 11 patients in SEAS and 15 in IMPROVE-IT with cancer death recorded but cancer incidence not recorded.
** As 12 independent tests are reported, exact p-values that are less than 1/12 are multiplied by 12 to correct for this.
NA=Not applicable.

Table 2: Death from cancer with onset since randomisation between active combination therapy (ezetimibe and simvastatin) and placebo
(NB. In 2 trials [SEAS & SHARP] control=double placebo, and in 1 trial [IMPROVE-IT] control=simvastatin + placebo)

	SEAS (hypothesis generating)				IMPROVE-IT & SHARP (hypothesis testing)			
	Active	Control	p-value (2-sided)	Bonferroni -corrected p-value*	Active	Control	p-value (2-sided)	Bonferroni -corrected p-value*
Number randomised	944	929			10319	10298		
Digestive tract	8 (0.8%)	4 (0.4%)	0.39	NA	15 (0.1%)	23 (0.2%)	0.20	NA
Hepatobiliary/pancreatic	5 (0.5%)	3 (0.3%)	0.73	NA	10 (0.1%)	10 (0.1%)	1.00	NA
Respiratory/intrathoracic	7 (0.7%)	8 (0.9%)	0.80	NA	21 (0.2%)	13 (0.1%)	0.23	NA
Skin	0 (0.0%)	0 (0.0%)		.	1 (0.0%)	1 (0.0%)	1.00	NA
Breast	1 (0.1%)	0 (0.0%)	1.00	NA	2 (0.0%)	0 (0.0%)	0.50	NA
Prostate	3 (0.3%)	1 (0.1%)	0.62	NA	4 (0.0%)	1 (0.0%)	0.37	NA
Kidney	1 (0.1%)	0 (0.0%)	1.00	NA	8 (0.1%)	1 (0.0%)	0.04	0.48
Bladder	3 (0.3%)	1 (0.1%)	0.62	NA	4 (0.0%)	2 (0.0%)	0.69	NA
Genital	3 (0.3%)	2 (0.2%)	1.00	NA	1 (0.0%)	0 (0.0%)	1.00	NA
Haematological	3 (0.3%)	2 (0.2%)	1.00	NA	6 (0.1%)	10 (0.1%)	0.33	NA
Other known sites	1 (0.1%)	0 (0.0%)	1.00	NA	7 (0.1%)	1 (0.0%)	0.07	0.84
Multiple/unspecified	4 (0.4%)	2 (0.2%)	0.69	NA	18 (0.2%)	10 (0.1%)	0.18	NA
Total: Any cancer	39 (4.1%)	23 (2.5%)	0.05	NA	97 (0.9%)	72 (0.7%)	0.06	NA

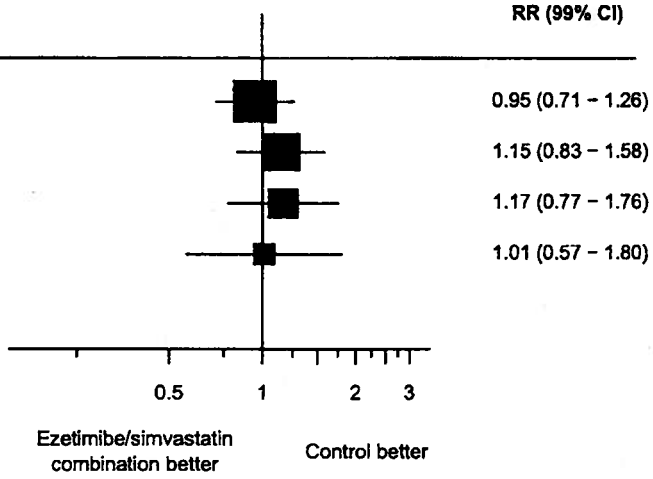
* As 12 independent tests are reported, exact p-values that are less than 1/12 are multiplied by 12 to correct for this.
NA=Not applicable.

Figure 1: Tests for trend in the cancer relative risk (RR, active vs control) in the 3 trials together (SEAS, SHARP and IMPROVE-IT including the 26 non-SAE cancers), by year

CANCER INCIDENCE (ANY SITE, 10th ICD C00-C99)

Years	Events/no. entering time period: Ezetimibe/ simvastatin	Control	O-E	Var of O-E	RR (99% CI)
0-1 year	154/11263	162/11227	-4.3	79.0	0.95 (0.71 - 1.26)
1-2 years	136/8066	118/8011	8.7	63.5	1.15 (0.83 - 1.58)
2-3 years	85/4539	73/4528	6.1	39.5	1.17 (0.77 - 1.76)
3+ years	40/2665	40/2682	0.3	20.0	1.01 (0.57 - 1.80)

Trend test: $\chi^2_1 = 0.45$ (NS)



CANCER DEATH (ANY SITE)

Years	Events/no. entering time period: Ezetimibe/ simvastatin	Control	O-E	Var of O-E	RR (99% CI)
0-1 year	34/11263	24/11227	4.9	14.5	1.41 (0.71 - 2.77)
1-2 years	43/8171	33/8130	4.9	19.0	1.29 (0.72 - 2.34)
2-3 years	33/4717	22/4694	5.4	13.7	1.49 (0.74 - 2.98)
3+ years	26/2827	16/2817	5.1	10.5	1.62 (0.73 - 3.59)

Trend test: $\chi^2_1 = 0.23$ (NS)