IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA	**:**	
v.	**:**	**CRIMINAL NO. 08-598**
CEPHALON, INC.	**:**	

GOVERNMENT'S MEMORANDUM FOR ENTRY OF PLEA AND SENTENCING

I. INTRODUCTION

The government submits this memorandum to assist the Court with the entry of a guilty plea and with sentencing in this case. Defendant Cephalon, Inc., has signed a guilty plea agreement under Fed.R.Crim.P. 11(c)(1)(C) under which, with the Court's approval, it will plead guilty to a one-count misdemeanor information charging it with misbranding under the Food, Drug and Cosmetic Act, 21 U.S.C. § 301 et seq. ("FDCA"), and pay a stipulated fine of $50 million (which includes $10 million in criminal forfeiture). The plea agreement also proposes that the Court proceed to impose sentence immediately, waiving a presentence investigation.

The plea agreement resolves a very significant investigation into the promotional practices in the United States of defendant Cephalon, Inc., a pharmaceutical manufacturer, for its drugs Actiq, Gabitril, and Provigil. The essence of the charge is that Cephalon marketed its drugs for uses that had not been approved by the Food and Drug Administration ("FDA"), a form of unlawful misbranding known as "off-label marketing." This plea is part of a global resolution that includes a civil settlement agreement with the United States and many states, a Corporate Integrity Agreement with the Department of Health and Human Services, Office of the Inspector

General, and resolution of several civil actions brought under the qui tam provisions of the False Claims Act.

II. THE CRIMINAL CHARGE

The information filed in this case charges Cephalon with one count of misdemeanor misbranding under the FDCA, 21 U.S.C. §§ 331(a), 333(a)(1), and 352(f)(1). A copy of this information is attached as Exhibit A.

As the information explains, the FDCA intensively regulates all aspects of the manufacture and distribution of drugs in the United States (pars. 2-3). In general, a drug manufacturer can not sell a drug here until the FDA approves the manufacturer's application, and determines that the drug was safe and effective, based on well controlled clinical studies, for the use proposed by the manufacturer. As part of its regulatory process, the FDA also reviews and approves the drug's "label" or "labeling," which must include adequate directions for the intended use – that is, the use that the manufacturer proposed in seeking the FDA's approval.

Under the FDCA, a drug is misbranded if the labeling does not contain "adequate directions for use." 21 U.S.C. § 352(f)(1). The FDA can not approve "adequate directions for use" until the drug is approved for that use, based on the FDA's finding that the drug is safe and effective, as established by proper clinical studies. Any uses for a drug that are not approved by FDA as safe and effective, and thus that were not included in the drug's approved labeling, are known as "off-label" indications or uses. A drug that is promoted for an off-label indication or use does not contain "adequate directions for use," because such an off-label indication or use was not included in the FDA-approved labeling for the drug. Promoting a drug for an off-label use constitutes misbranding of that drug.

The information alleges that Cephalon misbranded three of its drugs by marketing them off-label from 2001 through at least 2006 (pars. 6-11). Those drugs are the following:

- Actiq: approved by the FDA in 1998 for breakthrough cancer pain in opioid-tolerant patients. Cephalon improperly promoted Actiq for non-cancer pain uses.

- Gabitril: approved by the FDA in 1997 as an anti-epilepsy drug, for use as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures. Cephalon improperly promoted Gabitril to treat anxiety, insomnia, and pain.

- Provigil: approved by the FDA in 1998 for excessive daytime sleepiness associated with narcolepsy; in 2004, the FDA approved the expansion of Provigil's label to include the treatment of excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. Cephalon improperly promoted Provigil to treat sleepiness, tiredness, decreased activity, lack of energy and fatigue.

The information describes the defendant's off-label practices and its training of its sales staff to ignore the legal restrictions on promoting these drugs (pars. 12-18). In particular:

- Cephalon had its sales representatives call on doctors who would not normally prescribe the defendant's drugs in the course of the doctors' practice;

- Cephalon trained its sales representatives on techniques to prompt the doctors into off-label conversations;

- Cephalon's compensation and bonus structure encouraged off-label marketing;

- Cephalon had its sales representatives tell doctors how to document their off-label uses of drugs to get these uses paid by insurers, who often will not pay for off-label uses;

- Cephalon used its grants for continuing medical education to promote off-label uses; and

- Cephalon sent doctors to "consultant" meetings at lavish resorts to hear the company's off-label message.

The information also describes the risks to patients from Cephalon's off-label marketing campaign (pars. 19-23). Those risks were particularly high in the case of Actiq, an extremely powerful narcotic with a very narrow label, and Gabitril, an anti-seizure drug. Actiq was approved for use by opioid-tolerant patients suffering from breakthrough cancer pain, that is, patients whose cancer pain was so severe that their opioid therapies (such as morphine) were no longer effective. The label called for Actiq to be prescribed by oncologists or pain specialists familiar with opioids. Yet the defendant promoted Actiq to other doctors, including general practitioners, for more general pain uses. The use of Actiq by patients who are not yet tolerant of opioids poses particular dangers. Similarly, the FDA found that the use of Gabitril by non-epileptics was associated with seizures.

More generally, the information describes how off-label marketing can interfere with proper patient care and thus harm patients (pars. 19, 23). And as the information details, Cephalon proceeded with its off-label marketing campaigns despite directions from the FDA to stop (pars. 24-26).

The specific charge is that defendant Cephalon introduced and caused the introduction into interstate commerce of Provigil, Gabitril, and Actiq, drugs which were misbranded because they lacked adequate directions for their use in that Cephalon promoted them off-label, from January 2001 through October 2001 (par. 28). This is the charge to which Cephalon is pleading guilty.

III. THE GUILTY PLEA AGREEMENT

The essential terms of the plea agreement are set forth here. (A complete copy is attached for the Court's reference as Exhibit B.) In particular:

- Cephalon agrees to plead guilty to a one-count information charging misdemeanor misbranding of its drugs Provigil, Gabitril, and Actiq between January 2001 and October 1, 2001, in violation of the FDCA, 21 U.S.C. §§ 331(a), 333(a)(1), and 352(f)(1). The charge arises from Cephalon's unlawful promotional practices, known as "off-label" marketing. Cephalon also agrees not to contest forfeiture as set forth in the agreement. Plea Agreement, par. 1.

- The parties entered into this plea agreement under Fed.R.Crim.P. 11(c)(1)(C), with a stipulated sentence. If the Court rejects this plea under Rule 11(c)(1)(C), then the plea converts automatically to a plea under Rule 11(c)(1)(B), and the stipulated sentence becomes the sentence jointly recommended by the parties. Plea Agreement, par. 2.

- The agreed-upon sentence is: payment of $50 million ($40 million as the criminal fine, plus $10 million as the criminal forfeiture), all payable within 10 business days of sentencing; plus the special assessment of $125. In light of the Corporate Integrity Agreement signed by Cephalon, the parties agree that the defendant will not be placed on probation. Plea Agreement, par. 2.

- The parties stipulate to the following facts and basis for the plea, criminal fine and forfeiture (Plea Agreement, par. 6(A)):

  (1) Cephalon marketed Provigil, Gabitril, and Actiq, which were drugs within the meaning of 21 U.S.C. § 321(g)(1).

  (2) Shipments of a drug in interstate commerce must be accompanied by labeling bearing adequate directions for use for each of the drug's intended uses.

  (3) In 1998, Provigil was approved by the FDA to treat excessive daytime sleepiness associated with narcolepsy.

  (4) Between January 2001 and October 1, 2001, Cephalon promoted Provigil for uses not approved by the FDA, including as a daytime stimulant to treat sleepiness, tiredness, decreased activity, lack of energy and fatigue. Cephalon's promotion of Provigil for these additional intended uses violated 21 U.S.C. § 352(f)(1), because Provigil's labeling did not bear adequate directions for each of the drug's intended uses.

  (5) In 1997, Gabitril was approved by the FDA as an anti-epilepsy drug indicated as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures.

(6) Between January 2001 and October 1, 2001, Cephalon promoted Gabitril for certain uses not approved by the FDA, including as an agent for anxiety, insomnia, and pain. Cephalon's promotion of Gabitril for these additional intended uses violated 21 U.S.C. § 352(f)(1), because Gabitril's labeling did not bear adequate directions for each of the drug's intended uses.

(7) In 1998, Actiq was approved by the FDA for breakthrough cancer pain for patients with malignancies who were already tolerant to opioid therapy for their cancer pain.

(8) Between January 2001 and October 1, 2001, Cephalon promoted Actiq for uses not approved by the FDA, including for non-cancer pain uses, such as injuries and migraines. Cephalon's promotion of Actiq for these additional intended uses violated 21 U.S.C. § 352(f)(1), because Actiq's labeling did not bear adequate directions for each of the drug's intended uses.

(9) Between 2001 through October 1, 2001, Cephalon profited by misbranding Provigil, Gabitril and Actiq, and distributing these drugs in interstate commerce.

- The United States contends that, as a matter of relevant conduct, the conduct at issue continued past October 1, 2001. Cephalon does not admit that this conduct extended past October 1, 2001. Plea Agreement, par. 6(B).

- The Plea Agreement includes a non-prosecution clause for conduct which (a) falls within the scope of the grand jury investigation in this district relating to Provigil, Gabitril, and Actiq; or (b) was known to the United States Attorney's Office for the Eastern District of Pennsylvania and the Office of Consumer Litigation of the Department of Justice as of the date of the execution of this plea agreement, and which concerned the sale, promotion, or marketing of these three drugs in the United States. This non-prosecution clause is binding on the United States Attorney's Office for the Eastern District of Pennsylvania, the Office of Consumer Litigation of the Department of Justice, all other United States Attorney's Offices, and the Criminal Division of the United States Department of Justice. Plea Agreement, pars. 8-9.

- The Plea Agreement contains an appellate waiver. There can be no appeal if the Court enters the plea under Rule 11(c)(1)(C). If the plea is entered under Rule 11(c)(1)(B), then the defendant may appeal only to argue that the sentence exceeded the statutory maximum as set forth in the plea agreement, the Court erroneously departed upward under the Sentencing Guidelines, or the Court imposed an unreasonable sentence above the final Sentencing Guideline range.

Plea Agreement, par. 11.

- If acceptable to the Court, the parties agree to waive the presentence investigation and report pursuant to Fed.R.Crim.P. 32(c)(1), and ask that Cephalon be sentenced at the time the guilty plea is entered. Plea Agreement, par. 15.

IV. THE OTHER COMPONENTS OF THE GLOBAL RESOLUTION

As the Plea Agreement references, this is part of a global resolution of this investigation with the United States. In a separate civil settlement among Cephalon, the United States and various states, Cephalon will pay $375 million, plus interest, to resolve False Claims Act claims by the United States Medicaid and Medicare Trust Funds, and other federal programs and agencies, as well as claims by state Medicaid programs and the District of Columbia. This settlement also resolves the four qui tam actions filed in this district.

Along with the civil settlement agreement, Cephalon has signed a five-year Corporate Integrity Agreement with the Department of Health and Human Services, Office of the Inspector General. This agreement imposes a strict compliance program to ensure that the conduct does not recur.

V. THE ESSENTIAL ELEMENTS OF THE OFFENSE

A. Misbranding

The information charges one count of misbranding under the FDCA, in violation of 21 U.S.C. §§ 331(a), 333(a)(1), and 352(f)(1). Section 331 lists prohibited acts, including:

> (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

Under section 352 of the FDCA, a drug is "misbranded" under several circumstances, including (as relevant here):

A drug or device shall be deemed to be misbranded –

(f) Directions for use and warnings on label
Unless its labeling bears (1) adequate directions for use . . . .

Section 333 sets forth penalties, including:

(a) Violation of section 331 of this title; second violation; intent to defraud or mislead
(1) Any person who violates a provision of section 331 of this title shall be imprisoned for not more than one year or fined not more than $1,000, or both.

The information in this case charges a misdemeanor under this penalty provision. The offense would rise to the felony level either if the government charged and proved the defendant's intent to defraud or mislead, or if the defendant had already been convicted of an FDCA violation (the second-offender felony provision). 21 U.S.C. § 333(a)(2).

Thus, in order to prove the crime of misdemeanor misbranding, the government must establish the following elements beyond a reasonable doubt:

- that Actiq, Gabitril, and Provigil are drugs
- that they were misbranded, in that they lacked adequate directions for the uses intended by Cephalon, and
- that they were introduced into interstate commerce.

It is not illegal for a doctor to prescribe off-label, using his or her best medical judgment. However, it constitutes misbranding for a drug manufacturer to promote an off-label use to that doctor.

B. Forfeiture

The forfeiture component of the information and plea agreement arises from the FDCA's provision for seizing misbranded drugs. 21 U.S.C. § 334 (allowing proceedings on libel of information, for condemnation, against drugs that are misbranded or adulterated so that the

government can seize, destroy or sell them). These proceedings are by their nature classic civil forfeiture proceedings. Under federal forfeiture law, the government can pursue criminal forfeiture in any case where the defendant is charged with a violation of an Act of Congress which contains a civil forfeiture remedy. See 28 U.S.C. § 2461(c) (allowing criminal forfeiture where the defendant is charged "in a criminal case with a violation of an Act of Congress for which the civil or criminal forfeiture of property is authorized . . . ."). Thus, if civil forfeiture is authorized in a statute such as the FDCA, then criminal forfeiture is as well.

As the misbranded drugs are no longer available for seizure or destruction, the government can seek substitute assets. See 18 U.S.C. § 2461(c) (the procedures set forth in 21 U.S.C. § 853 apply to this criminal forfeiture); 21 U.S.C. § 853(p) (allowing the forfeiture of substitute assets if the items subject to forfeiture are no longer available).

VI. THE MAXIMUM PENALTIES

The maximum penalty for this offense is a fine of $200,000 (under 18 U.S.C. § 3571(c)(5)), or twice the gross gain or gross loss, whichever is greater (18 U.S.C. § 3571(d)); a special assessment of $125 (18 U.S.C. § 3013(a)(1)(B)(iii)); and a five-year term of Court supervision (18 U.S.C. § 3561(c)(2)); in addition, forfeiture may be ordered.

VII. THE FACTS AT TRIAL

In the plea agreement, the parties have stipulated to a factual basis sufficient to support the entry of this plea. Plea Agreement, par. 6(A). If the case were to proceed to trial, the government would prove these facts beyond a reasonable doubt, as well as the other allegations set forth in the information.

In summary, the government would show a concerted plan to maximize revenue

by the off-label marketing of Actiq, Gabitril, and Provigil, which for many of the years covered by the information were Cephalon's only drugs. The defendant's unlawful promotional efforts included several facets, set forth in the information, including training and compensating the sales staff to encourage off-label marketing, managing them to conduct this off-label marketing, co-opting the supposedly neutral continuing medical education process, and bestowing favors on doctors in the form of "consulting" sessions at lavish resorts where they attended off-label sessions. In fact, according to a Cephalon document, these meetings "proved incredibly effective in driving prescription growth among the attendees."

At trial, the government would show that the defendant's off-label marketing was no accident. Indeed, the proof would demonstrate that, for over six years, the very top levels of the company knew and approved of these efforts. This was a highly organized and deliberate effort to maximize revenue despite legal restrictions. Further, Cephalon continued its illegal promotional activities after January 2002, when the FDA specifically directed the company to stop promoting Provigil for off-label uses.

A. Actiq

The case of Actiq is particularly egregious, as this drug is 80-100 times more powerful than morphine. The FDA-approved label for Actiq is unusually restrictive:

> [Actiq] must not be used in opioid non-tolerant patients. Life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

The label calls for Actiq to be prescribed by oncologist or pain specialists familiar with the use of opioids. Because of the potency and risk of the drug, the FDA also mandated a risk management

program requiring Cephalon to submit quarterly reports concerning issues such as diversion.

In about 2001, Cephalon began a significantly expanded marketing effort for Actiq, including telling its sales representatives to target non-cancer physicians. In its marketing strategy for 2002, Cephalon described the Actiq patient profile as:

> any opioid tolerant patient suffering from breakthrough pain, regardless of disease state, is a potential candidate for Actiq. Additionally any patients suffering from moderate to severe episodic pain due to migraine headaches, sickle cell pain crises, etc. are potential candidates for Actiq. Lastly, Actiq may also be appropriate as a pre-procedural pain medication for any opioid naive or opioid tolerant patient about to undergo radiation therapy, wound dressing changes, physical therapy, etc. in a monitored setting. . . . By illustrating the true onset of analgesia and proving Actiq safe and effective in the treatment of other pain diagnoses, *including both opioid tolerant and opioid naive patients,* Actiq will be posed for tremendous growth in 2002 in both the BTP [breakthrough pain] and episodic pain segments of the opioid market.

(Emphasis added.) The marketing of Actiq for patients who were "opioid naive" directly contradicted the label and increased the risk for this population considerably.

Cephalon management conveyed its disregard for the FDA-approved label for Actiq (opioid-tolerant cancer patients with breakthrough cancer pain, to be prescribed by oncologist or pain specialists familiar with opioids) to the sales force. Using the mantra "pain is pain," Cephalon instructed the sales representatives to focus on physicians other than oncologists, and to promote Actiq for multiple uses other than breakthrough cancer pain.

B. Gabitril

Cephalon bought the rights to make and sell Gabitril in 2000, and started its promotions in 2001. The drug had been approved in 1997 as an anti-epilepsy drug indicated as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures. As of 2000, sales of Gabitril were declining. The anti-seizure field was crowded with other anti-epileptics, and Gabitril was only indicated as adjunctive therapy, meaning it had to be taken with

another drug to be effective. Cephalon knew that Gabitril was seen as "last in class as an anti-seizure medication." Cephalon attempted to identify "new market niches" for Gabitril.

Relying on market research showing a large growth in the use of anti-convulsants by psychiatrists, in 2001 Cephalon relaunched Gabitril, calling it the first Selective Gabapentin Reuptake Inhibitor, in hopes of taking advantage of the growing market among psychiatrists for SSRIs, (Selective Serotonin Reuptake Inhibitors such as Prozac, Paxil and Zoloft which are used to treat depression and also anxiety). To carry out its plan for Gabitril use beyond epilepsy, Cephalon instructed its sales representatives to focus on psychiatrists rather than neurologists (the specialty physicians who would ordinarily treat patients with epilepsy).

The Gabitril relaunch was successful. Cephalon tracked the rise in Gabitril prescriptions by psychiatrists from 8,065 in 2000 to 42,922 in 2001, and attributed this increase to its off-label promotion. Management told the sales representatives that it was "VITAL to develop MORE psychiatry writers, MORE psychiatry adopters, and MORE psychiatry product champions" because the company was committed "first and foremost" to psychiatry. This company call for the sales representatives to focus on psychiatrists, not neurologists, continued until Cephalon stopped promoting Gabitril in 2005.

In February 2005, after receiving adverse event reports that patients (mostly with psychiatric illnesses) were having seizures after taking Gabitril for conditions other than epilepsy, the FDA issued a public health advisory and required Cephalon to add a bolded warning on the Gabitril label advising physicians of the association between Gabitril and seizures in patients who did not have epilepsy. The FDA also required Cephalon to send a letter to physicians advising of the Gabitril-seizure association. At that point, Cephalon stopped promoting the drug.

C. Provigil

Cephalon's shift in focus from neurologists (on-label use) to psychiatrists (off-label use) included Provigil as well as Gabitril. Cephalon recognized that, because Provigil was the most-used drug in the limited narcolepsy population, the only avenue to greater sales was to expand the use beyond the label. Because psychiatrists were prescribing Provigil to treat conditions such as depression-related fatigue, Cephalon revised its promotional strategy to emphasize fatigue related to conditions other than narcolepsy. Instead of obtaining a broader indication for Provigil, however, Cephalon decided to "establish the product as a drug of choice for fatigue as well as sleepiness and to address the multiple symptoms that can be alleviated by the product in addition to the use of the product in adjunctive therapy beyond its indication" and to "better define benefits of 'wake-promotion' to expand use into other areas."

Shortly after Cephalon started promoting Provigil off-label for "wakefulness," in January 2002 the FDA directed Cephalon to stop disseminating false and misleading written promotional materials representing that Provigil was better, safer, more effective, or useful in a broader range of conditions or patients than had been approved. The company's promotional materials had included claims that Provigil was useful for sleepiness, tiredness, decreased activity, lack of energy and fatigue.

Although Cephalon stopped using these written promotional materials, its sales force continued to promote Provigil for those unapproved uses. For example, in November 2002, a Cephalon manager, accompanying a sales representative on calls to physicians, counseled the sales person: "Your best call of the day was with Dr. [a psychiatrist] . . . . Informing the physician of the transition that we have made with Provigil from narcolepsy to the variety of

areas in which it is currently being used was also effective."

In December 2002, Cephalon applied to the FDA to expand Provigil's label to cover excessive sleepiness, without regard to the patient's underlying medical condition. In January 2004, the FDA approved a more narrow expansion of the label, not for the requested excessive sleepiness, but instead for excessive sleepiness associated with two specific medical conditions: (1) obstructive sleep apnea, in certain patients, and (2) shift work sleep disorder. Despite these narrow expansions to the label, Cephalon continued to promote Provigil for off-label uses, behaving as if it had received the broader label it had been denied.

D. Sales

Cephalon's marketing and sales reports show the success of these off-label campaigns:

- Actiq: from $50.1 million in 2001 to $550.4 million in 2006
- Gabitril: from $24.6 million in 2001 to $ 87.3 million in 2004
- Provigil: from $146.2 million in 2001 to $691.7 million in 2006.

VIII. THE SENTENCING CONSIDERATIONS

The stipulated criminal fine of $50 million is the result of intensive negotiations between the parties. It represents a just resolution of the charge against Cephalon for its off-label marketing, particularly when coupled with the significant civil settlement and the obligations imposed by the Corporate Integrity Agreement. The total package is the largest resolution in this district's history.

The proposed criminal resolution accomplishes the goals of sentencing without being overly harsh. Off-label marketing is harmful, in general, in that it interferes with the

doctor-patient relationship, is misleading to doctors, and can harm patients. In this case, the harms go beyond the general. Promoting Actiq for use in patients who were not yet opioid-tolerant risked hypoventilation and death. Selling Gabitril for non-epileptics promoted seizures in that population. Expanding the use of Provigil beyond its indication also potentially over-medicates patients with a drug that has not been proven to be safe and effective for those uses.

The agreed-upon sentence also properly takes into account Cephalon's conduct. It reflects the fact that the company has no prior conviction and cooperated with the investigation, balanced against the breadth and length of the illegal conduct. The government believes that the global resolution will deter the company from further unlawful promotions.

A fine of this nature, coupled with all of the other aspects of this case, will also be just punishment for the offense, and serve as general deterrence to others who might be tempted to go down the road of off-label marketing. All of these factors are difficult to quantify, but the parties have engaged in lengthy discussions aimed at reaching a fair resolution of this matter.

The government therefore asks the Court to accept the plea and impose the agreed-upon sentence.

Respectfully submitted,

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/s/ Catherine Votaw
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CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing Memorandum was served upon defense counsel by hand-delivery and email, on this 29th day of September, 2008, as follows:

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