

## APPENDIX H

### CRITICISM OF VIOXX'S RENAL SAFETY PROFILE.

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## APPENDIX H

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#### A. Introduction.

As discussed in Appendix A, all NSAIDs, including selective Cox-2 inhibitors such as Vioxx, are associated with increases in blood pressure and fluid retention, or edema. The FDA-approved label for Vioxx identified these side effects and noted that they occurred more frequently at higher doses of Vioxx:

Clinical trials with VIOXX at daily doses of 12.5 and 25 mg have shown renal effects (e.g., hypertension, edema) similar to those observed with comparator NSAIDs; these occur with an increased frequency with chronic use of VIOXX at doses above the 12.5 to 25 mg range.<sup>1</sup>

From the time that Merck began marketing Vioxx, many at the Company believed that Searle/Pfizer representatives were attacking the renal safety of Vioxx so as to portray Vioxx as worse than both Celebrex and non-selective NSAIDs with respect to renal safety.<sup>2</sup> After the VIGOR Trial results were released, Merck representatives further believed that Searle/Pfizer representatives were attempting to link the increased incidence of hypertension and edema experienced by patients in the Vioxx arm of the VIGOR Trial

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<sup>1</sup> 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 507.

<sup>2</sup> See, e.g., Slide, "Pre-Launch Perspective," MRK-ACX0015446 (attached to 12/6/00 email from R. Rode to S. Reiss, MRK-ACX0015441) ("Pharmacia/Pfizer was pre-positioning VIOXX before it launched as a COX II inhibitor with a poor renal profile, causing hypertension and edema, unlike Celebrex."); 10/18/99 Reference Binder for Vioxx® (No. COX 99-079), MRK-AAR0008337, at 408 (noting that the "competition has been aggressively 'pre-positioning' our product," which was likely to prompt questions from doctors on three safety issues, including the drug's ability to cause edema); see generally List of Physicians to Neutralize, MRK-AFI0044570-96 (attached to 7/23/99 email from S. Baumgartner to S. Johnson, MRK-AFI0044569).

to the increased incidence of cardiovascular events among patients in the Vioxx arm of that trial.

These alleged efforts by Searle/Pfizer representatives to challenge Vioxx's renal and cardiorenal safety profile appeared to many at Merck to accelerate in the summer of 2000 after the initial presentation of SUCCESS VI, a Searle/Pfizer-sponsored study comparing the renal effects of Vioxx 25 mg versus Celebrex 200 mg conducted by Dr. Andrew Whelton\*, Adjunct Professor of Medicine at the Johns Hopkins University School of Medicine, together with a team of Searle/Pfizer-affiliated doctors. SUCCESS VI was the first of two twin studies conducted by Dr. Whelton\*, both of which showed an increased incidence of hypertension and edema with patients taking Vioxx as compared to Celebrex.

MRL scientists strongly disagreed with the methodology and results of the Whelton studies. This Appendix describes the two Whelton studies, as well as the response from MRL scientists and Merck's Marketing, Sales, and Public Affairs Departments.

B. SUCCESS VI and SUCCESS VII: The Whelton Studies.

SUCCESS VI and SUCCESS VII were twin six-week studies sponsored by Searle/Pfizer that compared the renal effects of Vioxx 25 mg and Celebrex 200 mg treatment in patients with treated hypertension and osteoarthritis. The first –

SUCCESS VI – enrolled 810 patients from October 1999 through April 2000.<sup>3</sup> The second – SUCCESS VII – involved 1,092 patients and was conducted between September 2000 and March 2001.<sup>4</sup> The primary endpoints of both studies focused on changes in systolic blood pressure and edema, two recognized indicators of renal effects. As discussed more fully below, both studies reached the same conclusion: that the renal side effects of Vioxx 25 mg – i.e., hypertension and edema – were worse than those of Celebrex 200 mg. The studies, individually and collectively, were routinely referred to within Merck as the “Whelton Study,” after their lead investigator, Dr. Andrew Whelton\*.

1. Results of SUCCESS VI.

As shown in Table 1, in the SUCCESS VI trial, Vioxx patients experienced more significant edema (defined as certain changes from baseline on a 5-point scale of peripheral edema, weight gain) and had greater increases in systolic blood pressure than did Celebrex patients.<sup>5</sup>

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<sup>3</sup> Whelton\* A, Fort\* JG, Puma\* JA, et al. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther. 2001;8: 85-95, at 88, MRK-ADY0002029.

<sup>4</sup> Whelton\* A, White\* WB, Bello\* AE, et al. Effects of celecoxib and rofecoxib on blood pressure and edema in patients ≥65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol. 2002;90: 959-963, at 959, MRK-ADY0004547.

<sup>5</sup> Whelton\* A, Fort\* JG, Puma\* JA, et al. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther. 2001;8: 85-95, at 89, MRK-ADY0002029.

Table 1

Rates of Significant Edema and Increased Systolic  
Blood Pressure in SUCCESS VI

Type of Event	Patients Treated with Celebrex	Patients Treated with Vioxx
Significant Edema	20	38
Significant Increase in Systolic Blood Pressure	45	66

At the end of the study, patients on Vioxx had experienced a mean increase of 2.6 mmHg in systolic blood pressure, and patients on Celebrex had experienced a mean decrease of 0.5 mmHg.<sup>6</sup> There were four incidents of Vioxx patients experiencing congestive heart failure, which may be correlated with increased systolic blood pressure, and no such incidents in the Celebrex arm.<sup>7</sup> In addition, 6 patients in each group developed minor but clinically significant levels of serum creatinine, blood urea nitrogen, or serum potassium – each an indicator of impaired renal function.<sup>8</sup> Nine percent of patients in each group withdrew from the study because of adverse events.<sup>9</sup>

Baseline characteristics among the two groups of patients in the SUCCESS VI

<sup>6</sup> Whelton\* A, Fort\* JG, Puma\* JA, et al. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther. 2001;8: 85-95, at 85, MRK-ADY0002029.

<sup>7</sup> 7/18/00 teleconference transcript, “Renal Safety Issues in Treating Arthritis Patients,” MRK-ABO0003972, at 75.

<sup>8</sup> Whelton\* A, Fort\* JG, Puma\* JA, et al. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther. 2001;8: 85-95, at 89, MRK-ADY0002029.

<sup>9</sup> Whelton\* A, Fort\* JG, Puma\* JA, et al. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther. 2001;8: 85-95, at 91, MRK-ADY0002029.

study were very similar. Mean treated baseline blood pressure – the blood pressure of subjects before beginning Vioxx or Celebrex treatment – was 137/76 for Vioxx and 138/76 for Celebrex patients; the historical rates of myocardial infarction and congestive heart failure in each group were identical.<sup>10</sup> All participants had been on a stable dose of antihypertensive medication for at least three months prior to entering the trial.<sup>11</sup>

## 2. Results of SUCCESS VII.

The results of SUCCESS VII, completed 11 months later, were consistent with those of SUCCESS VI, as illustrated by Table 2.<sup>12</sup>

Table 2

Rates of Clinically Significant Edema and Elevated Systolic  
Blood Pressure in SUCCESS VII

Type of Event	Patients Treated with Celebrex	Patients Treated with Vioxx
Clinically Significant Edema	26	42
Elevated Systolic Blood Pressure	38	81

Vioxx patients showed a mean increase of 3 mmHg from baseline systolic blood pressure over the course of the study, and Celebrex patients showed a mean decrease of 0.4 mmHg in systolic blood pressure.<sup>13</sup>

<sup>10</sup> 7/18/00 teleconference transcript, “Renal Safety Issues in Treating Arthritis Patients,” MRK-ABO0003972, at 74.

<sup>11</sup> Slide presentation by A. Whelton\*, “Celecoxib Safety and Tolerability Profile: The Renal and Cardiovascular Story,” MRK-AAA0002293, at 308.

<sup>12</sup> Whelton\* A, White\* WB, Bello\* AE, et al. Effects of celecoxib and rofecoxib on blood pressure and edema in patients ≥65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol. 2002;90: 959-963, at 961, MRK-ADY0004547.

As was the case with SUCCESS VI, the Vioxx patients enrolled in SUCCESS VII had baseline characteristics similar to those of the Celebrex patients: the mean ages of Vioxx and Celebrex patients were 73.1 and 73.3, respectively; mean baseline blood pressure was 136/78 for Vioxx patients and 136/76 for Celebrex patients; and 14 Vioxx patients (2.6%) compared to 16 Celebrex patients (2.9%) had a history of congestive heart failure.<sup>14</sup>

In SUCCESS VII, significant between-treatment differences developed among the subgroup of patients taking ACE-inhibitors either in conjunction with beta-blocker monotherapy or combined with diuretic therapy to control hypertension. Among these patients, more subjects taking Vioxx than Celebrex experienced significantly increased mean systolic blood pressure during the course of treatment. Differences in blood pressure changes were minimal between treatment groups for patients using calcium channel antagonists or diuretic therapy alone to treat hypertension.<sup>15</sup>

### 3. Publication of the Whelton Studies.

The findings of SUCCESS VI and VII were released at several scientific conferences and published in several journals over the course of two-and-a-half years.

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<sup>13</sup> Whelton\* A, White\* WB, Bello\* AE, et al. Effects of celecoxib and rofecoxib on blood pressure and edema in patients  $\geq 65$  years of age with systemic hypertension and osteoarthritis. Am J Cardiol. 2002;90: 959-963, at 961, MRK-ADY0004547.

<sup>14</sup> Whelton\* A, White\* WB, Bello\* AE, et al. Effects of celecoxib and rofecoxib on blood pressure and edema in patients  $\geq 65$  years of age with systemic hypertension and osteoarthritis. Am J Cardiol 2002;90: 959-963, at 961, MRK-ADY0004547.

<sup>15</sup> Whelton\* A, White\* WB, Bello\* AE, et al. Effects of celecoxib and rofecoxib on blood pressure and edema in patients  $\geq 65$  years of age with systemic hypertension and osteoarthritis. Am J Cardiol 2002;90: 959-963, at 961, MRK-ADY0004547.

This process began in June 2000, when Dr. Whelton\* presented the results of SUCCESS VI at a conference sponsored by the European League Against Rheumatism (“EULAR”). The following month, Dr. Whelton\* further discussed the data he had presented at EULAR with clinicians in a teleconference sponsored by Searle/Pfizer.<sup>16</sup> During the teleconference, Dr. Whelton\* opined that the differences in renal effects seen in SUCCESS VI resulted from a difference in the “primary molecule of rofecoxib or celecoxib and/or . . . an effect of [their] metabolites”<sup>17</sup> – in other words, that Vioxx was fundamentally different from Celebrex in its renal impact. Dr. Whelton\* also stated that increases in systolic blood pressure (such as those seen in SUCCESS VI) were linearly related to death rates due to coronary heart disease.<sup>18</sup>

In March 2001, an article authored by Dr. Whelton\* on the results of SUCCESS VI was published in the American Journal of Therapeutics, of which Dr. Whelton\* was a Senior Editor.<sup>19</sup> The article reiterated that relatively small, sustained changes in systolic blood pressure are associated with a 10%-to-20% increased risk of

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<sup>16</sup> 7/18/00 teleconference transcript, “Renal Safety Issues in Treating Arthritis Patients,” MRK-ABO0003972, at MRK-ABO0003972, at 72.

<sup>17</sup> 7/18/00 teleconference transcript, “Renal Safety Issues in Treating Arthritis Patients,” MRK-ABO0003972, at MRK-ABO0003972, at 77.

<sup>18</sup> Slide presentation by A. Whelton\*, “Celecoxib Safety and Tolerability Profile: The Renal and Cardiovascular Story,” MRK-AAA0002293, at 298.

<sup>19</sup> Whelton\* A, Fort\* JG, Puma\* JA, et al. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther. 2001;8: 85-95, MRK-ADY0002029.

congestive heart failure and a 15%-to-20% increased risk of stroke.<sup>20</sup> The article also noted that “[c]elecoxib and rofecoxib are different molecules with different pharmacokinetic profiles” and restated Dr. Whelton’s\* conclusion that the differential renal findings of SUCCESS VI “may be the result of direct renal effects of the rofecoxib molecule or its metabolites and not the result of a ‘class’-related COX-2 pharmacologic effect.”<sup>21</sup>

Two months later, the findings of SUCCESS VII were released at the Annual Scientific Meeting of the American Geriatric Society.<sup>22</sup> Approximately a year later, in April 2002, Dr. Whelton\* published an abstract on the pooled data from both trials in the Journal of the American Geriatric Society.<sup>23</sup> Finally, in November 2002, an article on the SUCCESS VII trial was published in the American Journal of Cardiology.<sup>24</sup>

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<sup>20</sup> Whelton\* A, Fort\* JG, Puma\* JA, et al. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther. 2001;8: 85-95, at 93, MRK-ADY0002029.

<sup>21</sup> Whelton\* A, Fort\* JG, Puma\* JA, et al. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am J Ther. 2001;8: 85-95, at 93, MRK-ADY0002029.

<sup>22</sup> 5/18/01 Final Standby Statement, MRK-ADG0055554, at 54; Whelton\* A. COX-2 specific inhibitors and the kidney: effect on hypertension and oedema. J Hypertens. 2002;20(Suppl. 6): S31-35, MRK-ADY0004792.

<sup>23</sup> Whelton\* A, Bello\* A, & Fort\* JG Cox-2 specific inhibitors, edema, and blood pressure in elderly treated hypertensive patients: a pooled analysis of 1,902 patients [abstract P413]. J Am Geriatr. April 2002;50(4, Suppl.), MRK-ADY0003606-07.

<sup>24</sup> Whelton\* A, White\* WB, Bello\* AE, et al. Effects of celecoxib and rofecoxib on blood pressure and edema in patients ≥65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol. 2002;90: 959-963, at 959, MRK-ADY0004547.

In addition to summarizing the difference in renal effects between Vioxx and Celebrex shown in the SUCCESS VII study, the November 2002 article also drew an implicit link between these results and the differential cardiovascular outcomes of the VIGOR Trial and the CLASS Trial. Specifically, the article noted that patients receiving Vioxx 50 mg in the VIGOR Trial experienced a mean 3.6 mmHg increase in blood pressure, while Searle/Pfizer's CLASS study showed significantly less new-onset or aggravated hypertension in Celebrex 800 mg patients (2.7%) than in the comparator NSAID groups (3.4%) (diclofenac 75 mg twice daily or ibuprofen 800 mg three times daily).<sup>25</sup> The article concluded that "a full exploration of pharmacokinetic, pharmacodynamic, correlations of BP [blood pressure] destabilization with drug dose and duration of drug action, together with molecular and metabolite considerations, will be necessary to elucidate the mechanisms responsible for these findings."<sup>26</sup>

C. Merck's Response to the Whelton Studies.

The initial presentation of SUCCESS VI at EULAR presented Searle/Pfizer with an opportunity to portray Celebrex as a safer drug than Vioxx in terms of its renal effects, and MRL scientists immediately began analyzing and criticizing the study.

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<sup>25</sup> Whelton\* A, White\* WB, Bello\* AE, et al. Effects of celecoxib and rofecoxib on blood pressure and edema in patients  $\geq 65$  years of age with systemic hypertension and osteoarthritis. Am J Cardiol 2002;90: 959-963, at 962, MRK-ADY0004547.

<sup>26</sup> Whelton\* A, White\* WB, Bello\* AE, et al. Effects of celecoxib and rofecoxib on blood pressure and edema in patients  $\geq 65$  years of age with systemic hypertension and osteoarthritis. Am J Cardiol 2002;90: 959-963, at 962-63, MRK-ADY0004547.

1. MRL Scientists' Response to Whelton Study.

MRL scientists believed that there was no significant difference between Vioxx and Celebrex with respect to renal function and that Dr. Whelton's\* conclusions were based on two design flaws in the SUCCESS Trials: (i) the doses of Vioxx and Celebrex selected, and (ii) the dosing intervals used.

a. Doses selected.

With respect to dose, Dr. Scolnick commented that the Whelton study "compared 200mg celebrex once a day to 25mg Vioxx once a day. In the crudest terms, this is like comparing a popgun to a cannon in efficacy."<sup>27</sup> Regarding the Whelton Study's suggestion that Celebrex had a renal safety advantage over Vioxx, Dr. Scolnick stated: "It is infuriating constantly and again to me that we cannot explain and counteract this kind of garbage."<sup>28</sup>

An analysis of the study by Dr. Jeffrey Melin, Associate Director of Medical Services, a sub-division of the Medical and Scientific Affairs Department, appeared to confirm Dr. Scolnick's reaction to the respective doses of Vioxx and Celebrex used. Dr. Melin concluded that 12.5 mg Vioxx would have produced the same level of Cox-2 inhibition as 200 mg Celebrex. Patients on Vioxx 25 mg – the dose used in the study –

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<sup>27</sup> 7/24/00 email from E. Scolnick to L. Sherwood, MRK-AFI0036540.

The recommended dose of Celebrex for the treatment of osteoarthritis was 200 mg per day. 12/13/98 approved Celebrex product label, MRK-ADN0010624, at 41. The recommended starting dose of Vioxx for the treatment of osteoarthritis was 12.5 mg, although the product label stated that some patients might benefit from increasing to the maximum recommended daily dose of 25 mg. 5/20/99 approved Vioxx product label, MRK-ACD0078494, at 516.

<sup>28</sup> 7/24/00 email from E. Scolnick to L. Sherwood, MRK-AFI0036540.

experienced double the degree of Cox-2 inhibition as those in the Celebrex arm.<sup>29</sup> As

Dr. Melin wrote to Dr. Sherwood:

The adverse events that Dr. Whelton showed for VIOXX validate the occurrence of Cox-2 inhibition before such data was reflected in the label. To not see adverse events is confirmation that COX-2 is only being weakly inhibited (as is the case with celecoxib). It is out of both frustration and desperation that Dr. Whelton attempts to implicate an active furanone-type metabolite of rofecoxib as causing these mechanism-based adverse events.<sup>30</sup>

Dr. Melin concluded that “[n]othing unexpected has been demonstrated by Dr. Whelton’s study. Double the dose of Celecoxib (to 400 mg qd) (in the same patient population) and one would expect to see the same rate of AEs as with 25 mg rofecoxib.”<sup>31</sup> Other MRL scientists, including Dr. Reicin, also criticized this aspect of the study’s methodology.<sup>32</sup>

b. Dosing intervals.

With respect to dosing intervals, Merck’s Dr. Ian Rodger suggested that the Whelton Study data might be biased depending on when in the dosing interval blood pressure and edema had been measured. He explained that Celebrex had a shorter

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<sup>29</sup> Analysis of Dr. Andrew Whelton’s EULAR Study of VIOXX vs. Celebrex in Elderly Osteoarthritic Patients with Systolic Hypertension, MRK-ABO0003045, at 46 (attached to 7/24/00 email from J. Melin to L. Sherwood, MRK-ABO0003044).

<sup>30</sup> Analysis of Dr. Andrew Whelton’s EULAR Study of VIOXX vs. Celebrex in Elderly Osteoarthritic Patients with Systolic Hypertension, MRK-ABO0003045, at 46 (attached to 7/24/00 email from J. Melin to L. Sherwood, MRK-ABO0003044) (emphasis omitted).

<sup>31</sup> Analysis of Dr. Andrew Whelton’s EULAR Study of VIOXX vs. Celebrex in Elderly Osteoarthritic Patients with Systolic Hypertension, MRK-ABO0003045, at 46 (attached to 7/24/00 email from J. Melin to L. Sherwood, MRK-ABO0003044) (emphasis in original).

<sup>32</sup> 2/26/03 deposition of A. Reicin at 182 (Calcaterra v. Merck & Co., No. 01-516-MJR, S.D. Ill.) (noting that selecting comparable doses was an important issue in study design).

half-life than Vioxx – i.e., its effects on the body dissipated more quickly than Vioxx's effect over the course of the dosing interval – and measuring subjects near the end of the dosing interval could therefore show a lesser effect of Celebrex. Dr. Rodger proposed that Merck conduct a study designed to account for this potential bias. The proposal was endorsed by Dr. Sherwood and Mr. Errol McKinney, head of the Vioxx marketing team within the Worldwide Human Health organization.<sup>33</sup>

Merck conducted at least two studies that addressed Dr. Rodger's concern about bias in dose-timing. One already ongoing two-week study conducted by Dr. Jules Schwartz, an MRL research scientist, compared Vioxx 25 mg, Celebrex 200 mg bid (400 mg), naproxen 500 mg bid (1000 mg), and placebo in 67 elderly volunteers. The trial measured blood pressure frequently and showed similar sodium excretion and blood pressure effects among the study drugs.<sup>34</sup>

Another study conducted by Merck, Protocol 155, measured blood pressure rates in hypertensive patients taking Celebrex 200 mg, Celebrex 200 mg bid (400mg), or placebo, but did not include Vioxx. The results, which were available in December 2001, showed that Celebrex increased blood pressure at both doses as compared to placebo, and that Celebrex 200 mg bid increased blood pressure more than Celebrex 200 mg once daily.<sup>35</sup>

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<sup>33</sup> 6/00 email correspondence among I. Rodger, E. McKinney, B. Gertz, L. Sherwood, et al., MRK-ADL0071626-27.

<sup>34</sup> 5/18/01 Final Standby Statement, MRK-ADG0055554, at 54.

<sup>35</sup> See 12/6/01 memorandum from W. Brady to G. Geba et al., MRK-ABC0034370-95.

2. Strategy of the Marketing, Sales, and Public Affairs Departments.

According to Merck market research, Searle/Pfizer publicized the Whelton Study through lectures, scientific conferences, reprint distribution, and press releases, and members of Merck's U.S. Human Health and Public Affairs Departments took active measures to counteract the perceived negative effects of Searle/Pfizer's campaign.<sup>36</sup>

a. Press release re: Whelton Study.

A June 23, 2000 CNBC.com report stated that Merck and Searle/Pfizer engaged in a "battle of the press releases" the day that the Whelton Study was presented at EULAR on June 22, 2000.<sup>37</sup> Searle/Pfizer's press release touted the superior renal safety of Celebrex as seen in the Whelton Study.<sup>38</sup> Merck's reported that a separate trial presented at EULAR – Merck's Protocol 106 – showed that the renal safety of Vioxx was not statistically different from that of Celebrex and that Vioxx showed superior efficacy

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<sup>36</sup> See 10/00 Position Paper on COX II Inhibitors and Hypertension/Edema, MRK-ADM0182542-64 (describing ways in which Searle/Pfizer allegedly disseminated the study results); 4/20/01 Bulletin for Vioxx: Action Required: Whelton Study Background Packet (No. COX 01-021) MRK-AAR0007222, at 24 ("While this is the first peer reviewed version from this trial it has been disseminated via CME, Press Releases, Medical Education (PIR) and HEL venues sponsored by Pharmacia and/or Pfizer."); Slide, "Current Renal and Cardiovascular Messages for Celebrex," MRK-ACX0015447 (attached to 12/6/00 email from R. Rode to S. Reiss, MRK-ACX0015441); Whelton Paper Q&A, MRK-ACZ0087203, at 203 (attached to 4/12/01 email from M. Buttala to L. Coppola et al., MRK-ACZ0087198) (instructing representatives to report instances of Searle/Pfizer representatives promoting the Whelton Study); 5/18/01 Final Standby Statement, MRK-ADG0055554, at 54 ("To counter Pharmacia, we plan to aggressively communicate the shortcomings in the design of the Whelton study. . . .").

<sup>37</sup> 6/26/00 email from M. Heinley to M. Basaman, MRK-ADI0006083-85 (circulating the text of the article. The article concluded that Merck "appear[ed] to be winning" the battle based on its stock price. *Id.* at 85.

<sup>38</sup> 6/22/00 Searle/Pfizer press release, "In large Head-to-Head Cox-2 Inhibitor Safety Study, Vioxx® Associated with Significant Increases in Blood Pressure and Edema vs. Celebrex," MRK-ACI0009326-27.

in pain relief.<sup>39</sup> Merck's press release further stated that an analysis of Merck-sponsored Phase III osteoarthritis safety and efficacy trials demonstrated that Vioxx had a renal safety profile similar to that of certain traditional non-selective NSAIDs. Merck's press release was reissued on March 19, 2001,<sup>40</sup> when data from SUCCESS VI were presented at a meeting of the American College of Cardiology, and again on May 11, 2001, in response to the initial presentation of SUCCESS VII.<sup>41</sup>

b. Development of marketing messages.

Behind the scenes, beginning prior to the initial presentation of the Whelton Study, senior members of MRL and senior members of U.S. Human Health discussed ways in which the Marketing Department could counter what they perceived as Searle/Pfizer's negative and erroneous messages about the renal profile of Vioxx.<sup>42</sup> Of particular concern was what many within the Company saw as an attempt by

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<sup>39</sup> 6/22/00 Merck press release, "Merck Confirms Renal Safety Profile of Vioxx," MRK-PRL0000128-30.

<sup>40</sup> 3/19/01 Merck press release, "Merck Confirms Renal Safety Profile of Vioxx," MRK-PRL0000175, at 75.

<sup>41</sup> 5/11/01 Merck press release, "Merck Confirms Renal Safety Profile of Vioxx," MRK-ACI0009067-69.

<sup>42</sup> At the May 2000 meeting, the Human Health Product Approval Committee ("HHPAC") was asked to approve messages to counter Searle/Pfizer's alleged attack, including that (i) there was no change in serum creatinine in two year-long rheumatoid arthritis trials; (ii) there was a small change in baseline blood pressure; (iii) incidence of edema and hypertension was the same as NSAID comparators in nine osteoarthritis trials "at therapeutic doses," and (iv) there were low discontinuation rates due to renal effects. 5/17/00 slide presentation, "Key Marketing Messages," MRK-ABL0000921, at 29. Mr. Anstice said that such approval would not have been an up or down vote but more of a general discussion of marketing themes. Similarly, Dr. Scolnick stated that the Human Health Product Approval Committee would not have approved specific marketing messages but rather general themes.

Searle/Pfizer to link the renal side effects of Vioxx with the myocardial infarction rates seen in the VIGOR Trial.

Dr. Dixon indicated that Dr. Scolnick did not believe that the Marketing Department was doing enough to combat the Searle/Pfizer campaign, and Dr. Scolnick offered to “help [the Marketing Department] to develop additional message[s] in response to the competitive environment” on these issues.<sup>43</sup> Dr. Dixon drafted at least two memoranda to Dr. Scolnick in April and May 2000 addressing what Merck perceived were Searle/Pfizer’s efforts to differentiate Celebrex from Vioxx based on superior cardiovascular and renal safety and the Marketing Department’s actions to combat those efforts.<sup>44</sup>

According to Dr. Dixon, the Marketing Department was constrained in its efforts to combat Searle/Pfizer’s campaign by the contents of the Vioxx label. Dr. Dixon believed that the Marketing Department could only say that Vioxx caused mechanism-based, dose-dependent increases in hypertension and edema – the data in the label – and nothing else. Furthermore, Dr. Dixon believed that Merck’s own data showed that Vioxx did, in fact, cause more renal effects than Celebrex. This view was echoed by a member of the Marketing Department, Mr. Thomas Cannell, to members of the Market Integration Team for Vioxx in an April 12, 2001 email:<sup>45</sup>

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<sup>43</sup> 5/8/00 memorandum from W. Dixon to E. Scolnick, MRK-ACR0010601, at 603.

<sup>44</sup> 4/26/00 memorandum from W. Dixon to E. Scolnick, MRK-AFI0015209-10; 5/8/00 memorandum from W. Dixon to E. Scolnick, MRK-ACR0010601-03.

<sup>45</sup> 4/12/01 email from T. Cannell to J. Dunn and M. Buttala, MRK-ADO0040848.

eventually I think we should step up to the fact that we probably do cause a little more HTN/edema [than Celebrex], particularly in the marketplace where V25 and C200 are the most common doses. The reason for that is that we are more effective at blocking COX-II, and you would expect this from any potent NSAID (since selective and non-selective NSAIDs inhibit COX-II).

Dr. Dixon stated that when the Marketing Department presented market research at a Management Committee meeting showing that doctors believed that Vioxx caused more serious renal side effects than Celebrex, Dr. Scolnick responded that the Marketing Department was not doing enough to defend against Searle/Pfizer's messaging.<sup>46</sup> Dr. Dixon said that she explained her view of the existing data and the constraints of the label but that Mr. Gilmartin sided with Dr. Scolnick and suggested that she was not thinking creatively about the matter. Dr. Scolnick, by contrast, stated that he wanted the Company's marketing campaign to concede that Vioxx caused slightly more dose-dependent hypertension and edema than Celebrex and to use this to support a claim of better efficacy in pain relief.

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<sup>46</sup> Dr. Dixon did not specify at which meeting this discussion occurred. Documents make clear that the Arthritis & Analgesia Worldwide Business Strategy Team ("WBST") presented to the Management Committee in December 2000 on topics including marketing challenges related to renal side effects of Vioxx, particularly as the Team believed that Searle/Pfizer was distorting the renal safety profile of Vioxx to the advantage of Celebrex. 12/14/00 slide presentation, "Management Committee presentation, Arthritis & Analgesia WBST," MRK-AAW0000194, at 271-90; 12/14/00 notes of Management Committee meeting, MRK-AAW0000192.

The need to address what was perceived to be Searle/Pfizer's aggressive strategy of distinguishing Celebrex from Vioxx based on renal safety continued to be discussed at senior levels into 2001. See, e.g., 2/8/01 email from L. Naphy to S. Kornowski, MRK-AHU0005965 (summarizing instructions from Mr. David Anstice to Dr. Wendy Dixon and the WBST to "reassess an approach for dealing with the hypertension/edema AE for VIOXX"); 3/13/01 background material for 3/20/01 HHPAC meeting, MRK-ABK0107661, at 690-91 (discussing need to neutralize concerns raised by competitor's attempts to portray Vioxx as unsafe because it caused hypertension and edema at rates higher than traditional NSAIDs or celecoxib).

As part of the above discussion, Riad El-Dada, then Senior Director of Marketing for the Arthritis and Analgesia Therapeutic Business Group, drafted a position paper in the fall of 2000 that outlined potential responses to Searle/Pfizer's purported claims that Vioxx caused more hypertension and edema than its competitors.<sup>47</sup> Mr. El-Dada said that he wrote the paper at the request of his supervisor, Ms. Lucine Beauchard, and that he understood that Dr. Dixon had requested a paper that reviewed whether Vioxx caused more hypertension and edema than Celebrex, and what Merck's position was on the issue, which was hurting Vioxx sales. Mr. El-Dada stated that Ms. Beauchard told him that the ultimate audience for the paper was Mr. Anstice.

The paper identified several concerns about Searle/Pfizer's promotion of the Whelton Study data, including the possibility that such promotion could increase the importance of hypertension issues in physicians' minds, generate new safety concerns about Vioxx, and allow Searle/Pfizer to present Celebrex as a "renal-sparing" NSAID compared to both Vioxx and non-specific NSAIDs.<sup>48</sup>

The paper acknowledged that there were differences between Vioxx and Celebrex in edema and hypertension results and suggested three potential explanations.<sup>49</sup> First, it stated that the incidence of hypertension with Vioxx appeared to be dose-related and might result from Vioxx's greater inhibition of Cox-2. Second, it explained that Celebrex

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<sup>47</sup> Position Paper on COX II Inhibitors and Hypertension/Edema, MRK-ADM0182542-64.

<sup>48</sup> Position Paper on COX II Inhibitors and Hypertension/Edema, MRK-ADM0182542, at 43.

<sup>49</sup> Position Paper on COX II Inhibitors and Hypertension/Edema, MRK-ADM0182542, at 45-46.

had a shorter half-life and was present in the kidney for less time than Vioxx and that this shorter half-life might allow the kidney of a patient on Celebrex to “recover,” resulting in less water retention than would be experienced by a patient on Vioxx. The position paper noted, though, that over several weeks the kidney should be able to readjust, which would be consistent with data that showed that the hypertension seen in Vioxx patients was transient. Third, the paper suggested – as had Dr. Whelton\* – that Vioxx’s molecular structure might determine the result, stating that certain non-selective NSAIDs caused greater hypertension and edema than others for unknown reasons.<sup>50</sup>

The paper also outlined four strategic objectives for the Marketing Department in combating Searle/Pfizer’s messages:<sup>51</sup>

- “Neutralize Pharmacia/Pfizer messages and maintain the non-GI safety image for the brand. This will defend VIOXX growth and also block celecoxib from staking out a differentiating position.”
- “Ensure that MIs in VIGOR are not linked by Pharmacia/Pfizer to increases in hypertension and edema.”
- “Block Pharmacia/Pfizer from convincing physicians that celecoxib is renal sparing.”
- “And most importantly, stay on the offensive with our own data demonstrating superior analgesic efficacy, the product attribute the physicians and patients rank as most important.”

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<sup>50</sup> Position Paper on COX II Inhibitors and Hypertension/Edema, MRK-ADM0182542, at 45-46.

<sup>51</sup> Position Paper on COX II Inhibitors and Hypertension/Edema, MRK-ADM0182542, at 46. These objective were echoed in a presentation by the Arthritis & Analgesia Worldwide Business Strategy Team to the Management Committee in December 2000. 12/14/00 slide presentation, “Management Committee presentation, Arthritis & Analgesia WBST,” MRK-AAW0000194, at 279.

To accomplish these objectives, the paper suggested a list of counter-messages for sales representatives to use with physicians. These messages included the following:<sup>52</sup>

- “Hypertension and edema are mechanism based class effects of all NSAIDs, specific and non-specific.”
- “Rates of hypertension and edema with VIOXX and celecoxib are low and consistent with incidences of these adverse events with non-specific NSAIDs.”
- “Rates of study discontinuation due to hypertension and edema are an important measure and are very low for both VIOXX (<0.2%) and celecoxib (<0.1%).”

c. Public Affairs strategy.

In May 2001, Public Affairs drafted a proposal entitled “Merck on the Offense” that recommended a new approach to communicating the gastrointestinal and cardio-renal safety of Vioxx.<sup>53</sup> The plan recommended “a very proactive media strategy on the renal issue in the context of upcoming medical meetings,” including a “traditional ‘high road’ strategy for usual competitors” and a “proposed offensive strategy for


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<sup>52</sup> Position Paper on COX II Inhibitors and Hypertension/Edema, MRK-ADM00182542, at 46.

<sup>53</sup> 5/4/01 slide presentation, “Spring 2001 Communications Plan for Vioxx: Supporting the GI & Cardio-renal Safety of Vioxx,” MRK-AFI0136807, at 19-29 (attached to 5/7/01 email from C. Fanelle to L. Beauchard et al., MRK-AFI0136806).

‘rule-breaking’ competitors.”<sup>54</sup> The plan contrasted these strategies in the page reproduced below:<sup>55</sup>

<b>Shifting Merck Strategic Approach to Competitor Data</b>	
<b><i>Traditional “High Road” Strategy for Usual Competitors</i></b>	<b><i>Proposed Offensive Strategy for “Rule-Breaking” Competitors</i></b>
Issue press release on our own relevant new data, use that release as the springboard for comments on competitor information	Issue materials and make proactive media calls to debunk information when we learn about it -- before it is promoted to the external world (assume it will be promoted by competitors)
Answer media calls and correct inaccurate stories	
Issue statements containing scientific product efficacy and safety messages, but that do not aggressively communicate flaws in competitor studies or flag related ethical issues	Issue statements containing simplified messages and that go to the next level -- “expose” the competitor’s practices (flawed science and conclusions)
Issue press releases and/or statements after competitors have pitched the media	Offer access to external physicians, MRL executives before the stories are developed
Offer internal and external experts to provide perspective to media <i>after</i> competitors’ presentations, reports	



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The issue of addressing data from the Whelton Study appeared repeatedly in the slides. In an email commenting on a draft of the plan Ms. Baumgartner noted:

One of [the] biggest flaws of [the] Whelton data is inappropriate use of V[ioux] 25 mg in this population. Should have started on V[ioux] 12.5 mg in hypertensive and elderly patients as recommended in our label. Need to

<sup>54</sup> 5/7/01 email from C. Fanelle to L. Beauchard et al., MRK-AFI0136806. The “upcoming medical meetings” listed in the presentation included the May 2001 meetings of the American Geriatric Society (at which the results of SUCCESS VII were released), the American Society of Hypertension, Digestive Disease Week. 5/4/01 slide presentation, “Spring 2001 Communications Plan for Vioxx: Supporting the GI & Cardio-renal Safety of Vioxx,” MRK-AFI0136807, at 29.

<sup>55</sup> 5/4/01 slide presentation, “Spring 2001 Communications Plan for Vioxx: Supporting the GI & Cardio-renal Safety of Vioxx,” MRK-AFI0136807, at 15.

capture this (prioritized as first weakness in our discussion  
and also main thrust of rep obstacle handling for  
consistency).<sup>56</sup>

Ms. Christine Fannelle of the Public Affairs Department responded with her comments  
embedded in the text of the email:<sup>57</sup>

To: Baumgartner, Susan L; Mills, Tracy L.  
From: Fannelle, Christine  
Cc: Bell, Angela; Ogden, Tracy C; Weiner, Jan D.  
Bcc:  
Date: 2001-05-09 14:24:42  
Subject: RE: Urgent: Renal Communications Plan5-4-01.ppt

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\* One of biggest flaws of Whelton data is inappropriate use of V 25 mg in this population. Should have started on V 12.5 mg in hypertensive and elderly patients as recommended in our label. Need to capture this (prioritized as first weakness in our discussion and also main thrust of rep obstacle handling for consistency). [Fannelle, Christine F] We understand the value of this message for certain audiences, but the PA/IR team recommended removing this explicit reference to the 12.5 dose because we felt that from a communications perspective, it feeds the Pharmacia argument that Vioxx at higher doses causes hypertension -- and given that Vioxx 25 mg is our most commonly prescribed dose, we didn't want to proactively feed the perception that Vioxx is a product that can only be used in lower doses in hypertensives (which would wipe out the efficacy advantage Vioxx has vs. Celecoxib 200 QD). Perhaps the way around this is to use a titration message? Do we have data that show that most physicians ACTUALLY do start their hypertensive patients on the 12.5 and THEN titrate up to 25 mg once the patient has adjusted to Vioxx? If not, this message may not be good as a press message, that is, if real world prescribing practices don't support it. Please advise.)

When the replicate Whelton Study (SUCCESS VII) was presented at the American Society of Hypertension in May 2001, the Public Affairs Department issued a short press release arguing that the study improperly employed twice the recommended starting dosage of Vioxx for elderly or hypertensive patients and simultaneously reissued the June 22, 2000 press release discussed above, which stated that the renal safety profile of Vioxx was not statistically different from that of Celebrex and was similar to that of

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<sup>56</sup> 5/9/01 email from S. Baumgartner to C. Fannelle et al., MRK-ADI0008767, at 67.

<sup>57</sup> 5/9/01 email from C. Fannelle to S. Baumgartner and T. Mills, MRK-ADI0008767, at 67.

certain traditional non-selective NSAIDs.<sup>58</sup> The Public Affairs Department also “spent the day on the phones with the media” publicizing Merck’s position on the study.<sup>59</sup>

d. Efforts to de-link renal effects from  
VIGOR Trial cardiovascular results.

One goal of Merck’s marketing campaign on renal issues was to de-link the renal effects of Vioxx from the cardiovascular events seen in the VIGOR Trial.<sup>60</sup> For example, Ms. Susan Baumgartner, commenting on the 2001 Communications Plan, suggested

[r]emov[ing] references to cardio-renal through the [Plan]  
and in all communications. The competition is trying to  
blur the renal and cardiovascular issues and to link  
hypertension and MI. We have to keep them distinct  
(edema, hypertension, and MI).<sup>61</sup>

Similarly, a Standby Statement approved for use when the second Whelton Study was presented at the American Society of Hypertension described a communications objective as: “Set record straight. Provide news media with reality check and context for Pharmacia data – get Merck position in stories and de-link renal issue from VIGOR, if

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<sup>58</sup> 5/11/01 Merck press release, “Merck Confirms Favorable Renal Safety Profile of Vioxx,” MRK-PRL0000190-92.

<sup>59</sup> 5/11/01 email from C. Fanelle to S. Baumgartner et al. (cc: J. Wainwright et al.), MRK-ADI0008881. Ms. Wainwright said she did not remember anything about this effort when shown the email.

<sup>60</sup> See, e.g., 12/14/00 slide presentation, “Management Committee presentation, Arthritis & Analgesia WBST,” MRK-AAW0000194, at 279 (slide of objectives for Vioxx, including “Ensure that the MIs in VIGOR are not linked by Pharmacia/Pfizer to increases in hypertension and edema”).

<sup>61</sup> 5/9/01 email from S. Baumgartner to C. Fanelle et al., MRK-ADI0008767, at 67. Ms. Baumgartner explained that MRL scientists had shown that in the VIGOR Trial there was no link between cardiovascular and renal issues with respect to Vioxx, and, therefore, she was recommending keeping discussions of the relevant data separate.

necessary.”<sup>62</sup> The Standby Statement went on to provide bullet points to support Merck’s claim that “Pharmacia’s linkage of the renal effects of Vioxx stated in the Whelton studies and the finding of VIGOR are false and misleading.”<sup>63</sup>

The Public Affairs Department successfully dissuaded at least one reporter from linking the renal findings of the second Whelton Study to the cardiovascular events in the VIGOR Trial by putting the reporter in touch with an outside consultant, Dr. Marvin Konstam\*.<sup>64</sup>

e. Letter to DDMAC.

In May and June 2001, Merck’s Office of Medical/Legal also sent two letters to the FDA’s Division of Drug Marketing, Advertising and Communication (“DDMAC”) complaining respectively about Searle/Pfizer’s marketing of the first and second Whelton studies and arguing that design flaws rendered the studies inadequate to support claims of superior renal safety over Vioxx.

The first letter was dated May 10, 2001 – the day before the results of the second Whelton study were released – and addressed only Searle/Pfizer’s marketing of SUCCESS VI. In that letter, Ms. Ellen Westrick, Executive Director of the Office of Medical/Legal at the time, asserted that

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<sup>62</sup> 5/18/01 Final Standby Statement, MRK-ADS0000127, at 28.

<sup>63</sup> 5/18/01 Final Standby Statement, MRK-ADS0000127, at 29.

<sup>64</sup> 5/11/01 email from C. Fanelle to S. Baumgartner et al. (cc: J. Wainwright et al.), MRK-ADI0008881 (journalist “was prepared to link the renal finding to the CV events in VIGOR with Vioxx, but I was able to dissuade her from that link and set her up to speak with Dr. Marv. Konstam”).

Pharmacia and Pfizer are disseminating a reprint of, and have issued four separate press releases on, the same single study purporting to compare cardiorenal profiles of Celebrex and VIOXX. Merck contends that, taken individually and together, Pharmacia/Pfizer's promotional activities constitute an aggressive campaign to misrepresent the cardiorenal and overall safety of Celebrex.<sup>65</sup>

Ms. Westrick advanced three arguments about the reprint distribution: First, the reprint allegedly was inconsistent with the precautions and adverse reactions sections of the Celebrex label, and a disclaimer on the reprint's coversheet stating that the document contained information not included on the approved label provided insufficient notice of this fact.<sup>66</sup> Second, the reprint ran afoul of FDA guidance on comparative claims between products because (i) it failed to provide equal prominence to comparative safety and efficacy claims, and (ii) SUCCESS VII was a single unreplicated study, which did not constitute "substantial evidence" of superior cardiorenal safety as required by FDA regulations on promotional claims.<sup>67</sup> Third, Merck claimed that the dosing regimen used for Vioxx was inconsistent with the recommended dosing for hypertensive and elderly patients and was an inappropriate basis for comparing dose-related side effects.<sup>68</sup> Additionally, Merck claimed that Searle/Pfizer's four separate press releases reporting on the same study used inappropriate promotional language, omitted material facts, and were

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<sup>65</sup> 5/10/01 letter from E. Westrick to S. Salis\*, MRK-ABW0002653, at 53.

<sup>66</sup> 5/10/01 letter from E. Westrick to S. Salis\*, MRK-ABW0002653, at 54-55.

<sup>67</sup> 5/10/01 letter from E. Westrick to S. Salis\*, MRK-ABW0002653.

<sup>68</sup> 5/10/01 letter from E. Westrick to S. Salis\*, MRK-ABW0002653, at 55.

“intended to and did present the cardiorenal profile of Celebrex as safer than has been demonstrated by substantial evidence and as set forth in its FDA-approved labeling.”<sup>69</sup>

Merck requested that DDMAC “take immediate action to address the false and misleading information disseminated through these activities.”<sup>70</sup>

After the results of the second Whelton Study were released on May 11, 2001, Merck submitted to DDMAC a follow up letter dated June 6, 2001 complaining about Searle/Pfizer’s press release regarding that study.<sup>71</sup> Merck argued that this press release also made comparative safety claims without presenting efficacy data as required by FDA guidance. Moreover, Merck noted that design flaws, including dosing of Vioxx in a manner inconsistent with the product label, rendered the study insufficient for making comparative claims between Vioxx and Celebrex. In response to Merck’s letters, the FDA stated that “some of the issues in your complaints appear to have merit and will be carefully evaluated for further action as deemed necessary.”<sup>72</sup> Mr. Thomas Casola, Executive Director of the Office of Medical/Legal, did not know the results of any such investigation (nor have any been found) and characterized Merck’s correspondence with DDMAC regarding Searle/Pfizer sales strategies as no more aggressive than similar correspondence related to other drugs.

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<sup>69</sup> 5/10/01 letter from E. Westrick to S. Salis\*, MRK-ABW0002653, at 56.

<sup>70</sup> 5/10/01 letter from E. Westrick to S. Salis\*, MRK-ABW0002653, at 56.

<sup>71</sup> 6/6/01 letter from E. Westrick to S. Salis\*, MRK-AAF0007589-90.

<sup>72</sup> 12/4/01 letter from L. Governale\* to E. Westrick, MRK-ABX0016212.

f. Letter to physicians.

In July 2001, sales personnel including both field representatives and Health Science Associates were given detailed letters about SUCCESS VI signed by Dr. Sherwood to hand out to physicians along with a copy of the Vioxx package insert.<sup>73</sup> The Whelton Study response letter stated Merck's view that "study design and patient population evaluated . . . may have influenced study results" and went on to list various points for doctors to consider in evaluating the study, the first being that "[a] starting dose of VIOXX 12.5 mg is particularly recommended" for osteoarthritis patients, as opposed to the 25 mg tested in the Whelton Studies.<sup>74</sup>

D. Project Offense.

On the heels of the negative publicity surrounding the promotion by Searle/Pfizer of the results of the Whelton Study as well as publication of an article by Dr. Eric Topol\* in JAMA that questioned the cardiovascular safety of selective Cox-2 inhibitors (discussed in Appendix J), Merck's Marketing and Sales Departments launched "Project Offense" in the fall of 2001.<sup>75</sup> The goal of the initiative was to: (i) promote new efficacy data comparing Vioxx to Oxycodone-Acetaminophen (Percocet); (ii) put renal and cardiovascular issues "into perspective;" and (iii) promote a Value Incentive Program

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<sup>73</sup> 7/9/01 Bulletin for Vioxx: Action Required: Dear Healthcare Provider/Dear Pharmacist Letter on Whelton Article (No. COX 01-045), MRK-ADJ0044399, at 399.

<sup>74</sup> 7/9/01 Bulletin for Vioxx: Action Required: Dear Healthcare Provider/Dear Pharmacist Letter on Whelton Article (No. COX 01-045), MRK-ADJ0044399, at 400.

<sup>75</sup> See generally, Slide presentation, "Vioxx® Going on OFFENSE," MRK-ABW0011849-64 (attached to 9/27/01 e-mail from J. Dunn to T. Cannell, MRK-ABW0011848).

(“VIP”) whereby hospitals that made Vioxx their preferred product and sold significant amounts of the drug could purchase Vioxx at a highly discounted rate.<sup>76</sup>

Mr. Thomas Cannell, who worked on the initiative, explained that in the wake of the negative publicity, representatives were spending much of their time responding to questions about safety issues rather than highlighting the positive, pain-relieving qualities of the drug.<sup>77</sup> Therefore, Project Offense aimed “to remind representatives in addition to providing a balanced discussion of all the appropriate safety information, to also talk about the reason doctors really use Vioxx, which is to relieve pain.”<sup>78</sup>

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<sup>76</sup> Slide presentation, “Vioxx® Going on OFFENSE,” MRK-ABW0011849, at 50 (attached to 9/27/01 e-mail from J. Dunn to T. Cannell, MRK-ABW0011848); Draft 10/3/01 MVX from J. Jerman re: “Project Offense,” MRK-ADW0037596, at 96; 11/2/01 email from J. Dunn to L. Brady, MRK-ADW0024614; SBD Cliff Notes: Vioxx – Project Offense: 10/1/01, MRK-ACZ0044537; 12/15/05 T. Cannell deposition at 36-37 (In re Vioxx Litig., MDL No. 1657, E.D. La.) (explaining the VIP program).

<sup>77</sup> 12/15/05 deposition of T. Cannell at 134 (In re Vioxx Litig., MDL No. 1657, E.D. La.).

<sup>78</sup> 12/15/05 deposition of T. Cannell at 134-35 (In re Vioxx Litig., MDL No. 1657, E.D. La.). To further this goal, representatives were provided with new detail pieces and encouraged to use their Hypertension and Whelton obstacle handlers with physicians.