EXPERT REPORT

DAVID A. KESSLER, M.D.

QUALIFICATIONS

1. My name is David A. Kessler, M.D. I received my M.D. degree from Harvard Medical School in 1979 and my J.D. degree from the University of Chicago Law School in 1978. I did my pediatrics training at Johns Hopkins Hospital.

2. I was appointed by President George H. W. Bush as Commissioner of the United States Food and Drug Administration and confirmed by the United States Senate. I served in that position also under President William Jefferson Clinton until February 1997.

3. I have taught food and drug law at Columbia Law School. I have testified many times before the United States Congress on food and drug issues. I have published numerous articles in legal, medical, and scientific journals on the federal regulation of food, drugs, and medical devices over the last thirty years. A list of my published books and articles, address, cases that I have appeared as witness in the last four years, and expert witness fee is attached in Appendix A.

4. As Commissioner, I acted to speed approval of new drugs and placed high priority on getting promising therapies for serious and life-threatening diseases to patients as quickly

as possible. I introduced changes in the device approval process to ensure that it meets high standards. During my tenure as Commissioner, the FDA announced a number of new programs, including: the regulation of the marketing and sale of tobacco products to children; nutrition labeling for food; user fees for drugs and biologics; preventive controls to improve food safety; measures to strengthen the nation's blood supply; and the MEDWatch program for reporting adverse events and product problems. I created an Office of Criminal Investigation within the agency.

5. I have served in numerous academic medical positions including Professor of Epidemiology and Biostatistics and Pediatrics.

THE FDA'S MISSION

6. The Food and Drug Administration (FDA) is one of the nation's most important consumer protection agencies. It is responsible for implementing the nation's food and drug laws. In 1962, as a result of the thalidomide tragedy where a drug that was marketed abroad, but not in the United States, was responsible for thousands of babies born with abnormal limbs, the United States Congress passed the Kefauver-Harris Amendments, which for the first time required the preclearance of all new drugs. Those Amendments required that before a drug company (called the "sponsor") could introduce in interstate commerce a new drug, the sponsor was required to scientifically establish that the drug was "safe and effective." The 1962 Amendments significantly changed how

the FDA regulated new drugs. [1] First, it required a positive act on the part of the FDA—prior to the Amendments, drugs were allowed to go on the market unless the FDA disapproved their use. Second, the Amendments added the requirement that new drugs must be proven to be "effective" as well as safe. [2] Third, they required that effectiveness be established by "substantial evidence" that demonstrated that the drug will have the effects it purports to have under the conditions of use set out in the drug's labeling.[3] And fourth, they defined "substantial evidence" as evidence consisting of "adequate and well-controlled investigations, including clinical investigations…." [4] The 1962 Amendments ushered in the modern era of drug development and evaluation. The statutory requirement of "adequate and well-controlled investigations" shifted drug development and testing to a scientifically based framework that has resulted in significant medical advances. Those Amendments helped shape the FDA requirements into the "gold standard" for the world.

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[1] Drug Efficacy and the 1962 Drug Amendments, 60 Geo. L. J 185, (1965)

[2] 21 U.S.C. § 355(d)

[3] 21 U.S.C. § 355(d)(5)

[4] 21 U.S.C. § 355(d)

THE FDA STANDARDS FOR APPROVAL

7. Under the nation's food and drug laws, a drug may not be introduced into interstate commerce unless its sponsor has shown that the drug is safe and effective for the intended conditions of use.[5]

8. The law requires that "adequate and well-controlled investigations" be used to demonstrate a drug's safety and effectiveness.[6]

9. The FDA approves a drug if there are "adequate and well-controlled clinical trials" that demonstrate a drug's safety and effectiveness for its "intended conditions" of use.[7]

10. The "intended conditions" for use of a drug are listed in the drug's labeling which is reviewed and approved by the FDA.[8]

11. Indications for use that are not listed in a drug's labeling have not been approved by the FDA.[9]

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[5] 21 U.S.C.§ 321

[6] 21 U.S.C. § 355(d)

[7] 21 U.S.C. § 355(d)(5)

[8] 21 U.S.C. § 355(d)(1) &(2)

[9] "The labeling is derived from the data submitted with the new drug application. It presents a full disclosure summarization of drug use information, which the supplier of the drug is required to develop from accumulated clinical experience and systemic drug trials of preclinical investigations and adequate, well-controlled clinical investigations that demonstrate the drug's safety and the effectiveness it purports or is represented to possess." 37 Fed. Reg. 16,503 (1972)

THE FDA'S SCIENTIFIC STANDARDS TO ESTABLISH SAFETY AND EFFECTIVENESS

12. The standards that govern the FDA safety and effectiveness requirements are contained in statutes, regulations, notices, and guidance documents.

13. The statutory requirement that a drug's effectiveness be demonstrated by "adequate and well-controlled clinical investigations" has been interpreted to mean a clinical study with 1) clear objectives; 2) adequate design to permit a valid comparison with a control group; 3) adequate selection of study subjects; 4) adequate measures to minimize bias; and 5) well defined and reliable methods of assessing subjects responses to treatment.[10]

14. The FDA has published a notice that set forth general principles for the conduct and performance of clinical trials. These principles have been adopted not only by the agency, but also by the International Conference on Harmonisation which includes the world's leading medicine control agencies. [11] Those principles include the following standards for the conduct of clinical trials to support an agency decision that a drug is safe and effective for its intended conditions for use:

a. The need for trials to be controlled --

"Trials should have an adequate control group. Comparisons may be made with placebo, no treatment, active controls, or of different doses of the drug under investigation. The

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[10] 21 C.F.R. § 314.26

[11] International Conference on Harmonisation : Guidance on General Considerations for Clinical Trials 62 Fed. Reg. 66113 (December 17, 1997)

choice of the comparator depends on, among other things, the objective of the trial… . Historical (external) controls can be justified in some cases, but particular care is important to minimize the likelihood of erroneous inference."

b. The need for trials to be randomized --

"In conducting a controlled trial, randomized allocation is the preferred means of assuring comparability of test groups and minimizing the possibility of selection bias."

c. The need for trials to be blinded --

"Blinding is an important means of reducing or minimizing the risk of biased study outcomes. A trial where the treatment assignment is not known by the study participant because of the use of placebo or other methods of masking the intervention is referred to as a single blind study. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and analysis of data are also unaware of the treatment assignments, the study is double blind."

d. The need for objective and prospectively determined trial endpoints --

A drug's effectiveness is determined if the drug has an effect on an "endpoint." That endpoint can be a clinical benefit, such as survival or a reduction of pain as measured on a validated pain scale; a clinical measurement, such as blood pressure; and, in some cases, a laboratory measurement, such as the amount of virus in the blood stream. All endpoints need to reflect clinical benefit. An endpoint that indirectly reflects a clinical benefit, such as a laboratory measurement, is known as a "surrogate endpoint. Endpoints should be defined prospectively (*i.e.*, before the trial begins), giving descriptions of

methods of observation and quantification. Objective methods of observation should be used where possible and when appropriate. A primary endpoint(s) should reflect clinically relevant effects and is typically selected based on the principal objective of the study. Secondary endpoints assess other drug effects that may or may not be related to the primary endpoint. Endpoints and the plan for their analyses should be prospectively specified in the protocol. The methods used to make the measurements of the endpoints, both subjective and objective, should be validated and meet appropriate standards for accuracy, precision, reproducibility, reliability, and responsiveness (sensitivity to change over time).

15. The FDA has addressed the need for reproducibility and reliability of clinical data in the trials that support a drug's approval. The FDA generally requires two pivotal adequate and well-controlled trials to support approval, except in certain circumstances. As stated by the FDA in the 1998 *Guidance to the Industry*,[12] "it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. (See e.g., Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); *Warner-Lambert Co. v. Heckler,* 787 F. 2d 147 (3d Cir. 1986)). FDA's position is based on the language in the statute and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence.

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[12] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*. May 1998

(S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962)). Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds. In section 115(a) of the Modernization Act, Congress amended section 505(d) of the Act to make it clear that the Agency may consider 'data from one adequate and well-controlled clinical investigation and confirmatory evidence' to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In making this clarification, Congress confirmed FDA's interpretation of the statutory requirements for approval and acknowledged the Agency's position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data."

16. The FDA usually considers one clinical trial insufficient to support approval.[13] The cases where the FDA has approved a drug on the basis of one clinical trial plus confirmatory evidence are rare. They include instances of large, independently conducted multicenter trials with strong empirical results, with internal consistency across multiple outcomes, such that "sponsors faced ethical boundaries" in conducting a second placebo-based trial.

17. Clinical trials that are not controlled, blinded, randomized and whose endpoints are not prospectively and objectively determined and measured may be used in early stage drug development phases, but are exceptionally unlikely to qualify as "adequate and well-controlled" clinical trials needed to support FDA approval.

REVIEW OF DOCUMENTS

18. I have reviewed the documents provided to me in Appendix B to this report. Based on a review of those documents, I have made a number of observations that are detailed below.

THE FDA APPROVED USES OF NEURONTIN

19. Neurontin was approved for adjunctive therapy (used in addition to other drugs) for specific types of seizures. On December 30, 1993,[14] The FDA's Robert Temple, M.D.

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[13] Peck CA, and Wechsler MA Report of a Workshop on Confirmatory Evidence to Support a Single Clinical Trial as a basis for New Drug Approval, *Drug Information Journal*, Vol. 36, pp. 517–534, 2002

[14] WLC FRANKLIN 0000151674-679

wrote to Parke Davis that the drug is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. The FDA concluded that the effectiveness of Neurontin as adjunctive therapy was established in three multicenter placebo-control double-blind parallel group clinical trials involving 705 adults with refractory partial seizures. The patients enrolled had a history of partial seizures in spite of receiving one or more anti-epileptic drugs.

20. The FDA concluded that the effective dose in the management of seizures is 900 to 1800 mg/day and is given in divided dose in adults.[15]

21. On October 12, 2000, FDA's Dr. Russell Katz wrote to Parke Davis that Neurontin was approved as adjunctive therapy in the treatment of partial seizures in pediatric patients age three years and above.[16]

22. On May 24, 2002, Neurontin was also approved for the management of postherpetic neuralgia. FDA's Dr. Cynthia McCormick[17] wrote to Parke Davis that, "This new drug application provides for the use of Neurontin (gabapentin) tablets, capsules and oral solution for the management of postherpetic neuralgia. We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text." FDA's approval of Neurontin for use in postherpetic neuralgia was based on the data in two randomized, double-blind, placebo-

[15] WLC FRANKLIN 0000151689

[16] Pfizer MPatel 0202487

[17] Pfizer MPatel 0202485, Pfizer LCastro 0012132-68

controlled, multicenter studies. The FDA concluded that there were significant differences in pain rating scales in those patients receiving the drug as compared to placebo at the doses tested. A significant reduction in weekly mean pain scores was seen by Week 1 in both studies, and significant differences were maintained to the end of treatment.

THE FDA REJECTED USES OF NEURONTIN AS MONOTHERAPY FOR SEIZURES IN ADULTS

23. The FDA refused to approve the use of Neurontin as monotherapy for certain seizures in adults. On August 26, 1997,[18] FDA's Paul Leber, M.D. wrote to Parke Davis and said that "we have concluded that a claim for Neurontin's use as monotherapy cannot be granted based on the evidence we have in hand."

24. Specifically, Dr. Leber stated that, "At the present time, you have submitted reports of four controlled clinical trials (Studies 945-088, 945-077, 945-082, 945-177) that, by design, should have been capable of assessing Neurontin's capacity, when used as monotherapy, to reduce the intensity and/or frequency of seizures in patients with epilepsy. In fact, two of the four studies (Study 945-088 and 945-077) have provided statistically significant results on the outcome measures identified in their protocols. However, although this evidence might, on face, seem sufficient to meet the regulatory test of substantial evidence of

[18] WLC CBU 041537-39

effectiveness, detailed examination of the data does not support the approval of a claim for Neurontin when given as the sole antiepilepsy drug (AED)."

"In our view, the evidence, taken as a whole, is inconclusive. While Study 945-088 does provide 'proof of principle' support for a conclusion that Neurontin has some capacity to reduce the incidence of partial seizures in patients with chronic recidivistic epilepsy, the time interval investigated (i.e., 8 days) is so short that the finding has little, if any, relevance to the proposed conditions of use of the marketed product either in chronic or newly diagnosed patients. The only other study in the chronic recidivistic population (Study 945-082) failed to yield evidence of effectiveness."

"Although Study 945-077 does provide what can be considered direct support for a monotherapy claim in patients with recently diagnosed epilepsy, the absence of a confirming corroborative study makes a conclusion that Neurontin is effective when given as monotherapy (even in this sub-group) unjustified. Moreover, the positive result of 945-077 is due to its effect on an outcome for which Neurontin is not currently approved for use (generalized tonic clonic seizures)."

"Consequently, we have concluded that a claim for Neurontin's use as monotherapy cannot be granted based on the evidence we have in hand. We acknowledge that, our present decision notwithstanding, available evidence does suggest that Neurontin may be effective in monotherapy, especially in newly diagnosed epileptic patients. However, before a claim for use in newly diagnosed patients could be approved, you would have to present results

from a second adequate and well-controlled clinical investigation corroborating the findings of Study 945-077."[19]

25. In response to the FDA's refusal to approve Neurontin for monotherapy for certain seizures in adults, Parke Davis amended its application[20] to include the use of Neurontin as monotherapy of partial seizures in adult patients who have not been previously treated with antiepileptic drugs.

26. On April 24, 1998, FDA's Paul Leber[21] again rejected Parke Davis's application for Neurontin use as "monotherapy in partial seizures in adults." Dr Leber wrote, "[W]e have concluded that your application fails to provide substantial evidence that Neurontin is effective in use when administered as monotherapy for partial seizures in adults. Accordingly, this supplemental application is *not* approvable under section 505(d) of the Act and 21 CFR 314.125(b)."

27. As a basis for its refusal of Neurontin as monotherapy, Dr. Leber wrote, "In the course of evaluating your application, the agency has considered not only the findings of the controlled clinical trials reported to the NDA file, but the arguments advanced by your firm, both in the NDA and in the course of verbal discussions with the Division's scientific/medical staff, explicating why it considers the evidence, despite the absence of independent substantiation of Neurontin's effectiveness when administered as the sole antiepileptic drug (AED) in a second adequate and well-controlled clinical trial, sufficient to support approval of the NDA." Dr.

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[19] WLC CBU 041538

[20] Pfizer LCastro 0001212

[21] Pfizer LCastro 0001212

Leber went on to write, "Basically, your firm argues that: 1) Study 077, on its own, provides what is tantamount to independent substantiation of Neurontin's effectiveness as monotherapy because the clinical outcomes of patients randomized to both the 900 and 1800 mg/day treatment groups were superior (i.e., statistically significantly different) to the average outcome of patients randomized to the placebo group; 2) the failure of Study 177 to confirm the effectiveness of Neurontin cannot be taken as evidence undermining the findings of Study 077 because Study 177 was not adequately powered to detect a treatment effect of the size realized in Study 077; 3) A draft of an agency document Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products indicates that the affirmative findings of one adequate and well-controlled clinical study could be sufficient to support a claim for an AED's use as monotherapy if the product was already known to be effective in use as a component of a multi-AED regimen for the same seizure type, and; 4) The Agency has in the past approved an NDA for the use of a drug as monotherapy in epilepsy on the basis of the results of but a single monotherapy study, and, accordingly, that is the standard of evidence that should be required of Neurontin."

Dr. Leber concluded, "These arguments are not compelling."[22]

THE FDA DID NOT APPROVE NEURONTIN FOR USE IN NEUROPATHIC PAIN

28. A supplemental New Drug Application was filed with the FDA for broad neuropathic pain on August 6, 2001. This application included two post herpetic neuralgia (PHN) studies, two

[22] Pfizer LCastro 0001213

Diabetic peripheral neuropathy (DPN) studies, and one study in mixed neuropathic pain (MNP).[23]

29. According to the minutes of a meeting May 14, 2001 between the FDA and the company, the FDA indicated that "a broad claim for the indication 'management of neuropathic pain' cannot be granted at this time."[24]

30. Pfizer's record of the meeting stated that "[t]he Division does not consider 'management of neuropathic pain' a viable indication at this time. They plan to hold an advisory committee meeting later this year to discuss the various conditions associated with neuropathic pain, and whether a number of conditions could be studied such that a general claim could be granted. This is the message they have given to sponsors since they became responsible for this area (approximately 10 months ago)."[25]

31. The FDA noted that "[i]n order for a general neuropathic indication to be granted, the sponsor must provide evidence that the underlying disease process is similar for DPN, PHN, and the pain of other neuropathic disorders and/or that the drug is effective for the neuropathic pain of all (or at least most) etiologies."

32. The FDA also noted that additional studies would be necessary. The FDA stated that "the sponsor must provide evidence of efficacy replicated in a second study for DPN. This trial must be 12 weeks in length at fixed doses, as required for a chronically administered drug. The

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[23] Pfizer LCastro 0010557

[24] Pfizer LCastro 0005155

[25] Pfizer LCastro 0005155

sponsor must also incorporate electrophysiological measurements in order to show that the improvement in pain is not due to sensory loss. Sensory exams are not easily reproduced and will not reliably detect sensory loss due to nerve death. The two studies for the PHN indication have shown efficacy at different doses. The sponsor must provide evidence of dose replication in order for clinicians to arrive at a proper prescribing dose."[26] Consistent with its policy on the quantum of evidence required to support approval,[27] the FDA required the company to replicate its clinical trial and would not approve the drug based on one clinical trial alone.

33. In an addendum to the FDA minutes, the FDA "indicated that an application with a general neuropathic pain indication would not be refused to file a priori. Rather, the indication will be a review issue with burden on the sponsor to scientifically support it."[28]

34. Pfizer's consultants counseled that the FDA would not approve Neurontin for use in neuropathic pain. Draft minutes of a September 6, 2001[29] meeting of company consultants stated, "[e]xpert opinion on general preclinical and clinical data to date is that the evidence is not convincing to support a broad neuropathic pain claim <u>based upon clinical results with one or two types of etiologies.</u>[30] Opinion on the Neurontin neuropathic pain package is that neither the FDA nor the Advisory Committee is likely to agree that adequate evidence is provided for a broad indication. New analyses/data not only do not support the broad claim, they provide evidence contrary to a broad

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[26] Pfizer LCastro 0005621

[27] See Paragraphs 15 and 16 *supra*

[28] Pfizer AGarrity 0002500

[29] Pfizer LKnapp 0024958

[30] Underlines appear in original apparently to reflect edits

indication." The minutes reflected that among the experts "[t]here was a clear consensus that a broad claim with any drug is not possible at this time. The available preclinical data are supportive of the theory, however, mechanisms are incompletely understood and insufficient to make a compelling case. There is insufficient-even less clinical evidence to make the general…[31] case." According to the minutes, the experts further counseled that "[w]hile the Neurontin package (2 studies in PHN and I study in DPN) alone was not considered adequate as supporting a broad claim, new analyses from the 945-306 study in the NDA and a recently completed Nordic study (945-271) add substantial evidence against a broad neuropathic pain claim. Statistical significance in 945-306 is the [*sic*] predominantly the result of the PHN patients (in addition to a small number of DPN patients) in the study. Patients with neuropathic pain types other than PHN or DPN had much less of a treatment effect (-0.3 for patients with other pain syndromes compared with -1.8 for PHN and DPN patients). Study 945-271, patients with posttraumatic and postsurgical neuropathic pain, was negative in primary outcome (VAS scale)."

35. On October 22, 2001, Pfizer informed the FDA[32] that it was "appropriate to amend the proposed indication in its pending New Drug Application" to "management of neuropathic pain associated with postherpetic neuraligia at this time," and that "narrowing the proposed indication may require some new analyzes and presentations" to allow the FDA to complete its review. On

[31] Underlines appear in original apparently to reflect edits

[32] Pfizer LCastro 0007275

November 6, 2001, Pfizer sent the FDA[33] a proposed timeline for submission of documents and datasets to support its amended application.

36. In its labeling review of Neurontin for use in post herpetic neuralgia, the FDA did not approve the indication submitted by Pfizer which stated "Neurontin® (gabapentin) is indicated for the management of neuropathic pain associated with-postherpetic neuralgia" but rather changed it to read "Neurontin® (gabapentin) is indicated for the management of post herpetic neuralgia."[34]

THE FDA DID NOT APPROVE NEURONTIN FOR USE IN DIABETIC PERIPHEREAL NEUROPATHIC PAIN

37. The FDA made clear to Pfizer that it would require certain tests to approve Neurontin for use in Diabetic Peripheral Neuropathy. According to minutes of a meeting with the FDA,[35] on May 14, 2001, the FDA stated "The sponsor must provide evidence of efficacy replicated in a second study for DPN. This trial must be 12 weeks in length at fixed doses, as required for a chronically administered drug. The sponsor must also incorporate electrophysiological measurements in order to show that the improvement in pain is not due to sensory loss. Sensory exams are not easily reproduced and will not reliably detect sensory loss due to nerve death.

[33] Pfizer LCastro 0008060

[34] Pfizer LCastro 0011577

[35] Pfizer LCastro 0005621

38. Based on the data submitted to the FDA, the FDA stated[36] "The Division does not believe that a Neurontin DPN submission would be fileable at this time, as efficacy has not been replicated. An additional trial would be needed."

39. Company consultants counseled Pfizer that obtaining the FDA approval for Neurontin in diabetic peripheral neuropathy was unlikely. Company minutes of a consultants meeting stated "Evidence for DPN is confounded by the negative DPN study. The Experts would not recommend the current package be presented at an Advisory Committee meeting." [37] "There was consensus that there was a low probability of success with current package; i.e., one positive study that evaluated 3600 mg, and one negative study (945-224). The large placebo effect and 2400 mg/day appearing worse than 120 (sic) mg/day in this dose-response study (600, 1200, 2400 mg/day) was particularly viewed as problematic. Another positive, well-controlled study is likely needed to overcome this study."[38]

40. As noted above, on May 14, 2001, the FDA told Pfizer that an application to support the indication for diabetic peripheral neuropathy needed to include a second study at fixed doses.[39] On January 17, 2002,[40] Pfizer submitted an investigational new drug application to undertake a 15-week randomized, double-blind, placebo-controlled, parallel group, multicenter study of Neurontin for efficacy and quality of life in patients with painful diabetic peripheral

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[36] Pfizer LKnapp 0047459

[37] Pfizer LKnapp 0013491

[38] Pfizer LKnapp 0013493

[39] Pfizer AGarrity 0002493-97; Pfizer LCastro 0005618

[40] Pfizer LCastro 0008368-69

neuropathy. Pfizer acknowledged that the trial it was submitting was not the trial the agency had requested. "We will submit another protocol (Protocol 945-440) in the near future that is intended to fulfill the Agency's expectations for that registration trial." On February 27, 2002,[41] Pfizer submitted the requested study (Protocol 945-440). On May 31, 2002,[42] Pfizer cancelled Protocol 945-440.

FDA DID NOT APPROVE DOSE RECOMMENDATIONS IN NEURONTIN'S LABELING GREATER THAN 1800 MG/DAY

41. In a letter dated August 26, 1997[43] from FDA's Paul Leber to Parke Davis , the FDA stated, "the supplemental application provides for the following: an increase in the effective dose range to include 3600 mg/day…. We are not able to grant changes in these labeling statements because experience gained at these higher doses in monotherapy trials cannot support the safety of these doses when given as adjunctive therapy, the only currently approved condition of use. If you make a suitable presentation of safe passage data gained at higher doses in adjunctive therapy, we would consider allowing that information to be included in labeling, provided it was accompanied by a statement advising that the evidence from controlled trials fails to provide evidence that higher doses of Neurontin are more effective than those recommended." In May 2002, the FDA did not approve the dosage for PHN submitted by Pfizer which stated, "The dose can subsequently be titrated up as needed for pain relief to a maximum daily dose of 3600 mg" and that there was "greater efficacy with increasing dose,"[44] but rather changed it to

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[41] Pfizer LCastro 0010379-81

[42] Pfizer MYoder 0000920

[43] WLC CBU 041537-39

[44] Pfizer LCastro 0011563

read: "Additional benefit of using doses greater than 1800 mg/day was not demonstrated."[45]

THE FDA DID NOT APPROVE NEURONTIN FOR USES BEYOND THOSE LISTED IN THE DRUG'S LABELING.

42. Neurontin's labeling states that the drug is approved for two indications, adjunctive therapy for partial seizures, and post herpetic neuralgia.

43. Other indications that are not listed on the drug's labeling are not FDA approved indications.

44. There is no evidence in the documents that I reviewed that Parke Davis or Pfizer submitted data to the FDA for Neurontin's use in bipolar and other mood disorders, migraine, nociceptive, and non neuropathic pain.

THE FDA NOTIFIED PARKE-DAVIS THAT IT WAS CONCERNED THAT PARKE DAVIS MAY HAVE BEEN PROMOTING NEUROTIN FOR "OFF LABEL" USES

45. On July 19, 1996,[46] FDA's Dr. Lesley Frank wrote to Parke Davis's Dr. William Merino that "FDA is concerned that Parke-Davis may be promoting Neurontin for 'off-label' uses, i.e., any use beyond the FDA-approved indications, in printed promotional materials, in detail or sales presentations to physicians, and through the use of company-solicited physician participation in a series of teleconferences. FDA is initiating an inquiry that will focus on these concerns. These

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[45] Pfizer LCastro 0011868; Pfizer MPatel 007787

[46] WLC CBU 057865-73

promotions of Neurontin for off-label uses include, but are not limited to, its use in chronic pain, bipolar disorders, and other psychiatric conditions. As you are aware, Neurontin's only approved indication is as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy."

THE FDA NOTIFIED PFIZER THAT CERTAIN PROMOTIONAL MATERIAL FOR NEURONTIN WAS MISLEADING AND IN VIOLATION OF THE FEDERAL FOOD DRUG AND COSMETIC ACT AND ITS APPLICABLE REGULATIONS

46. FDA's Dr. Lisa Stockbridge notified[47] Pfizer's Andrea Garrity in a letter of June 29, 2001, that certain of the company's promotional material "misleadingly claims improvement in quality of life (QOL) parameters based on the Neurontin Evaluation of Outcomes in Neurological Practice (NEON) study. Among other QOL parameters, the misleading presentation includes improvement in social limitations, memory difficulties, energy level, and work limitations. The NEON study is not considered to be substantial evidence for claims of QOL improvements because it is not a controlled study." The FDA asked the company to immediately discontinue use of the promotional materials and supply the agency with a list of all promotional materials with the same or similar issues and its methods for discontinuing these promotional materials.

47. An internal Pfizer slide presentation[48] concerning the FDA letter had listed the following bullets under "Action:"

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[47] Pfizer RGlanzman 0054596-609

[48] Pfizer LCastro 0006580-85

--"Discontinued used of Slim Jim and all other pieces with mention of NEON…"

--"Discontinued use of bounded materials that included STEPS quality of life data"

--"It was felt that DDMACs comments also applied to the use of STEPS efficacy and tolerability data"

--"No agreement at RC level regarding discontinuing use of STEPS data in promotion. Policy Committee"

--"Policy Committee agreed to the use of STEPS data if presentation on efficacy and tolerability was balanced with a similar presentation of the pivotal clinical trial data"

48. An internal Pfizer email[49] dated July 2, 2002 from Lucy Castro to JohnWolleben summarized the current situation. "Material currently being used contain information (QoL, efficacy & tolerability) based on another open label study - STEPS (this is data Andrea and I spoke to you about several months). We feel it presents the same risk as the use of NEON data and would like to remove the data from the next POA materials - particularly the QoL and efficacy data. Unfortunately, all of our promotional materials are based on these two studies. Without these data, we only have the pivotal data for promotion and that data is weak. We would like to present to the team the position that we should only be using the open label data to support our safety and tolerability message and would like your endorsement."

49. On July 9, 2001, [50] Pfizer's Dr. O. Lucy Castro wrote to the FDA in response to the FDA's letter of June 29, 2001 (see Paragraph 46 *supra*) that "In response to the FDA's request for

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[49] Pfizer AGarrity 0002142

[50] Pfizer Castro 0085965

action Pfizer has taken the following steps: 1. Discontinued use of the above mentioned slim jim. 2. Instructed the sales force to discontinue promotion of the QOL data in the NEON study. We are in the process of identifying other promotional materials with the same or similar messages. We will provide the Agency shortly with a detailed list of the identified pieces and a description of the action taken to remove them from the public domain."

50. On July 9, 2001,[51] Pfizer's Rick Burch wrote to the RON Specialty Sales Force stating "[o]n June 29, 2001, Pfizer received a Notice of Violation letter from the FDA for "Neurontin POA 1 Slim Jim (ID #NSJ5095A1)." The FDA cites the Slim Jim for misleading claims regarding improvement in quality of life (QOL) parameters based on the NEON study. The Agency does not consider the NEON study to be substantial evidence for claims of QOL improvements because it is not a controlled study. Pfizer has agreed to address these FDA objections as follows: Immediately discontinue the use of this Slim Jim and any other promotional material and practices with the same or similar study. Additionally, the Neurontin STEPs study contains QOL data and is not a controlled study. Therefore, Pfizer has decided to discontinue the use of any promotional material and practices containing STEPs QOL data as well. In order to comply with current FDA and Pfizer policy, you must discontinue use of and destroy any promotional materials containing reference to NEON or STEPS QOL data, including the following promotional items…"

[51] Pfizer MBrown 0000374

51. On July 11, 200,[52] Pfizer's Mark Brown, wrote to DL-K All Managers, "Just want to make sure that you and your team understand that only the QOL information needs to be discontinued. The remainder of the visaid material is still approved."

52. On July 31, 2001,[53] Pfizer's Dr. O. Lucy Castro again wrote to the FDA in reference to the FDA's June 29, 2001 letter (see Paragraph 46 *supra*) and Pfizer's July 9, 2001 letter to the FDA and stated: "In this correspondence we noted that we had complied with the Agency's recommendations by 1) discontinuing use of the above mentioned slim jim, 2) instructing the sales force to discontinue promotion of the QOL data in the NEON study and 3) identifying other promotional materials with the same or similar message. In addition, the following promotional materials have been withdrawn from circulation and the Field Force has been instructed to destroy these pieces… Pfizer trusts that the above information completes our address of the issues raised in your letter."

The foregoing is based on my experience, education and the information I have reviewed. I reserve the right to supplement this report if additional information is made available.

Submitted,

David A. Kessler M.D.

July 31, 2008

Date

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[52] Pfizer MBrown 000374

[53] Pfizer LCastro 0085964

APPENDIX A

PUBLICATIONS

Books

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ADDRESS

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San Francisco, California 94123

TESTIFIED AS IN WITNESS AT TRIAL OR IN DEPOSITION IN THE FOLLOWING CASES OVER THE LAST FOUR YEARS:

FOR THE UNITED STATES:
UNITED STATES OF AMERICA, Plaintiff,
v. PHILIP MORRIS USA INC. f/k/a PHILIP MORRIS INC., *et al.*,
Civil No. 99-CV-02496 (GK)

FOR THE STATE OF CALIFORNIA:
PEOPLE'S ADVOCATE AND NATIONAL TAX LIMITATION FOUNDATION
v. INDEPENDENT CITIZENS' OVERSIGHT COMMITTEE
(ALAMEDA COUNTY SUPERIOR COURT, STATE OF CALIFORNIA
(case # HG05206766)

EXPERT CONSULTATION RATE IN CURRENT CASE:

$1000/HR

APPENDIX B

PFIZER_AGARRITY_0002142
PFIZER_AGARRITY_0002490
PFIZER_AGARRITY_0002499
PFIZER_AGARRITY_0003834
PFIZER_AGARRITY_0005558
PFIZER_AGARRITY_0010045
PFIZER_LCASTRO_0001212
PFIZER_LCASTRO_0003662
PFIZER_LCASTRO_0005072
PFIZER_LCASTRO_0005618
PFIZER_LCASTRO_0006149
PFIZER_LCASTRO_0006580
PFIZER_LCASTRO_0007272
PFIZER_LCASTRO_0008052
PFIZER_LCASTRO_0008368
PFIZER_LCASTRO_0008371
PFIZER_LCASTRO_0010377
PFIZER_LCASTRO_0010557
PFIZER_LCASTRO_0011563
PFIZER_LCASTRO_0012132
PFIZER_LCASTRO_0011868
PFIZER_LCASTRO_0073127
PFIZER_LCASTRO_0085964
PFIZER_LESLIETIVE_0013555
PFIZER_LKNAPP_0009569
PFIZER_LKNAPP_0009645
PFIZER_LKNAPP_0009830
PFIZER_LKNAPP_0013491
PFIZER_LKNAPP_0023060
PFIZER_LKNAPP_0023078
PFIZER_LKNAPP_0024958
PFIZER_LKNAPP_0047459
PFIZER_LKNAPP_0047504
PFIZER_LKNAPP_0070705
PFIZER_MBROWN_0000374
PFIZER_MPATEL_0077867
PFIZER_MPATEL_0202485
PFIZER_MPATEL_0203692
PFIZER_MYODER_0000920
PFIZER_RGLANZMAN_0054596
WLC_CBU_041537
WLC_CBU_057865
WLC_FRANKLIN_0000039559
WLC_FRANKLIN_0000039956
WLC_FRANKLIN_0000039959
WLC_FRANKLIN_0000041545
WLC_FRANKLIN_0000151674