IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES	:	
	:	
v.	:	**Criminal No.** 1:12CR26
	:	
ABBOTT LABORATORIES	:	

AGREED STATEMENT OF FACTS

Introduction

1. Defendant ABBOTT LABORATORIES ("ABBOTT") is an Illinois corporation, headquartered in Illinois, which markets and distributes prescription drugs through its Pharmaceutical Products Division ("PPD"). ABBOTT's PPD is responsible for the unlawful conduct set forth herein. PPD's employees include sales representatives who market ABBOTT's prescription drugs throughout the United States.

2. ABBOTT markets and distributes several different forms of divalproex sodium, including Depakote (a/k/a Depakote DR), Depakote ER, and Depakote Sprinkle (hereinafter collectively referred to as "Depakote"). ABBOTT manufactures Depakote at facilities in Illinois and Puerto Rico and distributes it throughout the United States, including the Western District of Virginia.

3. Over the ten year period from 1998 to 2008, ABBOTT's gross sales of Depakote were approximately $13.8 billion.

4. From in or about 1998 to in or about December 2006, ABBOTT introduced and delivered, and caused the introduction and delivery for introduction, into interstate commerce Depakote which was misbranded in violation of the Food, Drug, and Cosmetic Act ("FDCA"),

21 U.S.C. §§ 331(a), 333(a)(1), and Section 352(f), in that the drugs' labeling lacked adequate directions for use for the control of agitation, aggression, and other behavioral symptoms exhibited by elderly patients with dementia. From in or about 2002 to December 2006, ABBOTT introduced and delivered, and caused the introduction and delivery for introduction, into interstate commerce Depakote which was misbranded in violation of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 331(a), 333(a)(1), and Section 352(f), in that the drugs' labeling lacked adequate directions for use for the treatment of schizophrenia. From December 2004 to December 2006, ABBOTT introduced and delivered, and caused the introduction and delivery for introduction, into interstate commerce Depakote which was misbranded in violation of the FDCA, 21 U.S.C. §§ 331(a), 333(a)(1), and Section 352(a), in that the drugs' labeling was misleading for use for the (a) control of agitation, aggression, and other behavioral symptoms exhibited by elderly patients with dementia and (b) treatment of schizophrenia..

Statutory Framework

5. The Food and Drug Administration ("FDA") is the federal agency responsible for protecting the health and safety of the public by enforcing the FDCA and ensuring, among other things, that drugs are safe and effective for each of their intended uses and that the labeling of such drugs bears true, complete, and accurate information.

6. The FDCA, 21 U.S.C. § 355, prohibits the distribution of a new drug in interstate commerce for any use proposed by the drug's manufacturer until FDA completes an intensive review of the safety and effectiveness of the drug and approves it for the proposed use(s). Under the FDCA, 21 U.S.C. §§ 331(d) and 355(b), a manufacturer seeking FDA approval to market a new drug is required to submit a New Drug Application ("NDA") that (1) identifies all of the proposed uses of the drug intended by the manufacturer; (2) includes data, generated in

randomized and well-controlled clinical trials, which demonstrates that the drug is safe and effective for each of those uses; and (3) includes proposed labeling setting forth detailed information about the drug with respect to those intended uses. The FDCA, 21 U.S.C. § 355(a), prohibits the manufacturer from introducing the new drug into interstate commerce until FDA approves the NDA and the proposed labeling after determining that the NDA provides sufficient evidence of the drug's safety and efficacy for its intended uses.

7. The FDA's approval of a drug for one use does not mean that the drug is safe and effective for another use. Uses not approved by FDA are known as "unapproved" or "off-label" uses. The FDCA requires a manufacturer seeking FDA approval for additional uses of a drug to file a new or supplemental NDA that includes the same information described in Paragraph 6 above. The manufacturer can distribute the drug for those additional uses only after FDA (1) concludes that the drug is safe and effective for those additional uses; (2) approves the new or supplemental NDA; and (3) approves revisions to the drug's labeling to describe those additional approved uses.

8. The FDCA, 21 U.S.C. §§ 331(a) and 333(a)(1), makes it unlawful for a drug manufacturer to introduce, deliver for introduction, or cause the introduction or delivery for introduction into interstate commerce of any "misbranded" drug. Under the law, 21 U.S.C. § 352(a), a misbranded drug includes a drug whose "labeling is false or misleading in any particular." The FDCA provides that determination of whether labeling is "misleading" should "take[] into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling ... fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article [which includes a drug] to

which the labeling ... relates under the conditions of use prescribed in the labeling ... or under such conditions of use as are customary or usual." 21 U.S.C. § 321(n). The FDCA also defines "labeling" as "all labels and other written, printed, or graphic matter (1) upon any article [which includes a drug] or any of its containers or wrappers, or (2) accompanying such article [which includes a drug]." 21 U.S.C. § 321(m). "Labeling" does not have to be physically attached to the drug and can include various written, printed, or graphic information that describes the drug and is disseminated by or on behalf of the drug manufacturer. Thus, a manufacturer can violate the FDCA by distributing written, printed, or graphic information about the drug that is false or misleading.

Depakote's Approved Uses and FDA-Approved Labeling

9. Depakote was approved by FDA to treat certain types of epileptic seizures and bipolar mania and to prevent the onset of migraines.[1] FDA has never approved Depakote as safe and effective for the control of agitation and aggression in patients with dementia or for the treatment of schizophrenia. ABBOTT, however, promoted Depakote for these unapproved uses.

10. The FDA-approved labeling includes information about safety risks associated with use of Depakote, including three "Black Box" warnings, other warnings and precautions, and information about adverse side effects associated with use of the drug. A Black Box warning is the most serious warning that FDA can require be placed on a drug's labeling.

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[1] On March 10, 1983, FDA approved Depakote for absence seizures. On May 26, 1995, FDA approved Depakote for manic episodes associated with bipolar disorder. On March 18, 1996, FDA approved Depakote for migraine prophylaxis. On June 20, 1996, FDA approved Depakote for complex partial seizures. On September 12, 1989, FDA approved Depakote Sprinkle for absence seizures. On June 20, 1996, FDA approved Depakote Sprinkle for complex partial seizures. On August 4, 2000, FDA approved Depakote ER for migraine prophylaxis. On December 20, 2002, FDA approved Depakote ER for complex partial seizures and absence seizures. On August 14, 2003, FDA approved Depakote ER for complex partial seizures and absence seizures in pediatric patients. On December 6, 2005, FDA approved Depakote ER for acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. Depakote, Depakote Sprinkle, and Depakote ER were never approved by FDA for any other uses.

11. In 1999, after an ABBOTT double-blind multicenter trial of valproate[2] in elderly patients with dementia (the "Dementia Study") was prematurely terminated due to serious side effects caused by Depakote, ABBOTT implemented a change to Depakote's approved labeling to include a warning about somnolence. In 2000, FDA approved the inclusion of the following warning for somnolence in the elderly as part of the approved labeling:

> In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age=83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence.

The dosage and administration section was also updated to include elderly dosing information, including that: "Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events."

Clinical Studies of the Unapproved Use of Depakote for the Control of Agitation and Aggression in Elderly Dementia Patients

12. Dementia occurs primarily in people older than 65 and arises from various causes but is most often associated with Alzheimer's disease. Dementia in the elderly often encompasses a slow, progressive decline in cognitive mental function including memory, language, thinking, judgment, and the ability to learn new information, and sometimes dementia patients became agitated and even aggressive. Dementia is a major reason why the elderly are

[2] Valproate is the active ingredient in Depakote.

admitted to nursing homes. Drugs used to control behaviors in elderly dementia patients in nursing homes are sometimes referred to as "chemical restraints."

13. In 1996, ABBOTT submitted an application to FDA to conduct a 15-patient study of Depakote to treat agitation in elderly dementia patients titled "A Double-Blind Placebo Controlled Study of Valproate in the Treatment of Behavioral Agitation Associated with Dementia" ("M96-491"). In a letter to ABBOTT dated January 28, 1997, FDA expressed its reservations about what inferences could be drawn from the study's outcome.[3] The results of the study showed that the six Depakote-treated patients demonstrated greater mean decreases in activity disturbances and aggressiveness scores over the placebo patients, although this result was not statistically significant. ABBOTT's analysis of the study noted that "No subject died or reported a serious adverse event during the study. One Depakote-treated subject had study drug prematurely discontinued due to a series of adverse events." The same analysis concluded that Depakote was "safe and well-tolerated in the sample of elderly subjects with dementia."

14. On November 18, 1997, ABBOTT submitted an application to FDA to conduct a study titled, "A Double-Blind Placebo-Controlled Study of Depakote in the Treatment of Signs and Symptoms of Mania in Elderly Patients with Dementia" (hereinafter referred to as "M97-738" or "ABBOTT's Dementia Study" or the "Dementia Study"). In a letter to Abbott dated January 15, 1998, FDA expressed reservations about Abbott obtaining FDA approval of a new or expanded use of Depakote for mania based on this study.[4]

15. ABBOTT began the Dementia Study in 1998. In March 1999, the study was suspended due to an increased incidence of adverse events in the Depakote treatment group. In

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[3] See Attachment 1.

[4] See Attachment 2.

June 1999, ABBOTT discontinued the Dementia Study. In the study, somnolence and thrombocytopenia (low blood platelet count that may cause easy or excessive bruising, superficial bleeding in the skin, prolonged bleeding from cuts, and spontaneous bleeding from the gums or nose) occurred statistically significantly more frequently with patients given Depakote than with the placebo patients. The results provided evidence that the dosing recommendations set forth in Depakote's labeling were too high and rapid for at least some elderly dementia patients. It was this evidence which resulted in the 1999 revision to the approved labeling referenced in Paragraph 11 above.

16. The results of the Dementia Study also failed to show that Depakote was effective in treating the "signs and symptoms of mania" in elderly dementia patients. ABBOTT concluded that "[t]he lack of effect on mania suggests the manic symptoms of this population may have a different basis than the manic symptoms of bipolar disorder." There were several measurement tools used as part of the Dementia Study to determine if Depakote improved any "signs or symptoms of mania." One of these tools was the Cohen-Mansfield Agitation Inventory ("CMAI"). This was the only measurement tool that showed a positive result. Improvement in the CMAI total score and its verbally agitated behavior subscore was statistically significantly greater for the Depakote treatment group than the placebo group. The data, however, indicated that this typically occurred when patients received the maximum dosage of the drug, a dosage that resulted in an increase in adverse events for many of the elderly patients. In the Clinical Study Report, ABBOTT concluded that the positive CMAI efficacy results "suggest[ed] a drug effect independent of effects of somnolence." Two years later, an associate medical director at ABBOTT expressed his opinion that "somnolence was the true 'treatment' effect for many [of

these patients]."[5] The results of the Dementia Study were published in a peer-reviewed medical journal in 2001.

17. In 2000, ABBOTT began another clinical trial – M99-082 – to evaluate Depakote's safety and effectiveness to treat agitation in elderly patients with dementia. The study protocol called for a lower dose of the drug for some patients than the dose used in the Dementia Study in part because the adverse events experienced by the patients in the Depakote treatment group in the Dementia Study were believed to be dose-related. ABBOTT started but never completed M99-082. In June 2003, ABBOTT submitted to FDA a final clinical study report that stated that the "trial was terminated for low enrollment. . . . . The study was seriously underpowered and definitive conclusions from the data were not possible." The report also stated that the two Depakote treatment groups and the placebo group all showed improvement on the primary and secondary endpoint measures. It also noted that "study drug was well tolerated by subjects in all 3 treatment groups [that is, the two Depakote treatment groups and the placebo group] and the safety profile was similar to previous Depakote studies in this population," including the Dementia Study. The data from this study was disclosed to the FDA, but it was not published in a medical journal or disseminated by ABBOTT's sales force.

18. ABBOTT never conducted another clinical trial of Depakote for the control of agitation and aggression in elderly patients with dementia and never submitted a supplemental new drug application to FDA seeking approval of Depakote for this use.

19. In two separate peer-reviewed medical journal articles in 2001 and 2003, the results of a 56-patient study called the Rochester Study were reported. The study was funded by

[5] See Attachment 3.

the Alzheimer Association, the National Institute of Aging, and an unrestricted, investigator-initiated grant from ABBOTT. According to the 2001 article, the results of the first phase of the study "suggest[ed], but did not prove" that the use of Depakote "can be associated with reduced agitation in some patients with dementia in the nursing home." The article stated that "[t]hese results support[ed] a larger, placebo-controlled trial definitively addressing the therapeutic potential of this agent." According to the 2003 article, the results of the second phase of the Rochester Study were consistent with the results of the first phase of the study "which suggested but did not prove that short-term [Depakote] therapy can result in decreased measures of agitation." It stated that the results from a study being conducted at the time by the Alzheimer's Disease Cooperative Study ("ADCS") (discussed below) would "likely further clarify the potential role of [Depakote] for treatment of" agitation in elderly patients with dementia.

20. A 153-patient, randomized, well-controlled clinical trial of the use of Depakote for the treatment of agitation in elderly patients with dementia was conducted by the ADCS from September 2000 to December 2002 ("ADCS Study"). The results of the study were published in the peer-reviewed American Journal of Geriatric Psychiatry in November 2005 and the authors concluded that "[t]reatment with [Depakote] did not show benefit over placebo in the treatment of agitation associated with possible or probable [Alzheimer's disease] in the nursing home residents included in this trial." The article also discussed the earlier studies, including ABBOTT's Dementia Study and the Rochester Study, and stated that "[n]one of the earlier placebo-controlled studies proved that [Depakote] is efficacious for agitation in dementia, and none were sufficient to define practice."

21. In May 2003, ABBOTT received an oral report of the preliminary results of the ADCS Study. According to this report, the preliminary results did not show that Depakote

reduced symptoms of agitation and aggression. However, an ABBOTT's Associate Medical Director who received these results questioned whether the study was designed properly to show efficacy, and believed the results could still prove positive for the drug if "a 'trend' for Depakote is shown, that could be seen as favorable data – especially if the safety data looks good."[6] In July 2003, ABBOTT's Associate Medical Director then included in a summary that the ADCS Study lead researcher's "verbal report of the preliminary findings [about the ADCS Study] suggest no evidence of a meaningful treatment difference between the Depakote and placebo groups."[7] In December 2004, ABBOTT received an advance copy of the to-be-published medical journal article about the ADCS Study which included the same conclusions about Depakote's lack of efficacy as well as the conclusions regarding the Dementia Study and the Rochester Study contained in the published article as described in Paragraph 20, above.

The Off-Label Promotion of Depakote for the Control of Agitation and Aggression in Elderly Dementia Patients

22. Beginning in or about 1998, and continuing until in or about December 2006, ABBOTT misbranded Depakote by marketing it for the control of agitation and aggression in elderly dementia patients. The off-label promotion of Depakote to control agitation and aggression in elderly dementia patients included:

a. In June 1997, ABBOTT developed its 1998 Strategic Marketing Plan entitled "Depakote – New Psychiatry Markets."[8]

b. In early 1998, ABBOTT created a Long Term Care ("LTC") sales force in substantial part to promote Depakote for the control of agitation and aggression in elderly

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6 See Attachment 4.

7 See Attachment 5.

8 See Attachment 6; see also Attachment 7.

dementia patients in nursing homes. ABBOTT trained its LTC sales force to promote Depakote to doctors and other healthcare providers as safe and effective for this unapproved use. For example, ABBOTT gave its LTC sales force a Dementia Backgrounder, which informed the sales force that Depakote had been shown effective in preliminary clinical trials to treat behavioral disturbances in dementia patients and that Depakote did not have some of the same side effects as antipsychotics for this unapproved use.[9]

c. ABBOTT trained the LTC sales force to promote Depakote to healthcare providers and employees of nursing homes as advantageous over atypical antipsychotics ("ATPs") for controlling agitation and aggression in elderly dementia patients because Depakote was not subject to certain provisions of the Omnibus Budget Reconciliation Act of 1987 ("OBRA") and its implementing regulations designed to prevent the use of unnecessary medications in nursing homes. See, e.g., training material titled "Maximizing the Long Term Care Market Opportunity."[10] Depakote was not subject to any specific use restrictions under OBRA Guidelines prior to December 2006. Until December 2006, ABBOTT trained the LTC sales representatives to state that, by using Depakote, nursing homes would avoid the administrative burdens and costs of complying with OBRA regulatory restrictions otherwise applicable to ATPs, namely the prohibition against giving such patients antipsychotic drugs unless indicated for a specific condition, the requirement that patients treated with ATPs should have drug holidays and gradual

[9] See Attachment 8.

[10] See Attachment 9.

dose reductions, and the requirement for behavior management rather than ATPs whenever possible.

d. ABBOTT paid its LTC sales force bonuses based on its sales of Depakote, which included sales of Depakote for the unapproved use of the drug.

e. ABBOTT provided the LTC sales force with materials to promote Depakote for the control of agitation and aggression in elderly dementia patients. For example, in 2001, ABBOTT funded via an unrestricted educational grant, a document called "A Pocket Guide to Dementia and Associated Behavioral Symptoms: Diagnosis, Assessment, and Management" (the "Guide").[11] A private entity, accredited by ACCME, designated the Guide as continuing medical education ("CME"). Physicians and other healthcare providers could earn CME credits free-of-charge by reviewing the Guide and taking a test set forth at the end of the Guide. As early as 2002, ABBOTT began providing the LTC sales representatives with copies of the Guide to promote Depakote to treat agitation and aggression in elderly dementia patients.[12] The sales representatives were instructed to become familiar with the Guide and to provide it to doctors and other healthcare providers to whom they were promoting Depakote. They were also told that the Guide would be a resource that physicians and pharmacists used to obtain additional continuing education credits. The Guide did not disclose the results of the Dementia Study. The somnolence and dosing issues identified by the Dementia Study were disclosed in the approved labeling but the approved labeling was not attached to the Guide and the Guide did not refer healthcare providers to the approved labeling. In

[11] See Attachment 10.

[12] See Attachment 11.

addition, the efficacy results of the Dementia Study were not disclosed in the approved labeling or the Guide.

f. ABBOTT funded and gave the LTC sales force funds for speaker programs promoting the use of Depakote to control agitation and aggression in elderly patients with dementia.

g. ABBOTT funded and caused the creation of educational programs and materials (such as videos and monographs) promoting the use of Depakote to control agitation and aggression in elderly patients with dementia.

h. ABBOTT entered into contracts with Long Term Care Pharmacy Providers (LTCPPs) that included provisions regarding the payment of rebates to the LTCPPs based on increases in the use of Depakote in the nursing homes serviced by the LTCPPs. Under these contracts, ABBOTT paid millions of dollars in rebates to the LTCPPs based on increases in the use of Depakote in these facilities, including the use of Depakote in the treatment of agitation and aggression in elderly dementia patients.

i. ABBOTT funded and created and caused the creation of programs and materials to train the LTCPPs' consultant pharmacists about the use of Depakote for the control of agitation and aggression in elderly dementia patients and to encourage them to recommend the drug for this unapproved use.

j. In March 2004, at the request of an LTCPP, ABBOTT sent a check in the amount of $16,250 to fund a letter sent by the LTCPP to 4,000 doctors who prescribed ATPs and 1,000 doctors who prescribed benzodiazepine medications to patients in

nursing homes.[13] ABBOTT's LTC National Account Manager ("NAM") emailed the LTC sales force stating that this LTCPP had "sent out a targeted Depakote ER mailing to the top 4,000 prescribers of [ATPs] and top 1000 prescribers of benzodiazepines within [the LTCPP's] facilities."[14] The LTC NAM further stated that "[t]he purpose of the mailing is to help increase the overall use of Depakote ER vs [ATPs] and benzodiazepines for patients with dementia related behaviors" and that the LTCPP's letter to the doctors "strongly position[ed] Depakote ER vs the [ATPs and] emphasize[d] the excellent side effect profile of Depakote ER."

k. In October 2003 ABBOTT produced its "Depakote Long Term Care – 2004 Strategic Investment Proposal," which included the strategy to market Depakote for this unapproved use in LTC facilities, including nursing homes.[15]

l. ABBOTT also promoted Depakote as effective to treat "manic-like symptoms" exhibited by elderly dementia patients based on Depakote's efficacy to treat bipolar mania.

23. In 2001, in anticipation of a review of ABBOTT's policy about the dissemination of clinical data, a staff member in ABBOTT's Regulatory Affairs office prepared a draft slide presentation which stated that ABBOTT's practice at that time did not "explicitly" address the "difference between dissemination and promotion," the "scope of data balance," or "failed studies." These draft slides also stated that ABBOTT needed to revise its practice to "clarify dissemination vs promotion," "assure that dissemination is a balanced representation of known

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[13] See Attachment 12.

[14] See Attachment 13.

[15] See Attachment 14.

information," and that the revised practice needed to "define options after failed applications/studies." This same staff member also wrote an earlier memorandum which noted that ABBOTT's then current practice and guidance documents left open several questions, including that:

> [T]here is no direction regarding how we will handle newly generated data related to indications that were the subject of failed applications or failed or disappointing studies. Responsibilities and accountability are not established in [ABBOTT's] guidance. The [guidance] document does not clearly define the difference between dissemination and promotion.

While ABBOTT continued to update and improve its compliance practices in accordance with industry practice and FDA guidance, some of the issues identified in this draft presentation and memo were not specifically addressed until after the time period relevant here.

24. ABBOTT's LTC sales representatives used reprints of medical journal articles about studies to promote the use of Depakote to control agitation and aggression in elderly patients with dementia, as set forth below:

a. ABBOTT trained its LTC sales representatives to use a reprint of an article based on a retrospective chart review of 22 nursing home patients in two nursing homes. Although this article was not based on a randomized, blinded, and controlled clinical study, ABBOTT trained its LTC sales representatives to use it to promote Depakote for this unapproved use.

b. Beginning in approximately 2001, ABBOTT made available to its LTC sales force reprints of the 2001 medical journal article about the Dementia Study and reprints of the 2001 medical journal article about the Rochester Study. ABBOTT trained its sales representatives to respond to inquiries about the Dementia Study's premature termination for safety reasons by advising healthcare providers that the dosages used in

the study were started too high and increased too fast. ABBOTT trained its sales force to promote the use of Depakote to control agitation and aggression in elderly patients with dementia at lower doses.

c. In 2003, ABBOTT made reprints of the 2003 medical journal article about the results of the second part of the Rochester Study available to its sales representatives and trained them to use the results of the study to promote the use of Depakote to control agitation and aggression in elderly patients with dementia.

25. ABBOTT continued to disseminate copies of reprints of the Rochester Study journal article to healthcare providers after receiving a report on the preliminary results of the ADCS Study in May 2003, and after receiving an advance copy of the article about the ADCS study in December 2004. ABBOTT continued to disseminate this article about the Rochester Study without disclosing the conflicting preliminary results of the ADCS Study including:

a. In or about December 2004, ABBOTT approved the continued reprinting of the 2003 Rochester Study article for its sales representatives to disseminate to healthcare providers.

b. In or about early 2006, ABBOTT provided its sales representatives with promotional materials, including the "T1 2006 Plan- O-Gram," which stated that ABBOTT's core marketing messages included telling nursing homes that Depakote had "broad-spectrum coverage," and listing among the "Core Selling Materials" for use to convey the core marketing messages a reprint of the Rochester Study article. The results of the ADCS study were not included.

c. In February 2006, for the first time, ABBOTT provided its sales force with a reprint of the ADCS Study article and marked it "For Representative Education Only."

Accordingly, under ABBOTT's policy, its sales force could not share this reprint with healthcare providers. In March 2006, ABBOTT also discontinued reprinting copies of the 2003 article about the Rochester Study. However, after March 2006, the sales force continued to obtain copies of already-existing reprints of the 2003 article about the Rochester Study from ABBOTT's supply contractor and continued to disseminate those reprints to healthcare providers because they were not directed by ABBOTT to stop distributing existing copies of the reprints.

d. ABBOTT's clinical science managers made presentations to healthcare providers about the use of Depakote for agitation and aggression in elderly dementia patients. Prior to April 2006, these presentations did not include any information about the results of the ADCS Study. In or about April 2006, Abbott revised the presentation to include two slides about the ADCS Study. The revised presentation, however, also included approximately a dozen slides about other studies, such as the Rochester Study, and slides about when healthcare providers should use Depakote to treat agitation and aggression in elderly dementia patients and how to dose Depakote for this off-label use.

e. ABBOTT sent medical information letters to healthcare providers who requested information about the use of Depakote to control agitation and aggression in elderly dementia patients. Prior to in or about January 2006, these letters did not disclose the results of the ADCS Study.

Clinical Studies of the Unapproved Use of Depakote for Schizophrenia

26. Schizophrenia is a common and serious mental disorder. FDA has approved various drugs as safe and effective to treat schizophrenia, including atypical antipsychotics ("ATPs").

27. ABBOTT conducted two clinical trials studying the safety and effectiveness of Depakote and ATPs together to treat patients with acute exacerbations of the symptoms of schizophrenia. In 1999, ABBOTT submitted an application to FDA to conduct a study (referred to as the "M99-010 Study") of the use of Depakote in combination with certain ATPs to treat acute schizophrenia. In January 2002, ABBOTT submitted the study results to FDA. The results showed that the study failed to meet its primary endpoint in that Depakote in combination with the ATPs did not result in statistically significant improvement in symptoms of psychosis associated with schizophrenia after 28 days of treatment as compared to the results for the ATPs alone. The results did show statistically significant improvement in symptoms as early as day 3 and continuing through day 21. FDA informed ABBOTT that it considered M99-010 a negative study because it failed to meet the predefined efficacy endpoint and, therefore, the results of the study could not be used to support an application for a new indication for Depakote for schizophrenia.

28. In 2003, the results of the M99-010 Study were published in a peer-reviewed medical journal article. While the article stated that the treatment difference for the primary efficacy endpoint (28 days) did not reach the level of statistical significance between Depakote combined with an ATP compared to an ATP alone, the article did state that the Depakote combination therapy was observed to show statistically significant improvement over ATP monotherapy as early as the third treatment day and persisting through day 21. A summary of a June 2002 meeting with an external consultant stated that the consultant viewed M99-010 Study to be "a positive trial (the effect size is robust)." The consultant also told ABBOTT that while the M99-010 Study "does not support combination use (as defined strictly the combination being

superior to each agent [i.e. ATP] alone), we could still argue for study 010's applicability to add-on" therapy.[16]

29. In March 2003, ABBOTT conducted another study (referred to as the "M02-547 Study") of Depakote ER combined with certain ATPs to treat acute schizophrenia. The results of the M02-547 Study, which was completed in or about August 2004, did not show a statistically significant treatment difference between Depakote ER combination therapy and the ATPs alone. The data also showed that somnolence, weight gain, and urinary incontinence were significantly higher for patients receiving Depakote ER combined with one of the ATPs than those treated with one of the ATPs alone. Patients treated with Depakote ER combination therapy also had a significant decrease in platelet counts compared to those treated with an ATP alone.

30. In August 2006, ABBOTT posted a synopsis of the M02-547 Study results on a public website (www.clinicalstudyresults.org). In December 2008, the results of the M02-547 Study were published in an article in the peer-reviewed medical journal, Neuropsychopharmacology. The article stated that there were no significant treatment differences between Depakote ER combination therapy and ATP monotherapy.

31. ABBOTT never conducted another clinical trial of the use of Depakote to treat schizophrenia and never submitted a supplemental new drug application to FDA seeking approval of Depakote for this use.

Promotion of Depakote for Off-Label Use in Schizophrenia

32. Beginning in or about 2002, and continuing until in or about December 2006, ABBOTT misbranded Depakote by marketing it for schizophrenia.

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[16] See Attachment 15.

33. ABBOTT used M99-010 Study's secondary endpoints to promote Depakote to healthcare providers as a treatment for schizophrenia. This included:

a. ABBOTT's 2001 "010 Communication Plan" set forth ABBOTT's strategies for dissemination of the results of the M99-010 Study,[17] and ABBOTT executed part of this plan by, among other things, providing the favorable results of the study to healthcare providers.

b. ABBOTT's 010 Communication Plan also included numerous meetings with healthcare providers. In 2002, ABBOTT held a "Depakote Psychosis Speaker/Faculty Development Meeting" to review with physicians the results of the M99-010 Study. The trainers for this meeting included an ABBOTT Product Manager. Physicians were paid $2,500 plus travel and lodging expenses to attend. One of the purposes of the meeting was to present the M99-010 Study data to physicians and on ABBOTT's invitation it noted "[a]fter participation in the meeting, you may be asked to present this data at various medical information programs in 2002."[18] In or about March 2002, ABBOTT provided its physician-speakers with a slide presentation regarding the M99-010 Study data for use in speaking engagements. Also in 2002, ABBOTT organized programs at an American Psychiatric Association ("APA") meeting to provide the M99-010 Study data to promote Depakote for the treatment of schizophrenia.

c. In 2002, an ABBOTT-funded message recall survey of 76 healthcare providers confirmed that a majority of those providers recalled that, during their most

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[17] See Attachment 16.

[18] See Attachment 17.

recent visit with an ABBOTT sales representative, the sales representative had discussed the off-label use of Depakote as combination therapy for the treatment of schizophrenia.

d. In 2003, ABBOTT funded and organized "Psychiatry Consultant Meetings," which were used to provide information about the results of the M99-010 Study to healthcare providers. For at least two of these meetings ABBOTT's sales force helped to target 30 and 45 psychiatrists, respectively, from around the United States. Abbott paid a $500 "honorarium" and travel expenses for each psychiatrist's attendance.

e. ABBOTT's 2003 "Schizophrenia Strategic Plan" called for the positioning of Depakote as the "ideal 1st line agent for adjunctive therapy for schizophrenia based upon proven clinical efficacy" by, among other things, generating materials or funding programs that communicated the results of the M99-010 Study to doctors; training the sales force about the dissemination of CME materials about the M99-010 Study; and developing a speakers bureau to deliver ABBOTT's message about the efficacy of the adjunctive use of Depakote to treat schizophrenia based on the data from the M99-010 Study.

f. In February 2003, ABBOTT made available to its sales representatives reprints of the published medical journal article about the M99-010 Study results, instructing its sales representatives that the reprint was approved for "dissemination only," was not for "promotional use," and they should "not discuss the reprint with physicians and customers."

34. ABBOTT decided not to conduct the two additional clinical trials required to obtain FDA approval of Depakote for schizophrenia, instead deciding to conduct one additional

study, the M02-547 Study, to generate positive data to support ABBOTT's marketing message that Depakote was safe and effective to treat schizophrenia.

a. In August 2004, ABBOTT completed the M02-547 Study. In November 2004, one of ABBOTT's vice presidents sent an email in which he stated that ABBOTT had concluded that the M02-547 Study did not show a statistically significant treatment difference between Depakote ER combination therapy and ATPs alone and in which he further explained:

> We are confident that there are no systematic [sic] issues with the study itself . . . [the] overall weight of the evidence from both studies [M99-010 and M02-547] suggest[ed] that there is not an obvious benefit of adding Depakote to ATPs in acute schizophrenia.

b. ABBOTT's January 2005 Executive Project Status Report described the M02-547 Study, stating "[t]rial completed. Results negative not confirming -010 trial." This report also described the status of ABBOTT's development of Depakote as a treatment for schizophrenia stating "[a] significant issue has been identified that most likely or definitively will negatively impact critical path, budget, or target product profile."

c. In November 2005, ABBOTT approved another reprint of the M99-010 medical journal article and made copies available to the sales force for dissemination to doctors and other customers, but ABBOTT failed to include any information about the results of the M02-547 Study.

d. ABBOTT's T1 2006 Plan-O-Gram issued in early 2006 included the reprint of the M99-010 journal article among the "CORE SELLING MATERIALS –

psychiatric resources available to all representatives," without any information about the M02-547 Study.

e. In or about August 2006, ABBOTT gave its sales representatives a Depakote ER T3/06 Plan-O-Gram which again included the reprint of the M99-010 medical journal article as an available sales resource, but without any information about the M02-547 Study.

f. In or about August 2006, ABBOTT posted a synopsis of the M02-547 Study on the public website clinicalstudyresults.org. The synopsis stated that "Depakote ER in combination with atypical antipsychotic therapy was as well tolerated as therapy with [certain ATPs] alone," despite the fact that the incidence of somnolence in the combination group of patients treated with an ATP and Depakote was more than twice as high as in the ATP monotherapy group and that this difference was statistically significant.

g. In or about August 2006, after it posted the results of the M02-547 Study on the public website, ABBOTT notified its sales force of this posting. This notification was the first time ABBOTT advised the sales force that the M02-547 Study had failed and its results were not consistent with the results of the M99-010 Study.[19]

35. ABBOTT sent medical information letters to healthcare providers who requested information about the off-label use of Depakote for schizophrenia. Through at least 2006, these letters disclosed the results of the M99-010 Study but not the results of the M02-547 Study.

36. The parties agree to the foregoing Agreed Statement of Facts.

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[19] See Attachment 18.

FOR THE UNITED STATES:

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