Facts supporting call for a criminal investigation of Purdue Pharma in Canada

1. The Agreed Statement of Facts, signed by United States executives of Purdue Frederick Company Inc. in their 2007 guilty plea, states that "PURDUE supervisors and employees, with the intent to defraud or mislead, marketed and promoted OxyContin as less addictive, less subject to abuse and diversion, and less likely to cause tolerance and withdrawal than other pain medications…" See Annex A.

2. An advertisement published in the journal *Canadian Family Physician* (September 2000) intended to promote sales of OxyContin stated that "Drug abuse is not a problem in patients with pain for whom the opioid is appropriately indicated", that there is "no ceiling to analgesic efficacy" and that there is "full 12 hours of pain relief". The advertisement shows pictures of a man holding his back in pain, a "small colour-coded" 80 mg OxyContin tablet, and an "Adapted" World Health Organization pain ladder with oxycodone added in red font alongside codeine. The advertisement bears a logo with the text "A TRUSTED PARTNER IN PAIN CARE, Purdue Frederick" and another with the text "Purdue Pharma Inc., Gen. Partner of Purdue Frederick, Pickering, Ontario, L1W 3W8". A similar advertisement was published in the *Canadian Medical Association Journal* in 2001. See Annex B

3. Physicians in Ontario recall being told by sales representatives of Purdue that long-acting opioids such as OxyContin were "less addictive", and they received written materials from Purdue indicating that long-acting opioids such as OxyContin have a "lower abuse potential". See Annex C and Annex D.

4. Dwayne May, a former Purdue Pharma Canada executive, has publicly stated that sales representatives of Purdue Pharma told physicians that long-acting opioids such as OxyContin had a low abuse potential, and also that Purdue Pharma Canada rewarded its sales representatives with bonuses based on the number of OxyContin prescriptions written by doctors, as it did in the United States. See Annex E.

5. In its application for a Canadian patent, Purdue claimed that long-acting oxycodone will "have substantially less inter-individual variation with regard to the dose of opioid analgesic required to control pain without unacceptable side effects" and that it was better than other opioid products. See Annex F.

6. Despite having two prior applications rejected, Purdue Pharma Canada persisted with a third application to have 5 mg OxyContin tablets publicly funded by the Government of Ontario. Purdue Pharma Canada's third application was rejected in 2007. The decision document indicates that the committee "repeatedly questioned the need for such a small dose of oxycodone in a long-acting preparation" and considered the "dramatic increase in the use of controlled-release oxycodone (OxyContin) over the past several years". See Annex G.

7. Long-acting opioids such as OxyContin were sold in the United States and Canada with similar approval details. Canadian physicians were paid by Purdue to communicate to other doctors about the use of opioid products such as OxyContin and some of these doctors report attending meetings in the United States. Dr Craig Landau was President and Chief Executive Officer of Purdue Pharma Canada from 2013 and is now the President and Chief Executive Officer of Purdue Pharma L.P. in the United States. Before heading Purdue Pharma in Canada, he was the Vice President and Chief Medical Officer of Purdue Pharma in the United States.

Annex A.

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

UNITED STATES OF AMERICA	)	
	)	
v.	)	Dkt. No. _____
	)	
THE PURDUE FREDERICK COMPANY, INC.	)	
D/B/A The Purdue Frederick Company	)	
MICHAEL FRIEDMAN	)	
HOWARD R. UDELL	)	
PAUL D. GOLDENHEIM	)	

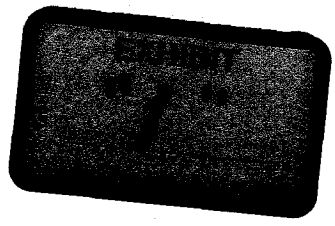
AGREED STATEMENT OF FACTS

Introduction

1. Defendant The PURDUE FREDERICK COMPANY, INC. (referred to in this Agreed Statement of Facts as "PURDUE"), doing business as The Purdue Frederick Company, was a New York corporation, headquartered in Connecticut. It was created in 1892 and was purchased by its current owners in 1952. At all times relevant to this Agreed Statement of Facts, PURDUE and other related and associated entities were engaged in the pharmaceutical business throughout the United States.

2. PURDUE developed and originally marketed OxyContin Tablets ("OxyContin"), an opioid analgesic approved to be taken every twelve hours. OxyContin is a controlled-release form of oxycodone and is a Schedule II controlled substance with an abuse liability similar to morphine.

3. Defendant MICHAEL FRIEDMAN joined PURDUE in 1985 as Vice President and Assistant to the President and Chairman. He was appointed Group Vice President in 1988, Executive Vice President and Chief Operating Officer in 1999, and President and Chief Executive Officer in 2003.



4. Defendant HOWARD R. UDELL joined PURDUE in 1977 as General Counsel. He was appointed Group Vice President and General Counsel in 1989, Executive Vice President and General Counsel in 1999, and Executive Vice President and Chief Legal Officer in 2003.

5. Defendant PAUL D. GOLDENHEIM joined PURDUE in 1985 as Medical Director. He was appointed Vice President and Medical Director in 1986, Vice President of Scientific and Medical Affairs and Executive Director of Purdue Frederick Research Center in 1988, Group Vice President of Scientific and Medical Affairs in 1989, Executive Vice President of Medical and Scientific Affairs in 1999, Executive Vice President of Worldwide Research & Development in 2000, and Executive Vice President of Worldwide Research & Development and Chief Scientific Officer in 2003. He left PURDUE in 2004.

6. From January 1996 through June 30, 2001, PURDUE received approximately $2.8 billion in revenue from the sale of OxyContin.

Statutory Framework

7. The United States Food and Drug Administration ("FDA") is the agency of the United States responsible for protecting the public health by ensuring the safety, efficacy, and security of human drugs and for enforcing the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301, *et seq.*

8. The FDCA, 21 U.S.C. § 355, required a sponsor of a new drug to receive FDA approval of a New Drug Application ("NDA"), before the sponsor could distribute the drug in interstate commerce.

9. The FDCA, 21 U.S.C. § 321(m), defined labeling to include "all labels and other written, printed, or graphic matter . . . accompanying [a drug]." Title 21, Code of Federal

Regulations, Section 202.1(*l*)(2) provided that labeling included brochures, booklets, mailing pieces, detailing pieces, bulletins, letters, motion picture films, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug which were disseminated by or on behalf of a drug's manufacturer, packer, or distributor. Such items "accompanied" a drug if they were designed for use and used in the distribution and sale of the drug.

10. The FDCA, 21 U.S.C. § 352(a), provided that a drug was misbranded "[i]f its labeling [was] false or misleading in any particular." The FDCA, 21 U.S.C. § 321(n), provided that "[i]n determining whether the labeling . . . [was] misleading there shall be taken 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 representation or material with respect to the consequences which may result from the use . . . 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."

11. The FDCA, 21 U.S.C. § 331(a), prohibited the introduction or delivery for introduction into interstate commerce of a misbranded drug. 21 U.S.C. § 333(a)(2) provided that such a violation committed with the intent to defraud or mislead was punishable as a felony. Under 21 U.S.C. § 333(a)(1) and the applicable case law, an individual could be held criminally liable for a misdemeanor violation of § 331(a) without having knowledge of, or intent to cause, the misbranding if that individual was a responsible corporate officer at the time of the misbranding. A responsible corporate officer for these purposes was one who had responsibility and authority either to prevent in the first instance or to promptly correct certain conduct resulting in the misbranding of a drug introduced or delivered for introduction into interstate commerce.

12. OxyContin was a drug within the meaning of the FDCA, 21 U.S.C. § 321(g)(1), and a new drug within the meaning of 21 U.S.C. § 321(p).

OxyContin Approval and Package Insert

13. On approximately December 28, 1994, PURDUE submitted the OxyContin NDA to the FDA. The NDA included clinical studies showing that OxyContin, when dosed every twelve hours, was as safe and as effective as immediate-release oxycodone dosed every six hours.

14. The NDA did not claim that OxyContin was safer or more effective than immediate-release oxycodone or other pain medications and PURDUE did not have, and did not provide the FDA with, any clinical studies demonstrating that OxyContin was less addictive, less subject to abuse and diversion, or less likely to cause tolerance and withdrawal than other pain medications.

15. On or about October 24, 1995, the FDA completed, with PURDUE's assistance, an internal Medical Officer Review ("MOR") of the Integrated Summary of Safety ("ISS") and a MOR of the Integrated Summary of Efficacy ("ISE"). While not binding on the company, the MORs were disclosed to certain PURDUE supervisors and employees. These MORs did not state that OxyContin was more effective than or superior to, safer, had less opioid effects, or caused fewer adverse events than any other marketed product.

16. The MOR of the ISS included these statements:

a. "The blood level data in clinical use suggests the opioid effects [of OxyContin and immediate-release oxycodone] would be similar;"

b. "The best conclusion is that the efficacy of [OxyContin] is equivalent to the [immediate-release oxycodone], with an adverse event profile that is as good as the [immediate-release oxycodone]. I would not allow a 'better' claim." (emphasis in original);

c. "The adverse experience profile of [OxyContin] is qualitatively similar to that of the parent drug, oxycodone;" and

d. "Withdrawal is possible in patients who have their dosage abruptly reduced or discontinued."

17. The MOR of the ISE included these statements:

a. "There is some evidence, both pharmacokinetic and clinical, that reduced acute opioid adverse effects may be expected in some patients, but there is not enough evidence to support an [adverse event] superiority claim [for OxyContin] against other marketed products." (emphasis in original); and

b. "Care should be taken to limit competitive promotion. [OxyContin] has been shown to be as good as current therapy, but has not been shown to have a significant advantage beyond reduction in frequency of dosing."

18. The FDA approved the OxyContin NDA on December 12, 1995, and from 1996 through June 30, 2001, the FDA-approved package insert for OxyContin stated that it was intended for "the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days." The package insert also included the statement: "Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug."

Misbranding of OxyContin

19. During the period February through March 1995, PURDUE supervisors and employees obtained market research that included focus groups of forty primary care physicians, rheumatologists, and surgeons to determine their receptivity to using OxyContin for non-cancer pain. According to this market research, some of these physicians had concerns, similar to their concerns about combination opioids, regarding OxyContin's addictive potential and side effect profile, including that "[t]he biggest negative of [OxyContin] was the abuse potential."

20. Beginning on or about December 12, 1995, and continuing until on or about June 30, 2001, certain PURDUE supervisors and employees, with the intent to defraud or mislead, marketed and promoted OxyContin as less addictive, less subject to abuse and diversion, and less likely to

cause tolerance and withdrawal than other pain medications, as follows:

a. Trained PURDUE sales representatives and told some health care providers that it was more difficult to extract the oxycodone from an OxyContin tablet for the purpose of intravenous abuse, although PURDUE's own study showed that a drug abuser could extract approximately 68% of the oxycodone from a single 10 mg OxyContin tablet by crushing the tablet, stirring it in water, and drawing the solution through cotton into a syringe;

b. Told PURDUE sales representatives they could tell health care providers that OxyContin potentially creates less chance for addiction than immediate-release opioids;

c. Sponsored training that taught PURDUE sales supervisors that OxyContin had fewer "peak and trough" blood level effects than immediate-release opioids resulting in less euphoria and less potential for abuse than short-acting opioids;

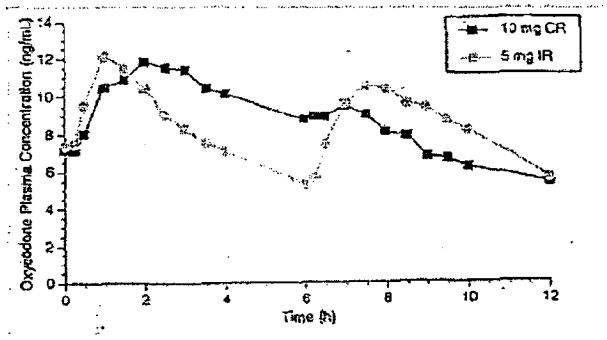
d. Told certain health care providers that patients could stop therapy abruptly without experiencing withdrawal symptoms and that patients who took OxyContin would not develop tolerance to the drug; and

e. Told certain health care providers that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to "weed out" addicts and drug seekers.

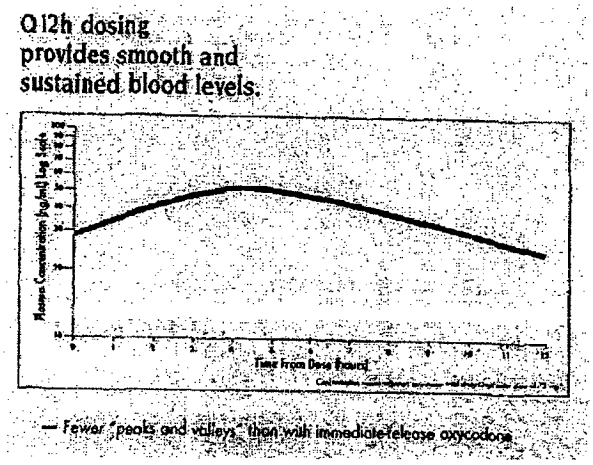
Misbranding of OxyContin: Use of Graphical Depictions by Sales Representatives

21. Data from one of PURDUE's clinical studies was used to create the following graphical demonstration of the difference in the plasma levels at steady state between patients who took OxyContin every twelve hours (the "10 mg CR" line) and patients who took immediate-release

oxycodone every six hours (the "5 mg IR" line):



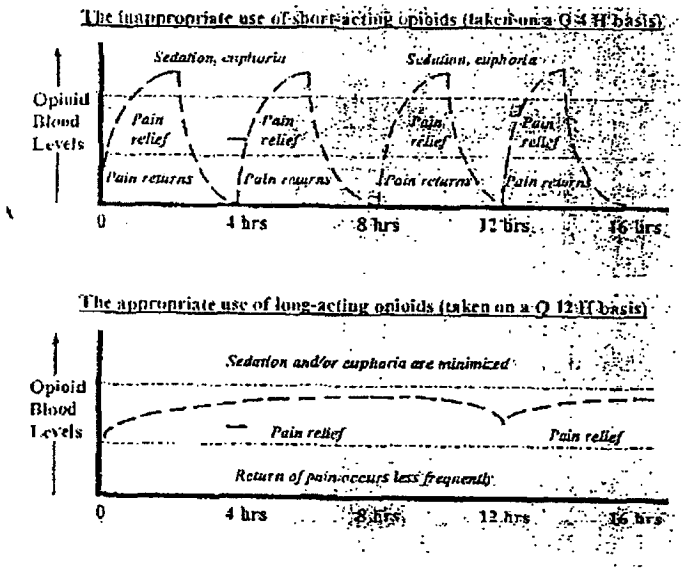
22. On October 12, 1995, PURDUE requested comments from the FDA's Division of Drug Marketing, Advertising, and Communication ("DDMAC") about its proposed launch marketing materials, which included the following graph and text showing the oxycodone plasma concentration provided by OxyContin on a logarithmic scale along with the statement that OxyContin's oxycodone blood plasma levels provided "fewer 'peaks and valleys' than with immediate-release oxycodone:"



23. On or about December 20, 1995, after reviewing the proposed OxyContin launch materials, DDMAC informed PURDUE that "[i]f [Purdue] wishes to compare blood levels in the text, then DDMAC suggests that the blood levels for both dosage forms be presented in the graphic so that the reader can accurately interpret this claim."

24. On or about January 11, 1996, PURDUE told DDMAC that it had "deleted" the statement "[f]ewer peaks and valleys than with immediate-release oxycodone."

25. In or about December 1998, PURDUE sponsored training for all of its district sales managers. During this meeting, a pharmacist retained by PURDUE to conduct a portion of the training used the following graphical demonstration (instead of the graphical demonstration of the actual clinical data described in paragraph 21 of this Agreed Statement of Facts), and falsely stated that OxyContin had significantly fewer "peak and trough" blood level effects than immediate-release opioids resulting in less euphoria and less potential for abuse than short-acting opioids:



26. Beginning in or around 1999, some of PURDUE's new sales representatives were permitted, during training at PURDUE's headquarters, to draw their own blood level graphs to falsely represent that OxyContin, unlike immediate-release or short-acting opioids, did not swing up and down between euphoria and pain, and resulted in less abuse potential.

27. During the period 1999 through June 30, 2001, certain PURDUE sales representatives used graphical depictions similar to the one described in paragraph 25 of this Agreed Statement of Facts and falsely stated to some health care providers that OxyContin had less euphoric effect and less abuse potential than short-acting opioids.

Misbranding of OxyContin: Misleading Use of Article to Claim No Withdrawal or Tolerance

28. On or about January 16, 1997, certain PURDUE supervisors and employees sent to the FDA the results of a clinical study pertaining to the use of low doses of OxyContin by osteoarthritis patients ("osteoarthritis study") and a final study report that included, in a section pertaining to respite periods, the statement "[n]o investigator reported 'withdrawal syndrome' as an adverse experience during the respite periods." In a section entitled "Adverse Experiences by Body System During Respite Periods," the report's summary of the major results listed the most frequently reported adverse experiences in respite periods to be nervousness, insomnia, nausea, pain, anxiety, depression, and diarrhea, followed by the statement: "Twenty-eight patients (26%) had symptoms recorded during 1 or more respite periods."

29. In or about May 1997, certain PURDUE supervisors and employees stated that while they were well aware of the incorrect view held by many physicians that oxycodone was weaker than morphine, they did not want to do anything "to make physicians think that oxycodone was stronger or equal to morphine" or to "take any steps in the form of promotional materials, symposia, clinicals,

publications, conventions, or communications with the field force that would affect the unique position that OxyContin ha[d] in many physicians mind (*sic*)."

30. On or about February 12, 1999, certain supervisors and employees of a United Kingdom company affiliated with PURDUE provided certain PURDUE supervisors and employees with an analysis of the osteoarthritis study together with another clinical study. This analysis included a list of eight patients in the osteoarthritis study and eleven patients in the other study "who had symptoms recorded that may possibly have been related to opioid withdrawal," including one patient in the other study who required treatment for withdrawal syndrome. The "Discussion" section of this analysis included the following: "It is not surprising that some patients in the clinical trials developed some degree of physical dependence and consequently experienced withdrawal symptoms as a result of abrupt discontinuation of OxyContin tablets. All patients who were suspected to have withdrawal symptoms have been reported but this may have resulted in a falsely high incidence. Of the patients who participated in [the osteoarthritis study] (in which patients entered respite periods without OxyContin tablets) many symptoms suspected to be due to opioid withdrawal may simply have resulted from the return of pain. After withdrawal of OxyContin tablets, patient 6007 complained of nervousness, patient 2004 complained of insomnia and felt restless and patients 2020 and 2028 were restless and anxious. Since these are symptoms which often accompany the return of significant pain, it may be wrong to label these as withdrawal symptoms. Nonetheless, the incidence of withdrawal syndromes in patients treated with OxyContin tablets is a concern and it is safer to over report, than under report this potential problem." The analysis' conclusions included the statement: "As expected, some patients did become physically dependent on OxyContin tablets but this is not expected to be a clinical problem so long as abrupt withdrawal of drug is avoided."

31. Certain PURDUE supervisors and employees participated in the drafting of an article regarding the osteoarthritis study that was published in a medical journal on or about March 27, 2000 ("osteoarthritis study article"). The "Results" section of the article included the following three statements pertaining to the incidence of withdrawal syndrome and withdrawal symptoms experienced by study patients: (1) One patient was hospitalized "for withdrawal symptoms.... The patient who was hospitalized with withdrawal symptoms had completed the study on the previous day and had been receiving CR oxycodone, 70 mg/d; symptoms resolved after 3 days." (2) "A second patient, who was receiving 60 mg/d CR oxycodone, experienced withdrawal symptoms after running out of study medication. The patient had not reported withdrawal symptoms during scheduled respites from doses of 30 or 40 mg/d." (3) "Withdrawal syndrome was not reported as an adverse event for any patient during scheduled respites. Adverse experiences reported by more than 10% of patients during scheduled respites were nervousness (9 patients) and insomnia (8 patients)."

32. The osteoarthritis study article also included a "Comment" section. The statement regarding withdrawal in this section largely summarized the information in the three statements in the "Results" section and further suggested that patients taking low doses could have their OxyContin treatment abruptly discontinued without experiencing withdrawal if their condition so warranted: "There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites, indicating that [OxyContin] at doses below 60 mg [per day] can be discontinued without tapering the dose if the patient's condition so warrants."

33. On or about May 18, 2000, after millions of OxyContin tablets had been sold and used by patients, PURDUE's Medical Services Department reported to certain PURDUE supervisors and

employees that it had recently received a report of a patient who said he or she was unable to stop taking OxyContin 10 mg every 12 hours without experiencing withdrawal symptoms and the report indicated that "this type of question, patients not being able to stop OxyContin without withdrawal symptoms has come up quite a bit here in Medical Services lately (at least 3 calls in the last 2 days)."

34. On or about June 26, 2000, certain PURDUE supervisors and employees sent the full text of the osteoarthritis study article together with a "marketing tip" to PURDUE's entire sales force. The marketing tip stated that a reprint of the osteoarthritis study article was available for use in achieving sales success. The marketing tip also included as one of the article's twelve key points: "There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites indicating that CR oxycodone at doses below 60 mg/d can be discontinued without tapering the dose if the patient condition so warrants."

35. On or about February 13, 2001, certain PURDUE supervisors and employees received a review of the accuracy of the withdrawal data in the osteoarthritis study that stated: "Upon a review of all comments for all enrolled patients, it was noted that multiple had comments which directly stated or implied that an adverse experience was due to possible withdrawal symptoms." This was followed by a list of eleven study patients who reported adverse experience due to possible withdrawal symptoms during these periods. 106 patients initially participated in the osteoarthritis study, 32 of them withdrew because of adverse events (not necessarily related to withdrawal), and 38 patients remained in the study at 12 months.

36. On or about March 28, 2001, a PURDUE employee emailed a PURDUE supervisor regarding the review of withdrawal data described in paragraph 35 of this Agreed Statement of Facts,

asking: "Do you think the withdrawal data from the [osteoarthritis] study . . . is worth writing up (an abstract)? Or would this add to the current negative press and should be deferred?" The supervisor responded: "I would not write it up at this point." No abstract was prepared.

37. Between approximately June 26, 2000, and June 30, 2001, certain PURDUE supervisors and employees distributed copies of the reprint of the osteoarthritis study article to all of PURDUE's sales representatives for use in the promotion and marketing of OxyContin to health care providers, including the distribution of 10,615 copies to certain PURDUE sales representatives between February 13, 2001, and June 30, 2001.

38. During the period June 26, 2000, through June 30, 2001, certain PURDUE sales representatives distributed the reprint of the osteoarthritis study article to some health care providers and falsely or misleadingly stated that patients taking OxyContin at doses below 60 milligrams per day can always be discontinued abruptly without withdrawal symptoms and that patients on such doses would not develop tolerance.

Misbranding of OxyContin: Use of Reduced Abuse Liability Claim in Marketing

39. The original OxyContin package insert approved by the FDA stated: "Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug" (the *Reduced Abuse Liability Statement*). Certain PURDUE supervisors and employees instructed PURDUE sales representatives to use this statement to market and promote OxyContin.

40. Certain PURDUE sales representatives, while promoting and marketing OxyContin, falsely told some health care providers that the *Reduced Abuse Liability Statement* meant that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used

to "weed out" addicts and drug seekers.

41. By March 2000, various PURDUE supervisors and employees in different parts of the company had received reports of OxyContin abuse and diversion occurring in different communities.

42. On or about November 27, 2000, certain PURDUE supervisors and employees amended the *Reduced Abuse Liability Statement* to state that "[d]elayed absorption, as provided by OxyContin tablets, when used properly for the management of pain, is believed to reduce the abuse liability of a drug," and instructed PURDUE sales representatives to use the amended statement to promote and market OxyContin.

43. From March 2000 through June 30, 2001, certain PURDUE sales representatives, while promoting and marketing OxyContin, falsely told some health care providers that the *Reduced Abuse Liability Statement* and the amended statement meant that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to "weed out" addicts and drug seekers.

Introduction of Misbranded OxyContin Into Interstate Commerce

44. In or about and between January 1996 and June 30, 2001, PURDUE manufactured, marketed, and sold quantities of OxyContin in interstate commerce from various locations outside the state of Virginia to various locations in the Western District of Virginia and elsewhere, which were misbranded within the meaning of 21 U.S.C. §§ 331(a), 333(a)(2), and 352(a), as described in paragraphs 19 through 43 of this Agreed Statement of Facts.

45. Between in or about January 1996 and on or about June 30, 2001, defendants MICHAEL FRIEDMAN, HOWARD R. UDELL, and PAUL D. GOLDENHEIM, were responsible

corporate officers of PURDUE under 21 U.S.C. §§ 331(a), 333(a)(1), and 352(a).

46. Defendants MICHAEL FRIEDMAN, HOWARD R. UDELL, and PAUL D. GOLDENHEIM ("individual defendants") do not agree that they had personal knowledge of all of the matters set forth in paragraphs 1 through 44 of this Agreed Statement of Facts. However, they agree that the Court may accept these facts, as agreed to by defendant THE PURDUE FREDERICK COMPANY, INC., as part of the factual basis supporting the guilty pleas by the individual defendants.

The parties agree to the foregoing Agreed Statement of Facts.

Date: May 9, 2007

FOR THE UNITED STATES:

John L. Brownlee

John L. Brownlee
United States Attorney
Western District of Virginia

Rick A. Mountcastle, Assistant United States Attorney
Randy Ramseyer, Assistant United States Attorney
Sharon Burnham, Assistant United States Attorney
Barbara T. Wells, Trial Attorney, U.S. Dept. Of Justice
Elizabeth Stein, Trial Attorney, U.S. Dept. Of Justice

FOR DEFENDANT THE PURDUE FREDERICK COMPANY, INC.:

Date: May 7, 2007

Robin E. Abrams, Esquire
Vice-President and Director of
The Purdue Frederick Company, Inc. and
Vice-President and Associate General Counsel
of Purdue Pharma L.P.
Authorized Corporate Officer for
The Purdue Frederick Company, Inc.

Date: May 8, 2007

Howard M. Shapiro, Esquire
Counsel for The Purdue Frederick Company, Inc.

FOR DEFENDANT MICHAEL FRIEDMAN:

Date: May 7, 2007

Michael Friedman, Defendant

Date: _____

Mark D. Pomerantz, Esquire
Counsel for Michael Friedman

FOR DEFENDANT HOWARD R. UDELL:

Date: May 7, 2007

Howard R. Udell, Defendant

Date: _____

Mary Jo White, Esquire
Counsel for Howard R. Udell

FOR DEFENDANT PAUL D. GOLDENHEIM:

Date: _____

Paul D. Goldenheim, Defendant

Date: _____

Andrew Good, Esquire
Counsel for Paul D. Goldenheim

FOR DEFENDANT THE PURDUE FREDERICK COMPANY, INC.:

Date: _____

Robin E. Abrams, Esquire
Vice-President and Director of
The Purdue Frederick Company, Inc. and
Vice-President and Associate General Counsel
of Purdue Pharma L.P.
Authorized Corporate Officer for
The Purdue Frederick Company, Inc.

Date: _____

Howard M. Shapiro, Esquire
Counsel for The Purdue Frederick Company, Inc.

FOR DEFENDANT MICHAEL FRIEDMAN:

Date: 5/7/07

Michael Friedman, Defendant

Date: 5/8/07

Mark F. Pomerantz, Esquire
Counsel for Michael Friedman

FOR DEFENDANT HOWARD R. UDELL:

Date: _____

Howard R. Udell, Defendant

Date: _____

Mary Jo White, Esquire
Counsel for Howard R. Udell

FOR DEFENDANT PAUL D. GOLDENHEIM:

Date: _____

Paul D. Goldenheim, Defendant

Date: _____

Andrew Good, Esquire
Counsel for Paul D. Goldenheim

FOR DEFENDANT THE PURDUE FREDERICK COMPANY, INC.:

Date: _____

Robin E. Abrams, Esquire
Vice-President and Director of
The Purdue Frederick Company, Inc. and
Vice-President and Associate General Counsel
of Purdue Pharma L.P.
Authorized Corporate Officer for
The Purdue Frederick Company, Inc.

Date: _____

Howard M. Shapiro, Esquire
Counsel for The Purdue Frederick Company, Inc.

FOR DEFENDANT MICHAEL FRIEDMAN:

Date: _____

Michael Friedman, Defendant

Date: _____

Mark D. Pomerantz, Esquire
Counsel for Michael Friedman

FOR DEFENDANT HOWARD R. UDELL:

Date: 5/7/07

Howard R. Udell, Defendant

Date: 5/8/07

Mary Jo White, Esquire
Counsel for Howard R. Udell

FOR DEFENDANT PAUL D. GOLDENHEIM:

Date: _____

Paul D. Goldenheim, Defendant

Date: _____

Andrew Good, Esquire
Counsel for Paul D. Goldenheim

FOR DEFENDANT THE PURDUE FREDERICK COMPANY, INC.:

Date: _____

Robin E. Abrams, Esquire
Vice-President and Director of
The Purdue Frederick Company, Inc. and
Vice-President and Associate General Counsel
of Purdue Pharma L.P.
Authorized Corporate Officer for
The Purdue Frederick Company, Inc.

Date: _____

Howard M. Shapiro, Esquire
Counsel for The Purdue Frederick Company, Inc.

FOR DEFENDANT MICHAEL FRIEDMAN:

Date: _____

Michael Friedman, Defendant

Date: _____

Mark D. Pomerantz, Esquire
Counsel for Michael Friedman

FOR DEFENDANT HOWARD R. UDELL:

Date: _____

Howard R. Udell, Defendant

Date: _____

Mary Jo White, Esquire
Counsel for Howard R. Udell

FOR DEFENDANT PAUL D. GOLDENHEIM:

Date: May 8, 2007

Paul D. Goldenheim, Defendant

Date: May 8, 2007

Andrew Good, Esquire
Counsel for Paul D. Goldenheim

Annex B.


OxyContin® q12h
Controlled release oxycodone tablets
• Rapid onset of analgesia within 46 minutes
Comparable to immediate-release oxycodone[†2,3]
46 min.
• Full 12 hours of pain relief[2-7]
Provides uninterrupted sleep for an improved quality of life[3,5]
• No risk of acetaminophen or ASA toxicity[2-4,7,8]
No ceiling to analgesic efficacy[††2,4,5,7]
Increasing pain
Step 3
• Oxycodone
• Hydromorphone
• Morphine
Step 2
• Oxycodone
• Codeine
Step 1
• ASA
• Acetaminophen
• NSAIDs
World Health Organization Pain Ladder (Adapted)[1,2]
The Only Step 2 And Step 3 q12h Analgesic
OxyContin® q12h
10 mg 20 mg 40 mg 80 mg
Small, colour-coded tablets
One to Start and Stay With ...Easy to Dose, Easy to Titrate
For prescribing information see page 452
For the relief of moderate to severe pain requiring the prolonged use of an opioid.
Side effects are similar to other opioid analgesics; the most frequently observed are constipation, nausea and somnolence.
Dosage limitations may be imposed by adverse effects if they occur.[5] Please refer to prescribing information.
Warning: Opioid analgesics should be prescribed and handled with the degree of caution appropriate to the use of a drug with abuse potential. Drug abuse is not a problem in patients with pain for whom the opioid is appropriately indicated.
†Median time to onset of analgesia after single dose Oxy-IR 15 mg (N=31/180) and OxyContin 30 mg (N=30/180) was 41 minutes and 46 minutes, respectively (N=60/180) (P≤0.05) in patients following abdominal or gynecologic surgery. (6 groups of 30 each).[2,3]
††With adequate dosing, there is no intrinsic limit to the analgesic effect of oxycodone.
Purdue Pharma Inc.
Purdue Frederick
Pickering, Ontario L1W 3W8
A TRUSTED PARTNER IN PAIN CARE
Purdue Frederick

Annex B (continued)

Annex B (continued)

"The Times investigation, based on thousands of pages of confidential Purdue documents and other records, found that:

- Purdue has known about the problem for decades. Even before OxyContin went on the market, clinical trials showed many patients weren't getting 12 hours of relief. Since the drug's debut in 1996, the company has been confronted with additional evidence, including complaints from doctors, reports from its own sales reps and independent research.
- The company has held fast to the claim of 12-hour relief, in part to protect its revenue. OxyContin's market dominance and its high price — up to hundreds of dollars per bottle — hinge on its 12-hour duration. Without that, it offers little advantage over less expensive painkillers**.**
- When many doctors began prescribing OxyContin at shorter intervals in the late 1990s, Purdue executives mobilized hundreds of sales reps to "refocus" physicians on 12-hour dosing. Anything shorter "needs to be nipped in the bud. NOW!!" one manager wrote to her staff.
- Purdue tells doctors to prescribe stronger doses, not more frequent ones, when patients complain that OxyContin doesn't last 12 hours. That approach creates risks of its own. Research shows that the more potent the dose of an opioid such as OxyContin, the greater the possibility of overdose and death.
- More than half of long-term OxyContin users are on doses that public health officials consider dangerously high, according to an analysis of nationwide prescription data conducted for The Times."

Los Angeles Times article.

http://www.latimes.com/projects/oxycontin-part1/

Annex C.

“I am a family doctor in Ontario since 1988. I can remember a drug rep telling me Oxycontin was less addictive… “

Email correspondence from Ontario physician.

Annex D.

"With respect to the reference to the 'lower abuse potential' that is listed as a benefit of Controlled Release / Sustained Release formulations vs Immediate Release in the 2002 version of the book, Health Canada wishes to clarify that the oxycodone Product Monograph never included information to the effect that it was more resistant to abuse, although some healthcare professionals might have supported that belief at the time. However, we note that this reference was removed from the 2008 version of the book and is no longer being used. Of course, should this issue had been brought to our attention back in 2002, Health Canada would have contacted Purdue Pharma to implement corrective measures."

Letter from Marketed Health Products Directorate of Health Canada dated 25 May 2012

Annex E.

“Mr. May confirmed, however, that reps did tell doctors initially — before evidence to the contrary emerged — that the drug had low abuse potential because of its special formulation.”

[…]

“Mr. May also confirmed reps were paid bonuses tied to the number of prescriptions doctors filled for OxyContin, as they were for other Purdue products and is common in the industry.”

http://nationalpost.com/news/canada/the-selling-of-oxycontin

Annex F.

The present invention can also provide a method and formulation(s) which substantially reduce the variability in daily dosages and formulation requirements necessary to control pain in substantially all patients.

In yet another aspect the present invention provides a method for substantially reducing the time and resources need to titrate patients requiring pain relief on opioid analgesics.

The present invention can also provide controlled release opioid formulations which have substantially less inter-individual variation with regard to the dose of opioid analgesic required to control pain without unacceptable side effects.

The above aspects and others are attained by virtue of the present invention, which is related to a solid controlled release oral dosage form, the dosage form comprising from about 10 to about 40 mg of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C is between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being substantially independent of pH, such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4.5 hours after administration of the dosage form.

USP Paddle Method is the Paddle Method described, e.g., in U.S. Pharmacopoeia XXII (1990).

In the present specification, "substantially independent of pH" means that the difference, at any given time, between the amount of oxycodone released at,

Canadian Intellectual Property Office, Patent 2098738

http://brevets-patents.ic.gc.ca/opic-cipo/cpd/eng/patent/2098738/summary.html

Oxycodone

Product:
OXYCODONE (OxyContin®), 5mg controlled-release tablet

Class of drugs:
Opioid analgesic (pain relief)

Indication:
Treatment of chronic moderate-to-severe pain

Manufacturer:
Purdue Pharma

CED Recommendation

The CED recommended that oxycodone (OxyContin) 5mg controlled-release tablet not be listed on the Ontario Drug Benefit (ODB) Formulary, on the basis that it does not provide any additional value given what is currently available on the Formulary.

Executive Officer Decision

Based on the CED's recommendation, the Executive Officer has decided not to list oxycodone (OxyContin) 5mg controlled-release tablets.

Status

No funding through the Ontario Public Drug Programs.

Highlights of Recommendation:

- Oxycodone controlled-release (OxyContin) is a long-acting narcotic used to manage moderate-to-severe pain by releasing medication over a 12 to 24-hour period. Specifically, oxycodone controlled-release tablet (OxyContin) is intended for patients with continuous pain who require treatment over an extended period of time (e.g., cancer pain).
- Other long-acting narcotic pain medicines that are currently listed on the Ontario Drug Benefit (ODB) Formulary include Codeine Contin, Hydromorph Contin, M-Eslon and MS Contin.
- OxyContin 5mg is a new strength of oxycodone controlled-release tablet. OxyContin 10mg, 20mg, 40mg, and 80mg tablets are currently listed on the Ontario Drug Benefit (ODB) Formulary.
- The price of the 5mg tablet, at $0.60, is more expensive on a price per mg basis than currently listed controlled-release oxycodone(OxyContin) tablets. The Committee indicated that the lower-strength 5mg tablet should be priced proportionately lower than the higher-strength controlled-release oxycodone (OxyContin) tablets.
- **Overall, the CED concluded that the oxycodone controlled-release (OxyContin) 5mg tablet does not provide added value for recipients of the ODB Program.** Therefore, the Committee recommended that oxycodone controlled-release tablet (OxyContin) 5mg not be listed on the Formulary.

Background:

Controlled-release oxycodone (OxyContin) is a long-acting form of oxycodone used to relieve moderate-to-severe pain. Oxycodone belongs to a group of medications called strong opioid analgesics, or narcotic analgesics, which are painkillers that can become addictive over time. These drugs are intended for patients with chronic, moderate-to-severe pain who require continuous treatment over a long period of time.

These products are not intended to treat everyday aches and pains. In studies of patients taking an opioid, typically 89% of them suffer common side effects such as constipation, nausea, sleepiness and dizziness, although these effects did decrease over time.

Controlled-release oxycodone is available as OxyContin 10mg, 20mg, 40mg and 80mg tablets on the ODB Formulary. It is designated to treat chronic pain in patients who cannot tolerate, or have failed treatment with another listed painkiller in this class.

Detailed Discussion:

- The manufacturer, Purdue Pharma, asked the Ministry of Health and Long-Term Care to list oxycodone controlled-release tablet (OxyContin) 5mg on the ODB Formulary in a similar manner as other OxyContin products.
- This is the third time the CED has reviewed oxycodone controlled-release (OxyContin) 5mg tablets. The Committee has repeatedly questioned the need for such a small dose of oxycodone in a long-acting preparation. The Committee noted that, even in the elderly population or in patients who are very sensitive to opioids, there are many Formulary alternatives available, including low dose short-acting preparations.

continued…

- The Committee noted that there has been a dramatic increase in the use of controlled-release oxycodone (OxyContin) over the past several years. The clinical reason for this is unclear, as oxycodone has not been demonstrated to be therapeutically superior to morphine or other opioid analgesics.
- The Committee reviewed recent consensus guidelines from the *Mayo Clinic Proceedings* (Assessment, Diagnosis and Treatment of Diabetic Peripheral Neuropathic Pain. Mayo Clin Proc, 2006). The Committee indicated that the data within the submission was not compelling, since it showed no therapeutic superiority over less costly alternatives such as morphine or other opioid analgesics. In addition, the Committee cited the dramatically increased and inappropriate use of controlled-release oxycodone (OxyContin) as a public health concern.
- With the current availability of multiple narcotic analgesics on the Formulary, the Committee maintained that controlled-release oxycodone (OxyContin) 5mg tablet does not serve an unmet therapeutic need.
- The price of the 5mg tablet, at $0.60, is more expensive on a price per mg than currently listed oxycodone controlled-release tablets (OxyContin). The 10mg tablet is priced at $0.80.
- Overall, the Committee concluded that oxycodone controlled-release (OxyContin) 5mg tablets do not provide added clinical or economic value for recipients of the ODB program.

CEDAC Recommendation:

(http://www.cadth.ca/index.php/en/cdr/recommendations)

The Canadian Expert Drug Advisory Committee (CEDAC) did not review oxycodone controlled-release (OxyContin) 5mg tablets.

Ontario

Ministry of
Health and Long-Term Care
Ontario Public Drug Programs

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