IN THE CHANCERY COURT OF THE FIRST JUDICIAL DISTRICT
OF HINDS COUNTY, MISSISSIPPI

STATE OF MISSISSIPPI, Plaintiff, v. PURDUE PHARMA L.P.; PURDUE PHARMA, INC.; THE PURDUE FREDERICK COMPANY, INC.; TEVA PHARMACEUTICALS USA, INC.; CEPHALON, INC.; JOHNSON & JOHNSON; JANSSEN PHARMACEUTICALS, INC.; ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC. n/k/a JANSSEN PHARMACEUTICALS, INC.; JANSSEN PHARMACEUTICA INC. n/k/a JANSSEN PHARMACEUTICALS, INC.; ENDO HEALTH SOLUTIONS INC.; ENDO PHARMACEUTICALS, INC.; ALLERGAN, PLC f/k/a ACTAVIS PLC ; ACTAVIS, INC. f/k/a WATSON PHARMACEUTICALS, INC.; WATSON LABORATORIES, INC.; ACTAVIS LLC; ACTAVIS PHARMA, INC. f/k/a WATSON PHARMA, INC.; MALLINCKRODT LLC; and SPECGX LLC, Defendants.	Case No. G.2015-1814 **AMENDED COMPLAINT**

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Plaintiff, the State of Mississippi, by and through its Attorney General (hereinafter "Mississippi" or "the State"), upon personal knowledge as to its own acts and beliefs, and upon information and belief as to all matters based upon the investigation of counsel, alleges as follows:

I. INTRODUCTION

1. A pharmaceutical manufacturer should never place its desire for profits above the health and well-being of its customers. Drug manufacturers have a legal duty to ensure their products are accompanied by full and accurate instructions and warnings to guide prescribing doctors and other health-care providers in making treatment decisions. They must tell the truth when marketing their drugs and ensure that their marketing claims are supported by science and medical evidence. Defendants broke these simple rules.

2. During the 1990s, Defendants had the ability to cheaply produce large quantities of opium-like painkillers ("opioids"), but the market was small. Defendants knew that opioids were effective treatments for short-term post-surgical and trauma-related pain, and for palliative (end-of-life) care. They also knew – and had known for years – that, except as a last resort, opioids were addictive and subject to abuse – particularly when used for long-term use for chronic non-cancer pain (pain lasting three months or longer, hereinafter referred to as "chronic pain"). Defendants further knew – and had known for years – that with prolonged use, the effectiveness of opioids wanes, requiring increases in doses and markedly increasing the risk of significant side effects and addiction.[1,2]

[1] *See, e.g.*, Russell K. Portenoy, *Opioid Therapy for Chronic Nonmalignant Pain: Current Status*, 1 Progress in Pain Res. & Mgmt., 247-287 (H.L. Fields and J.C. Liebeskind eds., 1994).

[2] The authoritative Diagnostic and Statistical Manual of Mental Disorders (5th ed. 2013) ("DSM-V"), classifies addiction as a spectrum of "substance use disorders" that range from misuse and abuse of drugs to addiction. Patients suffer negative consequences wherever they fall

3. Defendants also knew that controlled studies of the safety and efficacy of opioids were limited to short-term use (not longer than 90 days) and in managed settings (*e.g.*, hospitals), where the risk of addiction and other adverse outcomes was much less significant. Indeed, the U.S. Food and Drug Administration ("FDA") has expressly recognized that there have been no long-term studies demonstrating the safety and efficacy of opioids.[3]

4. Prescription opioids, which include well-known brand-name drugs like OxyContin and Percocet, and generics like oxycodone and hydrocodone, are narcotics. They are derived from or possess properties similar to opium and heroin, which is why they are regulated as controlled substances.[4] Like heroin, prescription opioids work by binding to receptors on the

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on the substance use disorder continuum. Throughout this Complaint, "addiction" refers to this range of substance abuse disorders.

[3] Letter from Janet Woodcock, M.D., Dir., Ct. for Drug Eval. & Res., to Andrew Kolodny, M.D., Pres. Physicians for Responsible Opioid Prescribing, Re Docket No. FDA-2012-P-0818 (Sept. 10, 2013).

[4] Since passage of the Controlled Substances Act ("CSA") in 1970, opioids have been regulated as controlled substances. Controlled substances are categorized in five schedules, ranked in order of their potential for abuse, with Schedule I being the highest. The CSA imposes a hierarchy of restrictions on prescribing and dispensing drugs based on their medicinal value, likelihood of addiction or abuse, and safety. Opioids generally had been categorized as Schedule II or Schedule III drugs. Schedule II drugs have a high potential for abuse, have a currently accepted medical use, and may lead to severe psychological or physical dependence. 21 U.S.C. § 812. Schedule II drugs may not be dispensed without an original copy of a manually signed prescription, which may not be refilled, from a doctor and filled by a pharmacist who both must be licensed by their state and registered with the DEA. 21 U.S.C. § 829. Opioids that have been categorized as Schedule II drugs include morphine (Avinza, Embeda, Kadian, MS Contin), fentanyl (Duragesic, Actiq, Fentora), methadone, oxycodone (OxyContin, Percocet, Percodan, Tylox), oxymorphone (Opana), and hydromorphone (Dilaudid, Palladone).

Schedule III drugs are deemed to have a lower potential for abuse, but their abuse still may lead to moderate or low physical dependence or high psychological dependence. 21 U.S.C. § 812. Schedule III drugs may not be dispensed without a written or oral prescription, which may not be filled or refilled more than six months after the date of the prescription or be refilled more than five times. 21 U.S.C. § 829. Some opioids had been categorized as Schedule III drugs, including forms of hydrocodone and codeine combined with other drugs, like acetaminophen. However, in October 2013, the FDA, following the recommendation of its advisory panel, reclassified all medications that contain hydrocodone from Schedule III to Schedule II.

spinal cord and in the brain, dampening the perception of pain. Opioids also can create a euphoric high, which can make them addictive. At certain doses, opioids can slow the user's breathing, causing respiratory depression and, ultimately, death.

5. In order to expand the market for opioids and realize blockbuster profits, Defendants needed to create a profound transformation in medical and public perception that would permit the use of opioids not only for acute and palliative care, but also for long periods of time to treat more common aches and pains, like lower back pain, arthritis, and headaches.

6. Defendants, through a common, sophisticated, and highly deceptive marketing campaign that began in the late 1990s, deepened around 2006, and continues to the present, set out to, and did, reverse the popular and medical understanding of opioids. Chronic opioid therapy – the prescribing of opioids to treat chronic pain long-term – is now commonplace.

7. In a "marketing blitz" designed to ensure that every piece of information regarding chronic opioid therapy assured physicians and consumers that the benefits of using their opioids outweighed the risks,[5] Defendants spent hundreds of millions of dollars: (a) developing and disseminating seemingly truthful scientific and educational materials that misrepresented the risks, benefits, and superiority of opioids used long-term to treat chronic pain as described in Section IV.B.2 and IV.C.2; (b) deploying sales representatives who visited doctors and other prescribers and delivered misleading messages about the use of opioids, as described in Section IV.B.2; (c) recruiting prescribing physicians as paid speakers, as means of both securing those physicians' future "brand loyalty" and extending their research to the physicians' peers, as described in Section IV.B.2; (d) funding, assisting, encouraging, and

[5] See Massimo Calabresi, The Price of Relief: Why America Can't Kick Its Painkiller Problem, TIME MAGAZINE (June 15, 2015).

directing doctors, known as "key opinion leaders" (KOLs), not only to deliver scripted talks, but to draft misleading studies, conduct continuing medical education programs (CMEs) that were deceptive and lacked balance, and serve on the boards and committees of professional societies and patient advocacy groups that delivered messages and developed guidelines supporting chronic opioid therapy as described in Section IV.C.2; and (e) funding, assisting, directing, and encouraging seemingly neutral and credible professional societies and patient advocacy groups (referred to hereinafter as Front Groups) that developed educational materials and treatment guidelines urging doctors to prescribe, and patients to use, opioids long-term to treat chronic pain as described in Section IV.C.2.f.

8. These efforts – developed, supported, and directed by Defendants – were designed not to present a fair view of how and when opioids could be safely and effectively used, but rather to convince doctors and patients that the benefits of using opioids to treat chronic non-cancer pain outweighed the risks and that opioids could be used safely by most patients.

9. Working individually, collectively, and through these Front Groups and KOLs, Defendants pioneered a new and far broader market for their potent and highly addictive drugs – the chronic pain market. Defendants persuaded doctors and patients that what they had long known – that opioids are addictive drugs, unsafe in most circumstances for long-term use – was untrue, and quite the opposite, that the compassionate treatment of pain *required* opioids. Ignoring the limitations and cautions in their own drugs' labels, Defendants: (a) overstated the benefits of chronic opioid therapy, promised improvement in patients' function and quality of life, and failed to disclose the lack of evidence supporting long-term use and the significant risks associated with such use; (b) trivialized or obscured the serious risks and adverse outcomes of chronic opioid therapy, including the risk of addiction, overdose, and death; (c) overstated the

superiority of opioids for chronic pain compared with other treatments, such as other non-opioid analgesics, physical therapy, and other alternatives; and (d) mischaracterized the difficulty of withdrawal from opioids and the prevalence of withdrawal symptoms. There was, and is, no reliable scientific evidence to support Defendants' marketing claims, and there was, and is, a wealth of scientific evidence to the contrary. Indeed, Defendants deceptively marketed these drugs for indications and benefits that were outside of the drugs' labels.

10. Even Defendants' KOLs initially were very cautious about whether opioids were safe and effective to treat chronic non-cancer pain. Some of these same KOLs have since recanted their pro-opioid marketing messages and acknowledged that Defendants' marketing went too far. Yet despite the voices of renowned pain specialists, researchers, and physicians who have sounded the alarm on the long-term use of opioids to treat chronic non-cancer pain, Defendants continue to disseminate their false and misleading marketing claims to this day.

11. Defendants' efforts were wildly successful. The United States is now awash in opioids. In 2010, 254 million prescriptions for opioids were filled in the U.S. – enough to medicate every adult in America around the clock for a month. Twenty percent of all doctors' visits result in the prescription of an opioid (nearly double the rate in 2000).[6] Opioids – once a niche category of drugs – are now the most prescribed class of drugs – more than blood pressure, cholesterol, or anxiety drugs. While Americans represent only 4.6% of the world's population, they consume 80% of the opioids supplied around the world and 99% of the global hydrocodone

[6] Matthew Daubresse, *et al*., Ambulatory Diagnosis and Treatment of Nonmalignant Pain in the United States, 2000-2010, 51(10) Med. Care 870-78 (2013).

supply.[7] Together, opioids generated $8 billion in revenue for drug companies in 2012, a number that is projected to reach $15.3 billion by 2016.[8]

12. Roughly 87% of opioids prescribed are used to treat chronic pain[9] – a practice doctors previously considered not just ineffective, but even reckless given the substantial risk of addiction. Among patients taking opioids for 90 days or more, two-thirds of those followed for 4.8 years were still taking opioids at the end of this period.[10]

13. It was Defendants' marketing – and not any medical breakthrough – that rationalized prescribing opioids for chronic pain and opened the floodgates of opioid use and abuse.

14. The result has been catastrophic. According to the U.S. Centers for Disease Control and Prevention ("CDC"), the nation has been swept up in an opioid-induced "public health epidemic."[11] Prescription opioid use contributed to 16,651 overdose deaths nationally in 2010;[12] 16,917 in 2011; and 16,007 in 2012.[13]

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[7] Laxmaiah Manchikanti, *et al*., Therapeutic Use, Abuse, and Nonmedical Use of Opioids: A Ten-Year Perspective, 13 Pain Physician 401-435 (2010).

[8] Barry Meier & Bill Marsh, *The Surging Cost of the Opioid Economy*, N.Y. TIMES (June 22, 2013).

[9] Michael Von Korff, Group Health Res. Inst., *The Epidemiology of Use of Analgesics for Chronic Pain*, Presentation to the FDA (2012), *available at* http://www.fda.gov/downloads/Drugs/NewsEvents/UCM308128.pdf.

[10] Bradley C. Martin, *et al.*, Long-Term Chronic Opioid Therapy Discontinuation Rates from the TROUP Study, 26(12) J. Gen. Internal Med. 1450-1457 (2011).

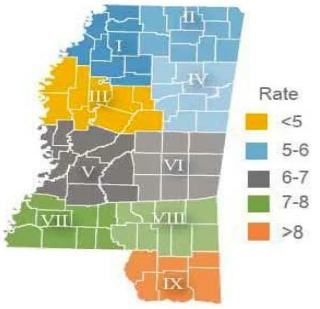
[11] CDC, *Examining the Growing Problems of Prescription Drug and Heroin Abuse* (Apr. 29, 2014), *available at* http://www.cdc.gov/washington/testimony/2014/t20140429.htm.

[12] CDC, *Opioids drive continued increase in drug overdose deaths* (Feb. 20, 2013), *available at*: http://www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.html.

[13] Evan Johnson, *Prescription Pill Deaths Down, Heroin Deaths on the Rise*, WBIR-TV (Oct. 15, 2014), *available at*: http://www.wbir.com/story/news/local/2014/10/15/prescription-pill-deaths-downheroin-death-on-the-rise/17326519/.

15. In 2012, 90 percent of drug overdose deaths in Mississippi were caused by prescription drugs, and most were accidental. The highest death rate (five-year average) is on the coast, which had a death rate 3 times the state average and 5 times the rate for the lower delta area.

UNINTENTIONAL DRUG POISONING DEATHS BY HEALTH DISTRICT, MISSISSIPPI 2007-2011



District	Number	Rate	District	Number	Rate
I (Northwest)	105	6.6	VI (East Central)	76	6.2
II (Northeast)	121	6.8	VII (Southwest)	63	7.2
III (Delta/Hills)	43	3.8	VIII (Southeast)	116	7.7
IV (Tombigbee)	64	5.2	IX (Coastal/Plains)	454	19.9
V (West Central)	187	5.9	Total	1,229	8.3

16. But even these alarming statistics do not fully communicate the toll of prescription opioid abuse on patients and their families, as the dramatic increase in opioid prescriptions to treat common chronic pain conditions has resulted in a population of addicts who seek drugs from doctors. Efforts by doctors to reverse course for a chronic pain patient with long-term dependence on opioids involve managing the physical suffering and psychological distress a patient endures while withdrawing from the drugs. This process is often thwarted by a secondary criminal market well-stocked by a pipeline of drugs that is diverted to supply these patients. Even though they never would have prescribed opioids in the first place, many doctors feel compelled to continue prescribing opioids to patients who have become dependent on them.

17. Indeed, opioid abuse has not displaced heroin, but rather triggered a resurgence in its use, imposing additional burdens on State agencies that address heroin use and addiction. Heroin produces a very similar high to prescription opioids, but is often cheaper. While a single opioid pill may cost $10-$15 on the street, users can obtain a bag of heroin, with multiple highs,

for the same price. It is hard to imagine the powerful pull that would cause a law-abiding, middle-aged person who started on prescription opioids for a back injury to turn to buying, snorting, or injecting heroin, but that is the dark side of opioid abuse and addiction.

18. Dr. Robert DuPont, former director of the National Institute on Drug Abuse and the former White House drug czar, opines that opioids are more destructive than crack cocaine:

> [Opioid abuse] is building more slowly, but it's much larger. And the potential[] for death, in particular, [is] way beyond anything we saw then.… [F]or pain medicine, a one-day dose can be sold on the black market for $100. And a single dose can [be] lethal to a non-patient. There is no other medicine that has those characteristics. And if you think about that combination and the millions of people who are using these medicines, you get some idea of the exposure of the society to the prescription drug problem.[14]

19. Between 600,000 and 700,000 Mississippians suffer from chronic pain, which takes an enormous toll on their health, their lives, and their families. These patients deserve both appropriate care and the ability to make decisions based on accurate, complete information about treatment risks and benefits. But Defendants' deceptive marketing campaign deprived Mississippi patients and their doctors of the ability to make informed medical decisions and, instead, caused important, sometimes life-or-death decisions to be made based not on science, but on hype. Defendants deprived patients, their doctors, and health care payors of the chance to exercise informed judgment and subjected them to enormous costs and suffering.

20. Defendants' actions are not permitted or excused by the fact that their labels (with the exception of Cephalon's labels for Fentora and Actiq) may have allowed or did not exclude the use of opioids for chronic non-cancer pain. The FDA's approval of the drugs themselves did

[14] Transcript, *Use and Abuse of Prescription Painkillers*, The Diane Rehm Show (Apr. 21, 2011), http://thedianerehmshow.org/shows/2011-04-21/use-and-abuse-prescription-painkillers/transcript.

not give Defendants license to misrepresent their risks, benefits, or superiority. Indeed, what makes Defendants' efforts particularly nefarious – and dangerous – is that, unlike other prescription drugs marketed unlawfully in the past, opioids are highly-addictive controlled substances. Defendants deceptively engaged a patient base that – physically and psychologically – could not turn away from their drugs, many of whom were not helped by the drugs or were profoundly damaged by them.

21. Nor is Defendants' causal role broken by the involvement of doctors. Defendants' marketing efforts were both ubiquitous and highly persuasive; their deceptive messages tainted virtually every source on which doctors could rely for information and prevented them from making informed treatment decisions. Defendants targeted not only pain specialists, but also primary care physicians (PCP), nurse practitioners, physician assistants and other health care providers not trained in pain treatment who were even less likely to be able to assess the companies' misleading statements. Defendants also were able to callously manipulate what doctors wanted to believe – namely, that opioids represented a means of relieving their patients' suffering and of practicing medicine more compassionately.

22. To redress and punish these violations of law, the State of Mississippi, by and through Attorney General Jim Hood, seeks a judgment requiring Defendants to pay damages, restitution, civil penalties, and attorneys' fees, costs, and expenses. The State also requests that the Court issue an order requiring Defendants to cease their unlawful promotion of opioids, to correct their misrepresentations, and to abate the public nuisance they have created, in addition to granting any other equitable relief authorized by law.

II. JURISDICTION AND VENUE

23. This Court has subject matter jurisdiction over this action pursuant to MISS. CODE ANN. § 75-24-9, because the State brings this action, in part, to restrain by permanent injunction the use of a method, act, or practice prohibited by MISS. CODE ANN. § 75-24-5.

24. This Court has personal jurisdiction over Defendants pursuant to MISS. CODE ANN. § 13-3-57, because they each conduct business in Mississippi; purposefully direct or directed their actions toward Mississippi; solicited and continue to solicit business, and performed and continue to perform business services, such as marketing, advertising, promoting, and distributing their products in Mississippi; and/or have the requisite minimum contacts with Mississippi necessary to constitutionally permit the Court to exercise jurisdiction.

25. Venue is proper in this Court pursuant to MISS. CODE ANN. §§ 11-11-3, 11-5-1, 75-24-9, and 9-5-81 and Section 159 of the Mississippi Constitution.

III. PARTIES

A. Plaintiff

26. This action is brought for and on behalf of the sovereign State, by and through Jim Hood, the duly elected and current Attorney General of the State, pursuant to, *inter alia*, MISS. CODE ANN. § 7-5-1, MISS. CODE ANN. §§ 43-13-219, *et seq*., Mississippi's Consumer Protection Act, MISS. CODE ANN. §§ 75-24-1, *et seq*., and the common law and statutory authority of the Attorney General to represent the State.

B. Defendants

27. PURDUE PHARMA L.P. is a limited partnership organized under the laws of Delaware. PURDUE PHARMA INC. is a New York corporation with its principal place of business in Stamford, Connecticut, and THE PURDUE FREDERICK COMPANY, INC. is a

Delaware corporation with its principal place of business in Stamford, Connecticut (collectively, "Purdue").

28. Purdue is primarily engaged in the manufacture, promotion, and distribution of opioids nationally and in Mississippi, including the following:

(a) OxyContin (oxycodone hydrochloride extended release) is a Schedule II opioid agonist[15] tablet first approved 1995 and indicated for the "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." Prior to April 2014,[16] OxyContin was indicated for the "management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."

(b) MS Contin (morphine sulfate extended release) is a Schedule II opioid agonist tablet first approved in 1987 and indicated for the "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." Prior to April 2014, MS Contin was indicated for the "management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."

(c) Dilaudid (hydromorphone hydrochloride) is a Schedule II opioid agonist first approved in 1984 (injection) and 1992 (oral solution and tablet) and indicated for the "management of pain in patients where an opioid analgesic is appropriate."

(d) Dilaudid-HP (hydromorphone hydrochloride) is a Schedule II opioid agonist injection first approved in 1984 and indicated for the "relief of moderate-to-severe pain in opioid-tolerant patients who require larger than usual doses of opioids to provide adequate pain relief."

[15] An opioid agonist is a drug that activates the opioid receptors in the brain, typically the mu-opioid receptor.

[16] The labels for OxyContin and other long-acting opioids were amended in response to a 2012 citizen's petition by doctors. The changes were intended to clarify the existing obligation to "make an individualized assessment of patient needs." The doctors also successfully urged that the revised labels heighten the requirements for boxed label warnings related to addiction, abuse, and misuse by changing "Monitor for signs of misuse, abuse, and addiction" to "[Drug name] exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death." Letter from Bob Rappaport, Dir. Ctr. for Drug Evaluations & Res., *Labeling Supplement and PMR [Post-Marketing Research] Required* (Sept. 10, 2013), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf.

(e) Butrans (buprenorphine) is a Schedule III opioid partial agonist transdermal patch first approved in 2010 and indicated for the "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." Prior to April 2014, Butrans was indicated for the "management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."

(f) Hysingla ER (hydrocodone bitrate) is a Schedule II opioid agonist tablet first approved in 2014 and indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

(g) Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride) is a Schedule II combination product of oxycodone, an opioid agonist, and naloxone, an opioid antagonist, first approved in 2014 and indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

29. OxyContin is Purdue's largest selling opioid, in both Mississippi and the nation. Since 2009, Purdue's national annual sales of OxyContin have fluctuated between $2.47 billion and $2.99 billion, up four-fold from its 2006 sales of $800 million. OxyContin constitutes roughly 30% of the entire market for analgesic drugs (painkillers).

30. In 2007, Purdue settled criminal and civil charges against it for misbranding OxyContin and agreed to pay the United States $635 million – at the time, one of the largest settlements with a drug company for marketing misconduct. Pursuant to its settlement, Purdue operated under a Corporate Integrity Agreement with the Office of Inspector General of the U.S. Department of Health and Human Services and 26 states, including Mississippi, and the District of Columbia, which required the company, *inter alia*, to ensure that its marketing was fair and accurate, and to monitor and report on its compliance with the Agreement.

31. CEPHALON, INC. is a Delaware corporation with its principal place of business in Frazer, Pennsylvania. In 2011, Teva, Ltd. acquired Cephalon, Inc.

32. TEVA PHARMACEUTICALS USA, INC. ("Teva USA") is a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd., an Israeli corporation. Teva USA is a Delaware corporation with its principal place of business in Pennsylvania.

33. Teva USA and Cephalon, Inc. work together closely to market and sell Cephalon products in the United States. Teva USA conducts Teva Ltd.'s sales and marketing activities for Cephalon in the United States through Teva USA and has done so since its October 2011 acquisition of Cephalon. Teva USA holds out Actiq and Fentora as Teva products to the public. Teva USA sells all former Cephalon branded products through its "specialty medicines" division. The FDA approved prescribing information and medication guide, which is distributed with Cephalon products marketed and sold in Mississippi, discloses that the guide was submitted by Teva USA, and directs physicians to contact Teva USA to report adverse events. (Teva USA and Cephalon, Inc. collectively are referred to herein as "Cephalon.")

34. Cephalon has been in the business of manufacturing, selling and distributing the following opioids, nationally and in Mississippi:

(a) Actiq (fentanyl citrate) is a Schedule II opioid agonist lozenge (lollipop) first approved in 1998 and indicated for the "management of breakthrough cancer pain in patients 16 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain."[17]

(b) Fentora (fentanyl citrate) is a Schedule II opioid agonist buccal tablet (similar to plugs of smokeless tobacco) first approved in 2006 and indicated for the "management of breakthrough pain in cancer patients 18 years of age and older who already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain."

[17] Breakthrough pain is a short-term flare of moderate-to-severe pain in patients with otherwise stable persistent pain.

35. In November 1998, the FDA granted restricted marketing approval for Actiq, limiting its lawful promotion to cancer patients experiencing pain. The FDA specified that Actiq should be prescribed solely to cancer patients. In 2008, Cephalon pled guilty to a criminal violation of the Federal Food, Drug and Cosmetic Act for its misleading promotion of Actiq and two other drugs and agreed to pay $425 million.

36. Teva USA is also in the business of selling generic opioids, nationally and in Mississippi, including a generic form of Oxycontin from 2005 through 2009.

37. On September 29, 2008, Cephalon entered into a five-year corporate integrity agreement with the Office of Inspector General of the U.S. Department of Health and Human Services. The agreement, *inter alia*, required Cephalon to send doctors a letter advising them of the settlement terms and giving them a means to report questionable conduct of its sales representatives; to disclose payments to doctors on its web site; and to regularly certify that the company has an effective compliance program.

38. JANSSEN PHARMACEUTICALS, INC. is a Pennsylvania corporation with its principal place of business in Titusville, New Jersey, and is a wholly owned subsidiary of JOHNSON & JOHNSON, a New Jersey corporation with its principal place of business in New Brunswick, New Jersey. Janssen Pharmaceuticals, Inc. was formerly known as Ortho-McNeil-Janssen Pharmaceuticals, Inc., which in turn, was formerly known as Janssen Pharmaceutica Inc. Defendant ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., now known as Janssen Pharmaceuticals, Inc., is a Pennsylvania corporation with its principal place of business in Titusville, New Jersey. JANSSEN PHARMACEUTICA, INC., now known as Janssen Pharmaceuticals, Inc., is a Pennsylvania corporation with its principal place of business in Titusville, New Jersey. Johnson & Johnson is the only company that owns more than 10% of

Janssen Pharmaceuticals' stock, and it corresponds with the FDA regarding Janssen's products. Upon information and belief, Johnson & Johnson controls the sale and development of Janssen Pharmaceutical's drugs and Janssen Pharmaceuticals' profits inure to Johnson & Johnson's benefit. (Janssen Pharmaceuticals, Inc., Ortho-McNeil-Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica, Inc., and Johnson & Johnson, collectively are referred to herein as "Janssen.")

39. Janssen manufactures, sells, and distributes a range of medical devices and pharmaceutical drugs in Mississippi and the rest of the nation, including Duragesic (fentanyl), which is a Schedule II opioid agonist transdermal patch first approved in 1990 and indicated for the "management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."

40. Until January 2015, when Depomed, Inc. acquired the rights to Nucynta and Nucynta ER for $1.05 billion from Janssen pursuant an Asset Purchase Agreement, Janssen developed, marketed, and sold Nucynta and Nucynta ER:

(a) Nucynta ER (tapentadol extended release) is a Schedule II opioid agonist tablet first approved in 2011 and indicated for the "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." Prior to April 2014, Nucynta ER was indicated for the "management of moderate to severe chronic pain in adults [and] neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults." The DPN indication was added in August 2012.

(b) Nucynta (tapentadol) is a Schedule II opioid agonist tablet and oral solution first approved in 2008 and indicated for the "relief of moderate to severe acute pain in patients 18 years of age or older."

41. Together, Nucynta and Nucynta ER accounted for $172 million in sales in 2014. Prior to 2009, Duragesic accounted for at least $1 billion in annual sales.

42. Prior to 2016, Janssen also had a global Active Pharmaceutical Ingredients (API) Manufacturing Network for opiate analgesics and antagonists and was among the largest narcotic API suppliers in the United States. Tasmanian Alkaloids created, manufactured, and patented a new, more potent strand of poppy (high thebaine) and delivered it via intercompany transfer to Noramco. Part of the J&J Family of Companies, Noramco and Tasmanian Alkaloids are "sister companies"[18] operating in a backward integration model to control the supply chain of opioid materials for production of "high-purity controlled substances." Noramco's product portfolio included Oxycodone (Oxycontin, Percocet, Roxicodone), and Hydrocodone (Vicodin, Lortab), Morphine (MS Contin, Embeda), in addition to Naloxone (Narcan, Exalgo) for overdose and abuse. Noramco supplied Cephalon, Endo, Purdue, Actavis, and Mallinckrodt. In 2015, 80% of Noramco's sales were via long-term supply agreements and/or majority controlled substance share with all seven of the top U.S. generic companies. Noramco steadily gained U.S. market share and capitalized on key brand-to-generic switches.

43. ENDO HEALTH SOLUTIONS INC. is a Delaware corporation with its principal place of business in Malvern, Pennsylvania. ENDO PHARMACEUTICALS, INC. is a wholly-owned subsidiary of Endo Health Solutions, Inc. and is a Delaware corporation with its principal place of business in Malvern, Pennsylvania. (Endo Health Solutions, Inc. and Endo Pharmaceuticals, Inc. collectively are referred to herein as "Endo.")

44. Endo develops, markets, and sells prescription drugs, including the following opioids, in Mississippi and nationally:

(a) Opana ER (oxymorphone hydrochloride extended release) is a Schedule II opioid agonist tablet first approved in 2006 and indicated for the "management of pain severe enough to require daily, around-the-clock,

[18] https://www.noramco.com/our-capabilities/ (Last visited: Aug. 15, 2019).

long-term opioid treatment and for which alternative treatment options are inadequate." Prior to April 2014, Opana ER was indicated for the "relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time."

(b) Opana (oxymorphone hydrochloride) is a Schedule II opioid agonist tablet first approved in 2006 and indicated for the "relief of moderate to severe acute pain where the use of an opioid is appropriate."

(c) Percodan (oxycodone hydrochloride and aspirin) is a Schedule II opioid agonist tablet first approved in 1950 and first marketed by Endo in 2004 and indicated for the "management of moderate to moderately severe pain."

(d) Percocet (oxycodone hydrochloride and acetaminophen) is a Schedule II opioid agonist tablet first approved in 1999 and first marketed by Endo in 2006 and indicated for the "relief of moderate to moderately severe pain."[19]

45. Opioids made up roughly $403 million of Endo's overall revenues of $3 billion in 2012. Opana yielded revenue of $1.16 billion from 2008 and 2012, and it alone accounted for 10% of Endo's total revenue in 2012. Endo also manufactures and sells generic opioids, nationally and in Mississippi, both itself and through its subsidiary, Qualitest Pharmaceuticals, Inc., including generic oxycodone, oxymorphone, hydromorphone, and hydrocodone products.

46. ALLERGAN PLC is a public limited company incorporated in Ireland with its principal place of business in Dublin, Ireland. ACTAVIS PLC acquired ALLERGAN PLC in March 2015, and the combined company changed its name to ALLERGAN PLC in March 2015. Prior to that, WATSON PHARMACEUTICALS, INC. acquired Actavis, Inc. in October 2012; the combined company changed its name to Actavis, Inc. as of January 2013 and then to Actavis plc in October 2013. WATSON LABORATORIES, INC. is a Nevada corporation with its

[19] In addition, Endo marketed Zydone (hydrocodone bitartrate and acetaminophen), a Schedule III opioid agonist tablet indicated for the "relief of moderate to moderately severe pain," from 1998 through 2013. The FDA's website indicates this product is currently discontinued, but it appears on Endo's own website.

principal place of business in Corona, California, and is a wholly owned subsidiary of ALLERGAN PLC (f/k/a Actavis, Inc., f/k/a Watson Pharmaceuticals, Inc.). ACTAVIS PHARMA, INC. (f/k/a Actavis, Inc.) is a Delaware corporation with its principal place of business in New Jersey, and was formerly known as WATSON PHARMA, INC. ACTAVIS LLC is a Delaware limited liability company with its principal place of business in Parsippany, New Jersey. Each of these defendants is owned by Allergan plc, which uses them to market and sell its drugs in the United States. Upon information and belief, Allergan plc exercises control over these marketing and sales efforts, and profits from the sale of Allergan/Actavis products ultimately inure to its benefit. (Allergan plc, Actavis plc, Actavis, Inc., Actavis LLC, Actavis Pharma, Inc., Watson Pharmaceuticals, Inc., Watson Pharma, Inc., and Watson Laboratories, Inc. hereinafter collectively are referred to as "Actavis.")

47. Actavis engages in the business of marketing and selling opioids in Mississippi and across the country, including the branded drugs Kadian and Norco, a generic version of Kadian, and generic versions of Duragesic and Opana. Kadian (morphine sulfate extended release) is a Schedule II opioid agonist capsule first approved in 1996 and indicated for the "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." Prior to April 2014, Kadian was indicated for the "management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time." Actavis acquired the rights to Kadian from King Pharmaceuticals, Inc. on December 30, 2008, and began marketing Kadian in 2009.

48. MALLINCKRODT LLC is a limited liability company organized and existing

under the laws of the State of Delaware. SPECGX LLC is a Delaware limited liability company with its headquarters in Clayton, Missouri. Mallinckrodt LLC and SpecGx LLC are wholly-owned subsidiaries of Mallinckrodt plc. Mallinckrodt LLC and SpecGx LLC, together with their registrant and licensee subsidiaries and affiliates (collectively, "Mallinckrodt"), manufacture, market, sell, and distribute pharmaceutical drugs throughout the United States, and in Mississippi. Mallinckrodt is the largest U.S. supplier of opioid pain medications and among the top ten generic pharmaceutical manufacturers in the United States based on prescriptions.

49. Mallinckrodt manufactures and markets two branded opioids: Exalgo, which is extended-release hydromorphone, sold in 8, 12, 16, and 32 mg dosage strengths, and Roxicodone, which is oxycodone, sold in 15 and 30 mg dosage strengths. In 2009, Mallinckrodt Inc., a subsidiary of Covidien plc, acquired the U.S. rights to Exalgo. Exalgo was approved for the treatment of chronic pain in 2012. Mallinckrodt further expanded its branded opioid portfolio in 2012 by purchasing Roxicodone from Xanodyne Pharmaceuticals. In addition, Mallinckrodt developed Xartemis XR, an extended-release combination of oxycodone and acetaminophen, which the FDA approved in March 2014, and which Mallinckrodt has since discontinued. Mallinckrodt promoted its branded opioid products with its own direct sales force.

50. While it has sought to develop its branded opioid products, Mallinckrodt has long been a leading manufacturer of generic opioids. Mallinckrodt estimated, based on IMS Health data for 2015, that its generics claimed an approximately 23% market share of DEA Schedules II and III opioid and oral solid dose medications.[20]

[20] Mallinckrodt plc 2016, Annual Report (Form 10-K), at 5 (Nov. 29, 2016), https://www.sec.gov/Archives/edgar/data/1567892/000156789216000098/0001567892-16-000098-index.htm.

51. Mallinckrodt operates a vertically integrated business in the United States: (1) importing raw opioid materials, (2) manufacturing generic opioid products, primarily at its facility in Hobart, New York, and (3) marketing and selling its products to drug distributors, specialty pharmaceutical distributors, retail pharmacy chains, pharmaceutical benefit managers that have mail-order pharmacies, and hospital buying groups.

52. Among the drugs Mallinckrodt manufactures or has manufactured are the following:

Product Name	**Chemical Name**
Exalgo	Hydromorphone hydrochloride, extended release
Roxicodone	Oxycodone hydrochloride
Xartemis XR	Oxycodone hydrochloride and acetaminophen
Methadose	Methadone hydrochloride
Generic	Morphine sulfate, extended release
Generic	Morphine sulfate oral solution
Generic	Fentanyl transdermal system
Generic	Oral transmucosal fentanyl citrate
Generic	Oxycodone and acetaminophen
Generic	Hydrocodone bitartrate and acetaminophen
Generic	Hydromorphone hydrochloride
Generic	Hydromorphone hydrochloride, extended release
Generic	Naltrexone hydrochloride
Generic	Oxymorphone hydrochloride
Generic	Methadone hydrochloride

Product Name	**Chemical Name**
Generic	Oxycodone hydrochloride
Generic	Buprenorphine and naloxone

53. Mallinckrodt made thousands of payments to physicians nationwide, ostensibly for activities including participating on speakers' bureaus, providing consulting services, assisting in post-marketing safety surveillance, and other services. In fact, these payments were made to deceptively promote and maximize the use of opioids.

54. Notably, in 2017, the Department of Justice fined Mallinckrodt $35 million for failing to report suspicious orders of controlled substances, including opioids, and for violating recordkeeping requirements.

55. At times relevant herein, each of the Defendants acted in concert with or conspired with one or more of the remaining defendants in committing the violations of law alleged herein. Each of the Defendants was the agent, employee or principal of each of the remaining Defendants and was acting within the course and scope of his or her agency and/or employment.

IV. FACTUAL ALLEGATIONS

A. The Science Behind Pain Medicine

1. Safe and effective treatment of chronic pain hinges on informed risk management.

56. The practice of medicine hinges on informed risk management. Prescribers must weigh the potential risks and benefits of each treatment option, as well as the risk of non-treatment. Accordingly, the safe and effective treatment of chronic pain requires that a physician

be able to weigh the relative risk of prescribing opioids against the relative benefits that may be expected during the course of treatment against the risks and benefits of alternatives.

57. This bedrock principle of full disclosure is particularly important in the context of chronic opioid therapy because of the risk that patients who use the drugs long-term will develop tolerance, thus requiring increasingly higher doses. At higher doses, opioids pose even greater risks and adverse effects; patients become physically and psychologically dependent on the drugs and find it difficult to manage or terminate their use.

58. A recent report released by pharmacy benefits manager Express Scripts found, after analyzing pharmacy claims of 6.8 million Americans who filled at least one prescription for an opioid between 2009 and 2013, that nearly half the people who took opioids for over 30 days were still using them three years later.[21] As another illustration, when MedPage Today followed up on seven individuals who had been profiled in a 1998 Purdue video distributed to 15,000 doctors to show how OxyContin had improved their lives, it was able to locate five of them. Of those five, three of them became addicted to the drug and/or other narcotic painkillers; one of them eventually fell asleep at the wheel while driving and died, another experienced excruciating withdrawal symptoms, and another was found dead of an overdose.[22]

59. The FDA-approved drug labels on each of Defendants' opioids do not attempt to advise physicians how to maximize the benefit and minimize risk for patients on long-term chronic opioid therapy. The labels contain no dosing cap above which it would be unsafe for any doctor to prescribe to any patient. Nor do any of the labels provide a duration limit, after which

[21] Express Scripts Lab, *A Nation in Pain: Focusing on U.S. Opioid Trends for Treatment of Short-Term and Longer-Term Pain* (Dec. 2014), *available at:* http://lab.express-scripts.com/publications/~/media/d48ef3ee579848e7bf3f14af536d7548.ashx.

[22] *See* https://vimeo.com/124857553.

the risks to a patient might change. Thus, doctors and patients rely more heavily on "educational" materials, such as treatment guidelines, CMEs, scientific and patient education articles, and websites, to inform their treatment decisions.

2. Known and substantial risks associated with the use of opioids.

60. The pain-relieving properties of opium have been recognized for millennia. So has the magnitude of its potential for abuse and addiction. Opioids, after all, are closely related to illegal drugs like opium and heroin.[23] During the Civil War, opioids, then known as "tinctures of laudanum," gained popularity among doctors and pharmacists for their ability to reduce anxiety and relieve pain – particularly on the battlefield – and they were popularly used in a wide variety of commercial products ranging from pain elixirs to cough suppressants to beverages. By 1900, an estimated 300,000 people were addicted to opioids in the United States,[24] and many doctors prescribed opioids solely to avoid patients' withdrawal. Both the numbers of opioid addicts and the difficulty in weaning patients from opioids made clear their highly addictive nature.

61. Minimizing addiction is a priority in the State of Mississippi. For that reason, since 2005 the State has participated in a Prescription Monitoring Program that collects prescription records and, where necessary, provides information to law enforcement. One of the stated purposes of the program is to facilitate and encourage the identification, intervention with

[23] *See* Jane Ballantyne & Jianren Mao, *Opioid Therapy for Chronic Pain*, 349 New Eng. J. Med. 1943-53 (2003).

[24] Substance Abuse and Mental Health Services Administration, *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs*, Treatment Improvement Protocol (TIP Series), No. 43 (2005), *available at*: http://www.ncbi.nlm.nih.gov/books/NBK64164/pdf/TOC.pdf.

and treatment of individuals addicted to controlled substances.[25] Mississippi law requires the Mississippi Bureau of Drug Enforcement and state board of education carry out educational programs designed to prevent and deter misuse and abuse of controlled substances,[26] and requires the Bureau of Narcotics, the State Board of Pharmacy, the State Board of Medical Licensure, the State Board of Dental Examiners, the Board of Nursing and the State Board of Optometry to "encourage research on misuse and abuse of controlled substances."[27]

62. Due to concerns about their addictive qualities, opioids have been regulated as controlled substances by the U.S. Drug Enforcement Administration ("DEA") since 1970. The labels for scheduled opioid drugs carry black box warnings of potential addiction and "[s]erious, life-threatening, or fatal respiratory depression," as a result of an excessive dose.

63. Most patients receiving more than a few weeks of opioid therapy will experience withdrawal symptoms if opioids are discontinued (commonly referred to as "dependence").[28] Once dependent, a patient experiences deeply unpleasant symptoms when his or her current dose of opioids loses effect and is not promptly replaced with a new dose. Among the symptoms reported in connection with opioid withdrawal are severe anxiety, nausea, vomiting, headaches, agitation, insomnia, tremors, hallucinations, delirium, pain, and other serious symptoms, which may persist for months, or even years, after a complete withdrawal from opioids, depending on how long opioids were used.[29]

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[25] *See* MISS. CODE § 73-21-127(d).

[26] MISS. CODE § 41-29-169.

[27] *Id.* § 41-29-171.

[28] Richard A. Deyo, *et al*., Opioids for Back Pain Patients: Primary Care Prescribing Patterns and Use of Services, 24 J. Am. Bd. Of Fam. Prac. 725 (2011).

[29] See Jane Ballantyne, New Addiction Criteria: Diagnostic Challenges Persist in Treating Pain With Opioids, 21(5) Pain Clinical Updates (Dec. 2013).

64. Dr. Andrew Kolodny, Chief Medical Officer for Phoenix House, a national addiction treatment program, has explained the effect of opioids as akin to "hijacking the brain's reward system," which in turn convinces a user that "the drug is needed to stay alive."[30] A patient's fear of the unpleasant effects of discontinuing opioids combined with the negative reinforcement during a period of actual withdrawal can drive a patient to seek further opioid treatment – even where ineffective or detrimental to quality of life – simply to avoid the deeply unpleasant effects of withdrawal.[31]

65. When under the continuous influence of opioids over a period of time, patients grow tolerant to their analgesic effects. As tolerance increases, a patient typically requires progressively higher doses in order to obtain the same levels of pain reduction he or she has become accustomed to – up to and including dosage amounts that are considered by many physicians to be "frighteningly high."[32] At higher doses, the effects of withdrawal are more substantial, leaving a patient at a much higher risk of addiction. The FDA has acknowledged that available data suggests a relationship between increased doses and the risk of adverse effects.[33]

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[30] David Montero, *Actor's Death Sows Doubt Among O.C.'s Recovering Opioid Addicts*, The Orange Cnty. Regi. (Feb. 3, 2014), http://www.ocregister.com/articles/heroin-600148-shaffer-hoffman.html.

[31] *See* Mary Jeanne Kreek, *et al.*, *Pharmacotherapy of Addictions*, 1(9) Nature Reviews: Drug Discovery 710-26 (Sept. 2002) (Describing counter-adaptive drug-induced changes that prompt "continued drug use through negative reinforcement mechanisms."); Ballantyne, *New Addiction Criteria*, *supra*.

[32] Mitchell H. Katz, *Long-term Opioid Treatment of Nonmalignant Pain: A Believer Loses His Faith*, 170(16) Archives of Internal Med., 1422-1424 (Sept. 13, 2010).

[33] Letter from Janet Woodcock, M.D., Dir., Ctr. for Drug Eval. & Res., to Andrew Kolodny, M.D., Pres. Physicians for Responsible Opioid Prescribing, Re Docket No. FDA-2012-P-0818 (Sept. 10, 2013); *see also* Laxmaiah Manchikanti, *et al.*, *American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part I – Evidence Assessment*, 15 Pain Physician S1-S66 (2012).

66. Patients receiving high doses of opioids as part of long-term opioid therapy are three to nine times more likely to suffer overdose from opioid-related causes than those on low doses.[34] As compared to available alternative pain remedies, scholars have suggested that tolerance to the respiratory depressive effects of opioids develops at a slower rate than tolerance to opioids' analgesic effects. Accordingly, the practice of continuously escalating dosages to match pain tolerance can, in fact, lead to overdose even where opioids are taken as recommended.[35]

67. Further, "a potential side effect from chronic use [of opioids] can be abuse and addiction.… [I]n fact, correct use and abuse of these agents are not polar opposites – they are complex, inter-related phenomena."[36] It is very difficult to tell whether a patient is physically dependent, psychologically dependent, or addicted. Drug-seeking behaviors, which are signs of addiction, will exist and emerge when opioids are suddenly not available, the dose is no longer effective, or tapering of a dose is undertaken too quickly.[37]

68. Studies have shown that between 30% and 40% of long-term users of opioids experience problems with opioid use disorders.[38]

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[34] Kate M. Dunn, *et al.*, *Opioid prescriptions for chronic pain and overdose: a cohort study*, 152(2) Annals of Internal Med., 85-92 (Jan. 19, 2010). Most overdoses were medically serious and 12% were fatal.

[35] *See* Laxmaiah Manchikanti, *et al.*, *Opioid Epidemic in the United States*, 15 Pain Physician ES9-ES38 (2012) (60% of opioid overdoses prescribed within guidelines).

[36] Wilson M. Compton & Nora D. Volkow, *Major Increases in Opioid Analgesic Abuse in the United States: Concerns and Strategies*, 81(2) Drug & Alcohol Dependence 103, 106 (Feb. 1, 2006).

[37] Jane Ballantyne, Opioid Dependence vs. Addiction: A Distinction without a Difference?, Archives of Internal Med. (Aug. 13, 2012).

[38] Joseph A. Boscarino, *et al.*, Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system, 105(10) Addiction 1776-82 (Oct. 2010); Joseph A. Boscarino, *et al.*, Prevalence of Prescription Opioid-Use Disorder Among Chronic Pain Patients:

69. Each of these risks and adverse effects – dependence, tolerance, and addiction – is fully disclosed in the labels for each of Defendants' opioids (though, as described below, not in Defendants' marketing).[39] Prior to Defendants' deceptive marketing scheme, each of these risks was well recognized by doctors and seen as a reason to use opioids to treat chronic pain sparingly and only after other treatments had failed.

70. Opioids vary by duration. Long-acting opioids are designed to be taken once or twice daily and provide continuous opioid therapy for, in general, twelve hours. Purdue's OxyContin and MS Contin, Janssen's Nucynta ER and Duragesic, Endo's Opana ER, and Actavis' Kadian are all examples of long-acting opioids. In addition, opioids may be taken in short-acting formulations, which last for approximately 4-6 hours. Short-acting opioids may be taken in addition to long-acting opioids to address "episodic pain." Cephalon's Actiq and Fentora are particularly fast-acting drugs that are explicitly indicated only for use in conjunction with continuous opioid therapy.

71. While it was once thought that long-acting opioids would not be as susceptible to abuse and addiction as short-acting ones, this view has been discredited. OxyContin's label now states, as do all labels of Schedule II long-acting opioids, that the drug "exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death." The FDA has required

Comparison of the DSM5 vs. DSM-4 Diagnostic Criteria, 30(3) Journal of Addictive Diseases 185-94 (July-Sept. 2011).

[39] For example, Purdue's OxyContin label (Oct. 5, 2011) states: "Physical dependence and tolerance are not unusual during chronic opioid therapy."

extended release and long-acting opioids to adopt "Risk Evaluation Mitigation Strateg[ies]" because they present "a serious public health crisis of addiction, overdose, and death."[40]

72. In 2013, in response to a petition to restrict the labels of long-acting opioid products, the FDA noted the "grave risks of opioids, the most well-known of which include addiction, overdose, and even death."[41] The FDA further warned that "[e]ven proper use of opioids under medical supervision can result in life-threatening respiratory depression, coma, and death."[42] The FDA required that – going forward – makers of long-acting opioid formulations clearly communicate these risks in their labels (defined, as noted in Section IV.C.1, to include promotional materials disseminated by or on behalf of the manufacturer of the drug). Thus, the FDA confirmed what had previously been accepted practice in the treatment of pain – that the adverse outcomes from opioid use include "addiction, unintentional overdose, and death" and that long-acting or extended release opioids "should be used ***only when alternative treatments are inadequate***."[43]

73. Notably, in reaching its conclusion, the FDA did not rely on new or otherwise previously unavailable scientific studies regarding the properties or effects of opioids.

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[40] FDA, Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting Opioids (Aug. 2014), *available at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

[41] Letter from Janet Woodcock, M.D., Dir., Ctr. for Drug Eval. & Res., to Andrew Kolodny, M.D., Pres. Physicians for Responsible Opioid Prescribing, Re Docket No. FDA-2012-P-0818 (Sept. 10, 2013).

[42] *Id.*

[43] *Id.* (emphasis in original).

3. The "benefits" offered by long-term continuous opioid use are unproven and contradicted.

74. Despite the fact that opioids are routinely prescribed, there never has been evidence of their efficacy for long-term use. Defendants always have been aware of these gaps in knowledge. While promoting opioids to treat chronic pain, Defendants have failed to disclose the lack of evidence to support their use long-term and have failed to disclose the contradictory evidence that chronic opioid therapy actually makes patients sicker.

75. There are no controlled studies of the use of opioids beyond 16 weeks, and no evidence that opioids improve patients' pain and function long-term.[44] The first random, placebo-controlled studies appeared in the 1990s and revealed evidence only for short-term efficacy and only in a minority of patients.[45] A 2004 study reviewed 213 randomized, controlled trials of treatments for cancer pain and found that, while opioids had short-term efficacy, the data was insufficient to establish long-term effectiveness. Subsequent reviews of the use of opioids for cancer and non-cancer pain consistently note the lack of data to assess long-term outcomes. For example, a 2007 systematic review of opioids for back pain concluded that opioids have limited, if any, efficacy for back pain and that evidence did not allow judgments regarding long-term use. Similarly, a 2011 systematic review of studies for non-cancer pain found that evidence of long-term efficacy is poor. One year later, a similar review reported poor evidence of long-term efficacy for morphine, tramadol, and oxycodone, and fair evidence for transdermal fentanyl (approved only for use for cancer pain).

[44] Id.; The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain, Agency for Healthcare Res. & Quality (Sept. 19, 2014).

[45] Nathaniel Katz, Opioids: After Thousands of Years, Still Getting to Know You, 23(4) Clin. J. Pain 303, 306 (2007); Roger Chou, *et al*., Research Gaps on Use of Opioids for Chronic Noncancer Pain, 10(2) J. Pain 147-159 (2009).

76. On the contrary, evidence exists to show that opioid drugs are not effective to treat chronic pain, and may worsen a patients' health. A 2006 study of studies found that opioids as a class did not demonstrate improvement in functional outcomes over other non-addicting treatments.[46] Most notably, it stated: "For functional outcomes, the other analgesics were significantly more effective than were opioids."[47] Another review of evidence relating to the use of opioids for chronic pain found that a review of evidence relating to the use of opioids for chronic pain found that up to 22.9% of patients in opioid trials dropped out before the study began because of the intolerable effects of opioids and that the evidence of pain relief over time was weak.[48]

77. Endo's own research shows that patients taking opioids, as opposed to other prescription pain medicines, report higher rates of obesity (30% to 39%); insomnia (9% to 22%); and self-described fair or poor health (24% to 34%).

78. Increasing duration of opioid use is strongly associated with an increasing prevalence of mental health conditions (depression, anxiety, posttraumatic stress disorder, or substance abuse), increased psychological distress, and greater health care utilization.[49]

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[46] Andrea D. Furlan, Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects, 174(11) Can. Med. Ass'n J. 1589-1594 (2006).

[47] *Id*. This same study revealed that efficacy studies do not typically include data on opioid addiction. In many cases, patients who may be more prone to addiction are pre-screened out of the study pool. This does not reflect how doctors actually prescribe the drugs, because even patients who have past or active substance use disorders tend to receive higher doses of opioids. Karen H. Seal, *Association of Mental Health Disorders With Prescription Opioids and High-Risk Opioids in US Veterans of Iraq and Afghanistan*, 307(9) J. Am. Med. Ass'n 940-47 (2012).

[48] Meredith Noble, *et al*., *Long-term opioid management for chronic noncancer pain (Review)*, 1 Cochrane Database of Systematic Reviews (2010).

[49] Richard A. Deyo, *et al*., Opioids for Back Pain Patients: Primary Care Prescribing Patterns and Use of Services, 24 J. Am. Bd. Of Fam. Prac. 717-27 (2011).

79. As a pain specialist noted in an article titled, *Are We Making Pain Patients Worse?*, "opioids may work acceptably well for a while, but over the long term, function generally declines, as does general health, mental health, and social functioning. Over time, even high doses of potent opioids often fail to control pain, and these patients are unable to function normally."[50]

80. This is true both generally and for specific pain-related conditions. Studies of the use of opioids long-term for chronic lower back pain have been unable to demonstrate an improvement in patients' function.[51] Instead, research consistently shows that long-term opioid therapy for patients who have lower back injuries does not enable patients to return to work or physical activity. This is due partly to addiction and other side effects.[52]

81. As many as 30% of patients who suffer from migraines have been prescribed opioids to treat their headaches.[53] Users of opioids had the highest increase in the number of headache days per month, scored significantly higher on the Migraine Disability Assessment (MIDAS), and had higher rates of depression compared to non-opioid users.[54] A survey by the National Headache Foundation found that migraine patients who used opioids were more likely

[50] Andrea Rubenstein, *Are we making pain patients worse?*, Sonoma Medicine (Fall 2009).

[51] Luis E. Chaparro, *et al*., *Opioids Compared to Placebo or Other Treatments for Chronic Low-Back Pain*, 8 Cochrane Database of Systematic Reviews (Aug. 27, 2013).

[52] Jeffrey Dersh, *et al*., Prescription opioid dependence is associated with poorer outcomes in disabling spinal disorders, 33(20) Spine 2219-27 (Sept. 15, 2008).

[53] Dawn C. Buse, Opioid Use and Dependence Among Persons With Migraine: Results of the AMPP Study, 52 Headache: The J. of Head & Face Pain 18-36 (Jan. 2012).

[54] *News Briefs – Opioid Treatment of Migraine is Associated with Multiple Risks*, Nat'l Headache Found (June 2012), *available at* http://www.headaches.org/sites/default/files/uploaded_files/News_to_Know1/pdf2/NHF_News_to_Know _June_20121.pdf.

to experience sleepiness, confusion, and rebound headaches, and reported a lower quality of life than patients taking other medications.[55]

82. The lack of evidence for the efficacy of long-term opioid use has been well-documented in the context of workers' compensation claims, where some of the most detailed data exists. Claims involving workers who take opioids are almost four times more likely to reach costs of over $100,000 than claims involving workers who do not take opioids because opioid patients suffer greater side effects and are slower to return to work.[56] Even adjusting for injury severity and self-reported pain score, receiving an opioid for more than seven days and receiving more than one opioid prescription increased the risk that a patient will be on work disability one year later.[57] A prescription for opioids as the first treatment for a workplace injury doubled the average length of the claim.[58]

4. Defendants' impact on the perception and prescribing of opioids.

83. Before Defendants began their marketing campaign, generally accepted standards of medical practice dictated that opioids should only be used short-term, for instance, for acute pain, pain relating to recovery from surgery, or for cancer or palliative care. In those instances, the risks of addiction are low or of little significance.

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[55] *Press Kits – Migraine Patients Taking Addictive Or Non Approved FDA Migraine Treatment*, Nat'l Headache Found (May 15, 2007), *available at* http://www.headaches.org/press/NHF Press_Kits/Press Press_Kits/Press_Kits_ _Migraine_Patients_Taking_Addictive_Or_Non_Approved_FDA_Migraine_ Treatments.

[56] Jeffrey A. White, *et al*., The Effect of Opioid Use on Workers' Compensation Claim Cost in the State of Michigan, 54(8) J. of Occupational & Environ. Med. 948-953 (2012).

[57] Gary M. Franklin, *et al*., Early Opioid Prescription and Subsequent Disability Among Workers with Back Injuries: The Disability Risk Identification Study Cohort, 33(2) Spine 199-204 (2008).

[58] Dongchun Wang, *et al*., *Longer-Term Use of Opioids*, Workers Comp. Res. Inst. (Oct. 2012).

84. In 1986, the World Health Organization ("WHO") published an "analgesic ladder" for the treatment of cancer pain. The WHO recommended treatment with over-the-counter or prescription acetaminophen or non-steroidal anti-inflammatory drugs ("NSAIDs") first, then use of unscheduled or combination opioids, and then stronger (Schedule II or III) opioids if pain persisted. The WHO ladder pertained only to the treatment of cancer pain, and did not contemplate the use of narcotic opioids for chronic pain – because the use of opioids for chronic pain was not considered appropriate medical practice at the time.

85. Studies and articles from the 1970s and 1980s made clear the reasons to avoid opioids.[59] Scientists observed negative outcomes from long-term opioid therapy in pain management programs: opioids' mixed record in reducing pain long-term and failure to improve patients' function; greater pain complaints as most patients developed tolerance to opioids; opioid patients' diminished ability to perform basic tasks; inability to make use of complementary treatments like physical therapy due to the side effects of opioids; and addiction. Leading authorities discouraged, or even prohibited, the use of opioid therapy for chronic non-cancer pain.[60]

86. For example, in 1986, Dr. Russell Portenoy, who later became Chairman of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York while at the same time serving as a top spokesperson for drug companies, published an article

[59] *See, e.g.*, Randal D. France, *et al*., *Long-term use of narcotic analgesics in chronic pain*, 19(12) Soc. Sci. Med. 1379 (1984); Maruta, T., *et al*., *Drug abuse and dependency in patients with chronic pain*, 54(4) Mayo Clinic Proc. 241 (1979); Judith A. Turner, *et al., Drug utilization pattern in chronic pain patients*, 12(4) Pain 357 (Apr. 1982); Scott L. McNairy, *et al., Prescription medication dependence and neuropsychologic function*, 18(2) Pain 169 (Feb. 1984).

[60] R.G. Black, *The clinical syndrome of chronic pain*, Pain, Discomfort & Humanitarian Care 207-209 (L.K.Y. Ng and J.J. Bonica eds. 1980). In addition, very few pharmacies routinely carried oral opioids. Russell K. Portenoy, *Opioid Therapy for Chronic Nonmalignant Pain*, 1 Progress in Pain Res. & Mgmt. 247-287 (H.L. Fields and J.C. Liebeskind eds. 1994).

reporting that "[f]ew substantial gains in employment or social function could be attributed to the institution of opioid therapy."[61]

87. Writing in 1994, Dr. Portenoy described the prevailing attitudes regarding the dangers from long-term use of opioids:

> The traditional approach to chronic nonmalignant pain does not accept the long-term administration of opioid drugs. This perspective has been justified by the perceived likelihood of tolerance, which would attenuate any beneficial effects over time, and the potential for side effects, worsening disability, and addiction. According to conventional thinking, the initial response to an opioid drug may appear favorable, with partial analgesia and salutary mood changes, but adverse effects inevitably occur thereafter. It is assumed that the motivation to improve function will cease as mental clouding occurs and the belief takes hold that the drug can, by itself, return the patient to a normal life. *Serious management problems are anticipated, including difficulty in discontinuing a problematic therapy and the development of drug seeking behavior induced by the desire to maintain analgesic effects, avoid withdrawal, and perpetuate reinforcing psychic effects. There is an implicit assumption that little separates these outcomes from the highly aberrant behaviors associated with addiction*.[62]

According to Portenoy, these could constitute "compelling reasons to reject long-term opioid administration as a therapeutic strategy in all but the most desperate cases of chronic nonmalignant pain."[63]

[61] Russell K. Portenoy & Kathleen M. Foley, Chronic Use of Opioid Analgesics in Non-Malignant Pain: Report of 38 cases, Pain. 171-186 (1986).

[62] Portenoy, Opioid Therapy for Chronic Nonmalignant Pain, supra (emphasis added).

[63] *Id*.

88. Thus, in the words of one researcher from the Harvard Medical School, "it did not enter [doctors'] minds that there could be a significant number of chronic pain patients who were successfully managed with opioids."[64] Defendants changed that.

B. Defendants' Plan to Change Prescriber Habits

1. Defendants are in the business of influencing prescriber habits and generating claims for payment.

89. Defendants are in the business of influencing prescriber and patient habits to generate prescriptions, claims for payment, and profits. That is the core of Defendants' sales functions and how they make money.

90. In 2012, the pharmaceutical industry spent more than $27 billion on drug promotion, the vast majority of which ($24 billion) was spent on marketing to physicians.[65] The sales force of every pharmaceutical company is a significant part of the company. Purdue currently has a 900-member sales force, which its website describes as having the role of "generating the sales that are the lifeblood of the company."[66] Indeed, even though it laid off approximately 9% of its work force on April 14, 2015, anticipating generic competition for OxyContin, it did not lay off any sales personnel, suggesting the importance of that sales force to Purdue's continued marketing of its pain medicine portfolio.[67]

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[64] Igor Kissin, *Long-Term Opioid Treatment of Chronic Nonmalignant Pain*, 6 J. Pain Research 513, 514 (2013) (quoting Loeser JD, *Five crises in pain management*, Pain Clinical Updates, 2012, 20(1):1-4)).

[65] PEW Charitable Trust Fact Sheet, *Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on Physicians and Patients* (Nov. 11, 2013), *available at*: http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients.

[66] *See* Business Unit Overviews, *available at*: http://www.purduepharma.com/business-unit-overviews.

[67] *See Purdue Pharma to Cut Nearly 300 Jobs in Connecticut, available at*: http://www.nytimes.com/2004/04/14/business/company-news-purdue-pharma-to-cut-nearly-300-jobs-in-connecticut.html.

91. Doctors are the gatekeepers for all prescription drugs so, not surprisingly, Defendants focused the bulk of their marketing efforts, and their multi-million dollar budgets, on the professional medical community. Particularly because of barriers to prescribing opioids, which are regulated as controlled substances, Defendants knew doctors would not treat patients complaining of common chronic pain with opioids unless doctors were persuaded that opioids had real benefits and minimal risks. Because Defendants were successful at doing so, Mississippi doctors began prescribing opioids long-term to treat chronic pain – something most would never have considered prior to Defendants' campaign.

92. Indeed, it is unusual for doctors to acknowledge having been swayed by a drug company's marketing. As learned professionals, they believe – genuinely – that they respond to scientific evidence, not other forms of persuasion. Nevertheless, numerous studies suggest that marketing can impact doctors' prescribing habits.[68]

93. Defendants would not spend billions of dollars on marketing to physicians if they did not believe that such efforts were successful in generating prescriptions. For that reason, they devote substantial resources to marketing their drugs to prescribers and patients and then meticulously tracking their return on that investment.

[68] Puneet Manchanda & Pradeep K. Chintagunta, *Responsiveness of Physician Prescription Behavior to Salesforce Effort: An Individual Level Analysis*, 15 Mktg. Letters 129 (2004) (detailing has a positive impact on prescriptions written); Ian Larkin, *Restrictions on Pharmaceutical Detailing Reduced Off-Label Prescribing of Antidepressants and Antipsychotics in Children*, 33 Health Affairs 1014 (June 2004) (finding academic medical centers that restricted direct promotion by pharmaceutical sales representatives resulted in a 34% decline in on-label use of promoted drugs); *see also* Art Van Zee, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99 Am J. Pub. Health 221 (2009) (correlating an increase of OxyContin prescriptions from 670,000 annually in 1997 to 6.2 million in 2002 to a doubling of its sales force and trebling of annual sales calls).

2. Defendants used their sales forces to sell opioids and recruit physician speakers.

94. Each Defendant promoted the use of opioids for chronic pain through "detailers" – sales representatives who visited individual physicians and their staff in their offices – and small group speaker programs. By establishing close relationships with doctors, Defendants' sales representatives were able to disseminate their misrepresentations in targeted, one-on-one settings that allowed them to differentiate their opioids and to address individual prescribers' concerns about prescribing opioids for chronic pain. Representatives were trained on techniques to build these relationships, with Actavis even rolling out an "Own the Nurse" kit as a "door opener" to time with doctors.

95. Defendants' sales representatives have visited hundreds of thousands of doctors, including thousands of visits to Mississippi prescribers, and as described herein, spread misinformation regarding the risks, benefits, and superiority of opioids for the treatment of chronic pain. This misinformation includes deceptive and unfair claims regarding the risks of opioids for chronic pain, particularly the risks of addiction, withdrawal, and high doses, as well as the benefits.

96. As described in more detail in Section IV.E below, each Defendant carefully trained its sales representatives to deliver company-approved messages designed to generate prescriptions of that company's drugs in particular and opioids in general. Pharmaceutical companies exactingly direct and monitor their sales representatives – through detailed action plans, trainings, tests, scripts, role-plays, supervisor tag-alongs, and other means – to ensure that individual detailers actually deliver the desired messages and do not veer off-script. Pharmaceutical companies likewise require their detailers to deploy sales aids reviewed, approved, and supplied by the company and forbid them to use, in industry parlance, "homemade

bread" – *i.e.*, promotional materials not approved by the company's marketing and compliance departments. Sales representatives' adherence to their corporate training typically is included in their work agreements. Departing from their company's approved messaging can and does lead to severe consequences, including termination of employment.

97. Besides carefully training their sales representatives, Defendants also used surveys of physicians – conducted by third-party research firms – to assess how well their core messages came across to prescribers. These "verbatim" recollections of detailers' messages are an integral tool in ensuring consistent message delivery. They also help Defendants gauge physicians' perceptions of, and willingness to prescribe, a particular Defendant's drugs.

98. In addition to making sales calls, Defendants' detailers also identified doctors to serve, for payment, on Defendants' speakers' bureaus and to attend programs with speakers and meals paid for by Defendants. Defendants almost always select physicians who are "product loyalists," since one question they will be asked is whether they prescribe the drug themselves. Endo, for instance, sought to use physicians – including high prescribers of its drugs – as local thought leaders to market Opana ER to primary care doctors. Such invitations are lucrative to the physicians selected for these bureaus; honorarium rates range from $800 to $2,000 per program, depending on the type of event, and even speaker training is typically compensated at $500/hour.

99. These speaker programs and associated speaker training serve three purposes: they provide an incentive to doctors to prescribe, or increase their prescriptions of, a particular drug; a forum in which to further market to the speaker him or herself; and an opportunity to market to the speaker's peers. Defendants grade their speakers, and future opportunities are based on speaking performance, post-program sales and product usage. Defendants also track

the prescribing of event attendees. It would make little sense for Defendants to devote significant resources to programs that did not increase their sales.

100. Like the sales representatives who select them, speakers are expected to stay "on message" – indeed, they agree in writing to follow the slide decks provided to them. This is important because the FDA regards promotional talks as part of product labeling, and requires their submission for review. Speakers thus give the appearance of providing independent, unbiased presentations on opioids, when in fact they are presenting a script prepared by Defendants' marketing departments. Although these meal-based speaker events are more expensive to host and typically have lower attendance than CMEs, they are subject to less professional scrutiny and thus afford Defendants greater freedom in the messages they present.

101. Defendants devoted massive resources to these direct sales contacts with prescribers. In 2014, Defendants collectively spent $168 million on detailing branded opioids to physicians nationwide. This figure includes $108 million spent by Purdue, $34 million by Janssen, $13 million by Cephalon, $10 million by Endo, and $2 million by Actavis. The total figure is more than double Defendants' collective spending on detailing in 2000.

3. Defendants are in the sole possession of proprietary data that shows how they directed their promotional efforts through detailed marketing plans.

102. In order to calibrate how to influence prescribers and monitor the effectiveness of their efforts, Defendants purchase, manipulate and analyze some of the most sophisticated data available in *any* industry, data available from IMS Health Holdings, Inc. ("IMS Health"), whose clients include "[a]ll of the top 100 global pharmaceutical and biotechnology companies."[69] As IMS Health reported in its most recent quarterly filing, it is "a leading global information and

[69] *See* Form S-1, IMS Health Holdings, Inc., filed Jan. 2, 2014.

technology services company providing clients in the healthcare industry with comprehensive solutions to measure and improve their performance" with "one of the largest and most comprehensive collections of healthcare information in the world, spanning sales, prescription and promotional data, medical claims, electronic medical records and social media."[70] Its dataset contains over 10 petabytes of unique data, and includes "over 85% of the world's prescriptions by sales value and approximately 400 million comprehensive, longitudinal, anonymous patient records."[71]

103. IMS data allows Defendants to track, precisely, the rates of initial prescribing and renewal by individual doctor, which in turn allows them to target, tailor, and monitor the impact of their appeals. Defendants relied on "influence mapping," *i.e.*, using decile rankings or similar breakdowns to identify the high-volume prescribers as to whom detailing would have the greatest sales impact. Endo, for example, identified prescribers representing 30% of its nationwide sales volume and planned to visit those physicians three times per month. Defendants also closely monitored doctors' prescribing after a sales representative's visit to allow them to refine their planning and messaging and to evaluate and compensate their detailers.

104. IMS data is expensive, proprietary and in the sole possession of Defendants. As IMS Health explained in its January 2, 2014 prospectus: "The breadth of the intelligent, actionable information we provide is not comprehensively available from any other source and would be difficult and costly for another party to replicate."[72]

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[70] *See* Form 10-Q, IMS Health Holdings, Inc., filed May 15, 2015.

[71] *See* Form S-1, IMS Health Holdings, Inc., filed Jan. 2, 2014.

[72] *See* Form S-1, IMS Health Holdings, Inc., filed Jan. 2, 2014.

105. Defendants use IMS Health data not only to analyze the effectiveness of their sales representatives, but also to measure the strength of the messages conveyed in the CMEs they sponsor, and talks given by KOLs and even determine the effectiveness of specific pieces of marketing literature.[73]

106. For example, Defendant Janssen began using SAS (Statistical Analysis System), a provider of business analytics software and services and the largest independent vendor in the "business intelligence market,"[74] to provide "predictive analysis" on the prescribing habits of physicians. SAS has developed "more complex and accurate propensity scoring models," showing which physicians are more likely to respond to certain sales techniques, including talks given by KOLs. Janssen is therefore able to "accurately predict which tactics – samples, vouchers, access to experts – will provide the greatest return for each specific product." [75]

107. To compile such models "requires a lot of data," including IMS sales data, census data, physician demographic information, call center activity, data on the distribution of samples, sales calls and other promotional activity and managed care data.[76] As Janssen's Senior Director of Sales Analytics explains: "so much of the value we get from SAS is through data manipulation."[77]

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[73] *See* Adriane Fugh-Berman, M.D., *Prescription Tracking and Public Health*, J. OF GEN. INTERN. MED., 1278-1280 (May 13, 2008) (Pharmaceutical companies use information tracking prescriptions "to allocate samples, to design continuing medical education programs and direct-to-consumer campaigns, and to evaluate the effects of specific promotions on sales.").

[74] *See* http://www.sas.com/en_us/company-information.html#stats.

[75] *See Millions in savings and smarter pharmaceutical marketing tactics*, *available at*: http://www.sas.com/en_us/customers/janssen-pharmaceuticals.html.

[76] *Id.*

[77] *Id.* Janssen's use of data to monitor physician prescribing habits, however, has not been limited to the time period of its relationship with SAS. The press release announcing the Janssen-SAS partnership explains that, prior to its formation, Janssen hired outside firms to, for example, develop physician "targeting lists" for product promotion.

108. Because Defendants' pervasive scheme affected literally every source of information on chronic opioid therapy to which Mississippi physicians had access, the State should not have to allege the names of specific doctors who received each of Defendants' marketing messages. Moreover, to make such a showing would require data from IMS Health and analyses created for Defendants by third parties such as SAS, which are in the sole possession of Defendants.

109. Further, there is no other legitimate or scientifically-accepted way to establish the effectiveness of Defendants' marketing mechanisms other than the measures used by Defendants themselves. It is well understood within the field of health care economics both that physicians are highly influenced by messages from pharmaceutical companies and, conversely, that they are unaware of that influence. Health care economics studies have repeatedly concluded that, due to "social desirability bias," physicians are reluctant to report that they may be influenced more by pharmaceutical marketing than by scientific literature.[78] This is true of messages delivered by sales representatives as well as industry messages contained in continuing medical education courses, talks given by KOLs and scientific literature. And it is particularly difficult for physicians to identify – much less resist – pharmaceutical industry influence when the materials they review appear to be "scientific" or "educational," or at least prepared by apparently neutral third parties.

110. Defendants, however, were intimately aware of the chain of events that would be required to generate prescriptions, designed their marketing to generate prescriptions, and knew that these prescriptions would result in claims that the State, along with other health care

[78] Sunita Sah and Adriane Fugh-Berman, *Physicians under the Influence: Social Psychology and Industry Marketing Strategies*, J. LAW, MEDICINE & ETHICS (Fall 2013) (describing studies).

providers, would ultimately pay. Defendants understood that their aim was to persuade patients to request, and doctors to write, more opioid prescriptions. Defendants also understood that they would not get paid for these prescriptions until they were approved by an insurance provider or paid for by the patients themselves.

111. Accordingly, Defendants used IMS and other data to guide their efforts to expand opioid prescribing through comprehensive marketing and business plans for each drug. These documents, based on the companies' extensive market research, laid out ambitious plans to bring in new prescribers and increase overall prescribing of Defendants' opioids.

a. Targeting categories of prescribers.

112. Defendants targeted, by zip codes and other local boundaries, individual health care providers for detailing. Defendants chose their targets based on the potential for persuading a provider to prescribe, ease of in-person access, and the likelihood of higher numbers of prescriptions at higher doses, with no correlation to demonstrated need or demand for opioid therapy, or to risk of abuse.

113. Collectively, Defendants' marketing plans evince dual strategies, which often operated parallel to one another. Defendants' sales representatives continued to focus their detailing efforts on pain specialists and anesthesiologists, who are the highest-volume prescribers of opioids but are also, as a group, more educated than other practitioners about opioids' risks and benefits. Seeking to develop market share and expand sales, however, Defendants also targeted increasing numbers and types of prescribers for marketing.

114. This expanded market of prescribers was, as a group, less informed about opioids and, market research concluded, more susceptible to Defendants' marketing messages. These prescribers included nurse practitioners and physician assistants, who, a 2012 Endo business plan

noted, were "share acquisition" opportunities because they were "3x times more responsive than MDs to details" and wrote "96% of [their] prescriptions … without physician consult."

115. The expanded market also included internists and general practitioners who were low- to mid-volume prescribers. Actavis, for example, rolled out a plan in 2008 to move beyond "Kadian loyalists" to an "expanded audience" of "low morphine writers."

b. Increasing direct-to-consumer marketing.

116. Defendants knew that physicians were more likely to prescribe their branded medications when patients asked for those medications. Endo's research, for example, found that such communications resulted in greater patient "brand loyalty," with longer durations of Opana ER therapy and fewer discontinuations. Defendants thus increasingly took their opioid sales campaigns directly to consumers, including through patient-focused "education and support" materials. These took the form of pamphlets, videos, or other publications that patients could view in their physician's office, as well as employer and workers' compensation plan initiatives to, as Endo put it, "[d]rive demand for access through the employer audience by highlighting cost of disease and productivity loss."

117. Defendants also knew that one of the largest obstacles to patients starting and remaining on their branded opioids – including by switching from a competitor's drug – was out-of-pocket cost. They recognized they could overcome this obstacle by providing patients financial assistance with their insurance co-payments, and each of Defendants did so through vouchers and coupons distributed during detailing visits with prescribers. A 2008 Actavis business review, for example, highlighted co-pay assistance, good for up to $600 per patient per year, as a way to drive conversions to Kadian from competitor drugs like Avinza and MS Contin. In 2012, Janssen planned to distribute 1.5 million savings cards worth $25 each.

c. Moving beyond office visits

118. Defendants sought to reach additional prescribers by expanding beyond traditional sales calls and speaker events to new channels for their messages. For their sales forces, these included marketing to prescribers through voice mail, postcards, and email – so-called "e-detailing." Defendants also created new platforms for their speakers by implementing "peer to peer" programs such as teleconferences and webinars that were available to prescribers nationally. These programs allowed Defendants to use this more seemingly credible vehicle to market to, among other hard-to-reach audiences, prescribers at hospitals, academic centers, and other locations that limit or prohibit in-person detailing. Employing these new approaches, each Defendant relied heavily on speakers to promote its drugs.

4. Defendants marketed opioids in Mississippi using the same strategies and methods they employed nationwide.

119. Defendants employed the same marketing plans and strategies and deployed the same messages in Mississippi as they did nationwide. Across the pharmaceutical industry, "core message" development is funded and overseen on a national basis by corporate headquarters. This comprehensive approach ensures that Defendants' messages are accurately and consistently delivered across marketing channels – including detailing visits, speaker events, and advertising – and in each sales territory. Defendants consider this high level of coordination and uniformity crucial to successfully marketing their drugs.

120. Defendants ensure marketing consistency nationwide through national and regional sales representative training; national training of local medical liaisons, the company employees who respond to physician inquiries; centralized speaker training; single sets of visual aids, speaker slide decks, and sales training materials; and nationally coordinated advertising. As noted above in Section IV.B.2, Defendants' sales representatives and physician speakers were

required to stick to prescribed talking points, sales messages, and slide decks, and supervisors rode along with them periodically to both check on their performance and compliance.

121. As they did nationwide, Defendants extensively tracked the prescribing behavior of Mississippi-area health care providers and used that data to target their detailing and speaker recruiting efforts. Top prescribers were profiled at the city, region, zip code, and sometimes facility levels, with information about their specialty, prescribing patterns (including product and dose), product loyalty and refill history. Providers' prescribing volume was ranked and sorted into deciles.

122. This information allowed Defendants to target, within each sales territory, prescribers who could have the biggest sales impact. Tracking prescribing behavior also enabled Defendants to zero in on trends: Actavis, for example, identified on a monthly basis the prescribers with the greatest increases and decreases in prescriptions written.

123. As described herein, misrepresentations and deceptions regarding the risks, benefits, and superiority of opioid use to treat chronic pain were part and parcel of Defendants' marketing campaigns in Mississippi.

C. Defendants Used "Unbranded" Marketing to Evade Regulations and Consumer Protection Laws

124. In addition to their direct marketing efforts, Defendants used unbranded, third-party marketing, which they deployed as part of their national marketing strategies for their branded drugs. Each Defendant executed these strategies through a network of third-party KOLs and Front Groups, with which it acted in concert by funding, assisting, encouraging and directing their efforts, while at the same time exercising substantial control over the content of the messages these third parties generated and disseminated, and distributing certain of those materials themselves. As with their other marketing strategies, Defendants' unbranded

marketing created and relied upon an appearance of independence and credibility that was undeserved but central to its effectiveness. Unlike their direct promotional activities, Defendants' unbranded marketing allowed them to evade the oversight of federal regulators and gave them greater freedom to expand their deceptive messages.

1. Regulations governing branded promotion require that it be truthful, balanced and supported by substantial evidence.

125. Drug companies that make, market, and distribute opioids are subject to generally applicable rules requiring truthful marketing of prescription drugs. A drug company's promotion must: (a) be consistent with prescribing information; (b) not include false or misleading statements or material omissions; (c) fairly balance the drug's benefits and risks; and (d) be supported by "substantial" scientific evidence.[79] The regulatory framework governing the marketing of drugs reflects a public policy designed to ensure that drug companies, which are best suited to understand the properties and effects of their drugs, are responsible for providing prescribers with the information they need to accurately assess the risks and benefits of drugs for their patients.

126. Accordingly, drug companies are prohibited from distributing materials that exclude contrary evidence or information about the drug's safety or efficacy or present conclusions that "clearly cannot be supported by the results of the study."[80] Drug companies also cannot make comparisons between their drugs and other drugs that represent or suggest that "a drug is safer or more effective than another drug in some particular when it has not been

[79] 21 U.S.C. § 352(a); 21 C.F.R. §§ 1.21(a); 202.1(e)(3), 202.1(e)(6).

[80] 21 C.F.R. § 99.101(a)(4).

demonstrated to be safer or more effective in such particular by substantial evidence or substantial clinical experience."[81]

127. While the FDA must approve a drug's label, it is the drug company's responsibility to ensure that the material in its label is accurate and complete and is updated to reflect any new information.[82] Non-binding guidance of the FDA likewise makes clear that patient awareness communications that fall outside of a drug's labels still must be "clear and accurate," and that the FDA is not alone responsible for ensuring compliance with this requirement.[83]

128. While promotional materials for prescription drugs also must be submitted to the FDA when they are first used or disseminated, the FDA does not have to approve these materials in advance. If, upon review, the FDA determines that materials marketing a drug are misleading, it can issue an untitled letter or warning letter. The FDA uses untitled letters for violations such as overstating the effectiveness of the drug or making claims without context or balanced information. Warning letters address promotions involving safety or health risks and indicate the FDA may take further enforcement action.

129. The Mississippi Consumer Protection Act reflects the same position that drug companies, like other businesses, have a duty to deal honestly with the government and other payors who purchase and use their products.

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[81] 21 C.F.R. § 202.1(e)(6)(ii).

[82] *See* 21 C.F.R. § 201.56 (providing general requirements for prescription drug labeling); *see also Wyeth v. Levine*, 555 U.S. 555 (2009) (holding that a drug company bears responsibility for the content of its drug labels at all times); 21 C.F.R. § 314.70(c)(2) (allowing manufacturers to make changes that "strengthen … A warning, precaution, or adverse reaction" or "strengthen a statement about drug abuse, dependence, psychological effect, or overdosage").

[83] U.S. Dep't of Health & Human Servs., Guidance for Industry, 'Help-Seeking' and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms (Jan. 2004).

2. Defendants deployed Front Groups and doctors to disseminate "unbranded" information on their behalf.

130. Drug companies market both directly and indirectly, using third party validators (such as scientists, physicians, or patient or professional organizations) that appear to be independent and therefore more credible. The FDA has made clear that Defendants are responsible for representations made by their own employees or by third parties:

> FDA's regulation of prescription drug product promotion extends both to promotional activities that are carried out by the firm itself, and to promotion conducted on the firm's behalf.
>
> ....
>
> Therefore, a firm is responsible for the content generated by its employees or any agents acting on behalf of the firm who promote the firm's product. For example, if an employee or agent of a firm, such as a medical science liaison or paid speaker (e.g., a key opinion leader) acting on the firm's behalf, comments on a third party site about the firm's product, the firm is responsible for the content its employee or agent provides. A firm is also responsible for the content on a blogger's site if the blogger is acting on behalf of the firm.[84]

131. In addition to being carried out directly or through third parties, drug companies' promotional activity can be branded or unbranded; unbranded marketing refers not to a specific drug, but more generally to a disease state or treatment. By using unbranded communications, drug companies can sidestep the extensive regulatory framework, described in Section IV.C.1, governing branded communications.

132. Defendants disseminated many of their false, misleading, imbalanced, and unsupported statements through unbranded marketing materials – materials that generally

[84] FDA, *Draft Guidance for Industry on Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics*, January 2014, at 1, 4, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm381352.pdf.

promoted opioid use but did not name a specific opioid while doing so – through KOLs and Front Groups. These KOLs and Front Groups were important elements of Defendants' marketing plans, which specifically contemplated their use, because they seemed independent and therefore outside of FDA oversight. Through these unbranded materials, Defendants presented information and instructions concerning opioids that were generally contrary to, or at best, inconsistent with, information and instructions listed on Defendants' branded marketing materials and drug labels and with Defendants' own knowledge of the risks, benefits and advantages of opioids. Defendants did so knowing that unbranded materials typically are not submitted to or reviewed by the FDA.

133. Even where such unbranded messages were channeled through third-party vehicles, Defendants adopted these messages as their own when they cited to, edited, approved, and distributed such materials knowing they were false, misleading, unsubstantiated, unbalanced, and incomplete. Unbranded brochures and other materials that are "disseminated by or on behalf of [the] manufacturer" constitute drug "labeling" that may not be false or misleading in any particular.[85] As described below and in Section IV.E, Defendants' sales representatives distributed third-party marketing material that was deceptive to Defendants' target audiences. Defendants are responsible for these materials.

[85] *See* 21. C.F.R. 202.1(e)(7)(l)(2) ("Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and the references published … containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling, as defined in section 201(m) of the act.").

134. Moreover, Defendants took an active role in guiding, reviewing, and approving many of the misleading statements issued by these third parties, ensuring that Defendants were consistently aware of their content. By funding, directing, editing, and distributing these materials, Defendants exercised control over their deceptive messages and acted in concert[86] with these third parties to fraudulently promote the use of opioids for the treatment of chronic pain.

135. For example, Defendants knew the FDA had admonished drug companies for making claims in *branded* materials that opioids allow patients to sleep, return to work, or walk more easily as lacking any scientific basis. Yet Defendants created and disseminated these same unsupported claims through *unbranded* marketing materials.

136. The third-party publications Defendants assisted in creating and distributing did not include the warnings and instructions mandated by their FDA-required drug labels and consistent with the risks and benefits known to Defendants. For example, these publications either did not disclose the risks of addiction, abuse, misuse, and overdose, or affirmatively denied that patients faced a serious risk of addiction.

137. By acting through third parties, Defendants were able both to avoid FDA scrutiny and to give the false appearance that these messages reflected the views of independent third parties. Later, Defendants would cite to these sources as "independent" corroboration of their own statements. Further, as one physician adviser to Defendants noted, third-party documents had not only greater credibility, but also broader distribution, as doctors did not "push back" at

[86] As used in this Complaint, the allegation that Defendants "acted in concert" with third parties is intended to mean *both* that they conspired with these third parties to achieve some end and that they aided and abetted these third parties in the commission of acts necessary to achieve it.

having materials from, for example, the non-profit American Pain Foundation ("APF") on display in their offices, as they would with first-party, drug company pieces. Nevertheless, the independence of these materials was a ruse – Defendants were in close contact with these third parties, paid for and were otherwise aware of the misleading information they were disseminating about the use of opioids to treat chronic pain, and regularly helped them to tailor and distribute their misleading, pro-opioid messaging.

138. As part of a strategic marketing scheme, Defendants spread and validated their deceptive messages through the following vehicles: (a) KOLs, who could be counted upon to write favorable journal articles and deliver supportive CMEs; (b) a body of biased and unsupported scientific literature; (c) treatment guidelines; (d) CMEs; (e) unbranded patient education materials; and (f) Front Group patient-advocacy and professional organizations, which exercised their influence both directly and through Defendant-controlled KOLs who served in leadership roles in those organizations.

a. Defendants' use of Key Opinion Leaders.

139. Defendants cultivated a small circle of doctors who, upon information and belief, were selected and sponsored by Defendants solely because they favored the aggressive treatment of chronic pain with opioids. Defendants' support helped these doctors become respected industry experts. In return, these doctors repaid Defendants by touting the benefits of opioids to treat chronic pain.

140. KOLs are retained by Defendants to influence their peers' medical practice, including but not limited to their prescribing behavior. KOLs give lectures, conduct clinical trials and occasionally make presentations at regulatory meetings or hearings. Pharmaceutical companies like using KOLs because physicians tend to give more credence to opinions of their

peers than they do marketing efforts, and therefore, if they can influence KOLs, they can influence exponentially more physicians who are on the receiving end of the KOLs' messages.[87]

141. Pro-opioid doctors have been at the hub of Defendants' promotional efforts, presenting the appearance of unbiased and reliable medical research supporting the broad use of opioid therapy for chronic pain. KOLs have written, consulted on, edited, and lent their names to books and articles, and given speeches and CMEs supportive of chronic opioid therapy. They have served on committees that developed treatment guidelines that strongly encourage the use of opioids to treat chronic pain (even while acknowledging the lack of evidence in support of that position) and on the boards of pro-opioid advocacy groups and professional societies that develop, select, and present CMEs. Defendants were able to exert control of each of these modalities through their KOLs.

142. In return, the KOLs' association with Defendants provided not only money, but prestige, recognition, research funding, and avenues to publish. This positioned them to exert even more influence in the medical community.

143. Although some KOLs initially may have advocated for more permissive opioid prescribing with honest intentions, Defendants cultivated and promoted only those KOLs who could be relied on to help broaden the chronic opioid therapy market. Defendants selected, funded, and elevated those doctors whose public positions were unequivocal and supportive of using opioids to treat chronic non-cancer pain.[88] These doctors' professional reputations were

[87] *See* Carl Elliott, *The Secret Lives of Big Pharma's 'Thought Leaders'*, The Chronicle of Higher Education (Sept. 12, 2010), *available at*: http://chronicle.com/article/The-Secret-Lives-of-Big/124335/.

[88] Opioid-makers were not the first to mask their deceptive marketing efforts in purported science. The tobacco industry also used KOLs in its effort to persuade the public and regulators that tobacco was not addictive or dangerous. For example, the tobacco companies funded a research program at Harvard and chose as its chief researcher a doctor who had expressed views

then dependent on continuing to promote a pro-opioid message, even in activities that were not directly funded by the drug companies.

144. Defendants cited and promoted favorable studies or articles by these KOLs. They did not support, acknowledge, or disseminate the publications of doctors critical of the use of chronic opioid therapy. Indeed, one prominent KOL sponsored by Defendants, Russell Portenoy, stated that he was told by a drug company that research critical of opioids (and the doctors who published that research) would never obtain funding. Some KOLs have even gone on to become direct employees and executives of Defendants, like Dr. David Haddox, Purdue's Vice President of Risk Management, and Dr. Bradley Galer, Endo's former Chief Medical Officer.[89]

145. Defendants provided substantial opportunities for KOLs to participate in research studies on topics Defendants suggested or chose, with the predictable effect of ensuring that many favorable studies appeared in the academic literature. As described by Dr. Portenoy, drug companies would approach him with a study that was well underway and ask if he would serve as the study's author. Dr. Portenoy regularly agreed.

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in line with industry's views. He was dropped when he criticized low tar cigarettes as potentially more dangerous, and later described himself as a pawn in the industry's campaign.

[89] Once a Purdue employee, Dr. Haddox's public statements became increasingly outrageous. He has been quoted as saying "If you are taking OxyContin for legitimate pain, you have nothing to worry about …. If I gave you a stalk of celery and you ate that, it would be healthy for you. But if you put it in a blender and tried to shoot it into your veins, it would not be good." Roger Alford, *Deadly OxyContin Abuse Expected to Spread in the U.S.*, Charleston Gazette & Daily Mail (Feb. 9, 2001). And, "A lot of these people say, 'Well, I was taking the medicine like my doctor told me to,' and then they start taking more and more and more[.] I don't see where that's my problem." Chris Kahn, *Lawsuits accuse OxyContin Maker*, Phila. Inquirer (July 27, 2001). Both of these statements were made in 2001, a year after Dr. Haddox was chosen to head up Purdue's task force responding to media reports of OxyContin abuse and diversion. *See* Paul Tough, *The Alchemy of OxyContin: From Pain Relief to Drug Addiction*, N.Y. TIMES MAG. (July 29, 2001).

146. Defendants also paid KOLs to serve as consultants or on their advisory boards and give talks or present CMEs, typically over meals or at conferences. From 2000 on, Cephalon, for instance, has paid doctors more than $4.5 million for programs relating to its opioids.

147. These KOLs were carefully vetted to ensure that they were likely to remain on message and supportive of a pharmaceutical industry agenda. One measure was a doctor's prior work for trusted Front Groups.

148. Defendants kept close tabs on the content of the misleading materials published by these KOLs. In many instances, they also scripted what these KOLs said – as they did with all their recruited speakers, as discussed above in Section IV.B.2. The KOLs knew or deliberately ignored the misleading way in which they portrayed the use of opioids to treat chronic pain to patients and prescribers, but they continued to publish those misstatements to benefit themselves and Defendants, all the while causing harm to Mississippi prescribers and patients.

149. In fact, while some pharmaceutical companies do this in-house, an entire industry has developed around developing pharmaceutical KOLs. There are dozens of companies that specialize in identifying potential KOLs, "mapping" their influence, and recruiting and managing them.

- Leadership in Medicine touts that it can identify "who are the most prominent, admired, and influential actors in healthcare, how they are interconnected, and why." It explains that, because the relationships among significant actors in healthcare are "vastly complex," "it is vital to focus on key opinion leaders (KOLs) at local, regional, and global levels, and to understand the ties among them. Equally essential is recognizing the roles played by key leading organizations (KLOs) such as medical institutions, payers, professional organizations, patient groups, government entities, and journals in structuring

KOL activities and relationships, since those are the stages on which KOLs perform."[90]

- Alpha Detail explains that, though "[t]he number of factors influencing physician prescribing decisions continues to grow," "one of the most impactful influences on physicians has remained consistent: national, regional and/or local key opinion leaders (KOL)." It claims that can provide "an innovative, on-line channel for understanding and mapping the sophisticated social networks that influence high prescribers in your therapeutic area."[91]

- Kantar Health makes clear that "Key opinion leaders (KOLs) play an important role in your marketing strategy at every stage of the product lifecycle" and states that it can "[m]ap the KOL's influence, including a visual layout of the network of influence."[92]

Similar types of information, in the sole possession of Defendants and/or the third parties they retain, can show how Defendants believed KOLs influenced other – and which – physicians. Defendants carefully managed these doctors and their messages, ensuring they were consistent with Defendants' own marketing messages.

(1) Russell Portenoy

150. Dr. Russell Portenoy, Chairman of the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York, is one example of a KOL whom Defendants identified and promoted to further their marketing campaign. Dr. Portenoy received research support, consulting fees, and honoraria from Cephalon, Endo, Janssen, and Purdue (among others), and was a paid consultant to Cephalon and Purdue.

151. Dr. Portenoy was instrumental in opening the door for the regular use of opioids to treat chronic pain. He served on the APS/AAPM Guidelines Committees, which endorsed the

[90] *See* http://www.leadershipinmedicine.com/.

[91] *See* http://www.alphadetail.com/corp/kol_mapping/AboutKOLMapping.do.

[92] *See* http://www.kantarhealth.com/services/kol-identification-and-influence-mapping.

use of opioids to treat chronic pain, first in 1997 and again in 2009. He was also a member of the board of APF, an advocacy organization almost entirely funded by Defendants.

152. Dr. Portenoy also made frequent media appearances promoting opioids and spreading misrepresentations. He appeared on *Good Morning America* in 2010 to discuss the use of opioids long-term to treat chronic pain. On this widely-watched program, broadcast in Mississippi and across the country, Dr. Portenoy claimed that:

> [a]ddiction, when treating pain, is distinctly uncommon. If a person does not have a history, a personal history, of substance abuse, and does not have a history in the family of substance abuse, and does not have a very major psychiatric disorder, most doctors can feel very assured that that person is not going to become addicted.[93]

153. To his credit, Dr. Portenoy has recently admitted that he "gave innumerable lectures in the late 1980s and '90s about addiction that weren't true" in which he claimed that less than 1% of patients would become addicted to opioids. According to Dr. Portenoy, because the primary goal was to "destigmatize" opioids, he and other doctors promoting them overstated their benefits and glossed over their risks. Dr. Portenoy also conceded that "[d]ata about the effectiveness of opioids does not exist."[94] Portenoy candidly stated "[d]id I teach about pain management, specifically about opioid therapy, in a way that reflects misinformation? Well … I guess I did."[95]

[93] Good Morning America television broadcast, ABC News (Aug. 30, 2010).

[94] Thomas Catan & Evan Perez, *A Pain-Drug Champion Has Second Thoughts*, WALL ST. J. (Dec. 17, 2012).

[95] *Id.*

(2) Lynn Webster

154. Another KOL, Dr. Lynn Webster, was the co-founder and Chief Medical Director of Lifetree Clinical Research, an otherwise-unknown pain clinic in Salt Lake City, Utah. Dr. Webster was President in 2013 and is a current board member of AAPM, a Front Group that ardently supports chronic opioid therapy. He is a Senior Editor of *Pain Medicine*, the same journal that published Endo/Portenoy special advertising supplements touting Opana ER. Dr. Webster was the author of numerous CMEs sponsored by Cephalon, Endo, and Purdue. At the same time, Dr. Webster was receiving significant funding from Defendants (including nearly $2 million from Cephalon).

155. Until September 2014, when the investigation was closed, Dr. Webster was under investigation for overprescribing by the U.S. Department of Justice's Drug Enforcement Agency, which raided his clinic in 2010. More than 20 of Dr. Webster's former patients at the Lifetree Clinic have died of opioid overdoses. Dr. Webster created and promoted the Opioid Risk Tool, a five question, one-minute screening tool relying on patient self-reports that purportedly allows doctors to manage the risk that their patients will become addicted to or abuse opioids. The claimed ability to pre-sort patients likely to become addicted is an important tool in giving doctors confidence to prescribe opioids long-term, and for this reason, references to screening appear in various industry-supported guidelines. Versions of Dr. Webster's Opioid Risk Tool, appear on, or are linked to, websites run by Endo, Janssen, and Purdue. In 2011, Dr. Webster presented, via webinar, a program sponsored by Purdue titled, *Managing Patient's Opioid Use: Balancing the Need and the Risk*. Dr. Webster recommended use of risk screening tools, urine testing, and patient agreements as ways to prevent "overuse of prescriptions" and "overdose deaths." This webinar was available to and intended to reach doctors in Mississippi.

156. Dr. Webster also was a leading proponent of the concept of "pseudoaddiction," the notion that addictive behaviors should be seen not as warnings, but as indications of undertreated pain. In Dr. Webster's description, the only way to differentiate the two was to *increase* a patient's dose of opioids. As he and his co-author wrote in a book entitled *Avoiding Opioid Abuse While Managing Pain* (2007), when faced with signs of aberrant behavior, increasing the dose "*in most cases … should be the clinician's first response*." Years later, Dr. Webster reversed himself, acknowledging that "[pseudoaddiction] obviously became too much of an excuse to give patients more medication."[96]

b. Defendants used "research" that lacked supporting evidence.

157. Rather than finding a way to actually test the safety and efficacy of opioids for long-term use, Defendants led everyone to believe that they had already done so. Defendants created a body of false, misleading, and unsupported medical and popular literature about opioids that (a) understated the risks and overstated the benefits of long-term use; (b) appeared to be the result of independent, objective research; and (c) was thus more likely to be relied upon by physicians, patients, and payors. This "literature" was in fact marketing material focused on persuading doctors and consumers that the benefits of long-term opioid use outweighed the risks.

158. To accomplish this, Defendants – sometimes through third-party consultants and/or advocacy organizations – commissioned, edited, and arranged for the placement of favorable articles in academic journals. Defendants' internal documents reveal plans to submit research papers and "studies" to long lists of journals, including back-up options and last resort,

[96] John Fauber & Ellen Gabler, *Networking Fuels Painkiller Boom*, MILWAUKEE WISC. J. SENTINEL (Feb. 19, 2012).

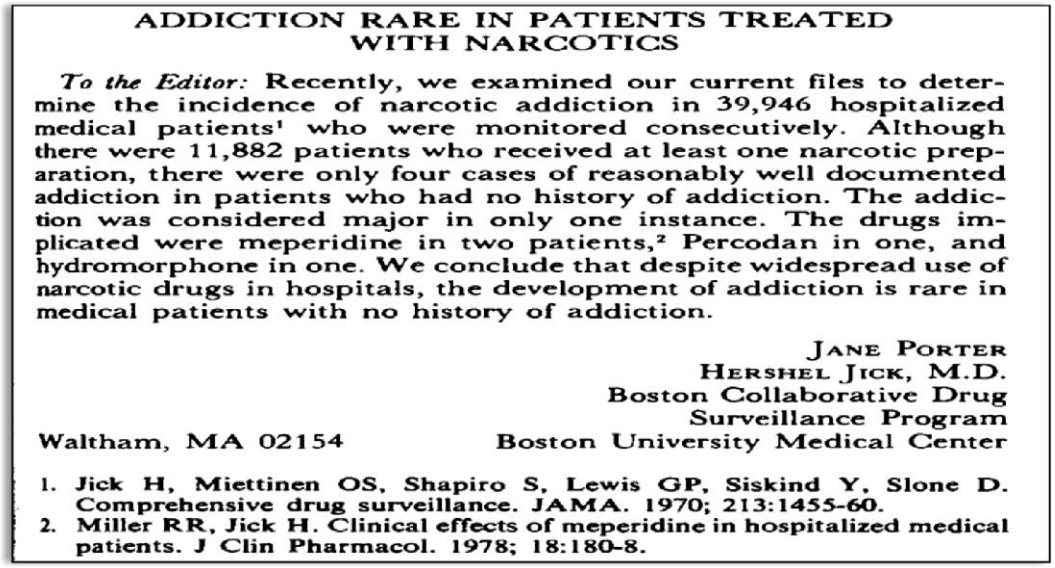
"fast-track" application journals that they could use if the pending paper was rejected everywhere else.

159. Defendants coordinated the timing and publication of manuscripts, abstracts, posters/oral presentations, and educational materials in peer-reviewed journals and other publications to support the launch and sales of their drugs. The plans for these materials did not originate in the departments within the Defendant organizations that were responsible for research, development or any other area that would have specialized knowledge about the drugs and their effects on patients, but in Defendants' marketing departments and with Defendants' marketing and public relations consultants. Defendants often relied on "data on file" or presented posters, neither of which are subject to peer review. They also published their articles not through a competitive process, but in paid journal supplements, which allowed Defendants to publish, in nationally circulated journals, studies supportive of their drugs.

160. Defendants also made sure that favorable articles were disseminated and cited widely in the medical literature, even where references distorted the significance or meaning of the underlying study. Most notably, Purdue promoted a 1980 reference in the well-respected New England Journal of Medicine: J. Porter & H. Jick, *Addiction Rare in Patients Treated with Narcotics*, 302(2) New Engl. J. Med. 123 (Jan. 1980) ("Porter-Jick Letter"). It is cited in Google Scholar a total of 856 times and 86 times since 2010. It appears as a reference in two CME programs in 2012 sponsored by Purdue and Endo.[97] Defendants and those acting on their behalf fail to reveal that this "article" is actually a letter-to-the-editor, not a peer-reviewed study (or any

[97] AAPM, Safe Opioid Prescribing Course, February 25-26, 2012, sponsored by Purdue and Endo; "Chronic Pain Management and Opioid Use," October 11, 2012, sponsored by Purdue. Each CME is available for online credit, including to prescribers in Mississippi.

kind of study at all). The Porter-Jick Letter, reproduced in full below, describes a review of the charts of hospitalized patients who had received opioids. (Because it was a 1980 study, standards of care almost certainly would have limited opioids to acute or end-of-life situations, not chronic pain.)



ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients[1] who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,[2] Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

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1. Jick H, Miettinen OS, Shapiro S, Lewis GP, Siskind Y, Slone D. Comprehensive drug surveillance. JAMA. 1970; 213:1455-60.
2. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. J Clin Pharmacol. 1978; 18:180-8.

161. The Porter-Jick Letter notes that, when these patients' records were reviewed, there were almost no references to signs of addiction, however, there was likewise no indication that caregivers were instructed to assess or document signs of addiction. None of these serious limitations are disclosed when Defendants, or those acting on their behalf, cite the Porter-Jick Letter, typically as the sole scientific support for the proposition that opioids are rarely addictive even when taken long-term. In fact, Dr. Jick later complained that his letter had been distorted and misused.

162. Defendants worked not only to create or elevate favorable studies in the literature, but to discredit or bury negative information. Defendants' studies and articles often challenged articles that contradicted Defendants' claims or raised concerns about chronic opioid therapy. In order to do so, Defendants – often with the help of third-party consultants – targeted a broad

range of media to get their message out, including negative review articles, letters to the editor, commentaries, case-study reports, and newsletters.

163. Defendants' strategies – first, to plant and promote supportive literature while burying unfavorable evidence, and then to cite that same pro-opioid evidence in their promotional materials, while failing to disclose evidence that contradicts those claims – are flatly inconsistent with their legal obligations, as laid out in Section IV.C.1. The strategies were intended to, and did, distort the truth regarding the risks and benefits of opioids for chronic pain relief and distorted prescribing patterns as a result.

c. Treatment Guidelines.

164. Treatment guidelines have been particularly important in securing acceptance for chronic opioid therapy. They are relied upon by doctors, especially the general practitioners and family doctors targeted by Defendants, who are neither experts in nor trained in the treatment of chronic pain.[98] Treatment guidelines not only directly inform doctors' prescribing practices, but are cited throughout the scientific literature and referenced by third-party payors in determining whether they should cover treatments for specific indications. Furthermore, Endo's internal documents indicate that pharmaceutical sales representatives employed by Endo, Actavis, and Purdue discussed treatment guidelines with doctors during individual sales visits.

165. Because treatment guidelines are intended to present a synthesis of current evidence and recommendations by expert clinicians, they may affect the practice of a large

[98] *See* Jerry Avorn, *Healing the Overwhelmed Physician*, New York Times (June 11, 2013) (discussing how even industry-influenced guidelines can influence physicians, who have little time to review scientific literature to stay current).

number of physicians. As a result, if those guidelines are prepared by physicians under the influence of pharmaceutical companies, that influence may be transmitted many times over.[99]

(1) FSMB

166. FSMB is a trade organization representing the various state medical boards in the United States. The state boards that comprise the FSMB membership have the power to license doctors, investigate complaints, and discipline physicians. The FSMB finances opioid- and pain-specific programs through grants from Defendants.

167. In 1998, the FSMB developed *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain* ("FSMB Guidelines"), which FSMB admitted were produced "in collaboration with pharmaceutical companies." The FSMB Guidelines taught not only that opioids could be appropriate in limited cases or after other treatments had failed, but also that opioids were "essential" for treatment of chronic pain, including as a first prescription option. The FSMB Guidelines failed to mention risks relating to respiratory depression and overdose, and discussed addiction only in the sense that "inadequate understandings" of addiction can lead to "inadequate pain control."

168. A 2004 iteration of the FSMB Guidelines and the 2007 book adapted from the 2004 guidelines, *Responsible Opioid Prescribing*, also make these same claims. These guidelines were posted online and were available to and intended to reach Mississippi physicians.

169. The publication of *Responsible Opioid Prescribing* was backed largely by drug manufacturers, including Cephalon, Endo, and Purdue. The FSMB financed the distribution of

[99] Niteesh K. Choudry, MD, FRCPC, Henry Thomas Stelfox, MD, FRCPC and Allan S. Detsky, MD, PhD, FRCPC, *Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry*, JAMA; 287:5 (Feb. 6, 2002).

Responsible Opioid Prescribing by its member boards by contracting with drug companies, including Endo and Cephalon, for bulk sales and distribution to sales representatives (for distribution to prescribing doctors).

170. In all, 163,131 copies of *Responsible Opioid Prescribing* were distributed to state medical boards (and through the boards, to practicing doctors), and the FSMB benefitted by earning approximately $250,000 in revenue and commissions from their sale. The FSMB website describes the book as the "leading continuing medication education (CME) activity for prescribers of opioid medications."

171. Drug companies relied on FSMB guidelines to convey the message that "undertreatment of pain" would result in official discipline, but no discipline would result if opioids were prescribed as part of an ongoing patient relationship and prescription decisions were documented. FSMB turned doctors' fear of discipline on its head – doctors, who used to believe that they would be disciplined if their patients became addicted to opioids, were taught that they would be punished instead if they failed to prescribe opioids to their patients with pain.

172. FSMB, more recently, has moderated its stance. Although the 2012 revision of *Responsible Opioid Prescribing* continues to teach that pseudoaddiction is real and that opioid addiction risk can be managed through risk screening, it no longer recommends chronic opioid therapy as a first choice after the failure of over the counter medication and has heightened the addiction and risk warnings.

(2) AAPM/APS Guidelines

173. AAPM and the APS are professional medical societies, each of which received substantial funding from Defendants from 2009 to 2013 (with AAPM receiving over $2 million). They issued a consensus statement in 1997, *The Use of Opioids for the Treatment of Chronic*

Pain, which endorsed opioids to treat chronic pain and claimed that the risk that patients would become addicted to opioids was low.[100] The co-author of the statement, Dr. Haddox, was at the time a paid speaker for Purdue. Dr. Portenoy was the sole consultant. The consensus statement, which also formed the foundation of the FSMB Guidelines, remained on AAPM's website until 2011, and was taken down only after a doctor complained, though it lingers on the internet elsewhere.[101]

174. AAPM and APS issued their own guidelines in 2009 ("AAPM/APS Guidelines") and continued to recommend the use of opioids to treat chronic pain. Fourteen of the 21 panel members who drafted the AAPM/APS Guidelines, including KOLs Dr. Portenoy and Dr. Perry Fine of the University of Utah, received support from Janssen, Cephalon, Endo, and Purdue.

175. The 2009 Guidelines promote opioids as "safe and effective" for treating chronic pain, despite acknowledging limited evidence, and conclude that the risk of addiction is manageable for patients regardless of past abuse histories. One panel member, Dr. Joel Saper, Clinical Professor of Neurology at Michigan State University and founder of the Michigan Headache & Neurological Institute, resigned from the panel because of his concerns that the 2009 Guidelines were influenced by contributions from drug companies, including Defendants, made to the sponsoring organizations and committee members. These AAPM/APS Guidelines have been a particularly effective channel of deception and have influenced not only treating physicians, but also the body of scientific evidence on opioids. The Guidelines have been cited

[100] *The Use of Opioids for the Treatment of Chronic Pain*, APS & AAPM (1997), *available at* http://opi.areastematicas.com/generalidades/OPIOIDES.DOLORCRONICO.pdf.

[101] *Id*.

732 times in academic literature, were disseminated in Mississippi during the relevant time period, are still available online, and were reprinted in the *Journal of Pain*.

176. Defendants widely referenced and promoted the 2009 Guidelines without disclosing the acknowledged lack of evidence to support them.

(3) American Geriatrics Society

177. The American Geriatrics Society ("AGS"), a nonprofit organization serving health care professionals who work with the elderly, disseminated guidelines regarding the use of opioids for chronic pain in 2002 (*The Management of Persistent Pain in Older Persons*, hereinafter "2002 AGS Guidelines") and 2009 (*Pharmacological Management of Persistent Pain in Older Persons*, hereinafter "2009 AGS Guidelines"). The 2009 AGS Guidelines included the following recommendations: "All patients with moderate to severe pain … should be considered for opioid therapy (low quality of evidence, strong recommendation)," and "the risks [of addiction] are exceedingly low in older patients with no current or past history of substance abuse."[102] These recommendations, which continue to appear on AGS' website, are not supported by any study or other reliable scientific evidence. Nevertheless, they have been cited 278 times in Google Scholar since their 2009 publication. A recent report by Express Scripts, a national pharmaceutical benefits manager, states that since the 2009 AGS Guidelines, there has been a 4.5% increase in elderly patients being prescribed only opioids for pain and a 5.1% decrease in NSAID drugs, which the 2009 AGS Guidelines discouraged.[103]

[102] Pharmacological Management of Persistent Pain in Older Persons, 57 J. Am. Geriatrics Society 1332 (Aug. 2009), *available at*: http://www.americangeriatrics.org/files/documents/2009_Guideline.pdf.

[103] Express Scripts Lab, *A Nation in Pain: Focusing on U.S. Opioid Trends for Treatment of Short-Term and Longer-Term Pain* (Dec. 2014), *available at:* http://lab.express-scripts.com/publications/~/media/d48ef3ee579848e7bf3f14af536d7548.ashx.

178. AGS contracted with Defendants Endo, Purdue, and Janssen to disseminate the 2009 Guidelines, and to sponsor CMEs based on them. These Defendants were aware of the content of the 2009 Guidelines when they agreed to provide funding for these projects. The 2009 Guidelines were released at the May 2009 AGS Annual Scientific Meeting in Chicago and first published online on July 2, 2009. AGS submitted grant requests to Defendants including Endo and Purdue beginning July 15, 2009. Internal AGS discussions in August 2009 reveal that it did not want to receive up-front funding from drug companies, which would suggest drug company influence, but would instead accept commercial support to disseminate the publication. However, by drafting the guidelines knowing that pharmaceutical company funding would be needed, and allowing these companies to determine whether to provide support only after they have approved the message, AGS ceded significant control to these companies. Endo, Janssen, and Purdue all agreed to provide support to distribute the guidelines.

179. According to one news report, AGS has received $344,000 in funding from opioid makers since 2009.[104] Five of the 10 experts on the Guidelines panel disclosed financial ties to Defendants, including serving as paid speakers and consultants, presenting CMEs sponsored by Defendants, receiving grants from Defendants, and investing in Defendants' stock. The Institute of Medicine recommends that, to ensure an unbiased result, that fewer than 50% of the members of a guidelines committee should have financial relationships with drug companies.

(4) Guidelines that did not receive Defendants' support

180. The extent of Defendants' influence on treatment guidelines is demonstrated by the fact that independent guidelines – the authors of which did not accept drug company

[104] John Fauber & Ellen Gabler, *supra*.

funding – reached very different conclusions. The 2012 *Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain*, issued by the American Society of Interventional Pain Physicians ("ASIPP"), warned that

> [t]he recent revelation that the pharmaceutical industry was involved in the development of opioid guidelines as well as the bias observed in the development of many of these guidelines illustrate that the model guidelines are not a model for curtailing controlled substance abuse and may, in fact, be facilitating it.[105]

ASIPP's Guidelines further advise that:

> therapeutic opioid use, specifically in high doses over long periods of time in chronic non-cancer pain starting with acute pain, not only lacks scientific evidence, but is in fact associated with serious health risks including multiple fatalities, and is based on emotional and political propaganda under the guise of improving the treatment of chronic pain.

ASIPP recommends long-acting opioids in high doses only "in specific circumstances with severe intractable pain" and only when coupled with "continuous adherence monitoring … in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse effects."[106]

181. Similarly, the 2011 *Guidelines for the Chronic Use of Opioids*, issued by the American College of Occupational and Environmental Medicine, recommend against the "routine use of opioids in the management of patients with chronic pain," finding "at least

[105] Laxmaiah Manchikanti, *et al*., American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part I – Evidence Assessment, 15 Pain Physician S1-S66 (2012).

[106] Laxmaiah Manchikanti, *et al*., American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part 2 – Guidance, 15 Pain Physician S67-S116 (2012).

moderate evidence that harms and costs exceed benefits based on limited evidence," while conceding there may be patients for whom opioid therapy is appropriate.[107]

182. *Clinical Guidelines on Management of Opioid Therapy for Chronic Pain*, issued by the U.S. Department of Veterans Affairs ("VA") and Department of Defense ("DOD") in 2010, notes that their review:

> revealed the lack of solid evidence based research on the efficacy of long-term opioid therapy. Almost all of the randomized trials of opioids for chronic non-cancer pain were short-term efficacy studies. Critical research gaps … include: lack of effectiveness studies on long-term benefits and harms of opioids …; insufficient evidence to draw strong conclusions about optimal approaches to risk stratification …; lack of evidence on the utility of informed consent and opioid management plans …; and treatment of patients with chronic noncancer pain at higher risk for drug abuse or misuse.[108]

d. Continuing medical education

183. CMEs are ongoing professional education programs required for doctors. Doctors must attend a certain number and, often, type of CME programs each year as a condition of their licensure. Since 2012, all Mississippi physicians with active DEA certificates are required to have five hours of CMEs related to "the prescribing of medication with an emphasis on controlled substances."[109] These programs are delivered in person, often in connection with professional organizations' conferences, and online, or through written publications. Doctors rely on CMEs not only to satisfy licensing requirements, but to get information on new

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[107] *American College of Occupational and Environmental Medicine's Guidelines for the Chronic Use of Opioids* (2011), *available at*: http://beta.acoem.org/uploadedFiles/ Knowledge_Centers/Practice_Guidelines/Chronic%20Pain%20Opioi d%202011.pdf.

[108] Management of Opioid Therapy for Chronic Pain Working Group, VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain (May 2010), *available at* http://www.healthquality.va.gov/guidelines/Pain/cot/COT_312_Full-er.pdf.

[109] MISS. ADM. CODE § 30-17-2610:2-1.

developments in medicine or to deepen their knowledge in specific areas of practice. Because CMEs are typically delivered by KOLs who are highly-respected in their fields and are thought to reflect their medical expertise, they can be especially influential with doctors.

184. The countless doctors and other health care professionals who participate in accredited CMEs constitute an enormously important audience for opioid reeducation.[110] As one target, Defendants aimed to reach general practitioners, whose broad area of focus and lack of specialized training in pain management made them particularly dependent upon CMEs and, as a result, especially susceptible to Defendants' deceptions.

185. In all, Defendants sponsored CMEs that were delivered thousands of times, promoting chronic opioid therapy and supporting and disseminating the deceptive and biased messages described in this Complaint. These CMEs, while often generically titled to relate to the treatment of chronic pain, focus on opioids to the exclusion of alternative treatments, inflate the benefits of opioids, and frequently omit or downplay their risks and adverse effects.

186. The American Medical Association ("AMA") has recognized that support from drug companies with a financial interest in the content being promoted "creates conditions in which external interests could influence the availability and/or content" of the programs and urges that "[w]hen possible, CME should be provided without such support or the participation of individuals who have financial interests in the educational subject matter."[111]

[110] *See* Lisa M. Schwartz & Steven Woloshin, *Medical Communication Companies and Continuing Medical Education: Clouding the Sunshine?*, 310(23) J. of the Am. Med. Ass'n 2507, 2507 (Dec. 18, 2013).

[111] *Opinion 9.0115 – Financial Relationships with Industry in CME*, Am. Med. Ass'n (Nov. 2011), http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion90115.page.

187. Dozens of CMEs that were available to and, upon information and belief, attended or reviewed by Mississippi doctors during the relevant time period did not live up to the AMA's standards.

188. The influence of Defendants' funding on the content of these CMEs is clear. One study by a Georgetown University Medical Center professor compared the messages retained by medical students who reviewed an industry-funded CME article on opioids versus another group who reviewed a non-industry-funded CME article. The industry-funded CME did not mention opioid-related death once; the non-industry-funded CME mentioned opioid-related death 26 times. Students who read the industry-funded article more frequently noted the impression that opioids were underused in treating chronic pain. The "take-aways" of those reading the non--industry funded CME included the risks of death and addiction much more frequently than the other group. Neither group could accurately identify whether the article they read was industry-funded, making clear the difficulty providers have in screening and accounting for source bias.[112]

189. By sponsoring CME programs put on by Front Groups like APF, AAPM, and others, Defendants could expect messages to be favorable to them, as these organizations were otherwise dependent on Defendants for other projects. The sponsoring organizations honored this principle by hiring pro-opioid KOLs to give talks that supported chronic opioid therapy, as described in Section IV.C.2.a.

190. CME sponsorships were smart investments for Defendants – both in content and reach. Having gained influence over a doctor's prescribing habits, they were able to profit from their entire patient base.

[112] Adriane Fugh-Berman, *Marketing Messages in Industry-Funded CME*, PharmedOut (June 25, 2010), www.pharmedout.org/Fugh-BermanPrescriptionforconflict6-25-10.pdf.

e. Unbranded patient education.

190. Pharmaceutical industry marketing experts see direct-to-consumer advertising as particularly valuable in "increas[ing] market share … by bringing awareness to a particular disease that the drug treats."[113] Evidence also demonstrates that physicians are willing to accede to patient demands for a particular drug – even for opioids and for conditions for which they are not generally recommended.[114] Recognizing this, Defendants put their relationships with Front Groups to work to engage in largely unbranded patient education about opioid treatment for chronic pain.

192. The drug companies expect that they will recoup their investment in direct-to-consumer advertisements because they will capture at least some of any additional prescriptions that result from patients "asking their doctor" about drugs that can treat their pain. Doctors also may review direct-to-consumer materials sales representatives give them to distribute to patients.

193. Defendants' influence was not restricted to ongoing medical education. Defendants' efforts to redirect medical literature and doctors' practice affected the teaching and training of medical students, as well, creating new generations of doctors who misunderstood the risks, benefits, and role of chronic opioid therapy.

f. Defendants' use of Front Groups.

194. As noted above, Defendants Cephalon, Endo, Janssen and Purdue entered into arrangements with numerous organizations to promote opioids. These organizations depended

[113] Kanika Johar, An Insider's Perspective: Defense of the Pharmaceutical Industry's Marketing Practices, 76 Albany L. Rev. 299, 308 (2013).

[114] Prescribers often accede to patient requests. According to one study, nearly 20% of sciatica patients requesting oxycodone would receive a prescription for it, compared with 1% making no request. More than half of patients requesting a strong opioid received one. John B. McKinlay, *et al.*, *Effects of Patient Medication Requests on Physician Prescribing Behavior*, MEDICAL CARE, 2014; 52(4): 294.

upon Defendants for significant funding and, in some cases, for their survival. They were involved not only in generating materials and programs for doctors and patients supporting chronic opioid therapy, but in assisting Defendants' marketing in other ways – for example, responding to negative articles and advocating against regulatory changes that would constrain opioid prescribing. They developed and disseminated pro-opioid treatment guidelines; conducted outreach to groups targeted by Defendants, such as veterans and the elderly; and developed and sponsored CMEs that focused exclusively on opioids to treat chronic pain. Defendants funded these Front Groups in order to ensure supportive messages from these seemingly neutral and credible third parties, and their funding did, in fact, ensure such supportive messages.

195. Several representative examples are highlighted below, but there are others, too, such as APS, AGS, FSMB, American Chronic Pain Association (ACPA), AAPM, American Society of Pain Educators ("ASPE"), NPF, and PPSG. Some of the available evidence demonstrating how Defendants controlled these Front Groups is laid out below.

(1) American Pain Foundation

196. The most prominent of Defendants' Front Groups was APF, which received more than $10 million in funding from opioid manufacturers from 2007 until it closed its doors in May 2012. Endo alone provided more than half that funding; Purdue was next, at $1.7 million.

197. APF issued education guides for patients, reporters, and policymakers that touted the benefits of opioids for chronic pain and trivialized their risks, particularly the risk of addiction. APF also launched a campaign to promote opioids for returning veterans, described in Section IV.C.4.b, which has contributed to high rates of addiction and other adverse outcomes – including death – among returning soldiers. APF also engaged in a significant multimedia

campaign – through radio, television, and the internet – to educate patients about their "right" to pain treatment – namely opioids. All of the programs and materials were available an intended to reach people nationally and in Mississippi.

198. In addition to Perry Fine, Russell Portenoy and Scott Fishman, who served on APF's Board and reviewed its publications, another APF board member, Lisa Weiss, was an employee of a public relations firm that worked for both Purdue and APF.

199. In 2009 and 2010, more than 80% of APF's operating budget came from pharmaceutical industry sources. Including industry grants for specific projects, APF received about $2.3 million from industry sources out of total income of about $2.85 million in 2009. Its budget for 2010 projected receipts of roughly $2.9 million from drug companies out of total income of about $3.5 million. By 2011, APF was entirely dependent on incoming grants from Defendants Purdue, Cephalon, Endo, and others to avoid using its line of credit. As one of its board members, Russell Portenoy, explained, the lack of funding diversity was one of the biggest problems at APF.

200. APF held itself out as an independent patient advocacy organization. It often engaged in grassroots lobbying against various legislative initiatives that might limit opioid prescribing, and thus the profitability of its sponsors. It was often called upon to provide "patient representatives" for Defendants' promotional activities, including for Purdue's *Partners Against Pain* and Janssen's *Let's Talk Pain.* As laid out below, APF functioned largely as an advocate for the interests of Defendants, not patients. Indeed, as early as 2001, Purdue told APF that the basis of a grant was Purdue's desire to "strategically align its investments in nonprofit organizations that share [its] business interests."

201. In practice, APF operated in close collaboration with opioid makers. On several occasions, representatives of the drug companies, often at informal meetings at Front Group conferences, suggested activities and publications for APF to pursue. APF then submitted grant proposals seeking to fund these activities and publications, knowing that drug companies would support projects conceived as a result of these communications.

202. APF assisted in other marketing projects for drug companies. One project funded by another drug company – the *APF Reporter's Guide: Covering Pain and Its Management* (2009) – recycled text that was originally created as part of the company's training document.

203. The same drug company made general grants, but even then it directed how APF used them. In response to a an APF request for funding to address a potentially damaging state Medicaid decision related to pain medications generally, the company representative responded, "I provided an advocacy grant to APF this year – this would be a very good issue on which to use some of that. How does that work?"

204. The close relationship between APF and the drug company was not unique, but mirrors relationships between APF and Defendants. APF's clear lack of independence – in its finances, management, and mission – and its willingness to allow Defendants to control its activities and messages support an inference that each Defendant that worked with it was able to exercise editorial control over its publications.

205. Indeed, the U.S. Senate Finance Committee began looking into APF in May 2012 to determine the links, financial and otherwise, between the organization and the manufacturers of opioid painkillers. The investigation caused considerable damage to APF's credibility as an objective and neutral third party and Defendants stopped funding it. Within days of being

targeted by Senate investigation, APF's board voted to dissolve the organization "due to irreparable economic circumstances." APF "cease[d] to exist, effective immediately."[115]

(2) The American Academy of Pain Medicine

206. The American Academy of Pain Medicine, with the assistance, prompting, involvement, and funding of Defendants, issued the treatment guidelines discussed in Section IV.C.2.c and sponsored and hosted medical education programs essential to Defendants' deceptive marketing of chronic opioid therapy.

207. AAPM has received over $2.2 million in funding since 2009 from opioid manufacturers. AAPM maintained a corporate relations council, whose members paid $25,000 a year (on top of other funding) to participate. The benefits include allowing members to present educational programs at off-site dinner symposia in connection with AAPM's marquee event – its annual meeting held in Palm Springs, California or other resort locations. AAPM describes the annual event as an "exclusive venue" for offering education programs to doctors. Membership in the corporate relations council also allows drug company executives and marketing staff to meet with AAPM executive committee members in small settings. Defendants Endo, Purdue, Cephalon, and Actavis were members of the council and presented deceptive programs to doctors who attended this annual event.

208. AAPM is viewed internally by Endo as "industry friendly," with Endo advisers and speakers among its active members. Endo attended AAPM conferences, funded its CMEs, and distributed its publications. The conferences sponsored by AAPM heavily emphasized sessions on opioids – 37 out of roughly 40 at one conference alone. AAPM's presidents have

[115] http://www.painfoundation.org.

included top industry-supported KOLs Perry Fine, Russell Portenoy, and Lynn Webster. Dr. Webster was even elected president of AAPM while under a DEA investigation. Another past President, Dr. Scott Fishman, stated he would place the organization "at the forefront" of teaching that "the risks of addiction are … small and can be managed."[116]

3. Defendants acted in concert with KOLs and Front Groups in the creation, promotion, and control of unbranded marketing.

209. Like cigarette makers, which engaged in an industry-wide effort to misrepresent the safety and risks of smoking, Defendants worked with each other and with the Front Groups and KOLs they funded and directed to carry out a common scheme to deceptively market the risks, benefits, and superiority of opioids to treat chronic pain.

210. Defendants acted through and with the same network of Front Groups, funded the same KOLs, and often used the very same language and format to disseminate the same deceptive messages. These KOLs have worked reciprocally with Defendants to promote misleading messaging regarding the appropriate use of opioids to treat chronic pain. Although participants knew this information was false and misleading, these misstatements were nevertheless disseminated to Mississippi prescribers and patients.

211. One vehicle for their collective collaboration was the Pain Care Forum ("PCF"). PCF was and continues to be run not by APF but by Defendant Purdue's in-house lobbyist, Burt Rosen. PCF began in 2004 with the stated goals of offering "a setting where multiple organizations can share information" and "promote and support taking collaborative action regarding federal pain policy issues." APF President Will Rowe described the Forum as "a

[116] Interview with Scott M. Fishman, MD, Professor of Anesthesiology and Pain Medicine, Chief of the Division of Pain Medicine, Univ. of Cal., Davis (2005), http://www.medscape.org/viewarticle/500829.

deliberate effort to positively merge the capacities of industry, professional associations, and patient organizations."

212. PCF is comprised of representatives from opioid manufacturers and distributors (including Cephalon, Endo, Janssen, and Purdue); doctors and nurses in the field of pain care; professional organizations (*e.g.*, American Academy of Pain Management, APS, and American Society of Pain Educators); patient advocacy groups (*e.g.*, APF and ACPA); and other like-minded organizations (*e.g.*, FSMB and Wisconsin Pain & Policy Studies Group), almost all of which received substantial funding from Defendants.

213. PCF, for example, developed and disseminated "consensus recommendations" for a Risk Evaluation and Mitigation Strategy ("REMS") for long-acting opioids that the FDA mandated in 2009 to communicate the risks of opioids to prescribers and patients.[117] This was critical because a REMS that went too far in narrowing the uses or benefits or highlighting the risks of chronic opioid therapy would deflate Defendants' marketing efforts. The recommendations – drafted by Will Rowe of APF – claimed that opioids were "essential" to the management of pain, and that the REMS "should acknowledge the importance of opioids in the management of pain and should not introduce new barriers."[118] As laid out below in Section IV.E, Defendants worked with PCF members to limit the reach and manage the message of the REMS, which enabled them to maintain, and not undermine, their deceptive marketing of opioids for chronic pain.

[117] The FDA can require a drug maker to develop a REMS – which could entail (as in this case) an education requirement or distribution limitation – to manage serious risks associated with a drug.

[118] Defendants also agreed that short-acting opioids should also be included in REMS as not to disadvantage the long-acting, branded drugs.

4. Defendants developed plans to target vulnerable and lucrative populations.

a. Elderly

214. Elderly patients taking opioids have been found to suffer elevated fracture risks, greater risk for hospitalizations, and increased vulnerability to adverse drug effects and interactions, such as respiratory depression, which, as Defendants acknowledge in their labels (but not in their marketing), occurs more frequently in elderly patients. A 2010 paper in the Archives of Internal Medicine reported that elderly patients who used opioids had a significantly higher rate of death, heart attacks, and strokes than users of NSAIDs. Defendants' targeted marketing to the elderly and the absence of cautionary language in their promotional materials flies in the face of scientific evidence and their own labels, and it creates a heightened risk of serious injury to elderly patients.

215. Defendants also promoted the notion – again without adequate scientific foundation – that the elderly are particularly unlikely to become addicted to opioids. AGS' 2009 Guidelines which Purdue, Endo, and Janssen publicized, for example, described the risk of addiction as "exceedingly low in older patients with no current or past history of substance abuse." Yet a 2010 study examining overdoses among long-term opioid users found that patients 65 or older were among those with the largest number of serious overdoses.[119]

216. Defendants' efforts have paid off. Since 2007, prescriptions for the elderly have grown at twice the rate of prescriptions for adults between the ages of 40 and 59.[120] Based on

[119] John Fauber & Ellen Gabler, *Narcotic Painkiller Use Booming Among Elderly*, Milwaukee Journal-Sentinel / Medpage Today (May 30, 2012).

[120] *Id.*

anecdotal evidence, many of these elderly patients started on opioids for chronic back pain or arthritis.

b. Veterans

217. Veterans, too, are suffering greatly from the effects of Defendants' targeted marketing. A 2008 survey showed prescription drug abuse among military personnel doubled from 2002 to 2005, and then nearly tripled again over the next three years. In 2009, military doctors wrote 3.8 million prescriptions for narcotic pain pills – four times as many as they did in 2001.[121] Further, one-third of veterans prescribed opioids as of 2012 remained on take-home opioids for more than 90 days.[122] Although many of these veterans are returning from service with traumatic injuries, the increase in opioid prescribing is disproportionate to the population and, in far too many cases, unsuited for their treatment. One survey of soldiers who had recently returned from combat showed that 15.1% had received opioid-based therapy to manage their chronic pain and, among those respondents, 23.2% said they had used opioids in the month before being surveyed, an indication that many of them were using the drugs long-term.[123] Among former service members receiving VA services nationally in a single year (2005), 1,013 had died of accidental drug overdoses – double the rate of the civilian population.[124]

[121] American-Statesman Investigative Team, Prescription drug abuse, overdoses haunt veterans seeking relief from physical, mental pain, Austin American-Statesman (Sept. 29, 2012).

[122] Bill Briggs, VA Docs Defied Opiate Rules in Treating Vets, Audit Finds, NBC News (May 15, 2014).

[123] Robin L. Toblin, Ph.D., *et al*., Chronic Pain and Opioid Use in US Soldiers After Combat Deployment, JAMA Intern Med 2014; 174[8]:1400-1401.

[124] American-Statesman Investigative Team, *supra*.

218. Mississippi has a substantial population of veterans who must cope with the consequences of overprescribing opioids. As of September 20, 2014, Mississippi had 220,389 veterans, according to the U.S. Department of Veterans Affairs.

219. Opioids are particularly dangerous to veterans. According to a study published in the 2013 Journal of American Medicine, veterans returning from Iraq and Afghanistan who were prescribed opioids have a higher incidence of adverse clinical outcomes, like overdoses and self-inflicted and accidental injuries, than the general population.[125] Additionally, 40% of veterans with post-traumatic stress disorder received opioids and benzodiazepines (anti-anxiety drugs) that, when mixed with alcohol, can cause respiratory depression and death. *Id*. Yet, according to a VA Office of Inspector General Report, 92.6% of veterans who were prescribed opioid drugs were also prescribed benzodiazepines.[126] Again, as with elderly patients, Defendants both purposefully sought to increase opioid prescribing to this vulnerable group and omitted from their promotional materials the known serious risks opioids posed to them.

220. *Exit Wounds*, a 2009 publication sponsored by Purdue and distributed by APF with grants from Janssen, written as a personal narrative of one veteran, describes opioids as "underused" and the "gold standard of pain medications" and fails to disclose the risk of addiction, overdose, or injury. It notes that opioid medications "increase a person's level of functioning" and that "[l]ong experience with opioids shows that people who are not predisposed to addiction are unlikely to become addicted to opioid pain medications." The book also asserts that "[d]enying a person opioid pain medication because he or she has a history of substance abuse or addiction is contrary to the model guidelines for prescribing opioids, published by the

[125] Seal, Association of Mental Health Disorders, *supra*.

[126] Briggs, *supra*.

U.S. Federation of State Medical Boards." As laid out above, the FSMB itself received support from Defendants during the time it created and published its guidelines.

221. *Exit Wounds* minimizes the risks from chronic opioid therapy and does not disclose the risk that opioids may cause fatal interactions with benzodiazepines taken by a significant number of veterans.[127] It is not the unbiased narrative of a returning war veteran. It is pure marketing, sponsored by Purdue, Endo, and Janssen. Yet, Janssen, for example, supported the marketing effort and its insufficient disclosures, despite acknowledging on the label for its opioid Duragesic that its use with benzodiazepines "may cause respiratory depression, hypotension, and profound sedation or potentially result in coma." A similar warning is found on the labels of other Defendants' opioids.

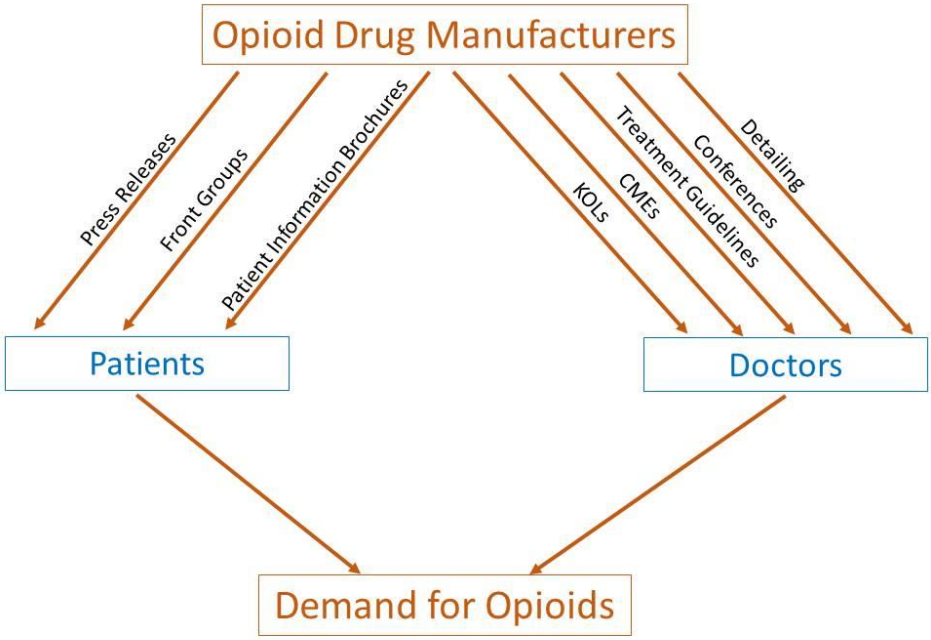
222. The deceptive nature of *Exit Wounds* is made obvious in comparing it to guidance on opioids published by the VA and DOD in 2010 and 2011. The VA's *Taking Opioids Responsibly* describes opioids as "dangerous." It cautions against taking extra doses and mentions the risk of overdose and the dangers of interactions with alcohol. The list of side effects from opioids includes decreased hormones, sleep apnea, hyperalgesia, addiction, immune system changes, birth defects and death – none of which is disclosed in *Exit Wounds*.

5. Why Defendants' plan worked.

223. Defendants succeeded in changing previously accepted medical and scientific beliefs about opioids because their marketing messages infected every source of information to

[127] FDA guidance states that materials designed to target a particular audience should disclose risks particular to that audience. *See* FDA Notice, Guidance for Industry, *Brief Summary and Adequate Directions for Use: Disclosing Risk Information in Consumer-Directed Print Advertisements and Promotional Labeling for Prescription Drugs* (Aug. 6, 2015).

which physicians turn. Even information that appeared to come from "independent" third parties like KOLs or Front Groups came from Defendants first.



As the above figure illustrates, marketing efforts by pharmaceutical companies include sponsoring CME events and conferences and developing peer networks through the use of KOLs who, in turn, discuss the drug at issue with other physicians and, because of the notoriety they gain from those activities, are selected to prepare treatment guidelines. It is not always obvious that these tactics are actually strategies developed by the pharmaceutical companies to market their drugs. Yet because of these tactics, there was no other source of information about the use of chronic opioid therapy other than Defendants.

224. And even though the medical community has spent over a decade accepting Defendants' marketing messages as science, it remains largely unaware that the purportedly "educational" materials on which they relied could, without exception, be traced back to Defendants. This is, in part, because the relationship between drug manufacturers and physicians

is not necessarily one of cause and effect. Pharmaceutical companies direct their marketing efforts at high prescribing physicians, who are in turn anointed KOLs, and therefore speak at CMEs, write articles, and give presentations to physicians, which then in turn generates increasing demand for Defendants' opioids, which creates more high prescribing physicians who became KOLs, and the cycle continues. As one physician author recently explained:

> [D]octors are badly placed to appraise the science around medications. They are the very group to which drugs are marketed. They are the ones who read the ghost-written journal articles. It is their continuing medical education that is largely funded by pharmaceutical companies. It is they who, in the interests of overcoming their cognitive dissonance, overload the myriad conflicts of interest they are confronted with in daily clinical life.[128]

D. Why Defendants' Claims Are Deceptive and Unfair

225. Defendants' marketing of opioids for long-term use to treat chronic pain, both directly and with and through third parties, included information that was false, deceptive, contract to credible scientific evidence and their own labels, and lacked balance and substantiation. Their marketing materials omitted material information about the risks of opioids, and overstated their benefits. Moreover, Defendants inaccurately suggested that chronic opioid therapy was supported by evidence, and failed to disclose the lack of evidence in support of treating chronic pain with opioids.

226. There are seven primary misleading and unfounded representations, laid out in greater detail below. Defendants:

- Misrepresented that opioids improve function;

[128] *See* Jeremy Wallace, MD, *A Long and Troubled Relationship*, *available at*: http://www.madinamerica.com/2015/03/long-troubled-relationship.

- Concealed the link between long-term use of opioids and addiction;
- Misrepresented that addiction risk can be managed;
- Masked the signs of addiction by calling it "pseudoaddiction;"
- Falsely claimed withdrawal is easily managed;
- Misrepresented or omitted the greater dangers from higher doses of opioids; and
- Deceptively minimized the adverse effects of opioids and overstated the risks of NSAIDs.

227. In addition to these misstatements, Purdue purveyed an eighth deception – laid out in detail below in Section IV.D.8 – that OxyContin provides a full 12 hours of pain relief.

228. Exacerbating each of these misrepresentations and deceptions was the collective effort of Defendants and third parties to hide from the medical community the fact that the FDA "is not aware of adequate and well-controlled studies of opioid use longer than 12 weeks."[129]

1. Defendants, directly or indirectly, misrepresented that opioids improve function.

229. Each of the following materials was created with the expectation that, by instructing patients and prescribers that opioids would improve patients' function and quality of life, patients would demand opioids and doctors would prescribe them. These claims also encouraged doctors to continue opioid therapy in the belief that failure to improve pain, function, or quality of life could be overcome by increasing doses or prescribing supplemental short-acting opioids to take on an as-needed basis for breakthrough pain.

[129] Letter from Janet Woodcock, M.D., Dir., Ctr. for Drug Eval. & Res., to Andrew Kolodny, M.D., Pres. Physicians for Responsible Opioid Prescribing, Re Docket No. FDA-2012-P-0818 (Sept. 10, 2013).

230. However, not only is there no evidence of improvement in long-term functioning, a 2006 study-of-studies found that "[f]or functional outcomes … other analgesics were significantly more effective than were opioids."[130] Studies of the use of opioids in chronic conditions for which they are commonly prescribed, such as low back pain, corroborate this conclusion and have failed to demonstrate an improvement in patients' function. Instead, research consistently shows that long-term opioid therapy for patients who have lower back injuries does not cause patients to return to work or physical activity.[131] Indeed, one Defendant's own internal marketing plans characterized functional improvement claims as "aspirational." Another acknowledged in 2012 that "[s]ignificant investment in clinical data [was] needed" to establish opioids' effect on mitigating quality of life issues, like social isolation.

231. As laid out below in Section IV.D.7, the long-term use of opioids carries a host of serious side effects, including addiction, mental clouding and confusion, sleepiness, hyperalgesia, immune-system and hormonal dysfunction, that degrade, rather than improve, patients' ability to function. Defendants often omitted these adverse effects from their publications, as well as omitting certain risks of drug interactions.

232. Yet each of the following statements by Defendants, which are further discussed, by Defendant, in Section IV.E, suggests that the long-term use of opioids improve patients' function and quality of life, and that scientific evidence supports this claim.

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[130] Andrea D. Furlan, *et al*., *Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects*, 174(11) Can. Med. Ass'n J. 1589-1594 (2006). This study revealed that efficacy studies do not typically include data on opioid addiction, such that, if anything, the data overstate effectiveness.

[131] Moreover, users of opioids had the highest increase in the number of headache days per month, scored significantly higher on the Migraine Disability Assessment (MIDAS), and had higher rates of depression, compared to non-opioid users. They also were more likely to experience sleepiness, confusion, and rebound headaches, and reported a lower quality of life than patients taking other medications.

Actavis	a. Documents from a 2010 sales training indicate that Actavis trained its sales force to instruct prescribers that "***most*** chronic benign pain patients do have ***markedly improved ability to function*** when maintained on chronic opioid therapy." (Emphasis added.) b. Documents from a 2010 sales training indicate that Actavis trained its sales force that increasing and restoring function is an expected outcome of chronic Kadian therapy, including physical, social, vocational, and recreational function. c. Actavis distributed a product advertisement that claimed that use of Kadian to treat chronic pain would allow patients to return to work, relieve "stress on your body and your mental health," and cause patients to enjoy their lives." The FDA warned Actavis such claims were misleading, writing: "We are not aware of substantial evidence or substantial clinical experience demonstrating that the magnitude of the effect of the drug has in alleviating pain, taken together with any drug-related side effects patients may experience … results in any overall positive impact on a patient's work, physical and mental functioning, daily activities, or enjoyment of life."[132]
Cephalon	d. Cephalon sponsored the FSMB's *Responsible Opioid Prescribing* (2007), which taught that relief of pain itself improved patients' function. *Responsible Opioid Prescribing* explicitly describes functional improvement as the goal of a "long-term therapeutic treatment course." Cephalon also spent $150,000 to purchase copies of the book in bulk and distributed the book through its pain sales force to 10,000 prescribers and 5,000 pharmacists. e. Cephalon sponsored the American Pain Foundation's *Treatment Options: A Guide for People Living with Pain* (2007), which taught patients that opioids when used properly "give [pain patients] a quality of life we deserve." The *Treatment Options* guide notes that non-steroidal anti-inflammatory drugs have greater risks with prolonged duration of use, but there was no similar warning for opioids. APF distributed 17,200 copies in one year alone, according to its 2007 annual report, and the publication is currently available online. f. Cephalon sponsored a CME written by key opinion leader Dr. Lynn Webster, titled *Optimizing Opioid Treatment for Breakthrough Pain*, which was offered online by Medscape, LLC from September 28, 2007,

[132] Warning Letter from Thomas Abrams, Dir., FDA Div. of Mktg., Adver., & Commc'ns, to Doug Boothe, CEO, Actavis Elizabeth LLC (Feb. 18. 2010), *available at*: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm259240.htm.

	through December 15, 2008. The CME taught that Cephalon's Actiq and Fentora improve patients' quality of life and allow for more activities when taken in conjunction with long-acting opioids.
Endo	g. Endo sponsored a website, painknowledge.com, through APF and NIPC, which claimed in 2009 that with opioids, "your level of function should improve; you may find you are now able to participate in activities of daily living, such as work and hobbies, that you were not able to enjoy when your pain was worse." Endo continued to provide funding for this website through 2012, and closely tracked unique visitors to it. h. A CME sponsored by Endo, titled *Persistent Pain in the Older Patient*, taught that chronic opioid therapy has been "shown to reduce pain and improve depressive symptoms and cognitive functioning." i. Endo distributed handouts to prescribers that claimed that use of Opana ER to treat chronic pain would allow patients to perform work as a chef. This flyer also emphasized Opana ER's indication without including equally prominent disclosure of the "moderate to severe pain" qualification.[133] j. Endo's sales force distributed FSMB's *Responsible Opioid Prescribing* (2007). This book taught that relief of pain itself improved patients' function. *Responsible Opioid Prescribing* explicitly describes functional improvement as the goal of a "long-term therapeutic treatment course." k. Endo provided grants to APF to distribute *Exit Wounds* to veterans, which taught that opioid medications "*increase* your level of functioning" (emphasis in the original). *Exit Wounds* also omits warnings of the risk of interactions between opioids and benzodiazepines, which would increase fatality risk. Benzodiazepines are frequently prescribed to veterans diagnosed with post-traumatic stress disorder.
Janssen	l. Janssen sponsored a patient education guide titled *Finding Relief: Pain Management for Older Adults* (2009), which its personnel reviewed and approved and its sales force distributed. This guide features a man playing golf on the cover and lists examples of expected functional improvement from opioids, like sleeping through the night, returning to work, recreation, sex, walking, and climbing stairs. The guide states as a "fact" that "opioids may make it *easier* for people to live normally" (emphasis in the original). The myth/fact structure implies authoritative backing for the claim that does not exist. The targeting of older adults also ignored heightened opioid risks in this population.

[133] FDA regulations require that warnings or limitations be given equal prominence in disclosure, and failure to do so constitutes "misbranding" of the product. 21 C.F.R. § 202.1(e)(3); *see also* 21 U.S.C. § 331(a).

	m. Janssen sponsored, developed, and approved content of a website, *Let's Talk Pain* in 2009, acting in conjunction with the APF, AAPM, and ASPMN, whose participation in *Let's Talk Pain* Janssen financed and orchestrated. This website featured an interview, which was edited by Janssen personnel, claiming that opioids were what allowed a patient to "continue to function," inaccurately implying her experience would be representative. This video is still available today on youtube.com. n. Janssen provided grants to APF to distribute *Exit Wounds* to veterans, which taught that opioid medications "*increase* your level of functioning" (emphasis in the original). *Exit Wounds* also omits warnings of the risk of interactions between opioids and benzodiazepines, which would increase fatality risk. Benzodiazepines are frequently prescribed to veterans diagnosed with post-traumatic stress disorder.
Purdue	o. Purdue ran a series of advertisements for OxyContin in 2012 in medical journals titled "Pain vignettes," which were case studies featuring patients, each with pain conditions persisting over several months, recommending OxyContin for each. One such patient, "Paul," is described to be a "54-yearold writer with osteoarthritis of the hands," and the vignettes imply that an OxyContin prescription will help him work more effectively. p. Purdue sponsored APF's *A Policymaker's Guide to Understanding Pain & Its Management*, which inaccurately claimed that "multiple clinical studies" have shown that opioids are effective in improving daily function, psychological health, and health-related quality of life for chronic pain patients." The sole reference for the functional improvement claim noted the absence of long-term studies and actually stated: "For functional outcomes, the other analgesics were significantly more effective than were opioids." The *Policymaker's Guide* is still available online. q. Purdue sponsored APF's *Treatment Options: A Guide for People Living with Pain* (2007), which counseled patients that opioids, when used properly, "give [pain patients] a quality of life we deserve." APF distributed 17,200 copies in one year alone, according to its 2007 annual report, and the guide currently is available online. r. Purdue sponsored APF's *Exit Wounds* (2009), which taught veterans that opioid medications "increase your level of functioning." *Exit Wounds* also omits warnings of the risk of interactions between opioids and benzodiazepines, which would increase fatality risk. Benzodiazepines are frequently prescribed to veterans diagnosed with post-traumatic stress disorder.

	s. Purdue sponsored the FSMB's *Responsible Opioid Prescribing* (2007), which taught that relief of pain itself improved patients' function. *Responsible Opioid Prescribing* explicitly describes functional improvement as the goal of a "long-term therapeutic treatment course." Purdue also spent over $100,000 to support distribution of the book.

2. Defendants, directly and indirectly, concealed the truth about how long-term opioid use leads to addiction.

233. The fraudulent representation that opioids are rarely addictive is central to Defendants' scheme. To reach chronic pain patients, Defendants, and the Front Groups and KOLs that they directed, assisted, and collaborated with, had to overcome doctors' legitimate fears that opioids would addict their patients. The risk of addiction is an extremely weighty risk – condemning patients to, among other things, dependence, compulsive use, haziness, a lifetime of battling relapse, and a dramatically heightened risk of serious injury or death. But for Defendants' campaign to convince doctors otherwise, finding benefits from opioid use for common chronic pain conditions sufficient to justify that risk would have posed a nearly insurmountable challenge.

234. Through their well-funded, comprehensive marketing efforts, Defendants and their KOLs and Front Groups were able to change prescriber perceptions, despite the well-settled historical understanding and clear evidence that opioids taken long-term are often addictive. Defendants and their third-party partners: (a) brazenly maintained that the risk of addiction for patients who take opioids long-term was low; and (b) omitted the risk of addiction and abuse from the list of adverse outcomes associated with chronic opioid use, even though the frequency and magnitude of the risk – and Defendants' own labels – compelled disclosure.

235. Further, in addition to falsely claiming opioids had low addiction risk or omitting disclosure of the risk of addiction altogether, Defendants employed language that conveyed to

prescribers that the drugs had lower potential for abuse and addiction. Further, in addition to making outright misrepresentations about the risk of addiction, or failing to disclose that serious risk at all, Defendants used code words that conveyed to prescribers that their opioid was less prone to abuse and addiction. For instance, sales representatives for Actavis, Endo, Janssen, and Purdue promoted their drugs as having "steady-state" properties with the intent and expectation that prescribers would understand this to mean that their drugs caused less of a rush or a feeling of euphoria, which can trigger abuse and addiction. Further, Endo actively promoted its reformulated Opana ER on the basis that it was "designed to be crush-resistant," suggesting both (a) that Endo had succeeded in making the drug harder to adulterate, and (b) that it was less addictive, in consequence. In fact, however, Endo knew that "the clinical significance of INTAC Technology or its impact on abuse/misuse has not been established for Opana ER" and that Opana ER could still be ground and cut into small pieces by those looking to abuse the drug. In the same vein, Janssen denied that Nucynta ER was an opioid and claimed that it was not addictive, and Purdue claimed that its opioids were not favored by addicts and did not produce a buzz, all of which falsely suggested that its opioids were less likely to be abused or addictive.

236. Each of the following was created with the expectation that, by instructing patients and prescribers that addiction rates are low and that addiction is unlikely when opioids are prescribed for pain, doctors would prescribe opioids to more patients. For example, one publication sponsored exclusively by Purdue – APF's 2011 *A Policymaker's Guide to Understanding Pain & Its Management* – claimed that opioids are not prescribed often enough because of "misconceptions about opioid addiction."

237. Acting directly or with and through third parties, each of the Defendants claimed the potential for addiction from its drugs was relatively small, or non-existent, even though there

was no scientific evidence to support those claims, and the available research contradicted them. A recent literature survey found that while ranges of "problematic use" of opioids ranged from <1% to 81%,[134] abuse averages between 21% and 29% and addiction between 8% and 12%.[135] These estimates are well in line with Purdue's own studies, showing that between 8% and 13% of OxyContin patients became addicted, but on which Purdue chose not to rely, citing instead the Porter-Jick letter.

238. The FDA has found as well that 20% of opioid patients use two or more pharmacies, 26% obtain opioids from two or more prescribers, and 16.5% seek early refills – all potential "red flags" for abuse or addiction.[136] The FDA in fact has ordered manufacturers of long-acting opioids to "[c]onduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose and death associated with long-term use of opioid analgesics for management of chronic pain," in recognition of the fact that it found "high rates of addiction" in the medical literature.[137]

239. Of course, the significant (and growing) incidence of abuse, misuse, and addiction to opioids also is powerful evidence that Defendants' statements regarding the low risk of addiction were and are untrue. This was well-known to Defendants, who had access to sales data

[134] Cited for the low end of that range was the 1980 Porter-Jick letter in the *New England Journal of Medicine.*

[135] Kevin Vowels, *et al.*, *Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis*, 156 PAIN 569-76 (April 2015).

[136] Len Paulozzi, M.D., "Abuse of Marketed Analgesics and Its Contribution to the National Problem of Drug Abuse," *available at*: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM233244.pdf.

[137] September 10, 2013 letter from Bob Rappaport, M.D., to NDA applicants of ER/LA opioid analgesics, *available at*: http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf ; Letter from Janet Woodcock, M.D., *supra*.

and reports, adverse event reports, federal abuse and addiction-related surveillance data, and other sources that demonstrated the widening epidemic of opioid abuse and addiction.

240. Acting directly or through and with third parties, each of the Defendants claimed the potential for addiction even from long-term use of its drugs was relatively small, or nonexistent, even though that was false and there was no scientific evidence to support it. Examples of these misrepresentations are laid out below, and further discussed, by Defendant, in Section IV.E:

Actavis	a. Documents from a 2010 sales training indicate that Actavis trained its sales force that long-acting opioids were less likely to produce addiction than short-acting opioids, although there is no evidence that either form of opioid is less addictive or that any opioids can be taken long-term without the risk of addiction. b. Actavis caused a patient education brochure to be distributed in 2007 that claimed addiction is possible, but it is "less likely if you have never had an addiction problem." Although the term "less likely" is not defined, the overall presentation suggests the risk is so low as not to be a worry.
Cephalon	c. Cephalon sponsored and facilitated the development of a guidebook, *Opioid Medications and REMS: A Patient's Guide*, which claims, among other things, that "patients without a history of abuse or a family history of abuse do not commonly become addicted to opioids." d. Cephalon sponsored APF's *Treatment Options: A Guide for People Living with Pain* (2007), which taught that addiction is rare and limited to extreme cases of unauthorized dose escalations, obtaining opioids from multiple sources, or theft.
Endo	e. Endo trained its sales force in 2012 that use of long-acting opioids resulted in increased patient compliance, without any supporting evidence. f. Endo's advertisements for the 2012 reformulation of Opana ER claimed it was *designed to be crush resistant*, in a way that conveyed that it was less likely to be abused. This claim was false; the FDA warned in a May 10, 2013 letter that there was no evidence Endo's design "would provide a reduction in oral, intranasal or intravenous abuse" and Endo's "postmarketing data submitted are insufficient to support any conclusion about the overall or route-specific rates of

	abuse." Further, Endo instructed its sales representatives to repeat this claim about "design," with the intention of conveying Opana ER was less subject to abuse. g. Endo sponsored a website, painknowledge.com, through APF and NIPC, which claimed in 2009 that: "[p]eople who take opioids as prescribed usually do not become addicted." Although the term "usually" is not defined, the overall presentation suggests the risk is so low as not to be a worry. The language also implies that as long as a prescription is given, opioid use will not become problematic. Endo continued to provide funding for this website through 2012, and closely tracked unique visitors to it. h. Endo sponsored a website, PainAction.com, which stated "Did you know? Most chronic pain patients do not become addicted to the opioid medications that are prescribed for them." i. Endo sponsored CMEs published by APF's NIPC, of which Endo was the sole funder, titled *Persistent Pain in the Older Adult* and *Persistent Pain in the Older Patient*. These CMEs claimed that opioids used by elderly patients present "possibly less potential for abuse than in younger patients[,]" which lacks evidentiary support and deceptively minimizes the risk of addiction for elderly patients. j. Endo distributed an education pamphlet with the Endo logo titled *Living with Someone with Chronic Pain*, which inaccurately minimized the risk of addiction: "Most health care providers who treat people with pain agree that most people do not develop an addiction problem." k. Endo distributed a patient education pamphlet edited by key opinion leader Dr. Russell Portenoy titled *Understanding Your Pain: Taking Oral Opioid Analgesics*. It claimed that "[a]ddicts take opioids for other reasons [than pain relief], such as unbearable emotional problems." This implies that pain patients prescribed opioids will not become addicted, which is unsupported and untrue. l. Endo contracted with AGS to produce a CME promoting the 2009 guidelines for the *Pharmacological Management of Persistent Pain in Older Persons*. These guidelines falsely claim that "the risks [of addiction] are exceedingly low in older patients with no current or past history of substance abuse." None of the references in the guidelines corroborates the claim that elderly patients are less likely to become addicted to opioids, and there is no such evidence. Endo was aware of the AGS guidelines' content when it agreed to provide this funding,

	and AGS drafted the guidelines with the expectation it would seek drug company funding to promote them after their completion. m. Endo provided grants to APF to distribute *Exit Wounds* (2009) to veterans, which taught that "[l]ong experience with opioids shows that people who are not predisposed to addiction are very unlikely to become addicted to opioid pain medications." Although the term "very unlikely" is not defined, the overall presentation suggests that the risk is so low as not to be a worry.
Janssen	n. Janssen sponsored a patient education guide titled *Finding Relief: Pain Management for Older Adults* (2009), which its personnel reviewed and approved and which its sales force distributed. This guide described a "myth" that opioids are addictive, and asserts as fact that "[m]any studies show that opioids are *rarely* addictive when used properly for the management of chronic pain." Although the term "rarely" is not defined, the overall presentation suggests the risk is so low as not to be a worry. The language also implies that as long as a prescription is given, opioid use is not a problem. o. Janssen contracted with AGS to produce a CME promoting the 2009 guidelines for the *Pharmacological Management of Persistent Pain in Older Persons*. These guidelines falsely claim that "the risks [of addiction] are exceedingly low in older patients with no current or past history of substance abuse." The study supporting this assertion does not analyze addiction rates by age and, as already noted, addiction remains a significant risk for elderly patients. Janssen was aware of the AGS guidelines' content when it agreed to provide this funding, and AGS drafted the guidelines with the expectation it would seek drug company funding to promote them after their completion. p. Janssen provided grants to APF to distribute *Exit Wounds* (2009) to veterans, which taught that [l]ong experience with opioids shows that people who are not predisposed to addiction are very unlikely to become addicted to opioid pain medications." Although the term "very unlikely" is not defined, the overall presentation suggests the risk is so low as not to be a worry. q. Janssen currently runs a website, *Prescriberesponsibly.com*, which claims that concerns about opioid addiction are "overstated."
Purdue	r. Purdue published a prescriber and law enforcement education pamphlet in 2011 entitled *Providing Relief, Preventing Abuse*, which under the heading, "Indications of Possible Drug Abuse," shows pictures of the stigmata of injecting or snorting opioids- skin popping, track marks, and perforated nasal septa. In fact, opioid addicts who resort to these extremes are uncommon; the far more typical reality is

	patients who become dependent and addicted through oral use.[138] Thus, these misrepresentations wrongly reassure doctors that as long as they do not observe those signs, they need not worry that their patients are abusing or addicted to opioids. s. Purdue sponsored APF's *A Policymaker 's Guide to Understanding Pain & Its Management,* which inaccurately claimed that less than 1% of children prescribed opioids will become addicted. This publication is still available online. This publication also asserted that pain is undertreated due to "misconceptions about opioid addiction." t. Purdue sponsored APF's *Treatment Options: A Guide for People Living with Pain* (2007), which asserted that addiction is rare and limited to extreme cases of unauthorized dose escalations, obtaining opioids from multiple sources, or theft. u. A Purdue-funded study with a Purdue co-author claimed that "evidence that the risk of psychological dependence or addiction is low in the absence of a history of substance abuse."[139] The study relied only on the 1980 Porter-Jick letter to the editor concerning a chart review of hospitalized patients, not patients taking Purdue's long-acting, take-home opioid. Although the term "low" is not defined, the overall presentation suggests the risk is so low as not to be a worry. v. Purdue contracted with AGS to produce a CME promoting the 2009 guidelines for the *Pharmacological Management of Persistent Pain in Older Persons*. These guidelines falsely claim that "the risks [of addiction] are exceedingly low in older patients with no current or past history of substance abuse." None of the references in the guidelines corroborates the claim that elderly patients are less likely to become addicted to opioids and the claim is, in fact, untrue. Purdue was aware of the AGS guidelines' content when it agreed to provide this funding, and AGS drafted the guidelines with the expectation it would seek drug company funding to promote them after their completion. w. Purdue sponsored APF's *Exit Wounds* (2009), which counseled veterans that "[l]ong experience with opioids shows that people who are not predisposed to addiction are very unlikely to become addicted to opioid pain medications." Although the term "very unlikely" is not

[138] Purdue itself submitted briefing materials in October 2010 to a meeting of the IDA's Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee in which it stated that OxyContin was used non-medically by injection 4-17% of the time.

[139] Watson, Controlled-release oxycodone, *supra*.

	defined, the overall presentation suggests it is so low as not to be a worry.

241. In addition to denying or minimizing the risk of addiction and abuse generally, and as laid out in Section IV.E, Defendants also falsely claimed that their particular drugs were safer, less addictive, and less likely to be abused or diverted than their competitors' or predecessor drugs. In making these claims, Defendants said or implied that because their drug had a "steady-state" and did not produce peaks and valleys, which cause drug-seeking behavior – either to obtain the high or avoid the low – it was less likely to be abused or addicting. Endo also asserted in particular that, because a reformulation of Opana ER was (or was designed to be) abuse-deterrent or tamper-resistant, patients were less likely to become addicted to them. Defendants had no evidence to support any of these claims, which, by FDA regulation, must be based on head-to-head trials;[140] the claims also were false and misleading in that they misrepresented the risks of both the particular drug and opioids as a class.

242. Further, rather than honestly disclose the risk of addiction, Defendants, and the third parties they directed and assisted and whose materials they distributed, attempted to portray those who were concerned about addiction as unfairly denying treatment to needy patients. To increase pressure on doctors to prescribe chronic opioid therapy, Defendants turned the tables; it was doctors who fail to treat their patients' chronic pains with opioids – not doctors who cause their patients to become addicted to opioids – who are failing their patients (and subject to discipline). Defendants, directly and through third parties, claimed that purportedly overblown worries about addiction cause pain to be under-treated and opioids to be over-regulated and

[140] *See Guidance for Industry*, "Abuse-Deterrent Opioids—Evaluation and Labeling," April 2015 (describing requirements for premarket and postmarket studies).

under-prescribed. This mantra of under-treated pain and under-used drugs reinforced Defendants' messages that the risks of addiction and abuse were not significant and were overblown.

243. For example, Janssen's website, *Let's Talk Pain*, warns in a video posted online that "strict regulatory control has made many physicians reluctant to prescribe opioids. The unfortunate casualty in all of this is the patient, who is often undertreated and forced to suffer in silence." The program goes on to say: "Because of the potential for abusive and/or addictive behavior, many healthcare professionals have been reluctant to prescribe opioids for their patients …. This prescribing environment is one of many barriers that may contribute to the undertreatment of pain, a serious problem in the United States."

244. In the same vein, a Purdue website called *In the Face of Pain* complains, under the heading of "Protecting Access," that, through at least mid-2013, policy governing the prescribing of opioids was "at odds with" best medical practices by "unduly restricting the amounts that can be prescribed and dispensed"; "restricting access to patients with pain who also have a history of substance abuse"; and "requiring special government-issued prescription forms only for the medications that are capable of relieving pain that is severe." This unsupported and untrue rhetoric aims to portray doctors who do not prescribe opioids as uncaring, converting their desire to relieve patients' suffering into a mandate to prescribe opioids.

3. Defendants, directly or indirectly, misrepresented that addiction risk can be avoided or managed.

245. Defendants each continue to maintain to this day that most patients can safely take opioids long-term for chronic pain without becoming addicted. Presumably to explain why doctors encounter so many patients addicted to opioids, Defendants have come to admit that some patients could become addicted, but that doctors can avoid or manage that risk by using

screening tools or questionnaires. These tools, they say, identify those with higher addiction risks (stemming from personal or family histories of substance abuse, mental illness, or abuse) so that doctors can more closely monitor patients at greater risk of addiction.

246. There are three fundamental flaws in Defendants' assurances that doctors can consistently identify and manage the risk of addiction. First, there is no reliable scientific evidence that doctors can depend solely on the screening tools currently available to substantially limit the risk of addiction. Even if the tools are effective, they may not always be applied correctly and are subject to manipulation by patients. Second, there is no reliable scientific evidence that high-risk or addicted patients can take opioids long-term without triggering addiction, even with enhanced monitoring. Third, there is no reliable scientific evidence that patients without these red flags can take opioids free of addiction risk.

247. Addiction is difficult to predict on a patient-by-patient basis, and there are no reliable, validated tools to do so. A recent Evidence Report by the Agency for Healthcare Research and Quality ("AHRQ"), which "systematically review[ed] the current evidence on long-term opioid therapy for chronic pain" identified "[n]o study" that had "evaluated the effectiveness of risk mitigation strategies, such as use of risk assessment instruments, opioid management plans, patient education, urine drug screening, prescription drug monitoring program data, monitoring instruments, more frequent monitoring intervals, pill counts, or abuse-deterrent formulations on outcomes related to overdose, addiction, abuse or misuse."[141] Furthermore, attempts to treat high-risk patients, like those who have a documented predisposition to substance abuse, by resorting to patient contracts, more frequent refills, or urine

[141] The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain, Agency for Healthcare Res. & Quality (Sept. 19, 2014).

drug screening are not proven to work in the real world, if busy doctors even in fact attempt them.[142]

248. Most disturbingly, despite the widespread use of screening tools, patients with past substance use disorders – which every tool rates as a risk factor – receive, on average, higher doses of opioids.

249. Defendants' misrepresentations regarding the risk of addiction from chronic opioid therapy were particularly dangerous because they were aimed at general practitioners or family doctors (collectively, "GPs"), who treat many chronic conditions but often lack the time and expertise to closely manage patients on opioids by reviewing urine screens, counting pills, or conducting detailed interviews to identify other signs or risks of addiction. One study conducted by pharmacy benefits manager Express Scripts concluded, after analyzing 2011-2012 narcotic prescription data of the type regularly used by Defendants to market their drugs, that, of the more than half million prescribers of opioids during that time period, only 385 were identified as pain specialists.[143]

250. As described below, and in Section IV.E, each Defendant claimed that the risk of addiction could be avoided or managed, claims that are deceptive and without scientific support:

Actavis	a. Documents from a 2010 sales training indicate that Actavis trained its sales force that prescribers can use risk screening tools to limit the development of addiction.
Cephalon	b. Cephalon sponsored APF's *Treatment Options: A Guide for People Living with Pain* (2007), which taught patients that "opioid

[142] Michael Von Korff, *et al*., Long-term opioid therapy reconsidered, 155(5) Annals Internal Med. 325 (Sept. 2011); Laxmaiah Manchikanti, *et al.*, American Society of Interventional Pain Physicians (ASIPP) Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part I – Evidence Assessment, 15 Pain Physician S1 (2012).

[143] Express Scripts Lab, *A Nation in Pain: Focusing on U.S. Opioid Trends for Treatment of Short-Term and Longer-Term Pain* (December 2014), *available at:* http://lab.express-scripts.com/publications/~/media/d48ef3ee579848e7bf3f14af536d7548.ashx.

	agreements" between doctors and patients can "ensure that you take the opioid as prescribed."
Endo	c. Endo paid for a 2007 supplement[82] available for continuing education credit in the *Journal of Family Practice* and written by a Chicago-based doctor who later became a member of Endo's speakers bureau. This publication, titled *Pain Management Dilemmas in Primary Care: Use of Opioids*, recommended screening patients using tools like the Opioid Risk Tool or the Screener and Opioid Assessment for Patients with Pain, and advised that patients at high risk of addiction could safely (*e.g.*, without becoming addicted) receive chronic opioid therapy using a "maximally structured approach" involving toxicology screens and pill counts.
Purdue	d. Purdue's unbranded website, *In the Face of Pain* (inthefaceofpain.com) states that policies that "restrict[] access to patients with pain who also have a history of substance abuse" and "requiring special government-issued prescription forms for the only medications that are capable of relieving pain that is severe" are "at odds with" best medical practices.[144] e. Purdue sponsored a 2012 CME program taught by a Chicago-based KOL titled *Chronic Pain Management and Opioid Use: Easing Fears, Managing Risks, and Improving Outcomes*. This presentation recommended that use of screening tools, more frequent refills, and switching opioids could treat a high-risk patient showing signs of potentially addictive behavior. f. Purdue sponsored a 2011 webinar taught by Dr. Lynn Webster, titled *Managing Patient's Opioid Use: Balancing the Need and Risk*. This publication taught prescribers that screening tools, urine tests, and patient agreements have the effect of preventing "overuse of prescriptions" and "overdose deaths."

4. Defendants, directly and indirectly, created confusion through the use of misleading terms like "pseudoaddiction."

251. Defendants, by themselves or through third parties, developed and disseminated each of the following misrepresentations with the intent and expectation that, by instructing patients and prescribers that signs of addiction are actually the product of untreated pain, doctors

[144] *See In the Face of Pain Fact Sheet: Protecting Access to Pain Treatment*, Purdue Pharma L.P., *available at*: www.inthefaceofpain.com/content/uploads/2011/12/factsheet_ProtectingAccess.pdf.

would prescribe opioids to more patients and would continue to prescribe, and patients to use, opioids despite signs that the patient was addicted. The concept of pseudoaddiction was coined by Dr. David Haddox, who went to work for Purdue, and popularized in opioid therapy for chronic pain by Dr. Russell Portenoy, who consulted for Defendants Cephalon, Endo, Janssen, and Purdue. Much of the same language appears in other Defendants' treatment of this issue, highlighting the contrast between "undertreated pain" and "true addiction," as if patients could not experience both. As KOL Dr. Lynn Webster wrote: "[Pseudoaddiction] obviously became too much of an excuse to give patients more medication…. It led us down a path that caused harm. It is already something we are debunking as a concept."[145]

252. Each of the publications and statements below, which are further discussed, by Defendant, in Section IV.E, falsely states or suggests that the concept of "pseudoaddiction" is substantiated by scientific evidence and accurately describes the condition of patients who only need, and should be treated with, more opioids:

Actavis	a. Documents from a 2010 sales training indicate that Actavis trained its sales force to instruct physicians that aberrant behaviors like self-escalation of doses constituted "pseudoaddiction."
Cephalon	b. Cephalon sponsored FSMB's *Responsible Opioid Prescribing* (2007), which taught that behaviors such as "requesting drugs by name," "demanding or manipulative behavior," seeing more than one doctor to obtain opioids, and hoarding are all signs of pseudoaddiction. Cephalon also spent $150,000 to purchase copies of the book in bulk and distributed it through its pain sales force to 10,000 prescribers and 5,000 pharmacists.
Endo	c. Endo distributed copies of a book by KOL Dr. Lynn Webster entitled *Avoiding Opioid Abuse While Managing Pain* (2007). Endo's internal planning documents describe the purpose of distributing this book as to "[i]ncrease the breadth and depth of the Opana ER prescriber base." The book claims that when faced with signs of aberrant behavior, the doctor should regard it as pseudoaddiction and thus, increasing the dose *in most cases … should be the clinician's first response.*" (emphasis added).

[145] John Fauber & Ellen Gabler, *Networking Fuels Painkiller Boom*, Milwaukee Wisc. J. Sentinel (Feb. 19, 2012).

	d. Endo spent $246,620 to buy copies of FSMB's *Responsible Opioid Prescribing* (2007), which was distributed by Endo's sales force. This book asserted that behaviors such as "requesting drugs by name," "demanding or manipulative behavior," seeing more than one doctor to obtain opioids, and hoarding, are all signs of "pseudoaddiction."
Janssen	e. Janssen's website, *Let's Talk Pain*, stated from 2009 through 2011 that "pseudoaddiction … refers to patient behaviors that may occur when *pain is under-treated"* and "[p]seudoaddiction is *different from true addiction* because such behaviors can be resolved with effective pain management." (emphasis added).
Purdue	f. Purdue published a prescriber and law enforcement education pamphlet in 2011 entitled *Providing Relief, Preventing Abuse*, which described pseudoaddiction as a concept that "emerged in the literature to describe the inaccurate interpretation of [drug-seeking behaviors] in patients who have pain that has not been effectively treated." g. Purdue distributed to physicians at least as of November 2006, and posted on its unbranded website, *Partners Against Pain*, a pamphlet copyrighted 2005 and titled *Clinical Issues in Opioid Prescribing*. This pamphlet included a list of conduct including "illicit drug use and deception" it defined as indicative of pseudoaddiction or untreated pain. It also states: "Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when *pain is undertreated*…. Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudoaddiction can be *distinguished from true addiction* in that the behaviors resolve when the pain is effectively treated." (Emphasis added.) h. Purdue sponsored FSMB's *Responsible Opioid Prescribing* (2007), which taught that behaviors such as "requesting drugs by name, "demanding or manipulative behavior," seeing more than one doctor to obtain opioids, and hoarding, are all signs of pseudoaddiction. Purdue also spent over $100,000 to support distribution of the book. i. Purdue sponsored APF's *A Policymaker's Guide to Understanding Pain & Its Management*, which states: "Pseudo-addiction describes patient behaviors that may occur when *pain is undertreated*…. Pseudo-addiction can be distinguished from true addiction in that this behavior ceases when pain is effectively treated." (Emphasis added.)

5. Defendants, directly or indirectly, deceptively claimed withdrawal is simply managed.

253. Defendants, directly and through third parties, promoted the false and misleading messages below with the intent and expectation that, by misdescribing the difficulty of withdrawing from opioids, prescribers and patients would be more likely to start chronic opioid therapy and would fail to recognize the actual risk of addiction.

254. In an effort to underplay the risk and impact of addiction, Defendants, either directly or through third parties, frequently claim that, while patients become physically "dependent" on opioids, physical dependence is not the same as addiction and can be addressed by gradually tapering patients' dosage to avoid the adverse effects of withdrawal. Defendants fail to disclose the extremely difficult and painful effects that patients can experience when they are removed from opioids – an adverse effect that also makes it less likely that patients will be able to stop using the drugs.

255. In reality, withdrawal is prevalent in patients after more than a few weeks of therapy, and common symptoms of withdrawal include: severe anxiety, nausea, vomiting, headaches, agitation, insomnia, tremors, hallucinations, delirium, and pain. Some symptoms may persist for months, or even years, after a complete withdrawal from opioids, depending on how long opioids were used. Withdrawal symptoms trigger a feedback loop that drives patients to seek opioids, contributing to addiction.

256. Each of the publications and statements below, which are further discussed, by Defendant, in Section IV.E, falsely states or suggests that withdrawal from opioids was not a problem and they should not be hesitant about prescribing or using opioids:

Actavis	a. Documents from a 2010 sales training indicate that Actavis trained its sales force that discontinuing opioid therapy can be

	handled "simply" and that it can be done at home. Actavis' sales representative training claimed opioid withdrawal would take only a week, even in addicted patients.
Endo	b. A CME sponsored by Endo, titled *Persistent Pain in the Older Adult*, taught that withdrawal symptoms can be avoided entirely by tapering the dose by 10-20% per day for ten days.
Janssen	c. A Janssen PowerPoint presentation used for training its sales representatives titled "Selling Nucynta ER" indicates that the "low incidence of withdrawal symptoms" is a "core message" for its sales force. This message is repeated in numerous Janssen training materials between 2009 and 2011. The studies supporting this claim did not describe withdrawal symptoms in patients taking Nucynta ER beyond 90 days or at high doses and would therefore not be representative of withdrawal symptoms in the chronic pain population. Patients on opioid therapy long-term and at high doses will have a harder time discontinuing the drugs and are more likely to experience withdrawal symptoms. In addition, in claiming a low rate of withdrawal symptoms, Janssen relied upon a study that only began tracking withdrawal symptoms in patients in patients two to four days after discontinuing opioid use, when Janssen knew or should have known that these symptoms peak earlier than that for most patients. Relying on data after that initial window painted a misleading picture of the likelihood and severity of withdrawal associated with chronic opioid therapy. Janssen knew or should have known that the patients involved in the study were not on the drug long enough to develop rates of withdrawal symptoms comparable to rates of withdrawal suffered by patients who use opioids for chronic pain – the use for which Janssen promoted Nucynta ER.
Purdue	d. Purdue sponsored APF's *A Policymaker's Guide to Understanding Pain & Its Management*, which taught that "Symptoms of physical dependence can often be ameliorated by gradually decreasing the dose of medication during discontinuation," but did not disclose the significant hardships that often accompany cessation of use.

6. Defendants, directly and indirectly, misrepresented that increased doses pose no significant additional risks.

257. Each of the following misrepresentations was created with the intent and expectation that, by misrepresenting and failing to disclose the known risks from high dose opioids, prescribers and patients would be more likely to continue to prescribe and use opioids, even when they were not effective in reducing patients' pain, and not to discontinue opioids even when tolerance required them to reach even higher doses.

258. Defendants, directly or through third parties, claimed that patients and prescribers could increase doses of opioids indefinitely without added risk, even when pain was not decreasing or when doses had reached levels that were "frighteningly high," suggesting that patients would eventually reach a stable, effective dose. Each of Defendants' claims also omitted warnings of increased adverse effects that occur at higher doses, and misleadingly suggested that there was no greater risk to higher dose opioid therapy.

259. These claims are false. Patients receiving high doses of opioids as part of long-term opioid therapy are three to nine times more likely to suffer overdose from opioid-related causes than those on low doses. As compared to available alternative pain remedies, scholars have suggested that tolerance to the respiratory depressive effects of opioids develops at a slower rate than tolerance to analgesic effects. Accordingly, the practice of continuously escalating doses to match pain tolerance can, in fact, lead to overdose even where opioids are taken as recommended. The FDA has itself acknowledged that available data suggest a relationship between increased doses and the risk of adverse effects. Moreover, it is harder for patients to terminate use of higher-dose opioids without severe withdrawal effects, which contributes to a cycle of continued use, even when the drugs provide no pain relief and are causing harm – the signs of addiction.

260. Each of the following claims, which are further discussed, by Defendant, in Section IV.E, suggests that high-dose opioid therapy is safe:

Actavis	a. Documents from a 2010 sales training indicate that Actavis trained its sales force that "individualization" of opioid therapy depended on increasing doses "until patient reports adequate analgesia" and to "set dose levels on [the] basis of patient need, not on [a] predetermined maximal dose." Actavis further counseled its sales representatives that the reasons some physicians had for not increasing doses indefinitely were simply a matter of physician "comfort level," which could be

	overcome or used as a tool to induce them to switch to Actavis' opioid, Kadian.
Cephalon	b. Cephalon sponsored APF's *Treatment Options: A Guide for People Living with Pain* (2007), which claims that some patients "need" a larger dose of their opioid, regardless of the dose currently prescribed. c. Cephalon sponsored a CME written by KOL Dr. Lynn Webster, *Optimizing Opioid Treatment for Breakthrough Pain*, which was offered online by Medscape, LLC from September 28, 2007, through December 15, 2008. The CME taught that non-opioid analgesics and combination opioids that include aspirin and acetaminophen are less effective to treat breakthrough pain because of dose limitations.
Endo	d. Endo sponsored a website, painknowledge.com, through APF and NIPC, which claimed in 2009 that opioids may be increased until "you are on the right dose of medication for your pain," and once that occurs, further dose increases would not occur. Endo funded the site, which was a part of Endo's marketing plan, and tracked visitors to it. e. Endo distributed a patient education pamphlet edited by KOL Dr. Russell Portenoy titled *Understanding Your Pain: Taking Oral Opioid Analgesics*. In Q&A format, it asked: "If I take the opioid now, will it work later when I really need it?" The response was: "The dose can be increased …. You won't 'run out' of pain relief."
Janssen	f. Janssen sponsored a patient education guide entitled *Finding Relief: Pain Management for Older Adults* (2009), which its personnel reviewed and approved and its sales force distributed. This guide listed dose limitations as "disadvantages" of other pain medicines but omitted any discussion of risks of increased doses from opioids. The publication also falsely claimed that it is a "myth" that "opioid doses have to be bigger over time."
Purdue	g. Purdue's *In the Face of Pain* website, along with initiatives of APF, promoted the notion that if a patient's doctor does not prescribe them what – in their view – is a sufficient dose of opioids, they should find another doctor who will. In so doing, Purdue exerted undue, unfair, and improper influence over prescribers who face pressure to accede to the resulting demands. h. Purdue sponsored APF's *A Policymaker's Guide to Understanding Pain & Its Management*, which taught that dose escalations are "sometimes necessary," even indefinitely high ones, which suggested that high dose opioids are safe and appropriate and did not disclose the risks from high dose opioids. This publication is still available online. i. Purdue sponsored APF's *Treatment Options: A Guide for People Living with Pain* (2007), which taught patients that opioids have "no

	ceiling dose" and are therefore the most appropriate treatment for severe pain. The guide also claimed that some patients "need" a larger dose of the drug, regardless of the dose currently prescribed. This language fails to disclose heightened risks at elevated doses. j. Purdue sponsored a CME issued by the American Medical Association in 2003, 2007, 2010, and 2013. The CME, *Overview of Management Options*, was edited by KOL Dr. Russell Portenoy, among others, and taught that other drugs, but not opioids, are unsafe at high doses. The 2013 version is still available for CME credit.

7. Defendants, directly or indirectly, deceptively omitted or minimized the adverse effects of opioids and overstated the risks of alternative forms of pain treatment.

261. Each of the following misrepresentations was created with the intent and expectation that, by omitting the known, serious risks of chronic opioid therapy, including the risks of addiction, abuse, overdose, and death, and emphasizing or exaggerating risks of competing products, prescribers and patients would be more likely to choose opioids. Defendants, directly or through third parties, routinely ignored the risks of chronic opioid therapy. These include (beyond the risks associated with misuse, abuse, and addiction): hyperalgesia, a "known serious risk associated with chronic opioid analgesic therapy in which the patient becomes more sensitive to certain painful stimuli over time;"[146] hormonal dysfunction; decline in immune function; mental clouding, confusion, and dizziness; increased falls and fractures in the elderly; neonatal abstinence syndrome (when an infant exposed to opioids prenatally withdraws from the drugs after birth); and potentially fatal interactions with alcohol or benzodiazapines, which are used to treat post-traumatic stress disorder and anxiety (disorders frequently coexisting with chronic pain conditions).[147]

[146] *See* Letter from Janet Woodcock, M.D., *supra*, at 10 n.41.

[147] Several of these risks do appear in the FDA-mandated warnings. *See, e.g.*, the August 13, 2015 OxyContin Label, Section 6.2, identifying adverse reactions including: "abuse, addiction … death, … hyperalgesia, hypogonadism … mood altered … overdose, palpitations (in

262. Despite these serious risks, Defendants asserted or implied that opioids were appropriate first-line treatments and safer than alternative treatments, including NSAIDs such as ibuprofen (Advil, Motrin) or naproxen (Aleve). While NSAIDs can pose significant gastrointestinal, renal, and cardiac risks, particularly for elderly patients, Defendants' exaggerated descriptions of those risks were deceptive in themselves, and also made their omissions regarding the risks of opioids all the more striking and misleading. Defendants, directly and through third parties, described over-the-counter NSAIDs as life-threatening and falsely asserted that they were responsible for 10,000-20,000 deaths annually (more than opioids), when the real number is closer to 3,200. This description of NSAIDs starkly contrasted with their representation of opioids, for which the listed risks were nausea, constipation, and sleepiness (but not addiction, overdose, or death). Compared with NSAIDs, opioids are responsible for roughly four times as many fatalities annually.

263. As with the preceding misrepresentations in Sections IV.D.1-6, Defendants' false and misleading claims regarding the comparative risks of NSAIDs and opioids had the effect of shifting the balance of opioids' risks and purported benefits. While opioid prescriptions have exploded over the past two decades, the use of NSAIDs has declined during that same time.

264. Each of the following, which are further discussed, by Defendant, in Section IV.E, reflects Defendants' deceptive claims and omissions about the risks of opioids, including in comparison to NSAIDs:

Actavis	a. Documents from a 2010 sales training indicate that Actavis trained its sales force that the ability to escalate doses during long-term opioid therapy, without hitting a dose ceiling, made opioid use safer than other forms of therapy that had defined maximum doses, such as acetaminophen or NSAIDs.

the context of withdrawal), seizures, suicidal attempt, suicidal ideation, syndrome of inappropriate antidiuretic hormone secretion, and urticaria [hives]."

	b. Actavis also trained physician-speakers that "maintenance therapy with opioids can be safer than long-term use of other analgesics," including NSAIDs, in older persons.
Cephalon	c. Cephalon sponsored APF's *Treatment Options: A Guide for People Living with Pain* (2007), which taught patients that opioids differ from NSAIDs in that they have "no ceiling dose" and are therefore the most appropriate treatment for severe pain. The publication attributed 10,000 to 20,000 deaths annually to NSAID overdose. *Treatment Options* also warned that risks of NSAIDs increase if "taken for more than a period of months," with no corresponding warning about opioids.
Endo	d. Endo distributed a "case study" to prescribers titled *Case Challenges in Pain Management: Opioid Therapy for Chronic Pain*. The study cites an example, meant to be representative, of a patient "with a massive upper gastrointestinal bleed believed to be related to his protracted use of NSAIDs" (over eight years), and recommends treating with opioids instead. e. Endo sponsored a website, painknowledge.com, through APF and NIPC, which contained a flyer called "Pain: Opioid Therapy." This publication included a list of adverse effects from opioids that omitted significant adverse effects like hyperalgesia, immune and hormone dysfunction, cognitive impairment, tolerance, dependence, addiction, and death. Endo continued to provide funding for this website through 2012, and closely tracked unique visitors to it. f. Endo provided grants to APF to distribute *Exit Wounds* (2009), which omitted warnings of the risk of interactions between opioids and benzodiazepines, which would increase fatality risk. *Exit Wounds* also contained a lengthy discussion of the dangers of using alcohol to treat chronic pain but did not disclose dangers of mixing alcohol and opioids.
Janssen	g. Janssen sponsored a patient education guide titled *Finding Relief: Pain Management for Older Adults* (2009), which its personnel reviewed and approved and its sales force distributed. This publication described the advantages and disadvantages of NSAIDs on one page, and the "myths/facts" of opioids on the facing page. The disadvantages of NSAIDs are described as involving "stomach upset or bleeding," "kidney or liver damage if taken at high doses or for a long time," "adverse reactions in people with asthma," and "can increase the risk of heart attack and stroke." The only adverse effects of opioids listed are "upset stomach or sleepiness," which the brochure claims will go away, and constipation. h. Janssen sponsored APF's *Exit Wounds* (2009), which omits warnings of the risk of interactions between opioids and benzodiazepines. Janssen's label for Duragesic, however, states that use with benzodiazepines "may cause respiratory depression, [low blood pressure], and profound sedation or

	potentially result in coma. *Exit Wounds* also contained a lengthy discussion of the dangers of using alcohol to treat chronic pain but did not disclose dangers of mixing alcohol and opioids.
Purdue	i. Purdue sponsored APF's *Exit Wounds* (2009), which omits warnings of the risk of interactions between opioids and benzodiazepines, which would increase fatality risk. *Exit Wounds* also contained a lengthy discussion of the dangers of using alcohol to treat chronic pain but did not disclose dangers of mixing alcohol and opioids. j. Purdue sponsored APF's *Treatment Options: A Guide for People Living with Pain* (2007), which advised patients that opioids differ from NSAIDs in that they have "no ceiling dose" and are therefore the most appropriate treatment for severe pain. The publication attributes 10,000 to 20,000 deaths annually to NSAID overdose. *Treatment Options* also warned that risks of NSAIDs increase if "taken for more than a period of months," with no corresponding warning about opioids. k. Purdue sponsored a CME issued by the American Medical Association in 2003, 2007, 2010, and 2013, and the 2013 version is still available for CME credit. The CME, *Overview of Management Options*, was edited by KOL Dr. Russell Portenoy, among others, and taught that NSAIDs and other drugs, but not opioids, are unsafe at high doses.
Mallinckrodt	l. Mallinckrodt distributed brochures to doctors, patients, and law enforcement officials that included deceptive statements concerning the indicators of possible opioid abuse. m. Mallinckrodt sponsored, directly distributed, and assisted in the distribution of publications that promoted the deceptive concept of "pseudoaddiction," even for high-risk patients. n. Mallinckrodt endorsed, directly distributed, and assisted in the distribution of publications that presented an unbalanced treatment of the long-term and dose-dependent risks of opioids versus NSAIDs.

8. Purdue Misleadingly Promoted OxyContin as Providing 12 Hours of Pain Relief.

265. In addition to making the deceptive statements above, Purdue also dangerously misled doctors and patients about OxyContin's duration and onset of action.

266. Purdue promotes OxyContin as an extended-release opioid, but the oxycodone does not enter the body on a linear rate. OxyContin works by releasing a greater proportion of oxycodone into the body upon administration, and the release gradually tapers, as illustrated in

the following chart, which was, upon information and belief, adapted from Purdue's own sales materials:[148]

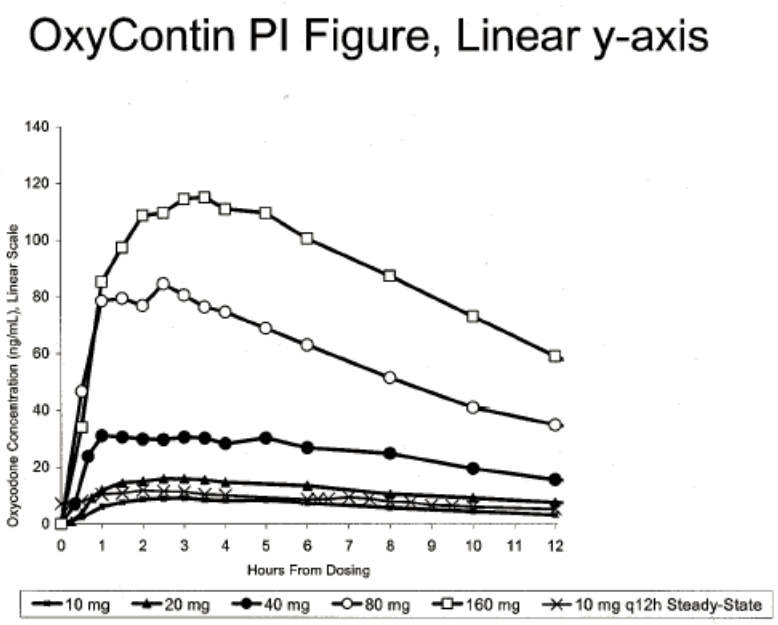


Figure 1

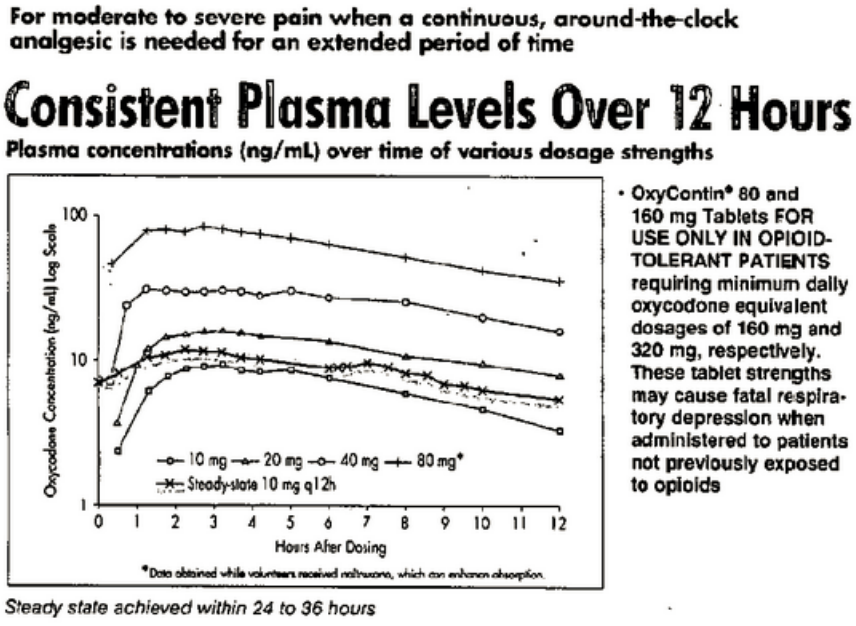
The reduced release of the drug over time means that the oxycodone no longer provides the same level of pain relief; as a result, in many patients, OxyContin does not last for the 12 hours for which Purdue promotes it – a fact that Purdue has known at all times relevant to this action.

267. OxyContin tablets provide an initial absorption of approximately 40% of the active medicine. This has a two-fold effect. First, the initial rush of nearly half of the powerful opioid – OxyContin is roughly twice as powerful as morphine – triggers a powerful psychological response. OxyContin thus behaves more like an immediate release opioid, which Purdue itself once claimed was more addicting in its original 1995 FDA-approved drug label.

[148] Jim Edwards, "*How Purdue Used Misleading Charts to Hide OxyContin's Addictive Power*," *CBSNews.com*, Sept. 28, 2011, http://www.cbsnews.com/news/how-purdue-used-misleading-charts-tohide-oxycontins-addictive-power/. The 160 mg dose is no longer marketed. Purdue's promotional materials in the past displayed a logarithmic scale, which gave the misleading impression the concentration remained constant.

Second, the initial burst of oxycodone means that there is less of the drug at the end of the dosing period, which results in the drug not lasting for a full 12 hours and precipitates withdrawal symptoms in patients, a phenomenon known as "end of dose" failure. (The FDA found in 2008 that a "substantial number" of chronic pain patients will experience "end-of-dose failure" with OxyContin.) The combination of fast onset and end-of-dose failure makes OxyContin particularly addictive, even compared with other opioids.

268. Purdue nevertheless has falsely promoted OxyContin as if it were effective for a full 12 hours. Purdue's advertising in 2000 included claims that OxyContin provides "Consistent Plasma Levels Over 12 Hours." That claim was accompanied by a chart depicting plasma levels on a logarithmic scale, which minimized the rate of end-of-dose failure by depicting 10 mg in a way that it appeared to be half of 100 mg in the table's y-axis. That chart, shown below, depicts the same information as the chart above but does so in a way that makes the absorption rate appear more consistent:



269. More recently, other Purdue advertisements also emphasized "Q 12h" (meaning twice-daily) dosing, as discussed in Section IV.E.5. These include an advertisement in the February 2005 *Journal of Pain* and 2006 *Clinical Journal of Pain* featuring an OxyContin logo with two pill cups, reinforcing the twice-a-day message. Other advertisements that ran in the 2005 and 2006 issues of the *Journal of Pain* depict a sample prescription for OxyContin, with "Q12h" handwritten for emphasis.

270. The information that OxyContin did not provide pain relief for a full 12 hours was known to Purdue, and Purdue's competitors, but was not disclosed to general practitioners. Purdue's knowledge of some pain specialists' tendency to prescribe OxyContin three times per day instead of two (which would have compensated for end-of-dose failure) was set out in Purdue's internal documents as early as 1999 and is apparent from MEDWATCH Adverse Event reports for OxyContin.[149] Even Purdue's competitor, Endo, was aware of the problem; Endo attempted to position its Opana ER drug as offering "durable" pain relief, which Endo understood to suggest a contrast to OxyContin. Endo even ran advertisements for Opana ER referring to "real" 12-hour dosing.

271. Purdue's failure to disclose the prevalence of end-of-dose failure meant that prescribers in Mississippi were not informed of risks relating to addiction, and that they received the misleading message that OxyContin would be effective for treating chronic pain for the advertised duration. Furthermore, doctors would compensate by increasing the dose or

[149] MEDWATCH refers to the FDA's voluntary adverse event reporting system.

prescribing "rescue" opioids, which has the same effect as increasing the amount of opioids prescribed to a patient, as described above in Section IV.D.6.[150,151]

E. Each Defendant Engaged in Unfair and Deceptive Marketing, Both Branded and Unbranded, that Targeted and Reached Mississippi Prescribers

272. Defendants – and the Front Groups and KOLs who depended on and worked under their direction – were able to effect a sea change in medical opinion in favor of accepting opioids as a medically necessary long-term treatment for chronic pain. As set forth below, each Defendant contributed to that result through a combination of both direct marketing efforts and third-party marketing efforts over which that Defendant exercised editorial control. These deceptive and misleading statements were directed to and reached Mississippi prescribers and patients, with the intent of distorting their views on the risks, benefits, and superiority of opioids for treatment of chronic pain.

273. Defendants engaged in their deceptive marketing campaign, both nationwide and in Mississippi, using a number of strategies. Defendants trained their sales forces and recruited physician speakers to deliver these deceptive messages and omissions, and they in turn conveyed them to prescribers. Defendants also broadly disseminated promotional messages and materials,

[150] Purdue's *Clinical Issues in Opioid Prescribing*, put out in 2005 under Purdue's unbranded *Partners Against Pain* banner, states that "it is recommended that a supplementary immediate-release medication be provided to treat exacerbations of pain that may occur with stable dosing." References to "rescue" medication appear in publications Purdue sponsored such as APF's *A Policymaker's Guide* (2011) and the 2013 CME *Overview of Pain Management Options*.

[151] The Connecticut Attorney General's office filed a citizens' petition with the FDA on January 27, 2004, requesting that the OxyContin label be amended with a warning not to prescribe the drug more than twice daily as a means of compensating for end-of-dose failure. The FDA denied this request on September 11, 2008. The FDA found that the state had failed to present sufficient evidence that more frequent dosing caused adverse outcomes, but the FDA did not challenge the Connecticut finding that end-of-dose failure of OxyContin was prevalent. Indeed, the FDA found that end-of-dose failure affected a "substantial" number of chronic pain patients prescribed OxyContin.

both by delivering them personally to doctors during detailing visits and by mailing deceptive advertisements directly to prescribers. Because they are disseminated by Defendant drug manufacturers and relate to Defendants' drugs, these materials are considered "labeling" within the meaning of 21 C.F.R. § 1.3(a), making Defendants liable for their content.

274. As described below, each of the misrepresentations received by Mississippi physicians – as well as other misrepresentations outlined above in Section IV.D – constitutes an integral piece of a centrally directed marketing strategy to change medical perceptions regarding the use of opioids to treat chronic pain. Defendants were aware of each of these misrepresentations, and Defendants approved of them and oversaw their dissemination at the national, corporate level.[152]

1. Actavis

275. As described below, Actavis promoted its branded opioid, Kadian, through a highly deceptive marketing campaign that it carried out principally through its sales force and recruited physician speakers. As internal documents indicate, this campaign rested on a series of misrepresentations and omissions regarding the risks, benefits, and superiority of opioids, and indeed incorporated each of the types of deceptive messages described above in Section IV.D.1-7. Based on the highly coordinated and uniform nature of Actavis' marketing, and as confirmed by both verbatim message data and prescriber interviews, Actavis conveyed these deceptive

[152] Even where Mississippi prescribers received Defendants' misrepresentations but failed to write prescriptions for Defendants' drugs paid for by the State, those still represent misstatements made by Defendants in connection with trade or commerce in Mississippi with the intent that these prescribers rely on those misrepresentations. Further, it is plausible – if not likely – that these prescribers wrote prescriptions for Mississippi consumers that were funded by another third-party payor or by Mississippi consumers themselves.

messages to Mississippi prescribers. Actavis did so with the intent that Mississippi prescribers and/or consumers would rely on the messages in choosing to use opioids to treat chronic pain.[153]

a. Actavis' deceptive direct marketing.

276. To help devise its marketing strategy for Kadian, Actavis commissioned a report from one of its consultants in January 2005 about barriers to market entry. The report concluded that two major challenges facing opioid manufacturers in 2005 were (i) overcoming "concerns regarding the safety and tolerability" of opioids, and (ii) the fact that "physicians have been trained to evaluate the supporting data before changing their respective practice behavior." To do that, the report advocated a "[p]ublication strategy based on placing in the literature key data that influence members of the target audience" with an "emphasis … on ensuring that the message is believable and relevant to the needs of the target audience." This would entail the creation of "effective copy points … backed by published references" and "developing and placing publications that demonstrate [the] efficacy [of opioids] and [their] safety/positive side effect profile." According to the report, this would allow physicians to "reach[] a mental agreement" and change their "practice behavior" without having first evaluated supporting data – of which Actavis (and other Defendants) had none.

277. The consulting firm predicted that this manufactured body of literature "w[ould], in turn, provide greater support for the promotional message and add credibility to the brand's advocates" based on "either actual or ***perceived*** 'scientific exchange'" in relevant medical literature (emphasis added). To this end, it planned for three manuscripts to be written during the first quarter of 2005. Of these, "[t]he neuropathic pain manuscript will provide evidence

[153] Actavis also sold various generic opioids, including Norco, which were widely prescribed in Mississippi and benefited from Actavis's overall promotion of opioids, but were not directly marketed by sales representatives.

demonstrating KADIAN is as effective in patients with presumptive neuropathic pain as it is in those with other pain types"; "[t]he elderly subanalysis … will provide clinicians with evidence that KADIAN is efficacious and well tolerated in appropriately selected elderly patients" and will "be targeted to readers in the geriatrics specialty"; and "[t]he QDF/BID manuscript will … call attention to the fact that KADIAN is the only sustained-release opioid to be labeled for [once or twice daily] use." In short, Actavis knew exactly what each study would show – and how that study would fit into its marketing plan – before it was published. Articles matching Actavis' descriptions later appeared in the *Journal of Pain* and the *Journal of the American Geriatrics Society*.

278. To ensure that messages based on this science reached individual physicians, Actavis deployed sales representatives, or detailers, to visit prescribers in Mississippi and across the country. At the peak of Actavis' promotional efforts in 2011, the company spent $6.7 million on detailing.

279. To track its detailers' progress, Actavis' sales and marketing department actively monitored the prescribing behavior of physicians. It tracked the Kadian prescribing activity of individual physicians, and assessed the success of its marketing efforts by tabulating how many Kadian prescriptions a prescriber wrote after he or she had been detailed.

280. Actavis also planned to promote Kadian by presenting at conferences of organizations where it believed it could reach a high concentration of pain specialists. Its choice of conferences also was influenced by the host's past support of opioids. For example, Actavis documents show that Actavis presented papers concerning Kadian at an annual meeting of AGS because AGS's guidelines "support the use of opioids."

281. Actavis targeted prescribers using both its sales force and recruited physician speakers, as described below.

(1) Actavis' deceptive sales training.

282. Actavis' sales representatives targeted physicians to deliver sales messages that were developed centrally and deployed uniformly across the country. These sales representatives were critical in delivering Actavis' marketing strategies and talking points to individual prescribers.

283. Actavis' strategy and pattern of deceptive marketing is evident in its internal training materials. A sales education module titled "Kadian Learning System" trained Actavis' sales representatives on the marketing messages – including deceptive claims about improved function, the risk of addiction, the false scientific concept of "pseudoaddiction," and opioid withdrawal – that sales representatives were directed and required, in turn, to pass on to prescribers nationally and in Mississippi.

284. The sales training module, dated July 1, 2010, includes the misrepresentations documented in this Complaint, starting with its promise of improved function. The sales training instructed Actavis sales representatives that "most chronic benign pain patients do have markedly improved ability to function when maintained on chronic opioid therapy," when, in reality, as described above in Section IV.D.1, data available at the time such representations were made demonstrate that patients on chronic opioid therapy are *less likely* to participate in daily activities like work. The sales training also misleadingly implied that the dose of prescription opioids could be escalated without consequence and omitted important facts about the increased risks of high dose opioids. First, Actavis taught its sales representatives, who would pass this message on to doctors, that pain patients would not develop tolerance to opioids, which would

require them to receive increasing doses: "Although tolerance and dependence do occur with long-term use of opioids, many studies have shown that tolerance is limited in most patients with [chronic pain]." Second, Actavis instructed its sales personnel that opioid "[d]oses are titrated to pain relief, and so no ceiling dose can be given as to the recommended maximal dose." Actavis failed to explain to its sales representatives and, through them, to doctors the greater risks associated with opioids at high doses, which are described in Section IV.D.6 above.

285. Further, the 2010 sales training module highlighted the risks of alternate pain medications without providing a comparable discussion of the risks of opioids, painting the erroneous and misleading impression that opioids are safer. Specifically, the document claimed that "NSAIDs prolong the bleeding time by inhibiting blood platelets, which can contribute to bleeding complications" and "can have toxic effects on the kidney." Accordingly, Actavis coached its sales representatives that "[t]he potential toxicity of NSAIDs limits their dose and, to some extent, the duration of therapy" since "[t]hey should only be taken short term." By contrast, the corresponding section related to opioids neglected to include a *single* side effect or risk associated with the use of opioids, including from long-term use.

286. This sales training module also severely downplayed the main risk associated with Kadian and other opioids – addiction. It represented that "there is no evidence that simply taking opioids for a period of time will cause substance abuse or addiction" and, instead, "[i]t appears likely that most substance-abusing patients in pain management practices had an abuse problem before entering the practice." This falsely suggests that few patients will become addicted, that only those with a prior history of abuse are at risk of opioid addiction, and that doctors can screen for those patients and safely prescribe to others. To the contrary, as described above in Section IV.D.2, opioid addiction will affect and has affected a significant population of

patients. While patients with a history of abuse may be more prone to addiction, all patients are at risk, and doctors may not be able to identify, or safely prescribe to, patients at greater risk.

287. The sales training also noted that there were various "signs associated with substance abuse," including past history or family history of substance or alcohol abuse, frequent requests to change medication because of side effects or lack of efficacy, and a "social history of dysfunctional or high-risk behaviors including multiple arrests, multiple marriages, abusive relationships, etc." This is misleading, as noted above, because it implies that only patients with these kinds of behaviors and history become addicted to opioids.

288. Further, the sales training module neglected to disclose that no risk-screening tools related to opioids have ever been scientifically validated. As noted in Section IV.D.3, the AHRQ recently issued an Evidence Report that could identify "[n]o study" that had evaluated the effectiveness of various risk mitigation strategies – including the types of patient screening implied in Actavis' sales training – on outcomes related to overdose, addiction, abuse or misuse.

289. The sales training module also directed representatives to counsel doctors to be on the lookout for the signs of "[p]seudoaddiction," which were defined as "[b]ehaviors (that mimic addictive behaviors) exhibited by patients with inadequately treated pain." However, as described above in Section IV.D.4, the concept of "pseudoaddiction" is unsubstantiated and meant to mislead doctors and patients about the risks and signs of addiction.

290. Finally, the 2010 national training materials trivialized the harms associated with opioid withdrawal by explaining that "[p]hysical dependence simply requires a tapered withdrawal should the opioid medication no longer be needed." This, however, overlooks the fact, described in Section IV.D.5, that the side effects associated with opiate withdrawal are severe and a serious concern for *any person* who wishes to discontinue long-term opioid therapy.

291. The Kadian Learning System module dates from July 2010, but Actavis sales representatives were passing deceptive messages on to prescribers even before then. A July 2010 "Dear Doctor" letter issued by the FDA indicated that "[b]etween June 2009 and February 2010, Actavis sales representatives distributed … promotional materials that … omitted and minimized serious risks associated with [Kadian]." Certain risks that were misrepresented included the risk of "[m]isuse, [a]buse, and [d]iversion of [o]pioids" and, specifically, the risk that "[o]pioid agonists have the potential for being abused and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion." The FDA also took issue with an advertisement for misrepresenting Kadian's ability to help patients "live with less pain and get adequate rest with less medication," when the supporting study did not represent "substantial evidence or substantial clinical experience."

292. Actavis' documents also indicate that the company continued to deceptively market its drugs after 2010. Specifically, a September 2012 Kadian Marketing Update, and the "HCP Detail" aid contained therein, noted that Kadian's "steady state plasma levels" ensured that Kadian "produced higher trough concentrations and a smaller degree of peak-to-trough fluctuations" than other opioids.

293. Actavis also commissioned surveys of prescribers to ensure Kadian sales representatives were promoting the "steady-state" message. That same survey – paid for and reviewed by Actavis – found repeated instances of prescribers being told by sales representatives that Kadian had low potential of abuse or addiction. This survey also found that prescribers were influenced by Actavis' messaging. A number of Kadian prescribers stated that they prescribed Kadian because it was "without the addictive potential" and wouldn't "be posing high risk for

addiction." As a result, Actavis' marketing documents celebrated a "perception" among doctors that Kadian had "low abuse potential".

294. Finally, the internal documents of another Defendant, Endo, indicate that pharmaceutical sales representatives employed by Endo, Actavis, and Purdue discussed the AAPM/APS Guidelines with doctors during detailing visits. As discussed above in Section IV.C.2.c.2, these guidelines deceptively concluded that the risk of addiction is manageable for patients regardless of past abuse histories.

(2) Actavis' deceptive speakers' training.

295. Actavis also increasingly relied on speakers – physicians whom Actavis recruited to market opioids to their peers – to convey similar marketing messages. Actavis set a goal to train 100 new Kadian speakers in 2008 alone, with a plan to set up "power lunch teleconferences" connecting speakers to up to 500 participating sites nationwide. Actavis sales representatives, who were required to make a certain number of sales visits each day and week, saw the definition of sales call expanded to accommodate these changes; such calls now included physicians' "breakfast & lunch meetings with Kadian advocate/speaker."

296. A training program for Actavis speakers included training on many of the same messages founded in the Kadian Learning System, described below. The deceptive messages in Actavis' speakers' training are concerning for two reasons: (a) the doctors who participated in the training were themselves prescribing doctors, and the training was meant to increase their prescriptions of Kadian; and (b) these doctors were trained, paid, and directed to deliver these messages to other doctors who would write prescriptions of Kadian.

297. Consistent with the training for sales representatives, Actavis' speakers' training falsely minimized the risk of addiction posed by long-term opioid use. Actavis claimed, without

scientific foundation and contrary to what Actavis knew, that "[o]pioids can be used with minimal risk in chronic pain patients without a history of abuse or addiction." The training also deceptively touted the effectiveness of "Risk Tools," such as KOL Lynn Webster's Opioid Risk Tool, in determining the "risk for developing aberrant behaviors" in patients being considered for chronic opioid therapy. In recommending the use of these screening tools, the speakers' training neglected to disclose that none of those tools has been scientifically validated.

298. The speakers' training also made reference to "pseudoaddiction," as a "[c]ondition characterized by behaviors, such as drug hoarding, that outwardly mimic addiction but are in fact driven by a desire for pain relief and usually signal undertreated pain." It then purported to assist doctors in identifying those behaviors that *actually* indicated a risk of addiction from those that did not. Behaviors it identified as "[m]ore suggestive of addiction" included "[p]rescription forgery," "[i]njecting oral formulations," and "[m]ultiple dose escalations or other nonadherence with therapy despite warnings." Identified as "[l]ess suggestive of addiction" were "[a]ggressive complaining about the need for more drugs," "[r]equesting specific drugs," "[d]rug hoarding during periods of reduced symptoms," and "[u]napproved use of the drug to treat another symptom." By portraying the risks in this manner, the speakers' training presentation deceptively gave doctors a false sense of security regarding the types of patients who can become addicted to opioids and the types of behaviors these patients exhibit.

299. The speakers' training downplayed the risks of opioids, while focusing on the risks of competing analgesics like NSAIDs. For example, it asserted that "Acetaminophen toxicity is a major health concern." The slide further warned that "Acetaminophen poisoning is the most common cause of acute liver failure in an evaluation of 662 US Subjects with acute

liver failure between1998-2003," and was titled "Opioids can be a safer option than other analgesics." However, in presenting the risks associated with opioids, the speakers' training focused on nausea, constipation, and sleepiness, and ignored the serious risks of hyperalgesia, hormonal dysfunction, decline in immune function, mental clouding, confusion, and dizziness; increased falls and fractures in the elderly, neonatal abstinence syndrome, and potentially fatal interactions with alcohol or benzodiazapines. As a result, the training exaggerated the risks of NSAIDs, both absolutely and relative to opioids, to make opioids appear to be a more attractive first-line treatment for chronic pain.

300. The speakers' training also misrepresented the risks associated with increased doses of opioids. For example, speakers were instructed to "[s]tart low and titrate until patient reports adequate analgesia" and to "[s]et dose levels on [the] basis of patient need, not on predetermined maximal dose." However, the speakers training neglected to warn speakers (and speakers bureau attendees) that patients on high doses of opioids are more likely to suffer adverse events.

b. Actavis' deceptive statements to Mississippi prescribers and patients.

301. The misleading messages and training materials Actavis provided to its sales force and speakers were part of a broader strategy to convince prescribers to use opioids to treat their patients' pain, without complete and accurate information about the risks, benefits, and alternatives. This deception was national in scope and included Mississippi. As described in Section IV.B.2 above, Actavis' nationwide messages reached Mississippi prescribers in a number of ways. For example, they were carried into Mississippi by Actavis' sales representatives during detailing visits as well as made available to Mississippi patients and prescribers through websites and ads, including ads in prominent medical journals. They have

also been delivered to Mississippi prescribers by Actavis' paid speakers, who were required by Actavis policy and by FDA regulations to stay true to Actavis' nationwide messaging.

302. Once trained, Actavis' sales representatives and speakers were directed to, and did, visit potential prescribers in Mississippi, as elsewhere, to deliver their deceptive messages. These contacts are demonstrated by Actavis' substantial effort in tracking the habits of individual Mississippi physicians in prescribing Kadian.

2. Cephalon

303. At the heart of Cephalon's deceptive promotional efforts was a concerted and sustained effort to expand the market for its branded opioids, Actiq and Fentora, far beyond their FDA-approved use in opioid-tolerant cancer patients. Trading on their rapid-onset formulation, Cephalon touted its opioids as the answer to "breakthrough pain" – a term its own KOLs planted in the medical literature – whether cancer pain or not. Cephalon promoted this message through its sales force, paid physician speakers, advertisements, and CMEs, even after the FDA issued the company warnings and rejected an expanded drug indication.

304. Even as it promoted Actiq and Fentora for a condition Cephalon itself planted in the medical literature, Cephalon also purveyed many of the deceptive messages described above in Section IV.D. It did so both directly – through detailing visits and speaker programs – and through the publications and CMEs of its third-party partners. These messages included misleading claims about functional improvement, addiction risk, pseudoaddiction, and the safety of alternatives to opioids.

305. Based on the highly coordinated and uniform nature of Cephalon's marketing, and as confirmed by both verbatim message data and prescriber interviews, Cephalon conveyed these deceptive messages to Mississippi prescribers. The materials that Cephalon generated in

collaboration with third-parties also were distributed or made available in Mississippi. Cephalon distributed these messages, or facilitated their distribution, in Mississippi with the intent that Mississippi prescribers and/or consumers would rely on them in choosing to use opioids to treat chronic pain.

a. Cephalon's deceptive direct marketing.

306. Like the other Defendants, Cephalon directly engaged in misleading and deceptive marketing of its opioids through its sales force and branded advertisements. These messages were centrally formulated and intended to reach prescribers nationwide, including those practicing in Mississippi. Cephalon also spent the money necessary to aggressively promote its opioid drugs, setting aside $20 million to market Fentora in 2009 alone.

(1) Cephalon's fraudulent and unfair marketing of Actiq and Fentora.

307. Chief among Cephalon's direct marketing efforts was its campaign to deceptively promote its opioids for "breakthrough pain." Cephalon reaps significant revenue from selling its opioids for treatment of chronic non-cancer pain. However, neither of its two opioid drugs – Actiq or Fentora – is approved for this purpose. Instead, both have indications that are very clearly and narrowly defined to limit their use to a particular form of cancer pain. Despite this restriction and in order to claim its piece of the broader chronic non-cancer pain market, Cephalon deceptively and unlawfully marketed Actiq and then Fentora for patients and uses for which they were not safe, effective, or allowed, causing prescriptions to be written and paid and, grievously, patients to be injured and die. As described below, Cephalon's efforts to expand the market for its drugs beyond cancer pain extended to Mississippi prescribers, few of whom were oncologists and at least one of whom was surprised to have received Cephalon's sales pitches because he ran a "headache clinic."

(a) Actiq

308. Cephalon's Actiq is a powerful opioid narcotic that is delivered to the bloodstream by a lollipop lozenge that dissolves slowly in the mouth. As described by one patient, Actiq "tastes like the most delicious candy you ever ate."[154]

309. Actiq is appropriately used only to treat "breakthrough" cancer pain that cannot be controlled by other medications. Breakthrough pain is a short-term flare of moderate-to-severe pain in patients with otherwise stable persistent pain. Actiq is a rapid-onset drug that takes effect within 10-15 minutes but lasts only a short time. It is also an extremely strong drug, considered to be at least 80 times more powerful than morphine. Fentanyl, a key ingredient in Actiq, has been linked to fatal respiratory complications in patients. Because of the significant number of fentanyl-related incidents such as overdoses and seizures, the DEA recently declared the drug to be a "threat to health and public safety."[155] Actiq is not safe in any dose for patients who are not opioid tolerant, that is, patients who have taken specific doses of opioids for a week or longer and whose systems have acclimated to the drugs.

310. In 1998, the FDA approved Actiq "***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."[156] (Emphasis in FDA document.)

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[154] *See* John Carreyrou, *Narcotic 'Lollipop' Becomes Big Seller Despite FDA Curbs*, WALL ST. J., Nov. 3, 2006.

[155] *See* Press Release, *DEA Issues Nationwide Alert on Fentanyl as a Threat to Health and Public Safety* (Mar. 18, 2015), *available at*: http://www.dea.gov/divisions/hq/2015/hq031815.shtml.

[156] FDA Approval Letter for NDA 20-747 (Nov. 4, 1998) at 5, http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/20747ltr.pdf.

Because of Actiq's dangers, wider, ambiguous uses – as the FDA label makes clear – are not permitted:

> This product ***must not*** be used in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason ACTIQ is contraindicated in the management of acute or postoperative pain.[157]

311. Actiq and Fentora are thus intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain. Unlike other drugs, as to which unapproved uses are permitted but cannot be promoted by the drug maker, Actiq and Fentora are so potent that unapproved use for opioid naïve patients is barred by the FDA, as their labels make clear.

312. Notwithstanding the drug's extreme potency and related dangers and the FDA's explicit limitations, Cephalon actively promoted Actiq for chronic non-cancer pain – an unapproved use. Cephalon marketed Actiq as appropriate for the treatment of various conditions including back pain, headaches, pain associated with sports-related injuries, and other conditions not associated with cancer for which it was not approved, appropriate, or safe.

313. Actiq's initial sales counted in the tens of millions of dollars, corresponding to its limited patient population. But by 2005, Actiq sales reached $412 million, making it Cephalon's second-highest selling drug. As a result of Cephalon's deceptive, unlawful marketing, sales exceeded $500 million by 2006.

[157] Actiq Drug Label, July 2011. The 1998 version does not substantively differ: "Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients." (Emphasis in original.)

(b) Cephalon's unfair and deceptive marketing of Fentora.

314. Actiq was set to lose its patent protection in September 2006. To replace the revenue stream that would be lost once generic competitors came to market, Cephalon purchased a new opioid drug, Fentora, from Cima Labs and, in August 2005, submitted a New Drug Application ("NDA") to the FDA for approval. Like Actiq, Fentora is an extremely powerful and rapid-onset opioid. It is administered by placing a tablet in the mouth until it disintegrates and is absorbed by the mucous membrane that lines the inside of the mouth.

315. On September 25, 2006, the FDA approved Fentora, like Actiq, only for the treatment of breakthrough cancer pain in cancer patients who were already tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Fentora's unusually strong and detailed black box warning label – the most serious medication warning required by the FDA – makes clear that, among other things:

> Fatal respiratory depression has occurred in patients treated with FENTORA, including following use in opioid non-tolerant patients and improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.
>
> Due to the risk of respiratory depression, FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients.[158]

316. When Cephalon launched Fentora on October 1, 2006, it picked up the playbook it developed for Actiq and simply substituted in Fentora. Cephalon immediately shifted 100 general pain sales representatives from selling Actiq to selling Fentora to the very same physicians for uses that would necessarily and predictably be unapproved. Cephalon's

[158] Fentora Drug Label, February 2013, http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021947s008lbl.pdf.

marketing of Actiq therefore "primed the market" for Fentora. Cephalon had trained numerous KOLs to lead promotional programs for Fentora, typically including unapproved uses for the drug. Cephalon billed Fentora as a major advance that offered a significant upgrade in the treatment of breakthrough pain generally – not breakthrough cancer pain in particular – from Actiq. Cephalon also developed a plan in 2007 to target elderly chronic pain patients, via a multi-city tour with stops at AARP events, YMCAs, and senior living facilities.

317. On February 12, 2007, only four months after the launch, Cephalon CEO Frank Baldino told investors:

> [W]e've been extremely pleased to retain a substantial portion, roughly 75% of the rapid onset opioid market. We executed our transition strategy and the results in our pain franchise have been better than we expected. With the successful launch of FENTORA and the progress in label expansion program, we are well positioned to grow our pain franchise for many years to come.[159]

318. On May 1, 2007, just seven months after Fentora's launch, Cephalon's then-Executive Vice President for Worldwide Operations, Bob Roche, boasted to financial analysts that Fentora's reach would exceed even Actiq's. He described the company's successful and "aggressive" launch of Fentora that was persuading physicians to prescribe Fentora for ever broader uses. He identified two "major opportunities" – treating breakthrough cancer pain and:

> The other opportunity of course is the prospect for FENTORA outside of cancer pain, in indications such as breakthrough lower back pain and breakthrough neuropathic pain….
>
> ….
>
> We believe that a huge opportunity still exists as physicians and patients recognize FENTORA as their first choice rapid onset

[159] *See Cephalon Q4 2006 Earnings Call Transcript*, Seeking Alpha (February 12, 2007, 8:48 PM EST) at 5, http://seekingalpha.com/article/26813-cephalon-q4-2006-earnings-call-transcript.

> opioid medication…. [opioids are] widely used in the treatment of … non-cancer patients ….
>
> ….
>
> Of all the patients taking chronic opioids, 32% of them take that medication to treat back pain, and 30% of them are taking their opioids to treat neuropathic pain. In contrast only 12% are taking them to treat cancer pain, 12%.
>
> We know from our own studies that breakthrough pain episodes experienced by these non-cancer sufferers respond very well to FENTORA. And for all these reasons, we are tremendously excited about the significant impact FENTORA can have on patient health and wellbeing and the exciting growth potential that it has for Cephalon.
>
> In summary, we have had a strong launch of FENTORA and continue to grow the product aggressively. Today, that growth is coming from the physicians and patient types that we have identified through our efforts in the field over the last seven years. In the future, with new and broader indications and a much bigger field force presence, the opportunity that FENTORA represents is enormous.[160]

319. On September 10, 2007, Cephalon sent letters to doctors warning of deaths and other "serious adverse events" connected with the use of Fentora and indicating that "[t]hese deaths occurred as a result of improper patient selection (*e.g.*, use in opioid non-tolerant patients), improper dosing, and/or improper product substitution."[161] The warning did not mention Cephalon's deliberate role in the "improper patient selection."

320. Two weeks later, the FDA issued its own Public Health Advisory. The FDA emphasized, once again, that Fentora only should be prescribed for approved conditions and that

[160] *See Cephalon Q1 2007 Earnings Call Transcript*, Seeking Alpha (May 1, 2007, 8:48 PM EST) at 23, http://seekingalpha.com/article/34163-cephalon-q1-2007-earnings-call-transcript?page=1.

[161] Letter from Jeffrey M. Dayno, M.D., Vice President, Medical Services, Cephalon, Inc., (Sept. 10, 2007), *available at*: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM154439.pdf.

dosage guidelines should be carefully followed. The FDA Advisory made clear that several Fentora-related deaths had occurred in patients who were prescribed the drug for unapproved use. The FDA Advisory warned that Fentora should not be used for any unapproved conditions, including migraines, post-operative pain, or pain due to injury, and that it should be given only to patients who have developed opioid tolerance. The Advisory reiterated that because Fentora contains a much greater amount of fentanyl than other opiate painkillers, it is not a suitable substitute for other painkillers.[162]

321. Cephalon's marketing of Actiq and Fentora for breakthrough pain continued notwithstanding the regulatory scrutiny. Cephalon's 2008 internal audit of its Sales & Marketing Compliance Programs concluded that marketing and tactical documents, as written, may be construed to promote unapproved use. The same report acknowledged that Cephalon lacked a process to confirm that speakers' program participants were following Cephalon's written, formal policies prohibiting promotion for unapproved use, and that "non-compliant [Cephalon Speaker Programs] may be taking place." Moreover, the report acknowledge the Cephalon's "call universe" may include "inappropriate prescribers" – prescribers who had nothing to do with cancer pain.

(2) After making detailed findings about its dangers, the FDA rejected Cephalon's request for expanded approval of Fentora for the treatment of chronic, non-cancer pain.

322. Cephalon filed a supplemental new drug application ("sNDA") asking the FDA to approve Fentora for the treatment of non-cancer breakthrough pain. Cephalon admitted that Fentora already had been heavily prescribed for non-cancer pain, but argued that such

[162] FDA Public Health Advisory, *Important Information for the Safe Use of Fentora (fentanyl buccal tablets*) (Sept. 26, 2007), *available at*: http://www.fda.gov/Drugs/DrugSafety/ PostmarketDrugSafetyInformationforPatientsandProviders/ucm05 1273.htm.

widespread use demonstrated why Fentora should be approved for these wider uses.[163] Cephalon's application also conceded that "[t]o date, no medication has been systematically evaluated in clinical studies or approved by the FDA for the management of [breakthrough pain] in patients with chronic persistent non-cancer-related pain." *Id*.

323. On May 6, 2008, the FDA's Anesthetic and Life Support Drugs Joint Committee and Drug Safety & Risk Management Joint Committee met in a joint session to discuss the risks of expanded prescribing of Fentora and whether those risks were great enough to preclude FDA approval of Fentora for treatment of non-cancer breakthrough pain. In outlining the topics of discussion, the designated FDA official, Teresa Watkins, described the Agency's concern that in the less than two years Fentora had been on the market: "We have already seen more reports of serious and life-threatening adverse events in both properly-prescribed and mis-prescribed patients then [sic] we have ever seen for Actiq over similar periods of time."[164] Watkins continued:

> We at the FDA are concerned that increased prescribing might also lead to an increased level of abuse, misuse, and diversion of Fentora. Due to the potency of this product, if this were to occur[,] the results may be an even more tragic public health crisis of increasing addiction, overdose, and death than we have seen with the currently available products and indications.

Id. at 18. "Fentora has attributes that make it particularly attractive for abuse and attributes that make it potentially dangerous for those who do abuse it." *Id*. at 20.

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[163] *See Fentora CII: Advisory Committee Briefing Document*, U.S. FDA Anesthetic & Life Support Drugs Advisory Comm. & Drug Safety & Risk Mgmt. Advisory Comm. (Apr. 4, 2008), http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4356b2-02-Cephalon.pdf.

[164] Transcript, Joint Meeting: Anesthetic and Life Support Drugs, Joint Committee and Drug Safety and Risk Management Advisory Committee (May 6, 2008), at 17, *available at*: http://www.fda.gov/ohrmsldockets/ac/cder08.html.

324. The FDA presented data showing that 95% of all Fentora use was for treatment of non-cancer pain.[165] Moreover, Dr. Joo Yung Chang, an FDA safety evaluator, presented post-marketing safety data for Fentora, which included five reports of death through February 2008. "Overall, four out of five deaths involved an overdose of Fentora." *Id*. at 122. Three of these deaths were directly caused by Fentora, two by accidental overdoses and one by suicide. The fourth death was related to, though it could not be determined that it was caused by, Fentora: a patient stole Fentora from his wife, overdosed, was taken to the hospital and diagnosed with myocardial infarction, after which he left the hospital against advice, returned home, and died. *Id.*

325. Of the 19 reported adverse events, only one was reported as within the FDA-approved indication, and more than half involved medication errors. *Id.* at 123-24. Lieutenant Commander Arnwine, from the FDA's Division of Medication Error Prevention, described reported medication errors in greater detail. Of the 43 reported medication errors, 35 occurred "in patients being treated for off-label use." *Id.* at 133. "One of these cases resulted in death of a patient because she took Fentora every 30 minutes for treatment of migraines." *Id.* at 135. Seven cases involved improper patient selection, including two in which patients were not on around-the-clock opioid therapy. "One of these cases resulted in respiratory depression and hospitalization…." *Id.* at 136.

326. Dr. Rob Shibuya, a Medical Officer in the Division of Anesthesia, Analgesia, and Rheumatology Products, presented evidence "that fentanyl may be more dangerous than other

[165] *See* Yoo Jung Chang & Lauren Lee, *Review of Fentora and Actiq Adverse Events from the Adverse Event Reporting System ("AERS") Database*, U.S. FDA Anesthetic & Life Support Drugs Advisory Comm. & Drug Safety & Risk Mgmt. Advisory Comm. (May 6, 2008), *available at*: http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4356s2-02-FDAcorepresentations.ppt#289,1.

opioids." *Id.* at 177. In its presentation to the Joint Committee, the FDA conveyed that it regarded Fentora's route of administration, which facilitated ease of use and resulted in rapid onset of effect, to be a key driver of the drug's increased abuse liability.

327. Citing data from the DAWN database, Shibuya stated that fentanyl "has the highest rate of [Emergency Department] visits per 10,000 prescriptions when compared to oxycodone and hydrocodone, and this has been very consistent for the three years of data shown." *Id.* at 178. Clinical trials accentuated Dr. Shibuya's concern that Fentora is particularly dangerous. Observations from clinical trials of Fentora in non-cancer patients included "worrisome terms from a risk management perspective … such as addictive behavior, physical trauma, and substance abuse, which are rarely seen in clinical trials." *Id.* at 187-88.

328. That finding was doubly troubling: not only was Fentora linked to greater safety risks than other opioids, but those risks were greatest in non-cancer patients – the very population for which Cephalon proposed to (and even in the absence of approval, did) promote Fentora. In two different analyses, "the events that portend risk management issues are more prevalent in the non-cancer population." *Id.* at 189. "[T]he non cancer population has an excess incidence of serious adverse events related to overdose, abuse, misuse, and those consistent with excessive CNS depression compared to analogous safety data from patients with cancer." *Id.*

329. Medical Officer Dr. Lori Love similarly emphasized that clinical trials in the non-cancer population indicate that Fentora poses unusually large risks of abuse and misuse. Out of 931 patients, three percent "exhibited high risk behavior" including "abuse, dependence, overdose, and a positive drug screen." *Id.* at 148. "Seventeen percent of patients, or 156, had at least one aberrant drug use behavior," and thefts occurred in 35 patients, or 4.2% of the population. *Id.* at 283. Dr. Love explained that these figures most likely *understate* the actual

risks associated with Fentora for two reasons. First, "[b]ecause this information is not available or perhaps was not gathered, the rates of abuse diversion, and aberrant behavior in general are likely unreported in these clinical trials." *Id.* at 153. Second, patients at high risk for abuse were excluded from entry to the clinical trials, meaning that those included in the trials were at low risk for substance abuse relative to the general population of would-be Fentora users. "[T]he rates of abuse and misuse observed in clinical trials of Fentora in non-cancer populations are not representative of what would occur if Fentora were approved for expanded indication in the general population with chronic pain." *Id.*

330. Dr. Love summarized:

> [T]he risks of unintentional potentially fatal overdose, misuse, abuse, or diversion of fentanyl and of Fentora in particular are extremely high, as demonstrated by instances of overdose, misuse, abuse, and diversion in the clinical studies, and from signals in post-marketing data where off-label use differed from the currently[-]approved indication. These clinical trials are not representative of potential risks of Fentora in the general population. This [clinical trial] population was highly screened to eliminate high-risk patients and, further, detection of aberrant drug use is uncommon in controlled clinical trials and appears to be much more frequent in the non-cancer patients who use Fentora long term.

Id. at 153-54. Warning against the risks of promoting Fentora for use in the non-cancer population, Dr. Love concluded that, "taken together, these findings suggest that expanded use of this product will raise serious public safety concerns and will result in significant abuse and diversion that further impacts the public health and safety." *Id.* at 154.

331. Following presentations by the FDA and Cephalon, as well as a period for public comments, the Joint Committee panelists discussed whether the benefits of an expanded indication for Fentora would justify the expected safety costs. Panelists agreed that expanded

use of Fentora would result in a significant increase in abuse, misuse, and diversion. *See id.* at 321-22, 332, 354-55, 415.

332. Thereafter, by a vote of 17-3, the relevant Advisory Committee – a panel of outside experts – voted against recommending approval of Cephalon's sNDA for Fentora, citing the potential harm from broader use. On September 15, 2008, the FDA denied Cephalon's application and requested, in light of its promotional activities, that Cephalon implement and demonstrate the effectiveness of proposed enhancements to Fentora's Risk Management Program. In December 2008, the FDA followed that up with a formal request directing Cephalon to submit a Risk Evaluation and Mitigation Strategy for Fentora.

(3) The FDA's division of Drug Marketing, Advertising and Communications ("DDMAC") warned Cephalon about its misleading advertising of Fentora.

333. Undeterred by the rejection of its sNDA, Cephalon continued to use its general pain sales force to promote Fentora to pain specialists as an upgrade over Actiq for the treatment of non-cancer breakthrough pain. Deceptively and especially dangerously, Cephalon also continued to promote Fentora for use by all cancer patients suffering breakthrough cancer pain, and not simply those who were opioid tolerant.

334. On March 26, 2009, the DDMAC issued a Warning Letter to Cephalon, advising that its promotional materials for Fentora amounted to deceptive and fraudulent promotion of the drug.[166] Specifically, the Warning Letter asserted that a sponsored link on Google and other search engines for Fentora, which said "Learn about treating breakthrough pain in patients with

[166] Letter from Michael Sauers to Carole S. Marchione (Mar. 26, 2009), *available at*: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166238.pdf.

cancer"[167] was improper because it "misleadingly broaden[ed] the indication for Fentora by implying that any patient with cancer who requires treatment for breakthrough pain is a candidate for Fentora therapy … when this is not the case."

335. DDMAC emphasized that Fentora's label was limited to cancer patients with breakthrough pain "*who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.*" (Emphasis in original.) DDMAC explained that the advertisement was "especially concerning given that Fentora must not be used in opioid non-tolerant patients because life-threatening hypoventilation and death could occur at any dose in patients not on a chronic regimen of opioids." (Emphasis in original.) DDMAC also warned Cephalon that, based on a review of Cephalon-sponsored links for Fentora on internet search engines, the company's advertisements were "misleading because they make representations and/or suggestions about the efficacy of Fentora, but fail to communicate any risk information associated with the use" of the drug. (Emphasis in original.)

(4) Cephalon continues to knowingly, deceptively, and illegally promote Fentora for unapproved uses.

336. Cephalon's own market research studies confirm that its Fentora promotions were not focused on the physicians who treat breakthrough cancer pain. Cephalon commissioned several market research studies to determine whether oncologists provided an "adequate" market potential for Fentora. These studies' central goal was to determine whether oncologists treat breakthrough cancer pain themselves, or whether they refer such patients to general pain specialists. The first study, completed in 2007, reported that 90% of oncologists diagnose and

[167] Screen shots of the sponsored link are available here: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166240.pdf.

treat breakthrough cancer pain themselves, and do not refer their breakthrough cancer pain patients to pain specialists. The second study, completed in 2009, confirmed the results of the 2007 study, this time reporting that 88% of oncologists diagnose and treat breakthrough cancer pain themselves and rarely, if ever, refer those patients to general pain specialists. (One reason that general pain specialists typically do not treat oncological pain is that the presence of pain can, in itself, be an indicator of a change in the patient's underlying condition that should be monitored by the treating oncologist.)

337. In 2011, Cephalon wrote and copyrighted an article titled "2011 Special Report: An Integrated Risk Evaluation and Risk Mitigation Strategy for Fentanyl Buccal Tablet (FENTORA®) and Oral Transmucosal Fentanyl Citrate (ACTIQ®)" that was published in *Pain Medicine News*. The article promoted Cephalon's drugs for unapproved uses by stating that the "judicious use of opioids can facilitate effective and safe management of chronic pain" and noted that Fentora "has been shown to be effective in treatment of [break through pain] associated with multiple causes of pain," not just cancer.

a. Cephalon's misrepresentation of the risks associated with the use of opioids for the long-term treatment of chronic pain.

338. Cephalon's conduct in marketing Actiq and Fentora for chronic non-cancer pain, despite their clear (and deadly) risks and unproved benefits, was an extension, and reaped the benefits, of Cephalon's generally deceptive promotion of opioids for chronic pain.

339. Along with its deploying its sales representatives, Cephalon also used speakers bureaus to help reach prescribers.

340. In addition, working with FSMB, Cephalon also trained its speakers to turn doctors' fear of discipline on its head – doctors, who used to believe that they would be disciplined if their patients became addicted to opioids, were taught instead that they would be

punished if they failed to prescribe opioids to their patients with pain. Through this messaging, Cephalon aimed to normalize the prescribing of opioids for chronic pain and failed to acknowledge the serious risks of long-term opioid use and its inappropriateness as a front-line treatment for pain.

341. Further, Cephalon also developed a guidebook called *Opioid Medications and REMS: A Patient's Guide*, which deceptively minimized the risks of addiction from the long-term use of opioids. Specifically, the guidebook claimed that "patients without a history of abuse or a family history of abuse do not commonly become addicted to opioids," which, as described in Section IV.D.2, is dangerously false. Cephalon distributed the guidebook broadly, and it was available to and intended to reach prescribers in Mississippi.

342. The misleading messages and materials Cephalon provided to its sales force and its speakers were part of a broader strategy to convince prescribers to use opioids to treat their patients' pain, without complete and accurate information about the risks, benefits, and alternatives. This deception was national in scope and included Mississippi. As described above in Section IV.B, Cephalon's nationwide messages would have reached Mississippi prescribers in a number of ways. For example, they were delivered in Mississippi by Cephalon's sales representatives in detailing visits and made available to Mississippi patients and prescribers through websites and ads, including ads in prominent medical journals. They have also been delivered to Mississippi prescribers by Cephalon's paid speakers, who were required by Cephalon policy to stay true to the company's nationwide messaging.

b. Cephalon's deceptive third-party statements.

343. Like the other Defendants, Cephalon also relied on third parties to disseminate its messages through deceptive publications and presentations. By funding, developing and

reviewing the content of, and distributing and facilitating the distribution of these messages, Cephalon exercised editorial control over them. Cephalon, in some instances, used its sales force to directly distribute certain publications by these Front Groups and KOLs, rendering those publications "labeling" within the meaning of § 21 C.F.R. § 1.3(a) and making Cephalon responsible for their contents. Cephalon also deployed its KOLs as speakers for talks and CMEs to selected groups of prescribers.

344. Cephalon's relationships with several such Front Groups and KOLs – and the misleading and deceptive publications and presentations those relationships generated – are described below.

(1) FSMB – *Responsible Opioid Prescribing*.

345. In 2007, for example, Cephalon sponsored and distributed through its sales representatives FSMB's *Responsible Opioid Prescribing*, which was drafted by "Medical Writer X," whose work for Janssen is described below in Section V.E.4. Medical Writer X was frequently hired by a consulting firm, Conrad & Associates LLC, to write pro-opioid marketing pieces disguised as science. Medical Writer X's work was reviewed and approved by drug company representatives, and he felt compelled to draft pieces that he admits distorted the risks and benefits of chronic opioid therapy in order to meet the demands of his drug company sponsors.

346. *Responsible Opioid Prescribing* was a signature piece of Medical Writer X's work and contained a number of deceptive statements. This publication claimed that because pain had a negative impact on a patient's ability to function, relieving pain – alone – would "reverse that effect and improve function." However, as described in Section IV.D.1 above, the

truth is far more complicated; functional improvements made from increased pain relief can be offset by a number of problems, including addiction.

347. *Responsible Opioid Prescribing* also misrepresented the likelihood of addiction by mischaracterizing drug-seeking behavior as "pseudoaddiction." It explained that "requesting drugs by name," engaging in "demanding or manipulative behavior," seeing more than one doctor to obtain opioids, and hoarding were all signs of "pseudoaddiction" and are likely the effects of undertreated pain, rather than true addiction. As described in Section IV.D.4 above, there is no scientific evidence to support the concept of pseudoaddiction, and any suggestion that addictive behavior masquerades as "pseudoaddiction" is false.

348. Cephalon spent $150,000 to purchase copies of *Responsible Opioid Prescribing* in bulk. It then used its sales force to distribute these copies to 10,000 prescribers and 5,000 pharmacists nationwide. These were available to and intended to reach prescribers and pharmacists in Mississippi.

(2) APF: *Treatment Options – A Guide for People Living with Pain*

349. Cephalon also exercised considerable control over the Front Group APF, which published and disseminated many of the most egregious falsehoods regarding chronic opioid therapy. Their relationship, and several of the APF publications, are described in detail below.

350. Documents indicate that Cephalon provided APF with substantial assistance in publishing deceptive information regarding the risks associated with the use of opioids for chronic pain. An April 3, 2008, Fentora Assessment Strategy Tactics Team Meeting presentation outlines Cephalon's strategy to prepare for a meeting at which the FDA Advisory Committee would consider expanding the indication of Fentora to include chronic, non-cancer pain. Cephalon prepared by "reaching out to third-party organizations, KOLs, and patients to

provide context and, where appropriate, encourage related activity." First among the Front Groups listed was APF.

351. Cephalon was among the drug companies that worked with APF to persuade the Institute of Medicine of the National Academies (IOM) on issues related to chronic opioid therapy. APF President Will Rowe circulated a document to Cephalon and other drug company personnel that contained key message points and suggested that they "[c]onsider using this document in your communications with the members of the IOM Committee." According to Rowe, recipients should "consider this a working document which you can add to or subtract from." Rowe also advised that, if recipients "have an ally on that Committee," they should "consider sharing this document with that person."

352. Cephalon personnel responded enthusiastically, with Cephalon's Associate Director for Alliance Development stating her belief that "the document does a good job of bringing together many important ideas." Cephalon reviewed and directed changes to this document, with the Cephalon Associate Director thanking Rowe "for incorporating the points we had raised." The close collaboration between Cephalon and APF on this project demonstrates their agreement to work collaboratively to promote the use of opioids as an appropriate treatment for chronic pain.

353. Cephalon's influence over APF's activities was so pervasive that APF's President, Will Rowe, even reached out to Defendants – including Cephalon – rather than his own staff to identify potential authors to draft an answer to an article critical of opioids that appeared in the *Archives of Internal Medicine* in 2011.

354. Cephalon also sponsored APF's *Treatment Options: A Guide for People Living with Pain*, starting in 2007. It is rife with misrepresentations regarding the risks, benefits, and superiority of opioids.

355. For example, *Treatment Options* deceptively asserts that the long-term use of opioids to treat chronic pain could help patients function in their daily lives by stating that, when used properly, opioids "give [pain patients] a quality of life [they] deserve." As described above in Section IV.D.1, there is no scientific evidence corroborating that statement, and such statements are, in fact, false because available data demonstrate that patients on chronic opioid therapy are *less likely* to participate in life activities like work.

356. *Treatment Options* also claims that addiction is rare and is evident from patients' conduct in self-escalating their doses, seeking opioids from multiple doctors, or stealing the drugs. *Treatment Options* further minimizes the risk of addiction by claiming that it can be avoided through the use of screening tools, like "opioid agreements," which can "ensure [that patients] take the opioid as prescribed." Nowhere does *Treatment Options* explain to patients and prescribers that neither "opioid agreements" nor any other screening tools have been scientifically validated to decrease the risks of addiction, and the publication's assurances to the contrary are false and deceptive as described above in Section IV.D.2-3.

357. *Treatment Options* also promotes the use of opioids to treat chronic pain by painting a misleading picture of the risks of alternate treatments, most particularly NSAIDs. *Treatment Options* notes that NSAIDs can be dangerous at high doses, and attributes 10,000 to 20,000 deaths a year annually to NSAID overdose. According to *Treatment Options*, NSAIDs are different from opioids because opioids have "no ceiling dose," which is beneficial since some patients "need" larger doses of painkillers than they are currently prescribed. These claims

misleadingly suggest that opioids are safe even at high doses and omit important information regarding the risks of high-dose opioids, as discussed above in Section IV.D.6.

358. Additionally, *Treatment Options* warns that the risks associated with NSAID use increase if NSAIDs are "taken for more than a period of months," but deceptively omits any similar warning about the risks associated with the long-term use of opioids. As discussed above in Section IV.D.7, this presentation paints a misleading picture of the risks and benefits of opioids compared with alternate treatments.

359. APF distributed 17,200 copies of *Treatment Options* in 2007 alone. It is currently available online and was intended to reach Mississippi prescribers and pharmacists.

(3) Key Opinion Leaders and misleading science.

360. Cephalon also knew that its misleading messages would be more likely to be believed by prescribers if they were corroborated by seemingly neutral scientific support. With funding from Cephalon, for example, Dr. Portenoy wrote an article that purported to expand the definition of breakthrough cancer pain to non-cancer indications, vastly expanding the marketing potential of Cephalon's Fentora. The article was published in the nationally circulated *Journal of Pain* in 2006 and helped drive a surge in Fentora prescriptions.

361. The concept of "breakthrough pain" ultimately formed the sole basis for the central theme of promotional messages Cephalon cited to support the approval and marketing of Actiq and Fentora, rapid-acting opioids which begin to work very quickly but last only briefly. Neither of these drugs had a natural place in the treatment of chronic pain before Cephalon's marketing campaign changed medical practice. A recent literature survey of articles describing non-cancer breakthrough pain calls into question the validity of the concept, suggesting it was

not a distinct pain condition but a hypothesis to justify greater dosing of opioids. In other words, Cephalon conjured the science of breakthrough pain in order to sell its drugs.

362. As one scholar has pointed out, references to breakthrough pain in articles published on the MEDLINE bibliographic database spiked in 1998 and again in 2006.[168] These spikes coincide with FDA's approval of Actiq and Fentora.

363. Cephalon also bolstered supportive studies with supportive KOLs. All told, Cephalon has paid doctors more than $4.5 million for programs relating to its opioids since 2000.

(4) Misleading Continuing Medical Education (CME).

364. Cephalon developed sophisticated plans for the deployment of its KOLs, broken down by sub-type and specialty, to reach targeted groups of prescribers through CMEs. Cephalon used the CME programs it sponsored to deceptively portray the risks related to the use of opioids to treat chronic non-cancer pain and promote the unapproved use of Actiq and Fentora.

365. In 2007 and 2008, Cephalon sponsored three CMEs that each positioned Actiq and Fentora, and only Actiq and Fentora, as "rapid onset opioids" that would provide effective analgesia within the time period during which "breakthrough pain" was at its peak intensity. Although the CMEs used only the generic names of the drugs, the description of the active ingredient and means of administration means that a physician attending the CME knew it referred only to Actiq or Fentora.

[168] Adriane Fugh-Berman, *Marketing Messages in Industry-Funded CME*, PharmedOut, Georgetown U. Med. Ctr. (June 25, 2010), *available at*: pharmedout.galacticrealms.com/Fugh-BermanPrescription forConflict6-25-10.pdf.

366. The CMEs each taught attendees that there was no sound basis for the distinction between cancer and non-cancer "breakthrough pain," and one instructed patients that Actiq and Fentora were commonly used in non-cancer patients, thus effectively endorsing this use. *Optimizing Opioid Treatment for Breakthrough Pain*, offered online by Medscape, LLC from September 28, 2007, through December 15, 2008, was prepared by KOL Dr. Lynn R. Webster and M. Beth Dove. It recommends prescribing a "short-acting opioid" (*e.g.*, morphine, hydromorphone, oxycodone) "when pain can be anticipated," or a rapid-onset opioid when it cannot. The only examples of rapid-onset opioids then on the market were oral transmucosal fentanyl citrate (*i.e.*, Actiq) or fentanyl effervescent buccal tablet (*i.e.*, Fentora): "Both are indicated for treatment of [breakthrough pain] in opioid-tolerant cancer patients *and are frequently prescribed to treat [breakthrough pain] in noncancer patients as well*." (Emphasis added.)

367. *Optimizing Opioid Treatment for Breakthrough Pain* not only deceptively promoted Cephalon's drugs for unapproved use, but also misleadingly portrayed the risks, benefits, and superiority of opioids for the treatment of chronic pain. For example, the CME misrepresented that Actiq and Fentora would help patients regain functionality by advising that they improve patients' quality of life and allow for more activities when taken in conjunction with long-acting opioids. The CME also minimized the risks associated with increased opioid doses by explaining that NSAIDs were less effective than opioids for the treatment of breakthrough pain because of their dose limitations, without disclosing the heightened risk of adverse events on high-dose opioids.

368. Cephalon similarly used an educational grant to sponsor the CME *Breakthrough Pain: Improving Recognition and Management*, which was offered online between March 31,

2008, and March 31, 2009, by Medscape, LLC. The direct result of Cephalon's funding was a purportedly educational document that echoed Cephalon's marketing messages: the CME deceptively omitted Actiq's and Fentora's tolerance limitations, cited examples of patients who experienced pain from accidents, not from cancer, and, like Cephalon's *Optimizing Opioid Treatment* CME, taught that Actiq and Fentora were the only products on the market that would take effect before the breakthrough pain episode subsided. This CME was available online and was intended to reach Mississippi prescribers.

369. Lastly, KOL Dr. Fine authored a CME, sponsored by Cephalon, titled *Opioid-Based Management of Persistent and Breakthrough Pain*, with KOLs Dr. Christine A. Miaskowski and Michael J. Brennan, M.D. Cephalon paid to have this CME published in a supplement of Pain Medicine News in 2009. It instructed prescribers that "clinically, broad classification of pain syndromes as either cancer- or noncancer-related has limited utility," and recommended dispensing "rapid onset opioids" for "episodes that occur spontaneously" or unpredictably, including "oral transmucosal fentanyl," *i.e.*, Actiq, and "fentanyl buccal tablet," *i.e.*, Fentora, including in patients with chronic non-cancer pain. Dr. Miaskowski disclosed in 2009, in connection with the APS/AAPM Opioid Treatment Guidelines, that she served on Cephalon's speakers bureau.[169] Dr. Fine also received funding from Cephalon for consulting services.

370. *Opioid-Based Management of Persistent and Breakthrough Pain* was available to and was intended to reach Mississippi prescribers.

[169] As described in Section IV.C.2.c.2 above, 14 of 21 panel members who drafted the AAPM/APS Guidelines received support from Janssen, Cephalon, Endo, and Purdue.

371. Cephalon's control over the content of these CMEs is apparent based on its advance knowledge of their content. A December 2005 Cephalon launch plan set forth key "supporting messages" to position Fentora for its product launch. Among them was the proposition that "15-minute onset of action addresses the unpredictable urgency of BTP." Years later, the same marketing messages reappeared in the Cephalon-sponsored CMEs described above. Echoing the Cephalon launch plan, *Optimizing Opioid Treatment for Breakthrough Pain* stated that "[t]he unpredictability of BTP will strongly influence the choice of treatment" and that Fentora "delivers an onset of analgesia that is similar to [Actiq] at ≤ 15 minutes." Similarly, *Opioid-Based Management of Persistent and Breakthrough Pain* defined "breakthrough pain" as "unpredictable," over a table describing both cancer and non-cancer "breakthrough pain."

372. Cephalon tracked the effectiveness of its deceptive marketing through third parties, demonstrating that Cephalon not only planned for but depended upon their activities as a key element of its marketing strategy.

c. Cephalon's deceptive statements to Mississippi patients and prescribers.

373. Cephalon used various measures to disseminate its deceptive statements regarding the risks of unapproved use of Actiq and Fentora and the risks, benefits, and superiority of opioids to Mississippi patients and prescribers.

374. Cephalon targeted Mississippi prescribers by recruiting them for its speakers bureaus for Actiq and Fentora. Based on the uniform and nationwide character of Cephalon's marketing and Cephalon's own speaker training materials, each of these speakers attended Cephalon' s speaker's training, was instructed to disseminate the misrepresentations outlined above, and did disseminate those misrepresentations in Mississippi.

375. Given that Cephalon's own studies demonstrated that the overwhelming majority of oncologists diagnose and treat breakthrough cancer pain themselves, Cephalon knew the only purpose in its representatives meeting with these prescribers was to promote unapproved use. Based on the uniform and nationwide character of Cephalon's marketing, Cephalon's deceptive messages would have been disseminated to Mississippi prescribers by Cephalon's sales representatives during these events.

3. Endo

376. Endo promoted its opioids through the full array of marketing channels. The company deployed its sales representatives, paid physician speakers, journal supplements, and advertising in support of its branded opioids, principally Opana and Opana ER. Misleading claims about the purportedly lower abuse potential of Opana ER featured prominently in this campaign, but Endo also made many of the other deceptive statements and omissions described above in Section IV.D. These included deceptive messages about functional improvement, addiction risk, pseudoaddiction, addiction screening tools, and the safety of alternatives to opioids.

377. At the same time, Endo also relied on a cast of third-party partners to promote the safety, efficacy, and superiority of opioids generally, through a combination of CMEs, websites, patient education pamphlets, and other publications. These materials echoed the misrepresentations described above, and also made deceptive statements about withdrawal symptoms and the safety of opioids at higher doses.

378. Based on the highly coordinated and uniform nature of Endo's marketing, Endo conveyed these deceptive messages to Mississippi prescribers. The materials that Endo generated in collaboration with third-parties also were distributed or made available in

Mississippi. Endo distributed these messages, or facilitated their distribution, in Mississippi with the intent that Mississippi prescribers and/or consumers would rely on them in choosing to use opioids to treat chronic pain.

a. Endo's deceptive direct marketing.

379. Like the other Defendants, Endo used deceptive direct marketing to increase the sales of its dangerous opioids. As set forth below, Endo conveyed these deceptive messages in training of its sales force and recruited speakers, who in turn conveyed them to physicians; in a misleading journal supplement; and in unbranded advertising.

(1) Endo's sales force and deceptive sales training.

380. Endo's promotion of Opana ER relied heavily on in-person marketing, including to Mississippi prescribers. Endo had an aggressive detailing program, with its sales representatives making nearly 72,000 visits to prescribers nationwide to detail Opana ER in the first quarter of 2010 alone. Between 2007 and 2013, Endo spent between $3 million and $10 million each quarter to promote opioids through its sales force.

381. Endo's sales representatives, like those of the other Defendants, targeted physicians to deliver sales messages that were developed centrally and deployed uniformly across the country. These sales representatives were critical in transmitting Endo's marketing strategies and talking points to individual prescribers.

382. Endo specifically directed its sales force to target physicians who would prescribe its drugs to treat chronic pain. For example, an Opana Brand Tactical Plan dated August 2007 aimed to increase "Opana ER business from [the Primary Care Physician] community" more than 45% by the end of that year. Indeed, Endo sought to develop strategies that would be most persuasive to primary care doctors – strategies that sought to influence the prescribing behavior

of primary care physicians through the use of subject matter experts. A February 2011 Final Report on Opana ER Growth Trends, for example, predicted that Endo's planned "[u]se of Pain Specialists as local thought leaders should affect increased primary care adoption."

383. Endo trained its sales force to make a number of misrepresentations to physicians nationwide and in Mississippi. Endo's sales representatives were trained to represent to these prescribers that Opana ER would help patients regain function they had lost to chronic pain; that Endo opioids had a lower potential for abuse because they were "designed to be crush resistant," even though the "clinical significance of INTAC Technology or its impact on abuse/misuse has not been established for Opana ER;" and that drug seeking behavior was a sign of undertreated pain rather than addiction.

384. Endo knew that its marketing reached physicians – repeatedly – because it tracked their exposure. Internal Endo documents dated August 23, 2006, demonstrate that the following percentages of physicians would view an Endo journal insert (or paid supplement) at least 3 times in an 8 month period: 86% of neurologists; 86% of rheumatologists; 85% of oncologists; 85% of anesthesiologists; 70% of targeted primary care physicians; and 76% of OB/Gyns.

385. Endo was not only able to reach physicians through its marketing, but also successfully imparted its marketing messages. The company found its promotional materials tripled prescribers' ability to recall the sales message and doubled their willingness to prescribe Opana ER in the future. This was true of marketing that contained its deceptions.

386. For example, according to internal Endo documents, up to 10% of physicians it detailed were able to recall without assistance the message that Opana ER had "Minimal/less abuse/misuse" potential than other drugs. The Endo message that prescribers retained was a

plain misrepresentation: that use of Opana ER was unlikely to lead to abuse and addiction. Although Opana ER always has been classified under Schedule II as a drug with a "high potential for abuse," and consistent with the pattern of misrepresentations described in Section IV.D.2, the largest single perceived advantage of Opana ER, according to a survey of 187 physicians who reported familiarity with the drug, was "perceived low abuse potential," cited by 15% of doctors as an advantage. As described in Section IV.E.3.c below, low abuse potential was among the deceptive messages that Mississippi prescribers received, and retained, from Endo sales representatives.

387. Endo's own internal documents, however, acknowledged the misleading nature of these statements, conceding that "Opana ER has an abuse liability similar to other opioid analgesics as stated in the [FDA-mandated] box warning." A September 2012 Opana ER Business Plan similarly stated that Endo needed a significant investment in clinical data – to support comparative effectiveness, scientific exchange, benefits and unmet need, while citing lack of "head-to-head data" as a barrier to greater share acquisition.

388. Nevertheless, Endo knew that its marketing was extremely effective in turning physicians into prescribers. Nationally, the physicians Endo targeted for in-person marketing represented approximately 84% of all prescriptions for Opana ER in the first quarter of 2010. Endo also observed that the prescribers its sales representatives visited wrote nearly three times as many prescriptions per month for Opana ER as those physicians who were not targeted for Endo's marketing – 7.4 prescriptions per month versus 2.5. The most heavily targeted prescribers wrote nearly 30 prescriptions per month. Internal Endo documents from May 2008 indicate that Endo expected that each of its sales representatives would generate 19.6

prescriptions per week by the end of 2008. As summarized by a February 2011 report on Opana ER growth trends, Endo's "[a]ggressive detailing [is] having an impact."

389. More broadly, Endo's sales trainings demonstrate that its sales force was trained to provide prescribers with misleading information regarding the risks of opioids when used to treat chronic pain. Foremost among these messages were misleading claims that the risks of addiction, diversion, and abuse associated with opioids – and Endo's products in particular – were low, and lower than other opioids.

(2) Endo's sales force deceptively minimized the risks of addiction associated with chronic opioid therapy.

390. By way of illustration, Endo's Opana ER INTAC Technology Extended-Release Sell Sheet Implementation Guide, which instructs Endo sales personnel how to effectively "support key messages" related to the marketing of Opana ER, states that it is an "approved message" for sales representatives to stress that Opana ER was "designed to be crush resistant," even though this internal document conceded that "the clinical significance of INTAC Technology or its impact on abuse/misuse has not been established for Opana ER."

391. Other Endo documents acknowledged the limitations on Opana ER's INTAC technology, conceding that while Opana ER may be resistant to pulverization, it can still be "ground" and "cut into small pieces" by those looking to abuse the drug.

392. Endo's claims about the crush-resistant design of Opana ER also made their way to the company's press releases. A January 2013 article in *Pain Medicine News*, based in part on an Endo press release, described Opana ER as "crush-resistant." This article was posted on the *Pain Medicine News* website, which was accessible to Mississippi patients and prescribers.

393. Endo could only have promoted the crush resistance of Opana ER in order to persuade doctors that there was less risk of abuse, misuse, and diversion of the drug.

394. On May 10, 2013, however, the FDA warned Endo that there was no evidence that Opana ER's design "would provide a reduction in oral, intranasal, or intravenous abuse" and that the post-marketing data Endo had submitted to the FDA "are insufficient to support any conclusion about the overall or route-specific rates of abuse." Even though it was rebuked by the FDA, Endo continued to market Opana ER as having been ***designed*** to be crush resistant, knowing that this would (falsely) imply that Opana actually ***was*** crush resistant and that this crush-resistant quality would make Opana ER less likely to be abused.

395. Endo's sales training and the promotional materials distributed by its sales representatives also minimized the risk of addiction. For example, Endo circulated an education pamphlet with the Endo logo titled *Living with Someone with Chronic Pain*, which implied to persons providing care to chronic pain patients that addiction was not a substantial concern by stating that "[m]ost health care providers who treat people with pain agree that most people do not develop an addiction problem." This program was downloadable from Endo's website and accessible to Mississippi prescribers.

396. Endo's sales training also misrepresented the risks of addiction associated with Endo's products by implying that Endo's prolonged absorption would make it less likely to lead to abuse. For example, a presentation titled "Deliver the Difference for the Opana Brand in POA II" sets out that one of the "[k]ey [m]essages" for the Endo sales force was that Opana ER provides "[s]table, steady-state plasma levels for true 12-hour dosing that lasts." As outlined in Section IV.E.3.c below, Endo's sales representatives used this messaging to imply to Mississippi prescribers that Opana ER provided "steady state" pain relief, making Opana less likely to incite euphoria in patients and less likely to lead to addiction.

397. Endo further instructed its sales force to promote the misleading concept of "pseudoaddiction," – *i.e.*, that drug-seeking behavior was not cause for alarm, but merely a manifestation of undertreated pain. In a sales training document titled "Understanding the Primary Care MD and their use of Opioids," Endo noted that the "biggest concerns" among primary care physicians were "prescription drug abuse (84.2%), addiction (74.9%), adverse effects (68%), tolerance (60.7%), and medication interaction (32%)." In response to these concerns, Endo instructed its sales representatives to ask whether their customers are "confus[ing] 'pseudo-addiction' with 'drug-seekers'" and how confident they are that their health care providers "know these differences (Tolerance, Dependence, Addiction, Pseudo-Addiction …)."

(3) Endo's sales force deceptively implied that chronic opioid therapy would improve patients' ability to function.

398. In addition to their deceptive messages regarding addiction, Endo's promotional materials and sales trainings also misleadingly claimed that patients using opioids for the long-term treatment of chronic pain would experience improvements in their daily function. In reality, long-term opioid use has not been shown to and does not improve patients' function, and, in fact, often is accompanied by serious side effects that degrade function. Endo's own internal documents acknowledged that claims about improved quality of life were unsubstantiated "off label claims."

399. Nevertheless, Endo distributed product advertisements that suggested that using Opana ER to treat chronic pain would allow patients to perform demanding tasks like work as a chef. One such advertisement states prominently on the front: "Janice is a 46-year-old chef with chronic low back pain. She needs a treatment option with true 12-hour dosing." The advertisement does not mention the "moderate to severe pain" qualification in Opana ER's

indication, except in the fine print. These advertisements were mailed to prescribers and distributed by Endo's sales force in detailing visits, which would have included Endo representatives' visits to Mississippi prescribers.

400. In a 2007 Sales Tool that was intended to be shown by Endo sales personnel to physicians during their detailing visits, Endo highlighted a hypothetical patient named "Bill," a 40-year-old construction worker who was reported to suffer from chronic low back pain. According to the Sales Tool, Opana ER will make it more likely that Bill can return to work and support his family.

401. Similarly, training materials for sales representatives from March 2009 ask whether it is true or false that "[t]he side effects of opioids prevent a person from functioning and can cause more suffering than the pain itself." The materials indicate that this is "[f]alse" because "[t]he overall effect of treatment with opioids is very favorable in most cases."

402. A sales training video dated March 8, 2012, that Endo produced and used to train its sales force makes the same types of claims. A patient named Jeffery explains in the video that he suffers from chronic pain and that "chronic pain […] reduces your functional level." Jeffery claims that after taking Opana ER, he "can go out and do things" like attend his son's basketball game and "[t]here's no substitute for that." This video was shown to Endo's sales force, which adopted its misleading messaging in its nationwide sales approach, including the approach it used in Mississippi.

403. Claims of improved functionality were central to Endo's marketing efforts for years. 2012 Endo Business Plan lists ways to position Opana ER, and among them is the claim that Opana ER will help patients "[m]aintain[] normal functionality, sleep, [and] work/life/performance productivity" and have a positive "[e]ffect on social relationships."

Indeed, that business plan describes the "Opana ER Vision" as "[t]o make the Opana franchise (Opana ER, Opana, Opana Injection) the choice that maximizes improvement in functionality and freedom from the burden of moderate-to-severe pain."

(4) Endo's sales force deceptively presented the risks and benefits of opioids to make them appear safer than other analgesics.

404. Endo further misled patients and prescribers by downplaying the risks of opioids in comparison to other pain relievers. For example, it distributed in Mississippi and elsewhere a presentation titled *Case Challenges in Pain Management*: *Opioid Therapy for Chronic Pain*. This study held out as a representative example one patient who had taken NSAIDs for more than eight years and, as a result, developed "a massive upper gastrointestinal bleed." The presentation recommended treating this patient with opioids instead. By focusing on the adverse side effects of NSAIDs, while omitting discussion of serious side effects associated with opioids, this presentation misleadingly portrayed the comparative risks and benefits of these drugs.

(5) Endo's speakers bureau programs deceptively minimized the risks of addiction associated with chronic opioid therapy.

405. In addition to its sales representatives' visits to doctors, Endo also used deceptive science and speaker programs to spread its deceptive messages.

406. Endo leaned heavily on its speakers' bureau programs. In 2008 alone, Endo spent nearly $4 million to promote up to 1,000 speakers programs around the country. Endo contracted with a medical communications firm to operate its speakers bureau program, planning to hold a total of 500 "fee-for-service … peer-to-peer promotional programs" for Opana ER in just the second half of 2011, including dinners, lunches and breakfasts. These programs were attended by sales representatives, which reveal their true purpose as marketing, rather than rather than educational, events.

407. Endo's internal reporting stated that the "return on investment" turned positive 8-12 weeks after such programs. Endo measured that return on investment in numbers of prescriptions written by physicians who attended the events. One internal Endo document concluded: "[w]e looked at the data for [the] 2011 program and the results were absolutely clear: physicians who came into our speaker programs wrote more prescriptions for Opana ER after attending than they had before they participated. You can't argue with results like that."

408. These speakers bureau presentations included the very same misrepresentations Endo disseminated through its sales representatives. A 2012 speaker slide deck for Opana ER – on which Endo's recruited speakers were trained and to which they were required to adhere to in their presentations – misrepresented that the drug had low abuse potential, in addition to suggesting that as many as one-quarter of the adult population could be candidates for opioid therapy.

409. In addition, a 2013 training module directed speakers to instruct prescribers that "OPANA ER with INTAC is the only oxymorphone designed to be crush resistant" and advised that "[t]he only way for your patients to receive oxymorphone ER in a formulation designed to be crush resistant is to prescribe OPANA ER with INTAC." This was a key point in distinguishing Opana ER from competitor drugs. Although Endo mentioned that generic versions of oxymorphone were available, it instructed speakers to stress that "[t]he generics are not designed to be crush resistant." This was particularly deceptive given that Opana ER was not actually crush-resistant.

410. In 2009, Endo wrote a talk titled *The Role of Opana ER in the Management of Chronic Pain*. The talk included a slide titled "Use of Opioids is Recommended for Moderate to Severe Chronic Noncancer Pain," which cited the AAPM/APS Guidelines – and, as described

above in Section V.C.2.c.2, their accompanying misstatements regarding the likelihood of addiction (by claiming that addiction risks were manageable regardless of patients' past abuse histories) while omitting their disclaimer regarding the lack of supporting evidence in favor of that position. This dangerously misrepresented to doctors the force and utility of the 2009 Guidelines.

411. The misleading messages and materials Endo provided to its sales force and its speakers were part of a broader strategy to convince prescribers to use opioids to treat their patients' pain, irrespective of the risks, benefits, and alternatives. This deception was national in scope and included Mississippi. As described above in Section IV.B.2, Endo's nationwide messages would have reached Mississippi prescribers in a number of ways. For example, they were carried into Mississippi by Endo's sales representatives during detailing visits as well as made available to Mississippi patients and prescribers through websites and ads. They also have been delivered to Mississippi prescribers by Endo's paid speakers, who were required by Endo policy and by FDA regulations to stay true to Endo's nationwide messaging.

(6) Endo's misleading journal supplement.

412. In 2007, Endo enlisted a Chicago prescriber to write a supplement available for CME credit in the *Journal of Family Practice* that Endo paid to have published. It was called *Pain Management Dilemmas in Primary Care: Use of Opioids*, and it deceptively minimized the risk of addiction by emphasizing the effectiveness of screening tools. Specifically, it recommended screening patients using tools like the Opioid Risk Tool or the Screener and Opioid Assessment for Patients with Pain. It also falsely claimed that, through the use of tools like toxicology screens, pill counts, and a "maximally structured approach," even patients at high

risk of addiction could safely receive chronic opioid therapy. Endo distributed 96,000 copies of this CME nationwide, and it was available to and was intended to reach Mississippi prescribers.

b. Endo's deceptive unbranded advertising.

413. Endo also used unbranded advertisements to advance its goals. By electing to focus on unbranded marketing, Endo was able to make claims about the benefits of its opioids that the FDA would never allow in its branded materials. The chart below compares an Endo unbranded statement with one of Endo's FDA-regulated, branded statements:

Living with Someone with Chronic Pain (2009) **(Unbranded)**	**Opana ER Advertisement (2011/2012/2013)** **(Branded)**
Patient education material created by Endo	Endo advertisement
"Most health care providers who treat people with pain agree that **most people do not develop an addiction problem**."	"[C]ontains oxymorphone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit." "All patients treated with opioids require careful monitoring for signs of abuse and addiction, since **use of opioid analgesic products carries the risk of addiction even under appropriate medical use**."

c. Endo's deceptive third party statements.

414. Endo's efforts were not limited to directly making misrepresentations through its marketing materials, its speakers, and its sales force. Endo believed that support for patient advocacy and professional organizations would reinforce Endo's position as "the pain management company."

415. Prior to, but in contemplation of, the 2006 launch of Opana ER, Endo developed a "Public Stakeholder Strategy." Endo identified "tier one" advocates to assist in promoting the approval and acceptance of its new extended release opioid. Endo also intended to enlist the support of organizations that engage or have the potential to advocate for public policy that would be "favorable" to Schedule II opioids from a sales perspective. Endo sought to develop its relationships with these organizations through its funding. In 2008, Endo spent $1 million per year to attend conventions of these pro-opioid medical societies, including meetings of AAPM, APS, and the American Society of Pain Management Nursing ("ASPMN").

416. APF's ability to influence professional societies and other third parties is demonstrated by its approach in responding to a citizens' petition filed with the FDA by the Physicians for Responsible Opioid Prescribing (the "PROP Petition"). The PROP petition, filed by a group of prescribers who had become concerned with the rampant prescribing of opioids to treat chronic pain, asked the FDA to require dose and duration limitations on opioid use and to change the wording of the approved indication of various long-acting opioids to focus on the severity of the pain they are intended to treat.

417. The PROP Petition set off a flurry of activity at Endo. It was a given that Endo would respond to the petition; the only question among Endo personnel was "[s]hould we […] consider filing a direct response to this [citizens' petition] or do you think we are better served by working through our professional society affiliations?" One Endo employee responded: "My sense is the societies are better placed to make a medical case than Endo." Endo's Director of Medical Science agreed that "a reply from an external source would be most impactful." These communications reflected Endo's absolute confidence that the professional societies would support its position in opposition to the Petition.

(1) APF

418. One of the societies with which Endo worked most closely was APF. Endo provided substantial assistance to, and exercised editorial control, over the deceptive and misleading messages that APF conveyed through its National Initiative on Pain Control ("NIPC"). Endo was one of the APF's biggest financial supporters, and Endo provided more than half of the $10 million APF received from opioid manufacturers during its lifespan. Endo spent $1.1 million on the NIPC program in 2008 alone, funding earmarked, in part, for the creation of CME materials that were intended to be used over and over again.

419. Endo's influence over APF's activities was so pervasive that APF President Will Rowe even reached out to Defendants – including Endo – rather than his own staff to identify potential authors to answer an article critical of opioids that appeared in the *Archives of Internal Medicine* in 2011. Personnel from Defendants Purdue, Endo, Janssen, and Cephalon worked with Rowe to formulate APF's response. The response suggested by Defendants was the one that APF ultimately published.

420. Documents also indicate that Endo personnel were given advance notice of materials APF planned to publish on its website and provided an opportunity to comment on the content of those materials before they were published. For example, in early July of 2009, APF's Director of Strategic Development wrote to Endo personnel to give them advance notice of content that APF planned to be "putting … up on the website but it's not up yet." This Endo employee also reassured the sender that she "will not forward it to anyone at all" and promised that she would "'double delete it' from [her] inbox." In response, APF's Director of Strategic Development replied internally with only four words: "And where's the money?"

421. Nowhere was Endo's relationship with APF closer than with its sponsorship of the NIPC. Before being taken over by APF, the NIPC was sponsored by Professional Postgraduate Services, but that company was determined to be a "commercial interest" by the ACCME and could no longer serve as a sponsor. In response, Endo reached out to APF. An August 2009 document titled "A Proposal for the American Pain Foundation to Assume Sponsorship of the National Initiative on Pain Control," pointed out that "[f]or the past 9 years, the NIPC has been supported by unrestricted annual grants from Endo Pharmaceuticals, Inc." According to this document, APF's sponsorship of the NIPC "[o]ffers the APF a likely opportunity to generate new revenue, as Endo has earmarked substantial funding: $1.2 million in net revenue for 2010 to continue the NIPC." Further, sponsorship of the APF would "[p]rovide[] numerous synergies to disseminate patient education materials," including "[h]andouts to attendees at all live events to encourage physicians to drive their patients to a trusted source for pain education – the APF website."

422. A September 14, 2009 presentation to APF's board contained a materially similar discussion of NIPC sponsorship, emphasizing the financial benefit to APF from assuming the role of administering NIPC. The proposal "offer[ed] a solution to continue the development and implementation of the NIPC initiative as non-certified … yet independent education to physicians and healthcare professionals in the primary care setting, while providing the APF with a dependable, ongoing source of grant revenue." A number of benefits related to NIPC sponsorship were listed, but chief among them was "a likely opportunity [for APF] to generate new revenue, as Endo has earmarked substantial funding: $1.2 million in net revenue for 2010 to continue the NIPC."

423. Internal Endo scheduling documents indicate that "NIPC module curriculum developing, web posting, and live regional interactive workshops" were Endo promotional tasks in 2010. Endo emails indicate that Endo personnel reviewed the content created by NIPC and provided feedback.

424. Behind the scenes, Endo exercised substantial control over NIPC's work. Endo exerted its control over NIPC by funding NIPC and APF projects; developing, specifying, and reviewing content; and taking a substantial role in distribution of NIPC and APF materials, which in effect determined which messages were actually delivered to prescribers and consumers. As described below, Endo projected that it would be able to reach tens of thousands of prescribers nationwide through the distribution of NIPC materials.

425. From 2007 until at least 2011, Endo also meticulously tracked the distribution of NIPC materials, demonstrating Endo's commercial interest in and access to NIPC's reach. Endo knew exactly how many participants viewed NIPC webinars and workshops and visited its website, *Painknowledge.com*. Endo not only knew how many people viewed NIPC's content, but what their backgrounds were (*e.g.*, primary care physicians or neurologists). Endo's access to and detailed understanding of the composition of the audience at these events demonstrates how deeply Endo was involved in NIPC's activities. Moreover, Endo tracked the activities of NIPC – ostensibly a third party – just as it tracked its own commercial activity.

426. Endo worked diligently to ensure that the NIPC materials it helped to develop would have the broadest possible distribution. Endo's 2008 to 2012 Opana Brand Tactical Plan indicates that it sought to reach 1,000 prescribers in 2008 through live NIPC events, and also to "[l]everage live programs via enduring materials and web posting." Endo also planned to disseminate NIPC's work by distributing two accredited newsletters to 60,000 doctors

nationwide for continuing education credit and sponsoring a series of 18 NIPC regional case based interactive workshops. Endo had earmarked more than one million dollars for NIPC activities in 2008 alone.

427. In short, NIPC was a key piece of Endo's marketing strategy. Indeed, internal APF emails question whether it was worthwhile for APF to continue operating NIPC given that the NIPC's work was producing far more financial benefit for Endo than for APF. Specifically, after Endo approved a $244,337.40 grant request to APF to fund a series of NIPC eNewsletters, APF personnel viewed it as "[g]reat news," but cautioned that "the more I think about this whole thing, [Endo's] making a lot of money on this with still pretty slender margins on [APF's] end." APF's commitment to NIPC's "educational" mission did not figure at all in APF's consideration of the value of its work, nor was Endo's motive or benefit in doubt.

(a) Misleading medical education.

428. NIPC distributed a series of eNewsletter CMEs focused on "key topic[s] surrounding the use of opioid therapy" and sponsored by Endo. These newsletters were edited by KOL Dr. Perry Fine and also listed several industry-backed KOLs, including Dr. Webster, as individual authors. Endo estimated that roughly 60,000 prescribers viewed each one, which were available to and would have included Mississippi prescribers. Before-and-after surveys, summarized in the chart below, showed that prescriber comfort with prescribing opioids ranged from 27% to 62% before exposure to the CME, and from 76% to 92% afterwards:

Topic	Comfort level *prior to reading the article*	Comfort level *after reading the article*
Patient Selection and Initiation of Opioid Therapy as a Component of Pain Treatment	47%	87%
Informed Consent and Management Plans to Optimize Opioid Therapy for Chronic Pain	48%	81%
Risk Stratification and Evaluation of High-Risk Behaviors for Chronic Opioid Therapy	28%	76%
Integration of Nonpharmacologic and Multidisciplinary Therapies Into the Opioid Treatment Plan	42%	85%
Addressing Patients' Concerns Associated With Chronic Pain Treatment and Opioid Use	62%	92%
Opioid Therapy in Patients With a History of Substance Use Disorders	35%	85%
Urine Drug Testing: An Underused Tool	54%	86%
Appropriate Documentation of Opioid Therapy: The Emergence of the 4As and Trust and Verify as the Paradigm	44%	86%
Opioid Rotation	27%	92%
Discontinuing Opioid Therapy: Developing and Implementing an "Exit Strategy"	37%	90%

429. Endo documents make clear that the persuasive power of NIPC speakers was directly proportional to their perceived objectivity. Accordingly, Endo personnel directed that, when giving Endo-sponsored talks, NIPC faculty would not appear to be "Endo Speakers." Nevertheless, the two parties understood that Endo and NIPC shared a common "mission to educate physicians" and working "through the APF … [wa]s a great way to work out … problems that could have been there without the APF's participation and support."

430. The materials made available on and through NIPC included misrepresentations. For example, Endo worked with NIPC to sponsor a series of CMEs titled *Persistent Pain in the Older Patient* and *Persistent Pain in the Older Adult*. These CMEs misrepresented the prevalence of addiction by stating that opioids have "possibly less potential for abuse" in elderly patients than in younger patients, even though there is no evidence to support such an assertion. Moreover, whereas withdrawal symptoms are always a factor in discontinuing long-term opioid therapy, *Persistent Pain in the Older Adult* also misleadingly indicated that such symptoms can be avoided entirely by tapering the patient's does by 10-20% per day for ten days. *Persistent*

Pain in the Older Patient, for its part, made misleading claims that opioid therapy has been "shown to reduce pain and improve depressive symptoms and cognitive functioning." NIPC webcast these CMEs from its own website, where they were available to and were intended to reach Mississippi prescribers.

(b) Painknowledge.com

431. Working with NIPC enabled Endo to make a number of misleading statements through the NIPC's website, *Painknowledge.com*. Endo tracked visitors to *Painknowledge.com* and used *Painknowledge.com* to broadcast notifications about additional NIPC programming that Endo helped to create.

432. APF made a grant request to Endo to create an online opioid "tool-kit" for NIPC and to promote NIPC's website, *Painknowledge.com*. In so doing, APF made clear that it planned to disseminate Defendants' misleading messaging. The grant request expressly indicated APF's intent to make misleading claims about functionality, noting: "Some of these people [in chronic pain] may be potential candidates for opioid analgesics, which can improve pain, function, and quality of life." Endo provided $747,517 to fund the project.

433. True to APF's word, *Painknowledge.com* misrepresented that opioid therapy for chronic pain would lead to improvements in patients' ability to function. Specifically, in 2009 the website instructed patients and prescribers that, with opioids, a patient's "level of function should improve" and that patients "may find [they] are now able to participate in activities of daily living, such as work and hobbies, that [they] were not able to enjoy when [their] pain was worse."

434. *Painknowledge.com* also deceptively minimized the risk of addiction by claiming that "[p]eople who take opioids as prescribed usually do not become addicted."

435. *Painknowledge.com* did not stop there. It deceptively portrayed opioids as safe at high doses and also misleadingly omitted serious risks, including the risks of addiction and death, from its description of the risks associated with the use of opioids to treat chronic pain.

436. Endo was the sole funder of *Painknowledge.com*, and it continued to provide that funding despite being aware of the website's misleading contents.

(c) *Exit Wounds.*

437. Finally, Endo also sponsored APF's publication and distribution of *Exit Wounds*, a publication aimed at veterans that also contained a number of misleading statements about the risks, benefits, and superiority of opioids to treat chronic pain. *Exit Wounds* was drafted by "Medical Writer X," whose extensive work for Janssen is described below in Section IV.E.4. Medical Writer X was frequently hired by a consulting Firm, Conrad & Associates LLC, to write pro-opioid marketing pieces disguised as science. Medical Writer X's work was reviewed and approved by drug company representatives, and he felt compelled to draft pieces that he admits distorted the risks and benefits of chronic opioid therapy in order to meet the demands of his drug company sponsors.

438. *Exit Wounds* is a textbook example of Medical Writer X's authorship on drug companies' behalf. The book misrepresented the functional benefits of opioids by stating that opioid medications "*increase* your level of functioning" (emphasis in original).

439. *Exit Wounds* also misrepresented that the risk of addiction associated with the use of opioids to treat chronic pain was low. It claimed that "[l]ong experience with opioids shows that people who are not predisposed to addiction are very unlikely to become addicted to opioid pain medications."

440. Finally, *Exit Wounds* misrepresented the safety profile of using opioids to treat chronic pain by omitting key risks associated with their use. Specifically, it omitted warnings of the risk of interactions between opioids and benzodiazepines – a warning sufficiently important to be included on Endo's FDA-required labels. *Exit Wounds* also contained a lengthy discussion of the dangers of using alcohol to treat chronic pain but did not disclose dangers of mixing alcohol and opioids – a particular risk for veterans.

441. As outlined above, Endo exercised dominance over APF and the projects it undertook in an effort to promote the use of opioids to treat chronic pain. In addition, as outlined above, Medical Writer X's work was being reviewed and approved by drug company representatives, motivating him to draft pro-opioid propaganda masquerading as science. Combined, these factors gave Endo considerable influence over the work of Medical Writer X and over APF. Further, by paying to distribute *Exit Wounds*, Endo endorsed and approved its contents.

(d) Other Front Groups: FSMB, AAPM and AGS.

442. In addition to its involvement with APF, Endo worked closely with other third-party Front Groups and KOLs to disseminate deceptive messages regarding the risks, benefits, and superiority of opioids for the treatment of chronic pain. As with certain APF publications, Endo in some instances used its sales force to directly distribute certain publications by these Front Groups and KOLs, making those publications "labeling" within the meaning of 21 C.F.R. § 1.3(a).

443. In 2007, Endo sponsored FSMB's *Responsible Opioid Prescribing*, which, as described in Section IV.D, in various ways deceptively portrayed the risks, benefits, and

superiority of opioids to treat chronic pain. *Responsible Opioid Prescribing* was drafted by "Medical Writer X."

444. Endo spent $246,620 to help FSMB distribute *Responsible Opioid Prescribing*. Based on the uniform and nationwide character of Endo's marketing campaign, and the fact that Endo purchased these copies specifically to distribute them, these copies were distributed to physicians nationwide, including physicians in Mississippi.

445. In December 2009, Endo also contracted with AGS to create a CME to promote the 2009 guidelines titled the *Pharmacological Management of Persistent Pain in Older Persons* with a $44,850 donation. As described in Section IV.C.2.c.3 above, these guidelines misleadingly claimed that "the risks [of addiction] are exceedingly low in older patients with no current or past history of substance abuse," since the study supporting this assertion did not analyze addiction rates by age. They also stated, falsely, that "[a]ll patients with moderate to severe pain … should be considered for opioid therapy (low quality of evidence, strong recommendation)" when in reality, opioid therapy was an appropriate treatment only for a subset of those patients, as Endo's FDA-mandated labels recognized.

446. AGS' grant request to Endo made explicit reference to the CME Endo was funding. Endo thus knew full well what content it was paying to distribute, and was in a position to evaluate that content to ensure it was accurate, substantiated, and balanced before deciding whether to invest in it. After having sponsored it, Endo's internal documents indicate that Endo's pharmaceutical sales representatives discussed the AGS guidelines with doctors during individual sales visits.

447. Endo also worked with AAPM, which it viewed internally as "Industry Friendly," with Endo advisors and speakers among its active members. Endo attended AAPM conferences, funded its CMEs, and distributed its publications.

448. A talk written by Endo in 2009, approved by Endo's Medical Affairs Review Committee,[170] and given by a Chicago-area KOL, titled *The Role of Opana ER in the Management of Chronic Pain,* includes a slide titled *Use of Opioids is Recommended for Moderate to Severe Chronic Noncancer Pain.* That slide cites the AAPM/APS Guidelines, which contain a number of misstatements as outlined in Section IV.C.2.c.2 above, while omitting their disclaimer regarding the lack of supporting evidence. This dangerously misrepresented to doctors the force and utility of the 2009 Guidelines. Furthermore, Endo's internal documents indicate that pharmaceutical sales representatives employed by Endo, Actavis, and Purdue discussed treatment guidelines with doctors during individual sales visits.

(e) Key Opinion Leaders and misleading science.

449. Endo also sought to promote opioids for the treatment of chronic pain through the use of key opinion leaders and biased, misleading science.

450. Endo's 2010 publication plan for Opana ER identified a corporate goal of making Opana ER the second-leading branded product for the treatment of moderate-to-severe chronic pain (after OxyContin). Endo sought to achieve that goal by providing "clinical evidence for the

[170] Although they were given slightly different names by each Defendant, each Defendant employed a committee that would review and approve materials for distribution. These committees included representatives from all relevant departments within Defendants' organizations, including the legal, compliance, medical affairs, and marketing departments. The task of these review committees was to scrutinize the marketing materials Defendants planned to distribute and to ensure that those materials were scientifically accurate and legally sound. Tellingly, these committees were called to review only materials that created a potential compliance issue for the company, an implicit recognition by Defendants that they ultimately would be responsible for the content under review.

use of Opana ER in chronic low back pain and osteoarthritis," and succeeded in having articles on this topic published.[171]

451. In the years that followed, Endo sponsored articles, authored by an Endo consultant and Endo employees, which argued that the metabolic pathways utilized by Opana ER made it less likely than other opioids to result in drug interactions in elderly low back and osteoarthritis pain patients. In 2010, Endo directed its publication manager to reach out to a list of consultants conducting an ongoing Endo-funded study, to assess their willingness to respond to an article[172] that Endo believed emphasized the risk of death from opioids, "without [] fair balance."[173]

452. Endo's reliance on flawed, biased research is also evident in its 2012 marketing materials and strategic plans. A 2012 Opana ER slide deck for Endo's speakers bureaus – on which these recruited physician speakers were trained and to which they were required to adhere – misrepresented that the drug had low abuse potential and suggested that as many as one-quarter of the adult population could be candidates for opioid therapy. Although the FDA requires such speaker slide decks to reflect a "fair balance" of information on benefits and risks, Endo's slides reflected one-sided and deeply biased information. The presentation's 28 literature citations were largely to "data on file" with the company, posters, and research funded by or

[171] These studies suffered from the limitations common to the opioid literature – and worse. None of the comparison trials lasted longer than three weeks. Endo also commissioned a six-month, open label trial during which a full quarter of the patients failed to find a stable dose, and 17% of patients discontinued, citing intolerable effects. In open label trials, subjects know which drug they are taking; such trials are not as rigorous as double-blind, controlled studies in which neither the patients nor the examiners know which drugs the patients are taking.

[172] Susan Okie, *A Flood of Opioids, a Rising Tide of Deaths*, 363 NEW ENGL. J. MED. 1981 (2010), finding that opioid overdose deaths and opioid prescriptions both increased by roughly 10-fold from 1990 to 2007.

[173] Endo did manage to get a letter written by three of those researchers, which was not published.

otherwise connected to Endo. Endo's speakers carried the information in these slides to audiences that were unaware of the skewed science on which the information rested.

453. A 2012 Opana ER Strategic Platform Review suffered from similar defects. Only a small number of the endnote references in that document, which it cites to indicate "no gap" in scientific evidence for particular claims, were to national-level journals. Many were published in lesser or dated journals, and written or directly financially supported by opioid manufacturers. Where the strategy document did cite independent, peer-reviewed research, it did so out of context. For example, it cited a 2008 review article on opioid efficacy for several claims, including that "treatment of chronic pain reduces pain and improves functionality," but it ignores that article's overall focus on "the lack of consistent effectiveness of opioids in reducing pain and improving functional status."[174]

454. Notwithstanding Endo's reliance upon dubious or cherry-picked science, in an Opana ER brand strategy plan it internally acknowledged the continuing need for a significant investment in clinical data to support comparative effectiveness. Endo also cited a lack of "head-to-head data" as a barrier to greater share acquisition and the "lack of differentiation data" as a challenge to addressing the "#1 Key Issue" of product differentiation. Nor did this acknowledged lack of support stop Endo from directing its sales representatives to tell prescribers that its drugs were less likely to be abused or less addictive than other opioids.

455. Endo also worked with various KOLs to disseminate various misleading statements about chronic opioid therapy. For example, Endo distributed a patient education

[174] Andrea M. Trescot, *et al*., Opioids in the management of non-cancer pain: an update of American Society of the Interventional Pain Physicians, Pain Physician 2008 Opioids Special Issue, S5-S2.

pamphlet edited by KOL Dr. Russell Portenoy titled *Understanding your Pain: Taking Oral Opioid Analgesics*. This pamphlet deceptively minimized the risks of addiction by stating that "[a]ddicts take opioids for other reasons [than pain relief], such as unbearable emotional problems," implying that patients who are taking opioids for pain are not at risk of addiction.

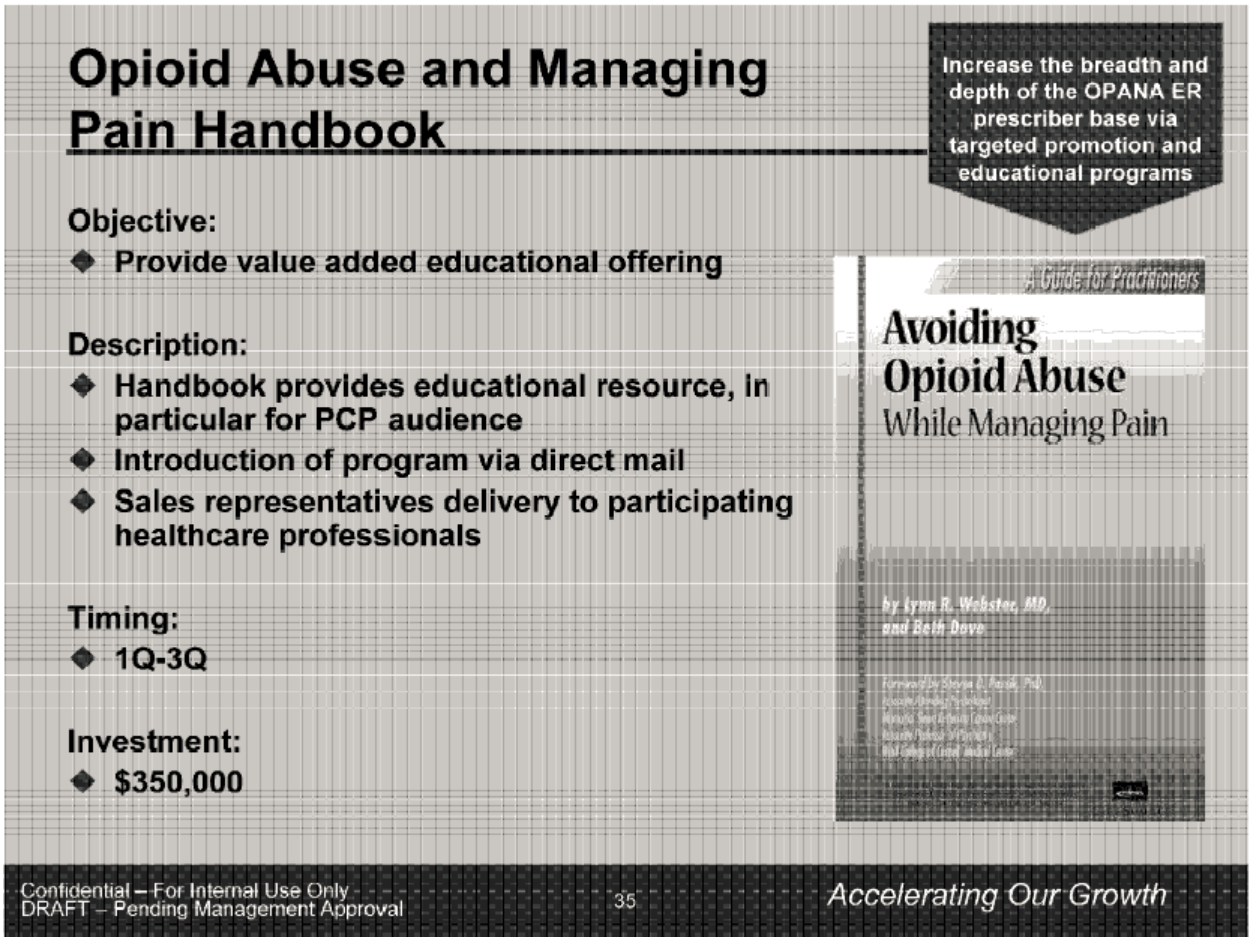
456. *Understanding your Pain: Taking Oral Opioid Analgesics* also misleadingly omitted any description of the increased risks posed by higher doses of opioid medication. Instead, in a Q&A format, the pamphlet asked "[i]f I take the opioid now, will it work later when I really need it?" and responded that "[t]he dose can be increased … [y]ou won't 'run out' of pain relief."

457. Dr. Portenoy received research support, consulting fees, and honoraria from Endo for editing *Understanding Your Pain* and other projects.

458. *Understanding Your Pain* was available on Endo's website during the time period of this Complaint and was intended to reach Mississippi prescribers.

459. Endo similarly distributed a book written by Dr. Lynn Webster titled *Avoiding Opioid Abuse While Managing Pain*, which stated that in the face of signs of aberrant behavior, increasing the dose "in most cases … should be the clinician's first response."

460. A slide from an Opana ER business plan contemplated distribution of the book as part of Endo's efforts to "[i]ncrease the breadth and depth of the OPANA ER prescriber base via targeted promotion and educational programs." The slide indicates that the book would be particularly effective "for [the] PCP audience" and instructed "[s]ales representatives [to] deliver [the book] to participating health care professionals." The slide, shown below, demonstrates Endo's express incorporation of this book by a KOL into its marketing strategy:



461. Endo documents indicate that, around 2007, the company purchased at least 50,000 copies of the book for distribution. Internal Endo documents demonstrate that the book had been approved for distribution by Endo's sales force, and Endo had fewer than 8,000 copies on hand in March of 2013. Based on the nationwide and uniform character of Endo's marketing, and the book's approval for distribution, this book was available to and was intended to reach Mississippi prescribers.

d. Endo's deceptive statements to Mississippi patients and prescribers.

462. Endo also directed the dissemination of the misstatements described above to Mississippi patients and prescribers, including through its sales force, speakers bureaus, CMEs, and the *Painknowledge.com* website.

463. Indeed, the significant response to *Painknowledge.com* also indicates that those websites were viewed by Mississippi prescribers, who were exposed to the site's misleading information regarding the effect of opioids on patients' ability to function and the deceptive portrayal of the risks of opioids. As of September 14, 2010, *Painknowledge.com* had 10,426 registrants, 86,881 visits, 60,010 visitors, and 364,241 page views. Upon information and belief, based on the site's nationwide availability, among the site's visitors were Mississippi-area patients and prescribers who were exposed to the site's misleading information regarding the effect of opioids on patients' ability to function and the deceptive portrayal of the risks of opioids.

4. Janssen

464. Janssen promoted its branded opioids, including Duragesic, Nucynta, and Nucynta ER, through its sales representatives and a particularly active speakers program. Deceptive messages regarding low addiction risk and low prevalence of withdrawal symptoms were a foundation of this marketing campaign. Janssen also conveyed other misrepresentations as described in Section IV.D, including that its opioids could safely be prescribed at higher doses and were safer than alternatives such as NSAIDs.

465. Janssen supplemented these efforts with its own unbranded website, as well as third-party publications and a Front Group website, to promote opioids for the treatment of chronic pain. These materials likewise made deceptive claims about addiction risk, safety at higher doses, and the safety of alternative treatments. They also claimed that opioid treatment would result in functional improvement, and further masked the risk of addiction by promoting the concept of pseudoaddiction.

466. Based on the highly coordinated and uniform nature of Janssen's marketing, and as confirmed by verbatim message data and interviews with prescribers, Janssen conveyed these deceptive messages to Mississippi prescribers. The materials that Janssen generated in collaboration with third-parties also were distributed or made available in Mississippi. Janssen distributed these messages, or facilitated their distribution, in Mississippi with the intent that Mississippi prescribers and/or consumers would rely on them in choosing to use opioids to treat chronic pain.

a. Janssen's deceptive direct marketing.

467. Janssen joined the other Defendants in propagating deceptive branded marketing that falsely minimized the risks and overstated the benefits associated with the long-term use of opioids to treat chronic pain. Like the other Defendants, Janssen sales representatives visited targeted physicians to deliver sales messages that were developed centrally and deployed identically across the country. These sales representatives were critical in transmitting Janssen's marketing strategies and talking points to individual prescribers. In 2011, at the peak of its effort to promote Nucynta ER, Janssen spent more than $90 million on detailing.

468. Janssen's designs to increase sales through deceptive marketing are apparent on the face of its marketing plans. For example, although Janssen knew that there was no credible scientific evidence establishing that addiction rates were low among patients who used opioids to treat chronic pain, its Nucynta Business Plans indicated that one of the "drivers" to sell more Nucynta among primary care physicians was the "[l]ow perceived addiction and/or abuse potential" associated with the drug. However, there is no evidence that Nucynta is any less addictive or prone to abuse than other opioids, or that the risk of addiction or abuse is low. Similarly, Janssen knew that there were severe symptoms associated with opioid withdrawal

including, severe anxiety, nausea, vomiting, hallucinations, and delirium, but Janssen touted the ease with which patients could come off opioids.

(1) Janssen's deceptive sales training.

469. Janssen encouraged its sales representatives to maximize sales of Nucynta and meet their sales targets by relying on the false and misleading statements described above, including in Sections IV.D.2 and IV.D.5.

470. For example, Janssen's sales force was trained to trivialize addiction risk. A June 2009 Nucynta training module warns that physicians are reluctant to prescribe controlled substances like Nucynta because of their fear of addicting patients, but this reluctance is unfounded because "the risks … are [actually] much smaller than commonly believed." Janssen also encouraged its sales force to misrepresent the prevalence of withdrawal symptoms associated with Nucynta. A Janssen sales training PowerPoint titled "Selling Nucynta ER and Nucynta" indicates that the "low incidence of opioid withdrawal symptoms" is a "core message" for its sales force. The message was touted at Janssen's Pain District Hub Meetings, in which Janssen periodically gathered its sales force personnel to discuss sales strategy.

471. This "core message" regarding a lack of withdrawal symptoms runs throughout Janssen's sales training materials. For example, Janssen's "Licensed to Sell" Facilitator's Guide instructs those conducting Janssen sales trainings to evaluate trainees, in part, on whether they remembered that "[w]ithdrawal symptoms after abrupt cessation of treatment with NUCYNTA ER were mild or moderate in nature, occurring in 11.8% and 2% of patients, respectively" and whether they were able to "accurately convey" this "core message." Janssen further claimed in 2008 that "low incidence of opioid withdrawal symptoms" was an advantage of the tapentadol molecule.

472. Similarly, a Nucynta Clinical Studies Facilitator's Guide instructs individuals training Janssen's sales representatives to ask trainees to describe a "key point" – that "83% of patients reported no withdrawal symptoms after abruptly stopping treatment without initiating alternative therapy" – "as though he/she is discussing it with a physician."

473. This misrepresentation regarding withdrawal was one of the key messages Janssen imparted to employees in the "Retail ST 101 Training" delivered to Nucynta sales representatives.

474. Indeed, training modules between 2009 and 2011 instruct training attendees that "most patients [who discontinued taking Nucynta] experienced no withdrawal symptoms" and "[n]o patients experienced moderately severe or severe withdrawal symptoms."

475. During the very time Janssen was making these representations, it knew or should have known that, as laid out above in Section IV.D.2, significant numbers of patients using opioids to treat chronic pain experienced issues with addiction. As laid out in Section IV.D.5, Janssen knew or should have known that its studies on withdrawal were flawed and created a misleading impression of the rate of withdrawal symptoms and, as a result, the risk of addiction.

476. The misleading messages and materials Janssen provided to its sales force were part of a broader strategy to convince prescribers to use opioids to treat their patients' pain, irrespective of the risks, benefits, and alternatives. This deception was national in scope and included Mississippi. As described above in Section IV.B.2, Janssen's nationwide messages reached Mississippi prescribers in a number of ways, including through its sales force in detailing visits, as well as through websites and ads. They also were delivered to Mississippi prescribers by Janssen's paid speakers, who were required by Janssen policy and by FDA regulations to stay true to Janssen's nationwide messaging.

(2) Janssen's deceptive speakers' bureau programs.

477. Janssen did not stop at disseminating its misleading messages regarding chronic opioid therapy through its sales force. It also hired speakers to promote its drugs and trained them to make the very same misrepresentations made by its sales representatives.

478. Janssen's speakers worked from slide decks – which they were required to present – reflecting the deceptive information about the risks, benefits, and superiority of opioids outlined above. For example, a March 2011 speaker's presentation titled *A New Perspective For Moderate to Severe Acute Pain Relief: A Focus on the Balance of Efficacy and Tolerability* set out the following adverse events associated with use of Nucynta: nausea, vomiting, constipation, diarrhea, dizziness, headache, anxiety, restlessness, insomnia, myalgia, and bone pain. It completely omitted the risks of misuse, abuse, addiction, hyperalgesia, hormonal dysfunction, decline in immune function, mental clouding, confusion, and other known, serious risks associated with chronic opioid therapy. The presentation also minimized the risks of withdrawal by stating that "more than 82% of subjects treated with tapentadol IR reported no opioid withdrawal symptoms."

479. An August 2011 speakers' presentation titled *New Perspectives in the Management of Moderate to Severe Chronic Pain* contained the same misleading discussion of the risks associated with chronic opioid therapy. It similarly minimized the risks of withdrawal by reporting that 86% of patients who stopped taking Nucynta ER "abruptly without initiating alternative opioid therapy" reported no withdrawal symptoms whatsoever. The same deceptive claims regarding risks of adverse events and withdrawal appeared in a July 2012 speaker's presentation titled *Powerful Pain Management: Proven Across Multiple Acute and Chronic Pain Models*.

480. These speakers presentations were part of Janssen's nationwide marketing efforts. Upon information and belief, a number of these events were available to and were intended to reach Mississippi prescribers.

(3) Janssen's deceptive unbranded advertising.

481. Janssen was aware that its branded advertisements and speakers programs would face regulatory scrutiny that would not apply to its unbranded materials, so Janssen also engaged in direct, unbranded marketing.

482. One such unbranded project was Janssen's creation and maintenance of *Prescriberesponsibly.com* (last updated July 2, 2015), a website aimed at prescribers and patients that claims that concerns about opioid addiction are "overstated." A disclaimer at the bottom of the website states that the "site is published by Janssen Pharmaceuticals, Inc., which is solely responsible for its content." This website was available to and intended to reach Mississippi prescribers and patients.

b. Janssen's deceptive third party statements.

483. Janssen's efforts were not limited to directly making misrepresentations through its sales force, speakers bureau, and website. To avoid regulatory constraints and give its efforts an appearance of independence and objectivity, Janssen obscured its involvement in certain of its marketing activities by "collaborat[ing] with key patient advocacy organizations" to release misleading information about opioids.

(1) AAPM and AGS – *Finding Relief: Pain Management for Older Adults*.

484. Janssen worked with AAPM and AGS to create a patient education guide entitled *Finding Relief: Pain Management for Older Adults* (2009). In doing so, Janssen contracted with a medical publishing firm, Conrad & Associates, LLC. The content was drafted by a writer

("Medical Writer X") hired by Conrad & Associates and funded by Janssen. These materials were reviewed, in detail, by Janssen's medical-legal review team, which conducted detailed reviews and gave him editorial feedback on his drafts, which was adopted in the published version.

485. Medical Writer X understood, without being explicitly told, that since his work was funded and reviewed by Janssen, the materials he was writing should aim to promote the sale of more drugs by overcoming the reluctance to prescribe or use opioids to treat chronic pain. He knew that the publication was undertaken in connection with the launch of a new drug and was part of its promotional effort. Medical Writer X knew of the drug company sponsoring the publication, and he would go to the company's website to learn about the drug being promoted. He also knew that his clients – including Janssen – would be most satisfied with his work if he emphasized that: (a) even when used long-term, opioids are safe and the risk of addiction is low; (b) opioids are effective for chronic pain; and (c) opioids are under-prescribed because doctors are hesitant, confused, or face other barriers.[175]

486. *Finding Relief* is rife with the deceptive content described above in Sections IV.D.2, IV.D.6, and IV.D.7. *Finding Relief* misrepresents that opioids increase function by featuring a man playing golf on the cover and listing examples of expected functional improvement from opioids, like sleeping through the night, returning to work, recreation, sex, walking, and climbing stairs. The guide states as a "fact" that "opioids may make it *easier* for

[175] Medical Writer X now acknowledges that the lists of adverse effects from chronic opioid use in the publications he authored, which excluded respiratory depression, overdose, and death and minimized addiction, were, "ridiculous" and "prime examples" of leaving out facts that the pharmaceutical company sponsors and KOLs knew at the time were true. His writings repeatedly described the risk of addiction as low. Medical Writer X stated that he understood that the goal was to promote opioids and, as a result, discussing addiction would be "counterproductive."

people to live normally" (emphasis in the original). The functional claims contained in *Finding Relief* are textbook examples of Defendants' use of third parties to disseminate messages the FDA would not allow them to say themselves. *Compare, e.g.*:

Branded Advertisement That Triggers an FDA Warning Letter (2008)[176]
Improvement in Daily Activities Includes: • Walking on a flat surface • Standing or sitting • Climbing stairs

with:

Seemingly-Independent Unbranded Publication: "Finding Relief: Pain Management for Older Adults" (Final Authority, Janssen 2009):
Your recovery will be measured by how well you reach functional goals such as: • Sleeping without waking from pain • Walking more, or with less pain • Climbing stairs with less pain • Returning to work

487. *Finding Relief* also trivialized the risks of addiction describing a "myth" that opioids are addictive, and asserting as fact that "[m]any studies show that opioids are *rarely* addictive when used properly for the management of chronic pain."

[176] This advertisement drew an FDA Warning Letter dated March 24, 2008. Though the advertisement was by the drug company King, which is not a defendant in this case, it is used here to demonstrate the types of claims that the FDA regarded as unsupported.

488. *Finding Relief* further misrepresented that opioids were safe at high doses by listing dose limitations as "disadvantages" of other pain medicines but omitting any discussion of risks from increased doses of opioids. The publication also falsely claimed that it is a "myth" that "opioid doses have to be bigger over time."

489. Finally, *Finding Relief* deceptively overstated the risks associated with alternative forms of treatment. It juxtaposes the advantages and disadvantages of NSAIDs on one page, with the "myths/facts" of opioids on the facing page. The disadvantages of NSAIDs are described as involving "stomach upset or bleeding," "kidney or liver damage if taken at high doses or for a long time," "adverse reactions in people with asthma," and "increase[d] … risk of heart attack and stroke." Conversely, the only adverse effects of opioids listed by *Finding Relief* are "upset stomach or sleepiness," which the brochure claims will go away, and constipation. The guide never mentions addiction, overdose, abuse, or other serious side effects of opioids.

490. Janssen was not merely a passive sponsor of *Finding Relief*. Instead, Janssen exercised control over its content and provided substantial assistance to AGS and AAPM to distribute it. A "Copy Review Approval Form" dated October 22, 2008, indicates that key personnel from Janssen's Advertising & Promotion, Legal, Health Care Compliance, Medical Affairs, Medical Communications, and Regulatory Departments reviewed and approved *Finding Relief*. All six Janssen personnel approving the publication checked the box on the approval form indicating that *Finding Relief* was "Approved With Changes." After the publication was modified at the behest of Janssen personnel, Janssen paid to have its sales force distribute 50,000 copies of *Finding Relief* in Mississippi and throughout the nation. Thus, *Finding Relief* is considered labeling for Janssen's opioids within the meaning of 21 C.F.R. § 1.3(a).

491. AAPM purchased and distributed copies of *Finding Relief* to all of its members.

492. *Finding Relief's* author, Medical Writer X, later said it was clear, from his perch at the intersection of science and marketing, that the money paid by drug companies to the KOLs and professional and patient organizations with which he worked distorted the information provided to doctors and patients regarding opioids. The money behind these and many other "educational" efforts also, he believes, led to a widespread lack of skepticism on the part of leading physicians about the hazards of opioids. It also led these physicians to accept without adequate scrutiny published studies that, while being cited to support the safety of opioids, were, in fact, of such poor methodological quality that they would not normally be accepted as adequate scientific evidence.

(2) AGS – Misleading medical education.

493. Janssen also worked with the AGS on another project – AGS's CME promoting the 2009 guidelines for the *Pharmacological Management of Persistent Pain in Older Persons*. As described above in Section V.C.2.c.3, these guidelines falsely claimed that "the risks [of addiction] are exceedingly low in older patients with no current or past history of substance abuse" when the study supporting this assertion did not analyze addiction rates by age. They also stated, falsely, that "[a]ll patients with moderate to severe pain … should be considered for opioid therapy (low quality of evidence, strong recommendation)." Based on Janssen's control over AGS's *Finding Relief*, Janssen also would have exercised control over this project as well.

(3) APF

494. Janssen also worked with APF to carry out its deceptive marketing campaign. Documents obtained from one of Janssen's public relations firms, Ketchum, indicate that Janssen and the firm enlisted APF as part of an effort to "draft media materials and execute [a] launch plan" for Janssen's drugs at an upcoming meeting of the AAPM. Janssen also drew on APF

publications to corroborate claims in its own marketing materials and its sales training. Janssen personnel participated in a March 2011 call with APF's "Corporate Roundtable," in which they worked with APF and drug company personnel to develop strategies to promote chronic opioid therapy. In particular, APF personnel spoke with Janssen employees, who "shar[ed] expertise from within their company for [a] public awareness campaign."

495. Their joint work on the "Corporate Roundtable" demonstrates the close collaboration between Janssen and APF in promoting opioids for the treatment of chronic pain. APF President Will Rowe also reached out to Defendants – including Janssen – rather than his own staff to identify potential authors to draft an answer to an article critical of opioids that appeared in the *Archives of Internal Medicine* in 2011. Additional examples of APF's collaboration with Janssen are laid out below:

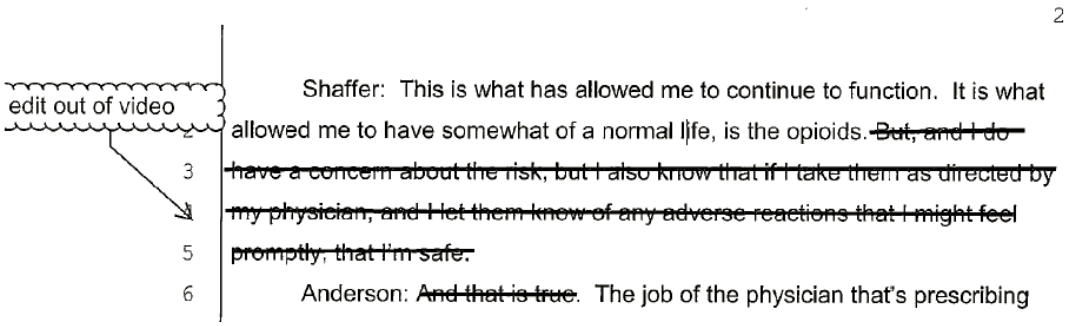
(a) Let's Talk Pain

496. Most prominent among these efforts was the *Let's Talk Pain* website. Janssen sponsored *Let's Talk Pain* in 2009, acting in conjunction with APF, American Academy of Pain Management, and American Society of Pain Management Nursing, whose participation in the website Janssen financed and orchestrated.

497. Janssen exercised substantial control over the content of the *Let's Talk Pain* website. Janssen's internal communications always referred to *Let's Talk Pain* as promoting tapentadol, the molecule it sold as Nucynta and Nucynta ER. Janssen regarded *Let's Talk Pain* and another website – *Prescriberesponsibly.com* – as integral parts of Nucynta's launch:

Janssen documents also reveal that Janssen personnel viewed APF and AAPM as "coalition members" in the fight to increase market share.

498. To this end, Janssen and APF entered into a partnership to "keep pain and the importance of responsible pain management top of mind" among prescribers and patients. They agreed to work to reach "target audiences" that included patients, pain management physicians, primary care physicians, and KOLs. One of the roles Janssen assumed in the process was to "[r]eview, provide counsel on, and approve materials." Janssen did in fact review and approve material for the *Let's Talk Pain* website, as evidenced by the following edits by a Janssen executive to the transcript of a video that was to appear on the site:



The final version of the video on *Let's Talk Pain* omitted the stricken language above.

499. This review and approval authority extended to the *Let's Talk Pain* website. Emails between Janssen personnel and a consultant indicate that, even though the *Let's Talk Pain* website was hosted by APF, Janssen had approval rights over its content. Moreover, emails describing Janssen's review and approval rights related to *Let's Talk Pain* indicate that this right extended to "major changes and video additions."

500. As a 2009 Janssen memo conceded, "[t]he *Let's Talk Pain Coalition* is sponsored by PriCara, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc." and "[t]he Coalition and PriCara **maintain editorial control of all *Let's Talk Pain* materials and publications**" (emphasis added).

501. A 2011 Consulting Agreement between Janssen and one of APF's employees, relating to the dissemination of national survey data, demonstrates the near-total control Janssen was empowered to exercise over APF in connection with the *Let's Talk Pain* website, including in requiring APF to circulate and post Janssen's promotional content. The agreement required APF to "participate in status calls between Janssen, APF, AAPM, ASPMN, and Ketchum as requested by Janssen" and required APF to "respond to requests to schedule status calls **within 48 hours** of the request" (emphasis in original). APF also was required to "[r]eview and provide

feedback to media materials, including a press release, pitch email, a key messages document, and social media messages, **within one week** of receipt" (emphasis in original).

502. The agreement further required APF to provide a summary of the survey results in APF's PAIN MONITOR e-newsletter, post a link to the survey results on APF's Facebook page, send out tweets related to the survey, serve as a spokesperson available for media interviews, "[s]hare information with any media contacts with whom APF has existing relationships to promote the announcement of the national survey findings," identify at least two patient spokespersons to talk about the survey data, and include the survey results in "any future APF materials, as appropriate." Tellingly, "any ideas made or conceived by [APF] in connection with or during the performance" of the Agreement "shall be the property of, and belong to, [Janssen]."

503. Janssen also exercised its control over *Let's Talk Pain*. Janssen was able to update the *Let's Talk Pain* website to describe its corporate restructuring and Janssen personnel asserted their control over "video additions" by reviewing and editing the interview touting the functional benefits of opioids described above in Section IV.D.1. Given its editorial control over the content of *Let's Talk Pain*, Janssen was at all times fully aware of – and fully involved in shaping – the website's content.[177]

504. *Let's Talk Pain* contained a number of the misrepresentations outlined above in Sections IV.D.1 and IV.D.4.

505. For example, *Let's Talk Pain* misrepresented that the use of opioids for the treatment of chronic pain would lead patients to regain functionality. *Let's Talk Pain* featured an

[177] It bears noting that Janssen does not publicly identify its role in creating *Let's Talk Pain*'s content. Instead, *Let's Talk Pain* represents that "coalition members" develop the content that appears on the website and lists Janssen as the only sponsor of that coalition.

interview claiming that opioids were what allowed a patient to "continue to function." This video is still available today on YouTube.com and is accessible to Mississippi prescribers and patients.

506. *Let's Talk Pain* in 2009 also promoted the concept of pseudoaddiction, which it described as patient behaviors that may occur when "*pain is under-treated*" but differs "*from true addiction* because such behaviors can be resolved with effective pain management" (emphasis added).

(b) *Exit Wounds*

507. Janssen also engaged in other promotional projects with and through APF. One such project was the publication and distribution of *Exit Wounds*, which, as described above in Section IV.D, deceptively portrayed the risks, benefits, and superiority of opioids to treat chronic pain. *Exit Wounds* was drafted by "Medical Writer X." It is fully representative of his work on behalf of drug companies.

508. Janssen gave APF substantial assistance in distributing *Exit Wounds* in Mississippi and throughout the nation by providing grant money and other resources.

509. Not only did Janssen manufacture its own branded drugs, its subsidiaries Tasmanian Alkaloids and Noramco were responsible for processing the active pharmaceutical ingredients ("API") for other opioid manufacturers. As a result, Janssen profited from the growth of both unbranded and branded opioids and was driven to develop the market as much as possible. Janssen had a global API manufacturing network for opiate analgesics and antagonists. Noramco and Tasmanian Alkaloids were the primary suppliers of the API provided to a number of opioid manufacturers. As stated above, eighty percent of Noramco's sales were with all seven of the top U.S. generic companies. Companies Noramco supplied included Cephalon, Endo,

Purdue, Actavis, and Mallinckrodt. Noramco's product portfolio includes Oxycodone (Oxycontin, Percocet, Roxicodone), Hydrocodone (Vicodin, Lortab), and Morphine (MS Contin, Embeda).

510. In 1994, Janssen's subsidiary, Tasmanian Alkaloids, established a research project "in order to develop a high thebaine poppy to meet the anticipated demand." This project resulted in the development of the "Norman" poppy. Its development "coincided with the release of a slow release formulation of oxycodone in the USA."[178] The company reported:

a. The new formulation was very successful, and there was greatly increased demand for the thebaine raw material used for its manufacture.

b. This new poppy variety is a major turning point in alkaloid production.

c. The high alkaloid content of the Tasmanian crop is our most important competitive advantage.

d. Patented, high thebaine poppy was a transformational technology that enabled the growth of oxycodone.

e. API volume growth linked to generics of branded drugs, new delivery systems, and abuse prevention claims.

511. Noramco steadily gained U.S. market share, reporting in 2014 alone U.S. sales of $94 million for Oxycodone and $52 million for Hydrocodone. In the five years from 2006 to 2011, Noramco's API volume growth doubled and continued climbing. Janssen's fully integrated supply chain provided security for continued growth.

512. Janssen fueled the opioid epidemic by providing a more potent poppy that could provide greater supply and/or profits. Because of Noramco and Tasmanian Alkaloids, Janssen had an incentive to fraudulently market opioids with other Manufacturer Defendants, since

[178] A.J. Fist, "The Tasmanian Poppy Industry: A Case Study of the Application of Science and Technology," Tasmanian Alkaloids Pty. Ltd., Westbury, Tasmania.

Janssen profited not only from its own opioid products, but also from the sale of its API to other manufacturers.

513. Ironically, Janssen also profited from the rising addictions and abuse of opioids by supplying API for use in Naloxone for opioid overdose and abuse, and in Naltrexone and Buprenorphine for opioid addiction.

5. Purdue

514. Purdue promoted its branded opioids – principally, Oxycontin, Butrans, and Hysingla – and opioids generally in a campaign that consistently mischaracterized the risk of addiction and made deceptive claims about functional improvement. Purdue did so through its sales force, branded advertisements, promotional materials, and speakers, as well as a host of materials produced by its third-party partners, most prominently APF. Purdue's sales representatives and advertising also misleadingly implied that OxyContin provides a full 12 hours of pain relief, and its allied Front Groups and KOLs conveyed the additional deceptive messages about opioids' safety at higher doses, the safety of alternative therapies, and the effectiveness of addiction screening tools.

515. Based on the highly coordinated and uniform nature of Purdue's marketing, Purdue conveyed these deceptive messages to Mississippi prescribers. The materials that Purdue generated in collaboration with third parties also were distributed or made available in Mississippi. Purdue distributed these messages, or facilitated their distribution, in Mississippi with the intent that Mississippi prescribers and/or consumers would rely on them in choosing to use opioids to treat chronic pain.

a. Purdue's deceptive direct marketing.

516. Like the other Defendants, Purdue directly disseminated deceptive branded and unbranded marketing focused on minimizing the risks associated with the long-term use of opioids to treat chronic pain. Purdue directed these messages to prescribers and consumers through its sales force and branded advertisements.

517. Purdue engaged in in-person marketing to doctors in Mississippi and operated speakers bureau programs that included and targeted Mississippi prescribers. Like the other Defendants' detailers, Purdue sales representatives visited targeted physicians to deliver sales messages that were developed centrally and deployed, identically, across the country. These sales representatives were critical in delivering Purdue's marketing strategies and talking points to individual prescribers.[179] Indeed, Endo's internal documents indicate that pharmaceutical sales representatives employed by Endo, Actavis, and Purdue discussed the AAPM/APS Guidelines, which as discussed above in Section IV.C.2.C.2 deceptively concluded that the risk of addiction is manageable for patients regardless of past abuse histories, with doctors during individual sales visits.

518. Purdue's spending on detailing reached its nadir in 2006 and 2007, as the company faced civil and criminal charges for misbranding OxyContin. Since settling those charges in 2007, however, Purdue has sharply increased its quarterly spending on promotion through its sales force, from under $5 million in 2007 to more than $30 million by the end of 2014.

[179] But Purdue did not stop there. It also tracked around 1,800 doctors whose prescribing patterns demonstrated a probability that they were writing opioid prescriptions for addicts and drug dealers. Purdue kept the program secret for nine years and, when it finally did report information about these suspicious doctors to law enforcement authorities, it only did so with respect to 8% of them.

519. Purdue also marketed its drugs through branded advertisements, which relied on, among other deceptive tactics, misleading statements about the efficacy and onset of OxyContin. As described above in Section IV.D.8, Purdue has marketed its drug as effective for 12 hours. Purdue knew, however, that these claims were misleading because, for many patients, the pain relief lasted for as little as eight hours, which led to end-of-dose failure and withdrawal symptoms and prompted doctors to prescribe or patients to take higher or more frequent doses of opioids, all of which increased the risk of abuse and addiction.

520. For example, a "Conversion and Titration Guide" submitted to the FDA and distributed to physicians by Purdue, prominently referred to "Q12h OxyContin Tablets," meaning that each tablet is intended to "offer your patient every-twelve-hour dosing." Other marketing materials directed at physicians and disseminated across the country in 2006 touted that OxyContin's "12-hour AcroContin Delivery System" is "designed to deliver oxycodone over 12 hours," which offered patients "life with Q12H relief." Those same marketing materials included a timeline graphic with little white paper pill cups only at "8AM" and, further down the line, at "8PM." They also proclaimed that OxyContin provides "Consistent Plasma Levels Over 12 Hours" and set forth charts demonstrating absorption measured on a logarithmic scale, which fraudulently made it appear levels of oxycodone in the bloodstream slowly taper over a 12 hour time period.

521. Purdue advertisements that ran in 2005 and 2006 issues of the *Journal of Pain* depict a sample prescription for OxyContin with "Q12h" handwritten. Another advertisement Purdue ran in 2005 in the *Journal of Pain* touted OxyContin's "Q12h dosing convenience" and displayed two paper dosing cups, one labeled "8 am" and one labeled "8 pm," implying that

OxyContin is effective for the 12 hour period between 8 a.m. and 8 p.m. Similar ads appeared in the March 2005 *Clinical Journal of Pain*.

522. Further, to this day, Purdue includes prominent 12-hour dosing instructions in its branded advertising, such as in a 2012 Conversion and Titration Guide, which states: "Because each patient's treatment is personal / Individualize the dose / Q12h OxyContin Tablets."

523. As outlined above in Section IV.D.8, however, these statements are misleading because they fail to make clear that a 12 hour dose does not equate to 12 hours of pain relief. Nevertheless, Purdue's direct marketing materials have misleadingly claimed OxyContin offers 12 hour "dosing convenience."

524. Purdue's direct marketing materials also misrepresented that opioids would help patients regain functionality and make it easier for them to conduct everyday tasks like walking, working, and exercising.

525. For example, in 2012, Purdue disseminated a mailer to doctors titled "Pain vignettes." These "vignettes" consisted of case studies describing patients with pain conditions that persisted over a span of several months and the vignettes imply that an OxyContin prescription will help him work. None of these ads, however, disclosed the truth – that there is no evidence that opioids improve patients' lives and ability to function (and there was substantial evidence to the contrary).

526. Some of the greatest weapons in Purdue's arsenal, however, were unbranded materials it directly funded and authored. These were in addition to the unbranded materials, described below, that Purdue channeled through third parties.

527. In 2011, Purdue published a prescriber and law enforcement education pamphlet titled *Providing Relief, Preventing Abuse*, which deceptively portrayed the signs – and therefore

the prevalence – of addiction. However, Purdue knew, as described above in Section IV.D.2, that OxyContin was used non-medically by injection less than 17% of the time. Yet, *Providing Relief, Preventing Abuse* prominently listed side effects of injection like skin popping and track marks as "Indications of Possible Drug Abuse" – downplaying much more prevalent signs of addiction associated with OxyContin use, such as asking for early refills, and making it seem that addiction only occurs when opioids are taken illicitly.

528. *Providing Relief, Preventing Abuse* also deceptively camouflaged the risk of addiction by falsely supporting the idea that drug-seeking behavior could, in fact, be a sign of "pseudoaddiction" rather than addiction itself. Specifically, it noted that the concept of pseudoaddiction had "emerged in the literature" to describe "[drug-seeking behaviors] in patients who have pain that has not been effectively treated." Nowhere in *Providing Relief, Preventing Abuse* did Purdue disclose the lack of scientific evidence justifying the concept of pseudoaddiction, nor that it was coined by a Purdue vice president.

529. *Providing Relief, Preventing Abuse* was available nationally and was intended to reach Mississippi prescribers. As described below, the deceptive statements in *Providing Relief, Preventing Abuse* regarding addiction were the very same messages Purdue directed at Mississippi prescribers through its sales force.

530. Purdue also disseminated misrepresentations through two of its unbranded websites, *In the Face of Pain* and *Partners Against Pain*.

531. Consistent with Purdue's efforts to portray opioid treatment as "essential" for the proper treatment of chronic pain and label skepticism related to chronic opioid therapy as an "inadequate understanding" that leads to "inadequate pain control," *In the Face of Pain* criticized policies that limited access to opioids as being "at odds with best medical practices" and

encouraged patients to be "persistent" in finding doctors who will treat their pain. This was meant to imply that patients should keep looking until they find a doctor willing to prescribe opioids.

532. *In the Face of Pain* was available nationally and was intended to reach Mississippi prescribers.

533. Purdue also used its unbranded website *Partners Against Pain* to promote the same deceptive messages regarding risk of addiction that are described in Section IV.D.2 and delivered by its sales representatives. On this website, Purdue posted *Clinical Issues in Opioid Prescribing*, a pamphlet that was copyrighted in 2005. Purdue distributed a hard-copy version of this pamphlet at least as of November 2006. *Clinical Issues in Opioid Prescribing* claimed that "illicit drug use and deception" were not indicia of addiction, but rather indications that a patient's pain was undertreated. The publication indicated that "[p]seudoaddiction can be distinguished from true addiction in that the behaviors resolve when the pain is effectively treated." In other words, Purdue suggested that when faced with drug-seeking behavior from their patients, doctors should prescribe more opioids – turning evidence of addiction into an excuse to sell and prescribe even more drugs.

534. Purdue's misleading messages and materials were part of a broader strategy to convince prescribers to use opioids to treat their patients' pain, irrespective of the risks, benefits, and alternatives. This deception was national in scope and included Mississippi. As described in Section IV.B.2 above, Purdue's nationwide messages would have reached Mississippi prescribers in a number of ways. For example, they were carried into Mississippi by Purdue's sales representatives during detailing visits as well as made available to Mississippi patients and prescribers through websites and ads, including ads in prominent medical journals. They would

have also been delivered to Mississippi prescribers by Purdue's paid speakers, who were required by Purdue policy and by FDA regulations to stay true to Purdue's nationwide messaging.

b. Purdue's deceptive third party statements.

535. Purdue's efforts were not limited to making misrepresentations through its own sales force and its own branded and unbranded marketing materials. As described above, Purdue knew that regulatory constraints restricted what it was able to say about its drugs through direct marketing. For this reason, like the other Defendants, Purdue enlisted the help of third parties to release misleading information about opioids. The most prominent of these was APF.

(1) APF

(a) Purdue's control of APF.

536. Purdue exercised considerable control over APF, which published and disseminated in many of the most blatant falsehoods regarding chronic opioid therapy. Their relationship, and several of the APF publications, is described in detail below.

537. Purdue exercised its dominance over APF over many projects and years. Purdue was APF's second-biggest donor, with donations totaling $1.7 million. Purdue informed APF that the grant money reflected Purdue's effort to "strategically align its investments in nonprofit organizations that share [its] business interests," making clear that Purdue's funding depended upon APF continuing to support Purdue's business interests. Indeed, Purdue personnel participated in a March 2011 call with APF's "Corporate Roundtable," where they suggested that APF "[s]end ambassadors to talk about pain within companies and hospitals." Thus, Purdue suggested what role APF could play that would complement its own marketing efforts. On that call, Purdue personnel also committed to provide APF with a list of "industry state advocates"

who could help promote chronic opioid therapy, individuals and groups that, upon information and belief, APF reached out to. Purdue personnel remained in constant contact with their counterparts at APF.

538. This alignment of interests was expressed most forcefully in the fact that Purdue hired APF to provide consulting services on its marketing initiatives. Purdue and APF entered into a "Master Consulting Services" Agreement on September 14, 2011. That agreement gave Purdue substantial rights to control APF's work related to a specific promotional project. Moreover, based on the assignment of particular Purdue "contacts" for each project and APF's periodic reporting on their progress, the agreement enabled Purdue to be regularly aware of the misrepresentations APF was disseminating regarding the use of opioids to treat chronic pain in connection with that project. The agreement gave Purdue – but not APF – the right to end the project (and, thus, APF's funding) for any reason. Even for projects not produced during the terms of this Agreement, the Agreement demonstrates APF's lack of independence and willingness to harness itself to Purdue's control and commercial interests, which would have carried across all of APF's work.

539. Purdue used this agreement to conduct work with APF on the *Partners Against Pain* website. *Partners Against Pain* is a Purdue-branded site, and Purdue holds the copyright. However, its ability to deploy APF on this project illustrates the degree of control Purdue exercised over APF. In 2011, it hired an APF employee to consult on the *Partners Against Pain* rollout, to orchestrate the media campaign associated with the launch of certain content on the website, and to make public appearances promoting the website along with a celebrity spokesperson. Purdue contemplated paying this consultant $7,500 in fees and expenses for 26 hours of work. Purdue would require this consultant to "to discuss and rehearse the delivery of

[Purdue's] campaign messages" and Purdue committed that "[m]essage points will be provided to [the] Consultant in advance and discussed on [a planned] call." At all times, decisions regarding the final content on the *Partners Against Pain* website were "at the sole discretion of Purdue."

540. APF also volunteered to supply one of its staff (a medical doctor or a nurse practitioner) to assist Purdue as a consultant and spokesperson in connection with the launch of one of Purdue's opioid-related projects, *Understanding & Coping with Lower Back Pain*, which appeared on *Partners Against Pain*. One of the consultants was APF's paid employee, Mickie Brown. The consultant's services would be provided in return for a $10,000 in consulting fees for APF and $1,500 in honoraria for the spokesperson. All documents used by the consultant in her media appearances would be reviewed and approved by individuals working for Purdue. Purdue initiated this project, and it was not until later that APF worried about "how Purdue sees this program fitting in with our [existing] grant request."

541. Given the financial and reputational incentives associated with assisting Purdue in this project and the direct contractual relationship and editorial oversight, APF personnel were acting under Purdue's control at all relevant times with respect to *Partners Against Pain*.

542. Purdue often asked APF to provide "patient representatives" for *Partners against Pain*, and APF fulfilled these requests. Moreover, APF staff and board members and Front Groups ACPA and AAPM, among others (such as Dr. Webster), appear on *Inthefaceofpain.com* as "Voices of Hope" – "champions passionate about making a difference in the lives of people who live with pain" and providing "inspiration and encouragement" to pain patients. APF also contracted with Purdue for a project on back pain where, among other things, it provided a patient representative who agreed to attend a Purdue-run "media training session."

543. According to an Assurance of Voluntary Compliance ("AVC") entered into between the New York Attorney General and Purdue Pharma on August 19, 2015, *Inthefaceofpain.com* received 251,648 page views between March 2014 and March 2015. Except in one document linked to the website, *Inthefaceofpain.com* makes no mention of opioid abuse or addiction. Purdue's copyright appears at the bottom of each page of the website, indicating its ownership and control of its content, and, in entering into its AVC with the New York Attorney General, Purdue agreed that those pages were "controlled or maintained by Purdue." There is no other indication that 11 of the individuals who provided testimonials on *Inthefaceofpain.com* received payments, according to the AVC, of $231,000 for their participation in speakers programs, advisory meetings and travel costs between 2008 and 2013. Therefore, the New York Attorney General found Purdue's failure to disclose its financial connections with these individuals had the potential to mislead consumers by failing to disclose the potential bias of these individuals.

544. Nowhere was Purdue's influence over APF so pronounced as it was with the APF's "Pain Care Forum" ("PCF"). PCF was and continues to be run not by APF, but by Defendant Purdue's in-house lobbyist, Burt Rosen. As described by a former drug company employee, Burt Rosen was able to tell PCF "what to do and how to do it," and also asserted that this allowed him to run APF. According to this employee, to Rosen's thinking, "PCF was APF, which was Purdue." The group meets regularly in-person and via teleconference and shares information through an email listserv.

545. In 2011, APF and another third-party advocacy group, the Center for Practical Bioethics, were contemplating working together on a project. Having reviewed a draft document provided by the Center for Practical Bioethics, the APF employee cautioned that "this effort will

be in cooperation with the efforts of the PCF" and acknowledged that "I know you have reservations about the PCF and pharma involvement, but I do believe working with them and keeping the lines of communications open is important." The Center for Practical Bioethics CEO responded by indicating some confusion about whom to speak with, asking "[i]s Burt Rosen the official leader" and reflecting what other sources have confirmed.

546. In 2007, the PCF Education Subgroup, consisting of drug companies Purdue and Alpharma, and Front Groups APF and ACPA (self-described as "industry-funded" groups), developed a plan to address a perceived "lack of coordination" among the industry and pro-opioid professional and patient organizations. PCF members agreed to develop simplified "key" messages" to use for public education purposes. Their messages were reflected in programs like NIPC's *Let's Talk Pain* (put together by Endo and APF), and Purdue's *In the Face of Pain*.

547. When the FDA required drug companies to fund CMEs related to opioid risks in connection with its 2009 REMS, Purdue, along with these Front Groups, worked through the PCF to ensure that, although it was mandatory for drug companies to fund these CMEs, it would not be mandatory for prescribers to attend them. A survey was circulated among Defendants Endo, Janssen, and Purdue, which predicted that the rates of doctors who would prescribe opioids for chronic pain would fall by 13% if more than four hours of mandatory patient education were required in connection with the REMS. With a push from PCF, acting under Purdue's direction, they were not.

548. APF showed its indebtedness to Purdue and its willingness to serve its corporate agenda by testifying on the company's behalf at a July 2007 hearing before the Senate Judiciary

Committee "evaluating the propriety and adequacy of the OxyContin criminal settlement."[180] Despite its ostensible role as a patient advocacy organization, APF was willing to overlook substantial evidence – resulting in the jailing of Purdue executives – that Purdue blatantly, and despite its clear knowledge to the contrary, told physicians and patients that OxyContin was "rarely" addictive and less addictive than other opioids. Like Purdue, and despite the leadership of numerous medical doctors and researchers on its board, APF ignored the truth about opioids and parroted Purdue's deceptive messaging. Purdue testified on Purdue's behalf that addiction was a "rare problem" for chronic pain patients and asserted: "[T]he scientific evidence suggests that addiction to opioids prescribed by legitimate chronic non-cancer pain patients without prior histories of substance abuse using the medication as directed is rare. Furthermore, no causal effect has been demonstrated between the marketing of OxyContin and the abuse and diversion of the drug." There was, and is, no scientific support for those statements.

549. APF President Will Rowe reached out to Defendants – including Purdue – rather than his own staff to identify potential authors to draft an answer to an article critical of opioids that appeared in the *Archives of Internal Medicine* in 2011.

550. Purdue's control over APF shaped and was demonstrated by specific APF, pro-opioid publications. These publications had no basis in science and were driven (and can only be explained) by the commercial interest of pharmaceutical companies – Purdue chief among them.

[180] *Evaluating the Propriety and Adequacy of the Oxycontin Criminal Settlement: Before the S. Comm. On the Judiciary*, 110th Cong. 46-50, 110-116 (2007) (statements of Dr. James Campbell, Chairman, APF). Purdue also was able to exert control over APF through its relationships with APF's leadership. Purdue-sponsored KOLs Russell Portenoy and Scott Fishman chaired APF's board. Another APF board member, Perry Fine, also received consulting fees from Purdue. APF board member Lisa Weiss was an employee of a public relations firm that worked for both Purdue and APF. Weiss, in her dual capacity, helped vet the content of the Purdue-sponsored *Policymaker's Guide*, which is described below.

(b) *A Policymaker's Guide.*

551. Purdue provided significant funding to and was involved with APF in creating and disseminating *A Policymaker's Guide to Understanding Pain & Its Management*, which was originally published in 2011 and is available online to this day. *A Policymaker's Guide to Understanding Pain & Its Management* misrepresented that there were studies showing that the use of opioids for the long-term treatment of chronic pain could improve patients' ability to function.

552. Specifically, *A Policymaker's Guide to Understanding Pain & Its Management* claimed that "multiple clinical studies" demonstrated that "opioids … are effective in improving [d]aily function, [p]sychological health [and] [o]verall health-related quality of life for people with chronic pain" and implied that these studies established that the use of opioids long-term led to functional improvement. The study cited in support of this claim specifically noted that there were no studies demonstrating the safety of opioids long-term and noted that "[f]or functional outcomes, the other [studied] analgesics were significantly more effective than were opioids."[181]

553. The *Policymaker's Guide* also misrepresented the risk of addiction. It claimed that pain generally had been "undertreated" due to "[m]isconceptions about opioid addiction" and that "less than 1% of children treated with opioids become addicted."

554. Moreover, the *Policymaker's Guide* attempted to distract doctors from their patients' drug-seeking behavior by labeling it as pseudoaddiction, which, according to the guide, "describes patient behaviors that may occur when pain is undertreated." Like *Partners Against Pain*, *A Policymaker's Guide* noted that "[p]seudo-addiction can be distinguished from true

[181] Andrea D. Furlan *et al.*, *Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects*, 174(11) CAN. MED. ASS'N J. 1589 (2006).

addiction in that this behavior ceases when pain is effectively treated." The similarity between these messages regarding pseudo-addiction highlights the common, concerted effort behind Purdue's deceptive statements.

555. The *Policymaker's Guide* further misrepresented the safety of increasing doses of opioids and deceptively minimized the risk of withdrawal. For example, the *Policymaker's Guide* claimed that "[s]ymptoms of physical dependence" on opioids in long-term patients "can often be ameliorated by gradually decreasing the dose of medication during discontinuation" while omitting the significant hardship that often accompanies cessation of use. Similarly, the *Policymaker's Guide* taught that even indefinite dose escalations are "sometimes necessary" to reach adequate levels of pain relief, but it completely omitted the safety risks associated with increased doses.

556. Purdue provided substantial assistance toward the creation and dissemination of the *Policymaker's Guide*, which APF ultimately disseminated on behalf of Defendants, including Purdue. Purdue provided $26,000 in grant money to fund the development and dissemination of its content. Purdue kept abreast of the content of the guide as it was being developed, and, based on the periodic reports APF provided to Purdue regarding its progress on the *Policymaker's Guide*, had editorial input into its contents.

557. The *Policymaker's Guide* was posted online, and was available to and intended to reach Mississippi prescribers and consumers. As described below, the deceptive statements in *Policymaker's Guide* regarding addiction and functionality were the very same messages Purdue directed at Mississippi through its own sales force.

(c) *Treatment Options – A Guide for People Living With Pain*.

558. Purdue's partnership with APF did not end with the *Policymaker's Guide*. Purdue also substantially assisted APF by sponsoring *Treatment Options: A Guide for People Living with Pain*, starting in 2007. Based on Purdue's control of other APF projects, Purdue also would have exercised control over *Treatment Options*.

559. *Treatment Options* is rife with misrepresentations regarding the safety and efficacy of opioids. For example, *Treatment Options* misrepresented that the long-term use of opioids to treat chronic pain could help patients function in their daily lives by stating that, when used properly, opioids "give [pain patients] a quality of life [they] deserve."

560. Further, as outlined above in Section IV.D.2, *Treatment Options* claimed that addiction is rare and, when it does occur, involves unauthorized dose escalations, patients who receive opioids from multiple doctors, or theft, which paints a narrow and misleading portrait of opioid addiction.

561. *Treatment Options* also promoted the use of opioids to treat long-term chronic pain by denigrating alternate treatments, most particularly NSAIDs. *Treatment Options* noted that NSAIDs can be dangerous at high doses and inflated the number of deaths associated with NSAID use, and distinguished opioids as having less risk. According to *Treatment Options*, NSAIDs were different from opioids because opioids had "no ceiling dose," which was beneficial since some patients "need" larger doses of painkillers than they are currently prescribed. *Treatment Options* warned that the risks associated with NSAID use increased if NSAIDs were "taken for more than a period of months," but deceptively omitted any similar warning about the risks associated with the long-term use of opioids.

562. *Treatment Options* was posted online and remains online today. It was available to and intended to reach Mississippi prescribers and patients. The deceptive statements in *Treatment Options* regarding addiction and functionality echo the messages Purdue directed at Mississippi through its own sales force.

(d) *Exit Wounds*.

563. Purdue also engaged in other promotional projects with and through APF. One such project was the publication and distribution of *Exit Wounds*, which, as described above in Section IV.D, deceptively portrayed the risks, benefits, and superiority of opioids to treat chronic pain.

564. Purdue provided APF with substantial assistance in distributing *Exit Wounds* in Mississippi and throughout the nation by providing grant money and other resources.

(2) Purdue's work with other third-party Front Groups and KOLs.

565. Purdue also provided other third-party Front Groups with substantial assistance in issuing misleading statements regarding the risks, benefits, and superiority of opioids for the long-term treatment of chronic pain.

(a) FSMB – *Responsible Opioid Prescribing*.

566. In 2007, Purdue sponsored FSMB's *Responsible Opioid Prescribing*, which, as described above in Section IV.D, deceptively portrayed the risks, benefits, and superiority of opioids to treat chronic pain. *Responsible Opioid Prescribing* also was drafted by "Medical Writer X."

567. Purdue spent $150,000 to help FSMB distribute *Responsible Opioid Prescribing*. The book was distributed nationally, and was available to and intended to reach prescribers in Mississippi.

(b) AGS – *Pharmacological Management of Persistent Pain in Older Persons*.

568. Along with Janssen, Purdue worked with the AGS on a CME to promote the 2009 guidelines for the *Pharmacological Management of Persistent Pain in Older Persons*. As discussed above in Section IV.C.2.c.3, these guidelines falsely claimed that "the risks [of addiction] are exceedingly low in older patients with no current or past history of substance abuse" when the study supporting this assertion did not analyze addiction rates by age. They also stated, falsely, that "[a]ll patients with moderate to severe pain should be considered for opioid therapy (low quality of evidence, strong recommendation)."

569. Controversy surrounding earlier versions of AGS guidelines had taught AGS that accepting money directly from drug companies to fund the guidelines' development could lead to allegations of bias and "the appearance of conflict." Accordingly, AGS endeavored to eliminate "the root cause of that flack" by turning down commercial support to produce the 2009 Guidelines. Having determined that its veneer of independence would be tarnished if it accepted drug company money to create the content, AGS decided to develop the guidelines itself and turn to the drug companies instead for funding to *distribute* the pro-drug company content once it had been created. As explained by AGS personnel, it was AGS's "strategy that we will take commercial support to disseminate [the 2009 Guidelines] if such support is forthcoming." AGS knew that it would be difficult to find such support unless the report was viewed favorably by opioid makers.

570. AGS sought and obtained grants from Endo and Purdue to distribute *Pharmacological Management of Persistent Pain in Older Persons*. As a result, the publication was distributed nationally, and was available to and was intended to reach Mississippi prescribers. Indeed, internal documents of another Defendant, Endo, indicate that

pharmaceutical sales representatives employed by Purdue discussed treatment guidelines that minimized the risk of addiction to opioids with doctors during individual sales visits.[182]

(c) *Chronic Pain Management and Opioid Use: Easing Fears, Managing Risks, and Improving Outcomes*.

571. Purdue sponsored a 2012 CME program taught by Steven Stanos, a Chicago-based KOL, called *Chronic Pain Management and Opioid Use: Easing Fears, Managing Risks, and Improving Outcomes*. The presentation deceptively instructed doctors that, through the use of screening tools, more frequent refills, and other techniques, high-risk patients showing signs of addictive behavior could be treated with opioids. This CME was presented at various locations in the United States.

(d) *Managing Patient's Opioid Use: Balancing the Need and Risk*.

572. Purdue also sponsored a 2011 CME taught by KOL Lynn Webster via webinar titled *Managing Patient's Opioid Use: Balancing the Need and Risk*. This presentation likewise deceptively instructed prescribers that screening tools, patient agreements, and urine tests prevented "overuse of prescriptions" and "overdose deaths." At the time, Dr. Webster was receiving significant funding from Purdue. Versions of Dr. Webster's Opioid Risk Tool appear on, or are linked to, websites run by Purdue (and other Defendants). The webinar was available to and was intended to reach Mississippi prescribers.

[182] As described above in Section IV.C.2.c.2, Purdue also provided substantial support for the AAPM/APS guidelines. The 1997 AAPM and APS consensus statement *The Use of Opioids for the Treatment of Chronic Pain* was authored by one of its paid speakers, and 14 out of 21 panel members who drafted the AAPM/APS Guidelines received support from Defendants Janssen, Cephalon, Endo, and Purdue.

(e) *Path of the Patient, Managing Chronic Pain in Younger Adults at Risk for Abuse*.

573. Purdue also sponsored a CME program entitled *Path of the Patient, Managing Chronic Pain in Younger Adults at Risk for Abuse*. *Path of the Patient* is devoted entirely to treating chronic pain with opioids. Although the program purports to instruct a treating physician how to manage chronic pain in younger adults at risk for abuse, it does no such thing. This "educational" program, addressing treatment of a population known to be particularly susceptible to opioid addiction, presents none of the alternative treatment options available, but only discusses treatment of chronic pain with opioids.

574. In a role-play in *Path of the Patient*, a patient who suffers from back pain tells his doctor that he is taking twice as many hydrocodone pills as directed. The doctor reports that the pharmacy called him because of the patient's early refills. The patient has a history of drug and alcohol abuse. Despite these facts, the narrator notes that, because of a condition known as "pseudoaddiction," the doctor should not assume his patient is addicted even if he persistently asks for a specific drug, seems desperate, hoards medicine, or "overindulges in unapproved escalating doses." The doctor in the role play treats this patient by prescribing a high-dose, long-acting opioid. This CME was available online and was intended to reach Mississippi prescribers.

(f) *Overview of Management Options*.

575. Purdue also sponsored a CME titled *Overview of Management Options* and issued by the American Medical Association in 2003, 2007, and 2013 (the latter of which is still available for CME credit). The CME was edited by KOL Russel Portenoy, among others. It deceptively instructed physicians that NSAIDs and other drugs, but not opioids, are unsafe at high doses. In fact, the data indicates that patients on high doses of opioids are more likely to experience adverse outcomes than patients on lower doses of the drugs. Dr. Portenoy received

research support, consulting fees, and honoraria from Purdue (among others), and was a paid Purdue consultant. This CME was presented online in the United States and was available to Mississippi prescribers.

(3) Purdue's misleading science.

576. Purdue also misrepresented the risks associated with long-term opioid use by promoting scientific studies in a deceptive way. In 1998, Purdue funded two articles by Dr. Lawrence Robbins in Chicago, which showed that between 8% and 13% of the patients he studied became addicted to opioids – a troubling statistic for Purdue, whose market, and marketing, depended upon the claim that opioids were rarely addictive.[183] Purdue had these articles placed in headache-specific journals, where they would be less likely to be encountered by pain specialists or general practitioners. The first of these articles has been cited a mere 16 times; the second does not even appear on Google scholar. Five years later, Purdue also funded a study of OxyContin in diabetic neuropathy patients, which was published in 2003. Notwithstanding that Purdue-funded studies, testing Purdue's own drugs, had previously indicated that addiction rates were between 8% and 13%, Purdue's 2003 article reached back to the 1980 Porter-Jick Letter to support its claim that OxyContin was not commonly addictive. This article was placed in a prominent pain journal and has been cited 487 times.[184] While this article was drafted over a decade ago, it continues to be relied upon to further the misrepresentations that opioids are not addictive.

[183] Lawrence Robbins, *Long-Acting Opioids for Severe Chronic Daily Headache*, 10(2) Headache Q. 135 (1999); Lawrence Robbins, *Works in Progress: Oxycodone CR, a Long-Acting Opioid, for Severe Chronic Daily Headache*, 19 Headache Q. 305 (1999).

[184] C. Peter N. Watson, *et al.*, *Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial I painful diabetic neuropathy*, 105 Pain 71 (2003).

(4) Purdue's deceptive statements to Mississippi patients and prescribers.

577. Purdue directed the dissemination of the misstatements described above to Mississippi patients and prescribers through the Front Groups, KOLs, and publications described above, as well as through its substantial sales force in Mississippi and through advertisements in prominent medical journals. The deceptive statements distributed through each of these channels reflect a common theme of misrepresenting the benefits of Purdue's opioids, unfairly portraying the risks of addiction associated with their use, and deceptively implying that they would improve patients' ability to function.

578. The deceptive message that OxyContin provided 12 hours of pain relief not only was available to and intended to reach Mississippi prescribers through nationally circulated advertising, but also was carried directly into the offices of Mississippi doctors by Purdue's sales representatives.

579. Likewise, the deceptive messages minimizing addiction were not only directed at Mississippi patients and prescribers through the publications circulated above, but also were disseminated directly by Purdue's sales force. Specifically, Purdue detailers omitted or minimized the risk of opioid addiction; claimed that Purdue's drugs would be less problematic for patients because they had extended release mechanisms, were tamper proof, and were "steady state"; claimed that OxyContin would provide 12 hours of pain relief; represented that screening tools could help manage the risk of addiction; minimized the symptoms of withdrawal; claimed or implied that opioids were safer than NSAIDs; and overstated the benefits of opioids, including by making claims of improved function.

6. Mallinckrodt

580. Mallinckrodt pursued a broader chronic pain market – marketing its branded and generic drugs by misrepresenting their addictive nature and falsely claiming that the drugs could be taken in higher doses, but without disclosing the greater risks of addiction. From 2009 to 2014, Mallinckrodt expanded its branded opioid portfolio while also maintaining its role as the leading manufacturer of generic opioids.

581. As described below, Mallinckrodt promoted its branded opioids Exalgo and Xartemis XR, and opioids generally, in a campaign that consistently mischaracterized the risk of addiction. Mallinckrodt did so through its website and sales force, as well as through unbranded communications distributed through the C.A.R.E.S. (Collaborating and Acting Responsibly to Ensure Safety) Alliance it created and led.

582. Mallinckrodt created the C.A.R.E.S. Alliance in 2010, which it describes as "a coalition of national patient safety, provider and drug diversion organizations that are focused on reducing opioid pain medication abuse and increasing responsible prescribing habits." The "C.A.R.E.S. Alliance" itself is a service mark of Mallinckrodt LLC (and was previously a service mark of Mallinckrodt, Inc.) copyrighted and registered as a trademark by Covidien, its former parent company. Materials distributed by the C.A.R.E.S. Alliance, however, include unbranded publications that do not disclose a link to Mallinckrodt.

583. By 2012, Mallinckrodt, through the C.A.R.E.S. Alliance, was promoting a book titled *Defeat Chronic Pain Now!* This book is still available online. The false claims and misrepresentations in this book include the following statements:

- "Only rarely does opioid medication cause a true addiction when prescribed appropriately to a chronic pain patient who does not have a prior history of addiction."

- "It is currently recommended that every chronic pain patient suffering from moderate to severe pain be viewed as a potential candidate for opioid therapy."
- "When chronic pain patients take opioids to treat their pain, they rarely develop a true addiction and drug craving."
- "Only a minority of chronic pain patients who are taking long-term opioids develop tolerance."
- "**The bottom line:** Only rarely does opioid medication cause a true addiction when prescribed appropriately to a chronic pain patient who does not have a prior history of addiction."
- "Here are the facts. It is very uncommon for a person with chronic pain to become 'addicted' to narcotics IF (1) he doesn't have a prior history of any addiction and (2) he only takes the medication to treat pain."
- "Studies have shown that many chronic pain patients can experience significant pain relief with tolerable side effects from opioid narcotic medication when taken daily and no addiction."

584. In a 2013 *Mallinckrodt Pharmaceuticals Policy Statement Regarding the Treatment of Pain and Control of Opioid Abuse*, which is still available online, Mallinckrodt stated: "Sadly, even today, pain frequently remains undiagnosed and either untreated or undertreated." It cites to a report that concludes that "the majority of people with pain use their prescription drugs properly, are not a source of misuse, and should not be stigmatized or denied access because of the misdeeds or carelessness of others."

F. Defendants Deliberately Disregarded Their Duties to Maintain Effective Controls to Prevent Diversion and to Identify, Report, and Take Steps to Halt Suspicious Orders.

585. Through their systematic and deceptive marketing schemes, Defendants created a vastly and dangerously larger market for opioids both in Mississippi and nationwide. Each of the Defendants then compounded this harm by facilitating the supply of far more opioids than could have been justified to serve that market.

586. "Suspicious orders" include orders of an unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency. These criteria are disjunctive and are not all-inclusive. For example, if an order deviates substantially from a normal pattern, the size of the order does not matter, and the order should be reported as suspicious. Likewise, the size of an order alone, whether or not it deviates from a normal pattern, is enough to trigger the responsibility to report the order as suspicious.

587. The failure of the Defendants to maintain effective controls and to investigate, report, and take steps to halt orders that they knew or should have known were suspicious breached both their State statutory and common law duties.

588. For over a decade, as the Defendants increased the demand for opioids, they aggressively sought to bolster their revenue, increase profit, and grow their share of the prescription painkiller market by unlawfully and surreptitiously increasing the volume of opioids they sold. However, Defendants are not permitted to engage in a limitless expansion of their sales through the unlawful sales of regulated painkillers. Rather, as described below, Defendants are subject to various duties to monitor such substances and prevent oversupply and diversion into the illicit market.

589. The Defendants have several responsibilities under Mississippi law with respect to control of the supply chain of opioids. First, they must set up a system to prevent diversion, including excessive volume and other suspicious orders. That would include reviewing their own data, relying on their observations of prescribers and pharmacies, and following up on reports or concerns of potential diversion. All suspicious orders must be reported to relevant enforcement authorities. Further, they must also stop shipment of any order that is flagged as suspicious and only ship orders that are flagged as potentially suspicious if, after conducting due

diligence, they can determine that the order is not likely to be diverted into illegal channels. Suspicious orders include orders of an unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.

G. All Defendants Have a Duty to Provide Effective Controls and Procedures to Guard Against Theft and Diversion, and to Report Suspicious Orders.

590. Multiple sources, including Mississippi statutes and regulations, impose duties on the Defendants to provide effective controls and procedures to guard against theft and diversion of opioid drugs. Multiple sources also impose duties on all the Defendants to report suspicious orders and to not ship such orders unless due diligence disproves those suspicions.

591. Under the common law, all Defendants had a duty to exercise reasonable care in delivering dangerous narcotic substances. By flooding the State with more opioids than could be used for legitimate medical purposes, by failing to provide effective controls and procedures against theft and diversion, and by filling and failing to report orders that they knew or should have known were likely being diverted for illicit uses, Defendants breached that duty and both created and failed to prevent a foreseeable risk of harm.

592. The Defendants also had multiple duties under Mississippi statutes and regulations. Opioids are Schedule II controlled substances. As such, opioids are defined as substances that pose a high potential for abuse that may lead to severe dependence.

593. Defendants are required to register with the Mississippi Board of Pharmacy. *See* Miss. Code Ann. § 41-29-127. Before allowing a pharmaceutical manufacturer to register, the Board of Pharmacy must determine that granting a registration is consistent with the public interest and, to be consistent with the public interest, a registrant must, among other things, demonstrate its ability to maintain effective controls against the diversion of opioids under

Mississippi law. *See* Miss. Code Ann. § 41-29-127(a)(1) and (4). Failure to maintain effective controls against diversion is inconsistent with the public interest as that term is used in 21 U.S.C. §§ 823 and 824 and Miss. Code Ann. § 41-29-127, and may result in the revocation of the registrant's DEA Certificate of Registration or registration with the State of Mississippi.

594. The Defendants had access to and possession of the information necessary to monitor, report, and prevent suspicious orders and to prevent diversion. The Defendants engaged in the practice of paying "chargebacks" to opioid distributors. A chargeback is a payment made by a manufacturer to a distributor after the distributor sells the manufacturer's product at a price below a specified rate. After a distributor sells a manufacturer's product to a pharmacy, for example, the distributor requests a chargeback from the manufacturer and, in exchange for the payment, the distributor identifies to the manufacturer the product, volume, and the pharmacy to which it sold the product. Thus, the Defendants knew the volume, frequency, and pattern of opioid orders being placed and filled. The Defendants built receipt of this information into the payment structure for the opioids provided to the opioid distributors.

595. In sum, all Defendants have many responsibilities under Mississippi law related to controlling the supply chain of opioids. They must set up a system to prevent diversion, including identifying excessive volume and other suspicious orders by reviewing their own data, relying on their observations of prescribers and pharmacies, and following up on reports or concerns of potential diversion. All suspicious orders must be reported to relevant enforcement authorities. They must also stop shipment of any order that is flagged as suspicious and only ship orders that are flagged as potentially suspicious if, after conducting due diligence, they can determine that the order is not likely to be diverted into illegal channels.

H. The Result of Defendants' Fraudulent Scheme

596. Through their direct promotional efforts, along with those of the third-party Front Groups and KOLs they assisted and controlled, and whose seemingly objective materials they distributed, Defendants accomplished exactly what they set out to do: change the institutional and public perception of the risk-benefit assessments and standard of care for treating patients with chronic pain. As a result, Mississippi doctors began prescribing opioids long-term to treat chronic pain – something most would never have considered prior to Defendants' campaign.

597. But for the misleading information disseminated by Defendants, doctors would not, in most instances, have prescribed opioids as medically necessary or reasonably required to address chronic pain. As outlined below, the impact of Defendants' deceptive marketing on doctors' prescribing and patients' use of opioids is evidenced by: (a) the increase in opioid prescribing nationally in concert with Defendants' marketing; and (b) the consequences of opioid over-prescription – including addiction, overdose, and death – that have been visited on Mississippi and its residents.

1. Defendants' fraudulent and deceptive marketing of opioids directly caused harm to the State of Mississippi.

598. Defendants' marketing of opioids caused health care providers to prescribe opioids to treat chronic pain. Because of Defendants' unbranded marketing, health care providers wrote and the State paid for prescriptions of opioids for chronic pain that were filled not only with their drugs, but with opioids sold by other manufacturers. All of these prescriptions were caused by Defendants' fraudulent marketing.

599. The fact that Mississippi would pay for these ineligible prescriptions is both the foreseeable and intended consequence of Defendants' fraudulent marketing scheme. Defendants set out to change the medical and general consensus supporting chronic opioid therapy *so that*

doctors would prescribe and government payors, such as the State, would pay for long-term prescriptions of opioids to treat chronic pain despite the absence of genuine evidence supporting chronic opioid therapy and the contrary evidence regarding the significant risks and limited benefits from long-term use of opioids.

a. Increase in opioid prescribing nationally.

600. Defendants' scheme to change the medical consensus regarding opioid therapy for chronic pain worked. During the year 2000, outpatient retail pharmacies filled 174 million prescriptions for opioids nationwide. During 2009, they provided 83 million more.

601. Opioid prescriptions increased even as the percentage of patients visiting the doctor for pain remained constant. A study of 7.8 million doctor visits between 2000 and 2010 found that opioid prescriptions increased from 11.3% to 19.6% of visits, as NSAID and acetaminophen prescriptions fell from 38% to 29%, driven primarily by the decline in NSAID prescribing.[185]

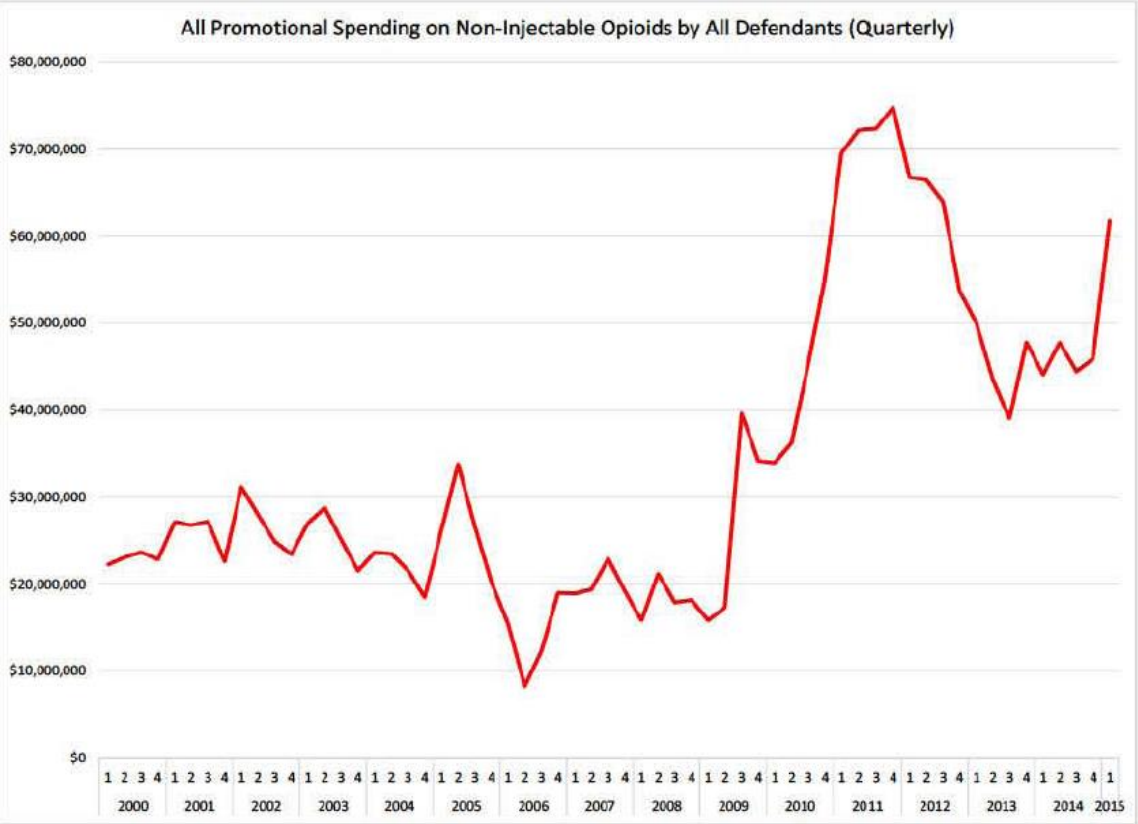
602. Approximately 20% of the population between the ages of 30 and 44 and nearly 30% of the population over 45 have used opioids. Indeed, "[o]pioids are the most common means of treatment for chronic pain."[186] From 1980 to 2000, opioid prescriptions for chronic pain visits doubled. This is the result not of an epidemic of pain, but an epidemic of prescribing. A study of 7.8 million doctor visits found that prescribing for pain increased by 73% between 2000 and 2010 – even though the number of office visits in which patients complained of pain did not change and prescribing of non-opioid pain medications ***decreased***. For back pain alone –

[185] Daubresse M, *et al*., *Ambulatory Diagnosis and Treatment of Nonmalignant Pain in the United States, 2000-2010*, Med. Care 2013; 51(10):870-78.

[186] Deborah Grady, *et al*., *Opioids for Chronic Pain*, 171(16) Archives of Internal Med. 1426 (Sept. 12, 2011).

one of the most common chronic pain conditions – the percentage of patients prescribed opioids increased from 19% to 29% between 1999 and 2010, even as the use of NSAIDs or acetaminophen declined and referrals to physical therapy remained steady.

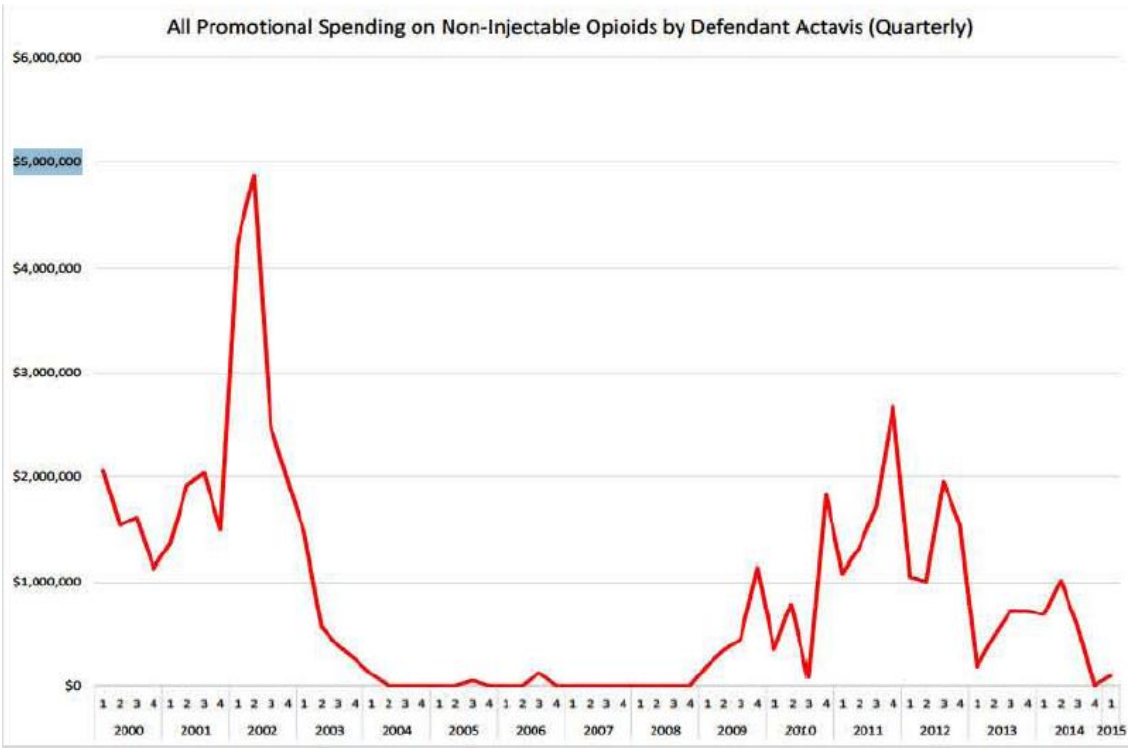
603. This increase corresponds with, and was caused by, Defendants' massive marketing push. As reflected in the chart below, according to data obtained from a marketing research company, Defendants' spending nationwide on marketing of opioids – including all of the drugs at issue here – stood at more than $20 million per quarter and $91 million annually in 2000. By 2011, that figure hit its peak of more than $70 million per quarter and $288 million annually, a more than three-fold increase. By 2014, the figures dropped to roughly $45 million per quarter and $182 million annually, as Defendants confronted increased concern regarding opioid addiction, abuse, and diversion, and as Janssen, which accounted for most of the spending reduction, prepared to sell its U.S. rights to Nucynta and Nucynta ER. Even so, Defendants still spend double what they spent in 2000 on opioid marketing.



604. By far the largest component of this spending was opioid manufacturers' detailing visits to individual doctors, with total detailing expenditures more than doubling between 2000 and 2014 and now standing at $168 million annually.

605. Each Defendant's promotional spending reflects its participation in this marketing blitz. Between 2000 and 2011:

- Actavis' promotional spending, which was virtually nonexistent in the 2004-2008 period, sharply rose beginning in 2009 to a quarterly peak of nearly $3 million at one point in 2011 (and nearly $7 million for the year), as shown below:



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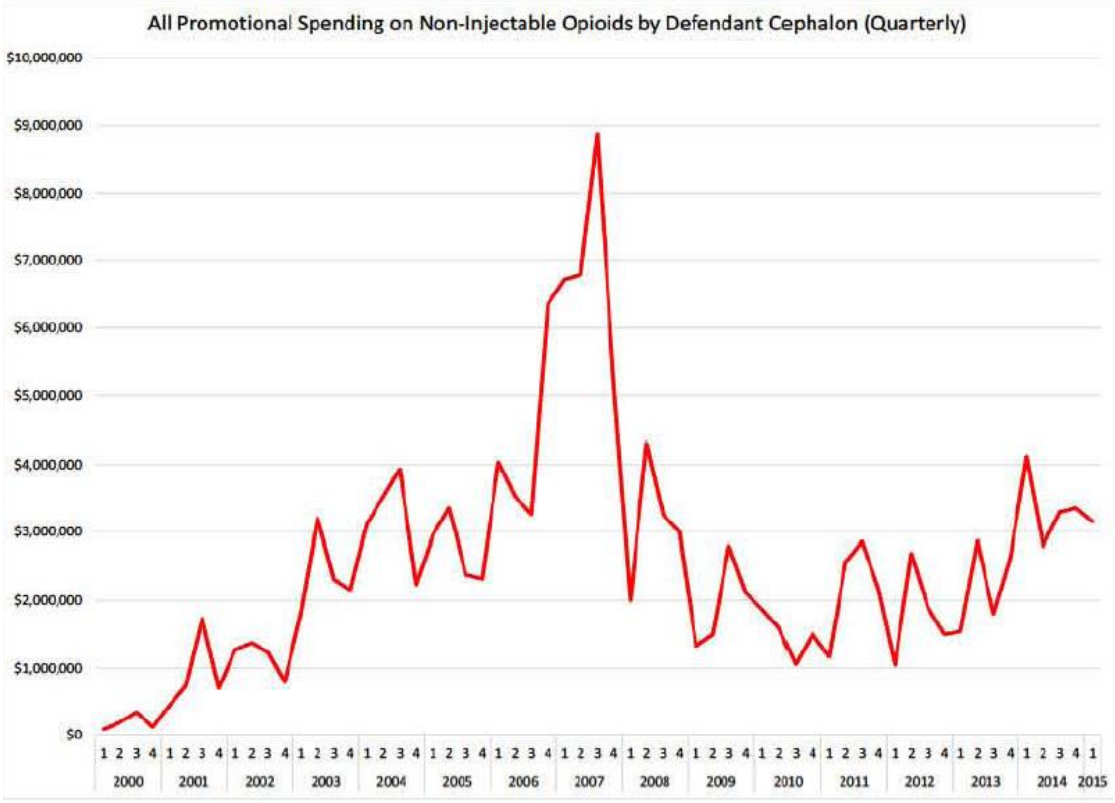
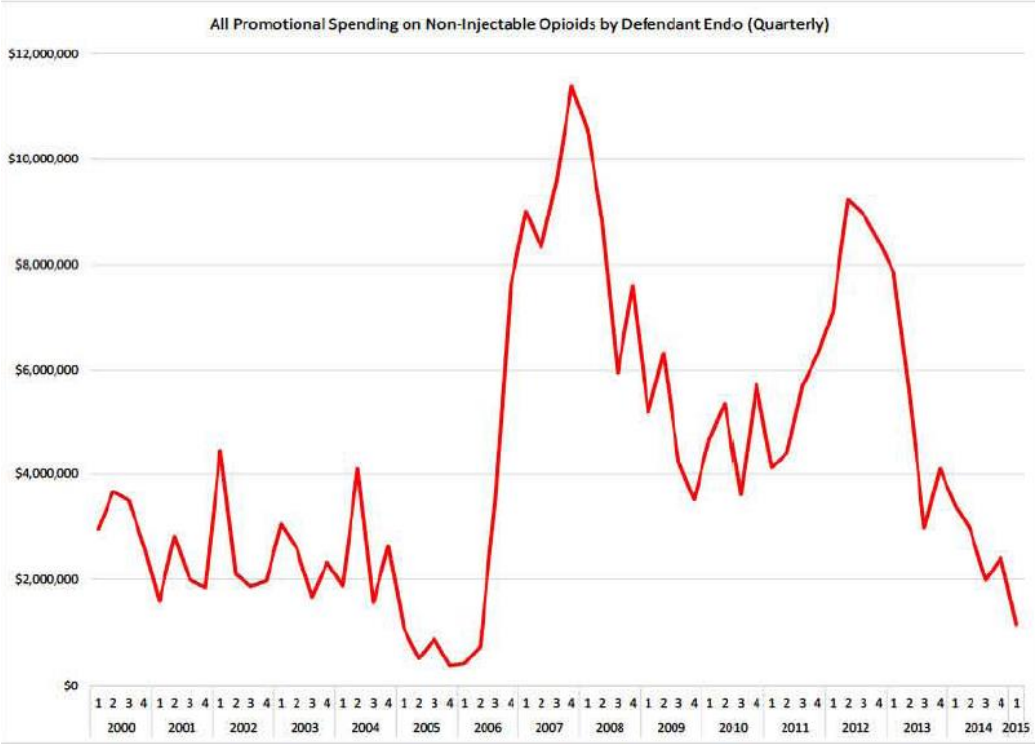
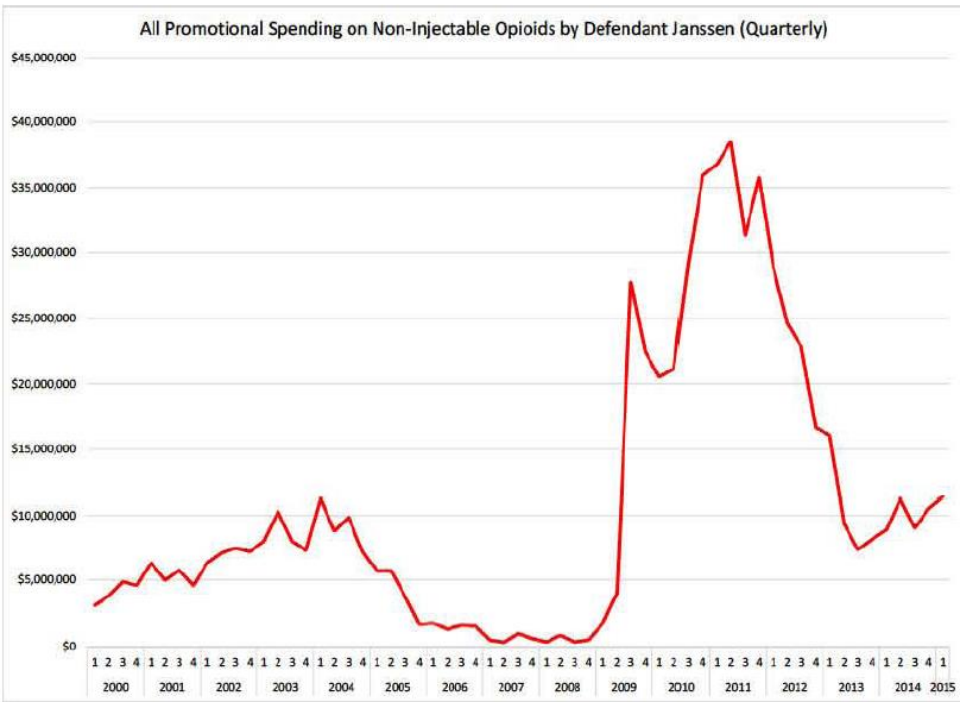
- Cephalon's quarterly spending steadily climbed from below $1 million in 2000 to more than $3 million in 2014 (and more than $13 million for the year), with a peak, coinciding with the launch of Fentora, of nearly $9 million for one quarter of 2007 (and more than $27 million for the year), as shown below:



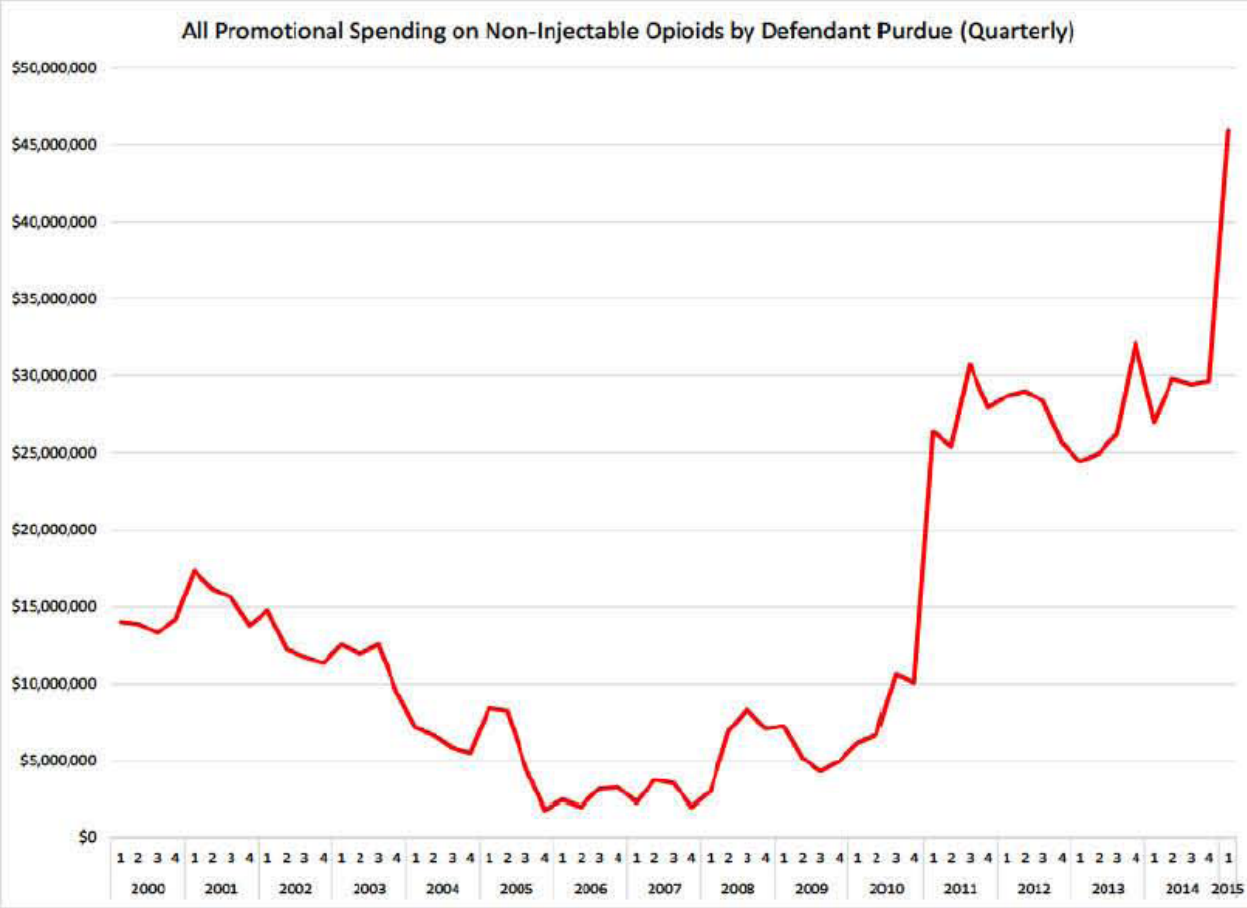
- Endo's quarterly spending went from the $2 million to $4 million range in 2000-2004 to more than $10 million following the launch of Opana ER in mid-2006 (and more than $38 million for the year in 2007) and more than $8 million coinciding with the launch of a reformulated version in 2012 (and nearly $34 million for the year), as shown below:



- Janssen's quarterly spending dramatically rose from less than $5 million in 2000 to more than $30 million in 2011, coinciding with the launch of Nucynta ER (with yearly spending at $142 million for 2011), as shown below:



- Purdue's quarterly spending notably decreased from 2000 to 2007, as Purdue came under investigation by the Department of Justice, but then spiked to above $25 million in 2011 (for a total of $110 million that year), and continues to rise, as shown below:



b. The State's increased spending on opioids.

606. Commensurate with Defendants' heavy promotion of opioids and the resultant, massive upswing in prescribing of opioids nationally, Mississippi has seen its own spending on opioids increase dramatically.

607. In all, based on a preliminary review, the State spent more than $5.6 million for opioids during this period. This includes approximately $2.5 million for Purdue Schedule II and III opioids, $1.3 million for Actavis Schedule II and III opioids, $940,000 for Janssen Schedule II and III opioids, $475,000 for Endo Schedule II and III opioids, and $375,000 for Cephalon and

Teva Schedule II and III opioids. The balance does not include prescriptions that also were caused by Defendants' deceptive marketing, including prescriptions for Defendants' generic opioid products and prescriptions for opioids from other manufacturers. These figures also do not reflect the cost to the State of prescribing opioids, such as doctors' visits or toxicology screens, or the costs of treating the adverse effects of prescribing opioids long-term, such as overdose and addiction.

2. Defendants' fraudulent and deceptive marketing of opioids directly caused harm to Mississippi consumers.

a. Increase in opioid use has led to an increase in opioid abuse, addiction and death.

608. Nationally, the sharp increase in opioid use has led directly to a dramatic increase in opioid abuse, addiction, overdose, and death. Scientific evidence demonstrates a very strong correlation between therapeutic exposure to opioid analgesics, as measured by prescriptions filled, and opioid abuse. "Deaths from opioid overdose have risen steadily since 1990 in parallel with increasing prescription of these drugs."[187] Prescription opioid use contributed to 16,917 overdose deaths nationally in 2011 – more than twice as many deaths as heroin and cocaine combined; drug poisonings now exceed motor vehicle accidents as a cause of death. More Americans have died from opioid overdoses than from participation in the Vietnam War.

609. Contrary to Defendants' misrepresentations, most of the illicit use stems from *prescribed* opioids; in 2011, 71% of people who abused prescription opioids got them through friends or relatives, not from drug dealers or the internet. According to the CDC, the 80% of

[187] Grady, *supra*, at 1426.

opioid patients who take low-dose opioids from a single prescriber (in other words, who are not illicit users or "doctor-shoppers") account for 20% of all prescription drug overdoses.

610. Opioids are by far the most commonly prescribed class of controlled substances in Mississippi. In January 2013 alone there were approximately 180,000 individual prescriptions for hydrocodone products, with over 10 million unit doses prescribed to Mississippi residents.[188] That quantity is sufficient for every man, woman, and child in Mississippi to receive more than three doses of hydrocodone in just that month.[189] Due in large part to this vast supply of opioids, the number of annual deaths in Mississippi attributable to unintentional drug overdoses (from Mississippi death certificate data) has increased 10-fold since 1990.[190] Shockingly, in 2011, out of 180 unintentional drug overdose deaths where Mississippi's Prescription Monitoring Program (MS PMP) records were available, 172 of the 180 decedents had filled at least one opioid prescription within two years of their death.[191]

611. Death statistics represent only the tip of the iceberg. According to 2009 data, for every overdose death that year there were nine abuse treatment admissions, 30 emergency department visits for opioid abuse or misuse, 118 people with abuse or addiction problems, and 795 non-medical users. Nationally, there were more than 488,000 emergency room admissions for opioids other than heroin in 2008 (up from almost 173,000 in 2004). Recent analysis by the CDC has documented increased rates of opioid abuse and addiction among women; nationally,

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[188] MISSISSIPPI STATE DEPARTMENT OF HEALTH, MISSISSIPPI MORBIDITY REPORT 2 (March 2013) *available at*: http://msdh.ms.gov/msdhsite/_static/resources/5321.pdf.

[189] *Id.*

[190] *Id.*

[191] CENTER FOR MISSISSIPPI HEALTH POLICY, CHART BOOK: FATAL UNINTENTIONAL DRUG OVERDOSES IN MISSISSIPPI 14 (September 2013) *available at*: http://www.mshealthpolicy.com/wp-content/uploads/2014/04/RxOD-Chart-Book-Sept-13.pdf.

every three minutes a woman goes to the emergency department for prescription painkiller misuse or abuse.[192]

612. Here in Mississippi, deaths by prescription drug overdose are also more prevalent in women. Analysis of the 180 decedent records with MS PMP data available from 2011 provided the following demographic information: 82 of the decedents with opioid prescription history during the period two years prior to death were men, and 98 were women.

613. The fraudulent and/or negligent marketing and overprescribing of opioids also has had a significant detrimental impact on children in Mississippi. The overprescribing of opioids for chronic pain has given young children access to opioids, nearly all of which were prescribed for adults in their household. One study documented over 9,000 children nationally exposed to prescription opioids, with a median age of two years old; the number of exposures in young children correlated to the number of prescriptions in the area.[193] Adolescents' ease of access to prescription medicines in the home is a key factor in drug misuse and abuse. A 2012 epidemiologic profile of Mississippi students, grades 6 through 11, reported that prescription drug use increased from around 2% of the student population when reported as "never" available at home or in the community to around 20% when reported as "always" available, representing a 12-fold increase in risk of adolescent abuse as availability increased.[194] This is particularly

[192] CDC, Prescription overdose deaths are a growing problem among women, *available at*: http://www.cdc.gov/vitalsigns/PrescriptionPainkillerOverdoses/.

[193] Bailey, JE, Campagna, E, Dart, RC, *The under recognized toll of prescription opioid abuse on young children*, Ann. Emerg. Med., 2009 Apr. 53(4), 419-24.

[194] Michael E Griswold, *et al., Underage Substance Use and Adverse Consequences in Mississippi: An Epidemiologic Profile (2001-2012)*, State Epidemiological Outcomes Workgroup (2012) *available at*: http://www.snapshots.ms.gov/mdemh/snapshots.nsf/webpages/Data_msdata?OpenDocument.

worrisome since a significant percentage of adolescent suicide attempts are carried out with opioids.

614. In addition, there has been a dramatic rise in the number of infants who are born addicted to opioids due to prenatal exposure and suffer from neonatal abstinence syndrome ("NAS," also known as neonatal opioid withdrawal syndrome, or "NOWS"). These infants painfully withdraw from the drug once they are born and cry nonstop from the pain and stress of withdrawal, experience convulsions or tremors, have difficulty sleeping and feeding, and suffer from diarrhea, vomiting, and low weight gain, among other serious symptoms. The long-term developmental effects are still unknown, though research in other states has indicated that these children are likely to suffer from continued, serious neurologic and cognitive impacts, including hyperactivity, attention deficit disorder, lack of impulse control, and a higher risk of future addiction.[195] When untreated, NAS can be life-threatening.[196] In 2009, more than 13,000 infants in the United States were born with NAS, or about one every hour.[197] According to data from Tennessee, which has most closely studied the issue, 52% of mothers of NAS newborns used only drugs prescribed to them; another 20% used a mix of their own prescriptions and illicitly obtained drugs.[198]

[195] Roland Gray presentation to FDA; *see* citations in FDA decision on Docket Nos. FDA-2013-P-1288 and FDA-2013-P-1289.

[196] *See* FDA decision on Docket Nos. FDA-2013-P-1288 and FDA-2013-P-1289.

[197] Patrick S, *et al*., Neonatal Abstinence Syndrome and Associated Health Care Expenditures, United States 2000-2009, JAMA Intern Med. May 9, 2012; 307(18).

[198] Jonel Aleccia, 'Just Flooding US': Tenn. Spike in drug-dependent newborns is warning to nation, NBC NEWS, October 11, 2013.

b. Increased opioid use has increased costs related to addiction treatment.

615. Opioid addiction is the primary reason that individuals seek admission for drug abuse treatment at Mississippi facilities. In 2012, more Mississippians sought treatment for opioid abuse than for cocaine, methamphetamines, or all other prescription drugs combined.[199] Of the 962 individuals who sought treatment primarily for opioid dependency, 52 percent were women, 75 percent were between the ages of 21 and 40, and 94 percent were Caucasian. Studies estimate the total medical and prescription costs of opioid addiction and diversion to public and private healthcare payers at $72.5 billion.[200]

616. By January 2013, Mississippi had 77 Certified Opioid Treatment Programs. By way of contrast, Tennessee, whose opioid epidemic is among the worst in the nation, has only twelve. These treatment programs do not even begin to meet the need for services.

617. In addition to intense counseling, many treatment programs prescribe additional drugs to treat opioid addiction. Nationally, in 2012, nearly 8 billion prescriptions of the two drugs commonly used to treat opioid addiction – buprenorphine/naloxone and naltrexone – were written and paid for. Studies estimate the total medical and prescription costs of opioid addiction and diversion to public and private healthcare payors at $72.5 billion. According to one estimate

[199] Substance Abuse & Mental Health Services Administration, Substance Abuse Treatment Admissions by Primary Substance of Abuse, http://wwwdasis.samhsa.gov/webt/quicklink/MS12.htm (current through July 7, 2014).

[200] Katz N, *Prescription Opioid Abuse: Challenges and Opportunities for Payers*, AmJManagCare, April 19 2013, p. 2, *available at*: http://www.ajmc.com/publications/issue/2013/2013-1-vol19-n4/Prescription-Opioid-Abuse-Challenges-and-Opportunities-for-Payers/.

based on 2007 data showing $25 billion spent in health care costs from opioid abuse, Mississippi has spent $141,709,137 in such costs, amounting to $47 per capita.[201]

c. Increased opioid use has fueled an illegal secondary market for narcotics and the criminals who support it.

618. Defendants' success in extending the market for opioids to new patients and chronic conditions has created an abundance of drugs available for criminal use and fueled a new wave of addiction, abuse, and injury.

619. Defendants' scheme supplies both ends of the secondary market for opioids – producing both the inventory of narcotics to sell and the addicts to buy them. One researcher who has closely studied the public health consequences of opioids has found, not surprisingly, that a "substantial increase[] in the nonmedical use of opioids is a predictable adverse effect of substantial increases in the extent of prescriptive use."[202] It has been estimated that the majority of the opioids that are abused come, directly or indirectly, through doctors' prescriptions.

620. In Mississippi, the Division of Medicaid (DOM) recently began using the MS PMP to identify beneficiaries suspected of abusing or diverting prescription drugs and restrict their access. In 2011 alone, the DOM identified 494 beneficiaries who were obtaining prescription drugs from 7 or more pharmacies or providers.

[201] See Matrix Global Advisors, LLC, Health Care Costs from Opioid Abuse: A State-by-State Analysis (Apr. 2015).

[202] G. Caleb Alexander *et al*., *Rethinking Opioid Prescribing to Protect Patient Safety and Public Health*, 308(18) JAMA 1865 (2012).

621. In Mississippi, the street value for a single tablet of oxycodone can range from $10 to $20.[203] These prices have given rise to a significant black market in prescription opioids, which has not only created and supplied additional addicts, but fueled other criminal activities.

622. In addition, because heroin is cheaper than prescription painkillers, many prescription opioid addicts migrate to heroin. Thus, prescription drug abuse is fueling the rise of heroin usage in Mississippi. According to Mississippi Bureau of Narcotics Director Marshall Fisher, "[w]hat is happening, the addicts are figuring out they can get heroin on the street, cheaper, and with much less risk than prescription drugs."[204] As a result, self-reported heroin use nearly doubled in the U.S. between 2007 and 2012, from 373,000 to 669,000 individuals and, in 2010, more than 3,000 people in the U.S. died from heroin overdoses, also nearly double the rate in 2006; nearly 80% of those who used heroin in the past year previously abused prescription opioids.[205] Patients become addicted to opioids and then move on to heroin because these prescription drugs are roughly four times more expensive than heroin on the street. In the words of one federal Drug Enforcement Agency official, "Who would have ever thought in this country it would be cheaper to buy heroin than pills and obtain them more easily. That is the reality we're facing."[206]

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[203] S. Randy Easterling, *A Look at the Mississippi State Board of Medical Licensure*, 23 (June 2013) *available at*: http://www.msmaonline.com/Docs/Documents/Prescription%20Drug%20Abuse%20Crisis%20-%20Randy%20Easterling%20MD%20-%205.26.pdf

[204] Chip Ward, *Prescription Drug Abuse Blamed for Rise of Heroin*, NEWSMS. (October 7, 2013), http://www.newsms.fm/prescription-drug-abuse-blamed-rise-heroin/.

[205] NPR Staff, *With Rise of Painkiller Abuse, A Closer Look At Heroin*, NPR, Nov. 2, 2013, *available at*: www.npr.org/2013/11/02/242594489/with-rise-of-painkiller-abuse-a-closer-look-at-heroin.

[206] Matt Pearce and Tina Susman, Philip Seymour Hoffman dies amid major comeback of heroin in the U.S., LA TIMES, Feb. 3, 2014.

623. The toll on patients who abuse or become addicted to opioids does not lend itself to quantification, or even easy descriptions. Many of them will lose their jobs and some of them will lose their homes and their families. Some of them will get treatment and fewer will successfully complete it; many of those patients will relapse, returning to opioids or some other drug. As noted above, some will become so desperate for drugs that they will switch to heroin – moving from taking prescription drugs to buying and even injecting illegal drugs. Of those who continue to take opioids, some will overdose – some fatally, some not. Others will die prematurely from related causes – falls, traffic accidents, assaults, or from premature heart or neurological disease that hastens their death by 10 or 20 years.

3. Defendants' fraudulent marketing has led to record profits.

624. While the use of opioids has taken an enormous toll on the State of Mississippi and its residents, Defendants have realized blockbuster profits. In 2012, health care providers nationwide wrote 259 million prescriptions for painkillers – roughly one prescription per American adult.[207] Opioids generated $8 billion in revenue for drug companies just in 2010.[208]

625. Financial information – where available – indicates that Defendants each experienced a material increase in sales, revenue, and profits from the fraudulent, misleading, and unfair market activities laid out above. Purdue's OxyContin sales alone increased from

[207] *CDC Vital Signs, Opioid Painkiller Prescribing*, CDC (July 2014), *available at*: http://www.cdc.gov/vitalsigns/opioid-prescribing/.

[208] Barry Meier & Bill Marsh, *The Surging Cost of the Opioid Economy*, NEW YORK TIMES (June 22, 2013), *available at*: http://www.nytimes.com/interactive/2013/06/23/sunday-review/the-soaring-cost-ofthe-opioid-economy.html?_r=0.

$45 million in 1996 to $3.1 billion in 2010.[209] In 2010, Research Firm Frost & Sullivan projected an increase to $15.3 billion in overall revenue from opioid sales by 2016.[210]

I. Defendants Fraudulently Concealed Their Misrepresentations

626. At all times relevant to this Complaint, Defendants took steps to avoid detection of and fraudulently conceal their deceptive marketing and conspiratorial behavior.

627. First, and most prominently, Defendants disguised their own roles in the deceptive marketing of chronic opioid therapy by funding and working through patient advocacy and professional front organizations and KOLs. Defendants purposefully hid behind these individuals and organizations to avoid regulatory scrutiny and to prevent doctors and the public from discounting their messages.

628. While Defendants were listed as sponsors of many of the publications described in this Complaint, they never disclosed their role in shaping, editing, and exerting final approval over their content. Defendants exerted their considerable influence on these promotional and "educational" materials.

629. In addition to hiding their own role in generating the deceptive content, Defendants manipulated their promotional materials and the scientific literature to make it appear these items were accurate, truthful, and supported by substantial scientific evidence. Defendants distorted the meaning or import of studies they cited and offered them as evidence for propositions the studies did not support. The true lack of support for Defendants' deceptive

[209] Katherin Eban, *Purdue Pharma's Painful Medicine*, Fortune Magazine (November 9, 2011), *available at*: http://fortune.com/2011/11/09/oxycontin-purdue-pharmas-painful-medicine/.

[210] Frost & Sullivan, *U.S. Opioid Pain Management Market* (July 12, 2010), *available at:* http://www.frost.com/prod/servlet/report-brochure.pag?id=N72F-01-00-00-00.

messages was not apparent to the medical professionals who relied upon them in making treatment decisions, nor could they have been detected by the State.

630. Thus, while the opioid epidemic was evident, Defendants, in furtherance of their marketing strategy, intentionally concealed their own role in causing it. Defendants successfully concealed from the medical community, patients, and health care payers facts sufficient to arouse suspicion of the existence of claims that the State now asserts. The State was not alerted to the existence and scope of Defendants' industry-wide fraud and could not have acquired such knowledge earlier through the exercise of reasonable diligence.

631. Through their public statements, marketing, and advertising, Defendants' deceptions deprived the State of actual or presumptive knowledge of facts sufficient to put it on notice of potential claims.

V. CLAIMS FOR RELIEF

COUNT I

VIOLATIONS OF MISSISSIPPI'S CONSUMER PROTECTION ACT
(MISS. CODE ANN. § 75-24-1, *et seq.*)

632. Plaintiff realleges and incorporates by reference all preceding paragraphs as if fully set forth herein.

633. Defendants' actions, as complained of herein, constitute unfair methods of competition and unfair or deceptive trade practices in violation of MISS. CODE ANN. § 75-24-5. Specifically, and without limitation, Defendants:

a. knowingly, or with reason to know, and willfully used unfair and deceptive trade practices in violation of MISS. CODE ANN. § 75-24-5(1), in general, consisting of:

1. knowingly or with reason to know, making, and continuing to make, false representations regarding the risks of long-term use of prescription opioids for chronic non-cancer pain;

2. before, during, and after consumer transactions, making, and continuing to make, misrepresentations and omissions and engaging, and continuing to engage, in deceptive trade practices that have deceived or misled, or could have reasonably been expected to deceive or mislead, the State regarding the risks of long-term use of prescription opioids for chronic non-cancer pain; and

3. engaging, and continuing to engage, in unfair trade practices that are immoral, unethical, oppressive, unscrupulous, or substantially injurious to aggrieved consumers such as the State, including misrepresenting, failing to state, concealing, suppressing and/or omitting facts regarding the risks of long-term use of opioids for chronic non-cancer pain, and targeting vulnerable consumers and consumer groups by sponsoring and disseminating materials that contained such untrue, false and misleading statements.

b. knowingly, or with reason to know, and willfully misrepresented the source, sponsorship, approval, or certification of good or services in violation of MISS. CODE ANN. § 75-24-5(2)(b), by, in general;

1. Providing significant financial support to pro-opioid KOLs and Front Groups which misrepresented the risks of the use of opioids to treat chronic non-cancer pain, and then assisting in the dissemination of literature written by those KOLs and Front Groups that made misrepresentations concerning the risks and benefits of the use of opioids to treat chronic non-cancer pain;

2. Assisting in the distribution of guidelines written by KOLs and Front Groups that contained misrepresentations concerning the use of opioids to treat chronic non-cancer pain and the risks of opioid addiction;

3. Endorsing and assisting in the distribution of CMEs containing misrepresentations concerning the use of opioids to treat chronic non-cancer pain;

4. Developing and disseminating scientific studies that misrepresented that opioids are safe and effective for the long-term treatment of chronic non-cancer pain and that opioids improve quality of life, while concealing contrary data; and

5. Creating, endorsing, and supporting the distribution of other "unbranded" materials that misrepresented the data regarding the

safety and efficacy of opioids for the long-term treatment of chronic non-cancer pain, including known rates of abuse and addiction.

c. knowingly, or with reason to know, and willfully misrepresenting the affiliation, connection, or association with, or certification of another in violation of MISS. CODE ANN. § 75-24-5(2)(c), by, in general:

1. Providing significant financial support to pro-opioid KOLs and Front Groups which misrepresented the risks of the use of opioids to treat chronic non-cancer pain, and then assisting in the dissemination of literature written by those KOLs and Front Groups that made misrepresentations concerning the risks and benefits of the use of opioids to treat chronic non-cancer pain;

2. Assisting in the distribution of guidelines written by KOLs and Front Groups that contained misrepresentations concerning the use of opioids to treat chronic non-cancer pain and the risks of opioid addiction;

3. Endorsing and assisting in the distribution of CMEs containing misrepresentations concerning the use of opioids to treat chronic non-cancer pain;

4. Developing and disseminating scientific studies that misrepresented that opioids are safe and effective for the long-term treatment of chronic non-cancer pain and that opioids improve quality of life, while concealing contrary data; and

5. Creating, endorsing, and supporting the distribution of other "unbranded" materials that misrepresented the data regarding the safety and efficacy of opioids for the long-term treatment of chronic non-cancer pain, including known rates of abuse and addiction.

d. knowingly, and with reason to know, and willfully misrepresented that goods or services have sponsorship, approval, characteristics, ingredients, uses, benefits, or quantities that they do not have, in violation of MISS. CODE ANN. § 75-24-5(2)(e), by, in general:

1. Creating and disseminating advertisements that misrepresented the ability of opioids to improve function long-term and the evidence supporting the efficacy of opioids long-term for the treatment of chronic non-cancer pain;

2. Misrepresenting the true risk of addiction and promoting the misleading concept of pseudoaddiction, even for high risk patients;

3. Endorsing, directly distributing, and assisting in the distribution of statements that presented an unbalanced treatment of the long-term and dose-dependent risks of opioids versus non-steroidal anti-inflammatory drugs;

4. Providing significant financial support to pro-opioid KOLs and Front Groups which misrepresented the risks of the use of opioids to treat chronic non-cancer pain, and then assisting in the dissemination of literature written by those KOLs and Front Groups that made misrepresentations concerning the risks and benefits of the use of opioids to treat chronic non-cancer pain;

5. Assisting in the distribution of guidelines that contained misleading statements concerning the use of opioids to treat chronic non-cancer pain and misrepresented the risks of opioid addiction;

6. Endorsing and assisting in the distribution of CMEs that misrepresented the risks of the use of opioids to treat chronic non-cancer pain;

7. Developing and disseminating scientific studies that misleadingly concluded opioids are safe and effective for the long-term treatment of chronic non-cancer pain and that opioids improve quality of life, while concealing contrary data;

8. Creating, endorsing, and supporting the distribution of "unbranded" materials that misrepresented the data regarding the safety and efficacy of opioids for the long-term treatment of chronic non-cancer pain, including known rates of abuse and addiction;

9. Through in-person detailing and speakers bureau events, making misrepresentations to a wide range of Mississippi doctors, including general practitioners, neurologists and sports medicine specialists concerning the use of opioids to treat chronic non-cancer pain; and

10. Targeting the elderly and veterans by sponsoring and disseminating patient education marketing materials that contained misrepresentations concerning the use of opioids to treat chronic non-cancer pain.

e. knowingly, or with reason to know, and willfully misrepresenting that a person has a sponsorship, approval, status, affiliation, or connection that he does not have, in violation of MISS. CODE ANN. § 75-24-5(2)(e), by, in general:

1. Providing significant financial support to pro-opioid KOLs and Front Groups which misrepresented the risks of the use of opioids to treat chronic non-cancer pain, and then assisting in the dissemination of literature written by those KOLs and Front Groups that made misrepresentations concerning the risks and benefits of the use of opioids to treat chronic non-cancer pain;

2. Assisting in the distribution of guidelines written by KOLs and Front Groups that contained misrepresentations concerning the use of opioids to treat chronic non-cancer pain and the risks of opioid addiction;

5. Endorsing and assisting in the distribution of CMEs containing misrepresentations concerning the use of opioids to treat chronic non-cancer pain;

6. Developing and disseminating scientific studies that misrepresented that opioids are safe and effective for the long-term treatment of chronic non-cancer pain and that opioids improve quality of life, while concealing contrary data; and

7. Creating, endorsing, and supporting the distribution of other "unbranded" materials that misrepresented the data regarding the safety and efficacy of opioids for the long-term treatment of chronic non-cancer pain, including known rates of abuse and addiction.

f. knowingly, or with reason to know, and willfully misrepresented that goods or services are of a particular standard, quality, or grade, if they are of another, in violation of MISS. CODE ANN. § 75-24-5(2)(g), by, in general:

1. Creating and disseminating advertisements that misrepresented the ability of opioids to improve function long-term and the evidence supporting the efficacy of opioids long-term for the treatment of chronic non-cancer pain;

2. Misrepresenting the true risk of addiction and promoting the misleading concept of pseudoaddiction, even for high risk patients;

3. Endorsing, directly distributing, and assisting in the distribution of statements that presented an unbalanced treatment of the long-term and dose-dependent risks of opioids versus non-steroidal anti-inflammatory drugs;

4. Providing significant financial support to pro-opioid KOLs and Front Groups which misrepresented the risks of the use of opioids to treat chronic non-cancer pain, and then assisting in the dissemination of literature written by those KOLs and Front Groups that made misrepresentations concerning the risks and benefits of the use of opioids to treat chronic non-cancer pain;

5. Assisting in the distribution of guidelines that contained misleading statements concerning the use of opioids to treat chronic non-cancer pain and misrepresented the risks of opioid addiction;

6. Endorsing and assisting in the distribution of CMEs that misrepresented the risks of the use of opioids to treat chronic non-cancer pain;

7. Developing and disseminating scientific studies that misleadingly concluded opioids are safe and effective for the long-term treatment of chronic non-cancer pain and that opioids improve quality of life, while concealing contrary data;

8. Creating, endorsing, and supporting the distribution of "unbranded" materials that misrepresented the data regarding the safety and efficacy of opioids for the long-term treatment of chronic non-cancer pain, including known rates of abuse and addiction;

9. Through in-person detailing and speakers bureau events, making misrepresentations to a wide range of Mississippi doctors, including general practitioners, neurologists and sports medicine specialists concerning the use of opioids to treat chronic non-cancer pain; and

10. Targeting the elderly and veterans by sponsoring and disseminating patient education marketing materials that contained misrepresentations concerning the use of opioids to treat chronic non-cancer pain.

634. Defendants' unfair and deceptive acts or practices were in or affected commerce, and proximately caused injury to the State. As a result of Defendants' unfair and deceptive conduct, the State has suffered millions of dollars in inflated or excessive payments for prescription opioids prescribed for long-term treatment of chronic non-cancer pain.

635. Defendants' actions as alleged herein were an inequitable assertion of their power or position to the detriment of payors like Plaintiff, leading to unfair and deceptive practices.

636. The State is also entitled to civil penalties of up to $10,000.00 for each violation resulting from each Defendant's unlawful conduct, investigative costs, and attorneys' fees pursuant to MISS. CODE ANN. § 75-24-19(1)(b).

637. In addition, the State seeks a permanent injunction against Defendants' future unfair and deceptive trade practices pursuant to MISS. CODE ANN. § 75-24-9.

COUNT II

FRAUD

638. Plaintiff realleges and incorporates by reference all preceding paragraphs as if fully set forth herein.

639. As alleged herein, Defendants engaged in false representations and concealments of material fact regarding the use of opioids to treat chronic non-cancer pain.

640. Defendant Purdue made and/or disseminated untrue, false, and misleading statements, including, but not limited to, the following:

- Creating, sponsoring, and assisting in the distribution of patient education materials that contained misleading statements;
- Creating and disseminating advertisements that contained false, misleading, and untrue statements concerning the ability of opioids to improve function long-term and concerning the evidence supporting the efficacy of opioids long-term for the treatment of chronic non-cancer pain;

- Disseminating misleading statements concealing the true risk of addiction and promoting the misleading concept of pseudoaddiction through Purdue's own unbranded publications and on internet sites Purdue operated;

- Distributing brochures to doctors, patients, and law enforcement officials that included misleading statements concerning the indicators of possible opioid abuse;

- Sponsoring, directly distributing, and assisting in the distribution of publications that promoted the misleading concept of pseudoaddiction, even for high-risk patients;

- Endorsing, directly distributing, and assisting in the distribution of publications that presented an unbalanced treatment of the long-term and dose-dependent risks of opioids versus NSAIDs;

- Providing significant financial support to pro-opioid KOL doctors who made untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain;

- Providing needed financial support to pro-opioid pain organizations that made untrue, false, and misleading statements, including in patient education materials, concerning the use of opioids to treat chronic non-cancer pain;

- Assisting in the distribution of guidelines that contained misleading statements concerning the use of opioids to treat chronic non-cancer pain and misrepresented the risks of opioid addiction;

- Endorsing and assisting in the distribution of CMEs containing untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain;

- Developing and disseminating scientific studies that misleadingly concluded opioids are safe and effective for the long-term treatment of chronic non-cancer pain and that opioids improve quality of life, while concealing contrary data;

- Assisting in the dissemination of literature written by pro-opioid KOLs that contained false, misleading, and untrue statements concerning the use of opioids to treat chronic non-cancer pain;

- Creating, endorsing, and supporting the distribution of patient and prescriber education materials that misrepresented the data regarding the safety and efficacy of opioids for the long-term treatment of chronic non-cancer pain, including known rates of abuse and addiction and the lack of validation for long-term efficacy;

- Targeting veterans by sponsoring and disseminating patient education marketing materials that contained untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain;

- Targeting the elderly by assisting in the distribution of guidelines that contained misleading statements concerning the use of opioids to treat chronic non-cancer pain and misrepresented the risks of opioid addiction in this population;

- Exclusively disseminating misleading statements in education materials to Mississippi hospital doctors and staff while purportedly educating them on new pain standards;

- Making untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain to Mississippi prescribers through in-person detailing; and

- Withholding from Mississippi law enforcement the names of prescribers Purdue believed to be facilitating the diversion of its products, while simultaneously marketing opioids to these doctors by disseminating patient and prescriber education materials and advertisements and CMEs they knew would reach these same prescribers.

641. Defendant Endo made and/or disseminated untrue, false, and misleading statements, including, but not limited to, the following:

- Creating, sponsoring, and assisting in the distribution of patient education materials that contained misleading statements;

- Creating and disseminating advertisements that contained false, misleading, and untrue statements concerning the ability of opioids to improve function long-term and concerning the evidence supporting the efficacy of opioids long-term for the treatment of chronic non-cancer pain;

- Creating and disseminating paid advertisement supplements in academic journals promoting chronic opioid therapy as safe and effective for long term use for high-risk patients;

- Creating and disseminating advertisements that falsely and inaccurately conveyed the impression that Endo's opioids would provide a reduction in oral, intranasal, or intravenous abuse;

- Disseminating misleading statements concealing the true risk of addiction and promoting the misleading concept of pseudoaddiction through Endo's own unbranded publications and on internet sites Endo sponsored or operated;

- Endorsing, directly distributing, and assisting in the distribution of publications that presented an unbalanced treatment of the long-term and dose-dependent risks of opioids versus NSAIDs;

- Providing significant financial support to pro-opioid KOLs, who made untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain;

- Providing needed financial support to pro-opioid pain organizations – including over $5 million to the organization responsible for many of the most egregious misrepresentations – that made untrue, false, and misleading statements, including in patient education materials, concerning the use of opioids to treat chronic non-cancer pain;

- Targeting the elderly by assisting in the distribution of guidelines that contained misleading statements concerning the use of opioids to treat chronic non-cancer pain and misrepresented the risks of opioid addiction in this population;

- Endorsing and assisting in the distribution of CMEs containing untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain;

- Developing and disseminating scientific studies that misleadingly concluded opioids are safe and effective for the long-term treatment of chronic non-cancer pain and that opioids improve quality of life, while concealing contrary data;

- Directly distributing and assisting in the dissemination of literature written by pro-opioid KOLs that contained false, misleading, and untrue statements concerning the use of opioids to treat chronic non-cancer pain, including the concept of pseudoaddiction;

- Creating, endorsing, and supporting the distribution of patient and prescriber education materials that misrepresented the data regarding the safety and efficacy of opioids for the long-term treatment of chronic non-cancer pain, including known rates of abuse and addiction and the lack of validation for long-term efficacy; and

- Making untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain to Mississippi prescribers through in-person detailing.

642. Defendant Janssen made and/or disseminated untrue, false and misleading statements, including, but not limited to, the following:

- Creating, sponsoring, and assisting in the distribution of patient education materials that contained misleading statements;

- Directly disseminating misleading statements through internet sites over which Janssen exercised final editorial control and approval stating that opioids are safe and effective for the long-term treatment of chronic non-cancer pain and that opioids improve quality of life, while concealing contrary data;

- Disseminating misleading statements concealing the true risk of addiction and promoting the misleading concept of pseudoaddiction through internet sites over which Janssen exercised final editorial control and approval;

- Promoting opioids for the treatment of conditions for which Janssen knew, due to the scientific studies it conducted, that opioids were not efficacious and concealing this information;

- Sponsoring, directly distributing, and assisting in the dissemination of patient education publications over which Janssen exercised final editorial control and approval, which presented an unbalanced treatment of the long-term and dose-dependent risks of opioids versus NSAIDs;

- Providing significant financial support to pro-opioid KOLs, who made untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain;

- Providing necessary financial support to pro-opioid pain organizations that made untrue, false, and misleading statements, including in patient education materials, concerning the use of opioids to treat chronic non-cancer pain;

- Targeting the elderly by assisting in the distribution of guidelines that contained misleading statements concerning the use of opioids to treat chronic non-cancer pain and misrepresented the risks of opioid addiction in this population;

- Targeting the elderly by sponsoring, directly distributing, and assisting in the dissemination of patient education publications targeting this population that contained false and misleading statements about the risks of addiction and the adverse effects of opioids, and made false statements that opioids are safe and effective for the long-term treatment of chronic non-cancer pain and improve quality of life, while concealing contrary data;

- Endorsing and assisting in the distribution of CMEs containing untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain;

- Directly distributing and assisting in the dissemination of literature written by pro-opioid KOLs that contained false, misleading, and untrue statements

concerning the use of opioids to treat chronic non-cancer pain, including the concept of pseudoaddiction;

- Creating, endorsing, and supporting the distribution of patient and prescriber education materials that misrepresented the data regarding the safety and efficacy of opioids for the long-term treatment of chronic non-cancer pain, including known rates of abuse and addiction and the lack of validation for long-term efficacy;

- Targeting veterans by sponsoring and disseminating patient education marketing materials that contained untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain; and

- Making untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain to Mississippi prescribers through in-person detailing.

643. Defendant Cephalon made and/or disseminated untrue, false and misleading statements, including, but not limited to, the following:

- Creating, sponsoring, and assisting in the distribution of patient education materials that contained misleading statements;

- Sponsoring and assisting in the distribution of publications that promoted the misleading concept of pseudoaddiction, even for high-risk patients;

- Providing significant financial support to pro-opioid KOL doctors who made untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain and breakthrough chronic non-cancer pain;

- Developing and disseminating scientific studies that misleadingly concluded opioids are safe and effective for the long-term treatment of chronic non-cancer pain in conjunction with Cephalon's potent rapid-onset opioids;

- Providing needed financial support to pro-opioid pain organizations that made untrue, false, and misleading statements, including in patient education materials, concerning the use of opioids to treat chronic non-cancer pain;

- Endorsing and assisting in the distribution of CMEs containing untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain;

- Endorsing and assisting in the distribution of CMEs containing untrue, false and misleading statements concerning the use of Cephalon's rapid-onset opioids;

- Directing its marketing of Cephalon's rapid-onset opioids to a wide range of doctors, including general practitioners, neurologists, sports medicine specialists, and workers' compensation programs, serving chronic pain patients;

- Making untrue, false, and misleading statements concerning the use of Cephalon's opioids to treat chronic non-cancer pain to Mississippi prescribers through in-person detailing and speakers bureau events, when such uses are unapproved and unsafe; and

- Making untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain to Mississippi prescribers through in-person detailing and speakers bureau events.

644. Defendant Actavis made and/or disseminated untrue, false and misleading statements, including, but not limited to, the following:

- Making untrue, false, and misleading statements concerning the use of opioids to treat chronic non-cancer pain to Mississippi prescribers through in-person detailing;

- Creating and disseminating advertisements that contained false, misleading, and untrue statements that opioids are safe and effective for the long-term treatment of chronic non-cancer pain and that opioids improve quality of life;

- Creating and disseminating advertisements that concealed the risk of addiction in the long-term treatment of chronic, non-cancer pain; and

- Developing and disseminating scientific studies that misleadingly concluded opioids are safe and effective for the long-term treatment of chronic non-cancer pain and that opioids improve quality of life while concealing contrary data.

645. Defendant Mallinckrodt made and/or disseminated deceptive statements, including, but not limited to, the following:

- Creating, sponsoring, and assisting in the distribution of patient education materials throughout the United States—including, upon information and belief, to Mississippi prescribers—that contained deceptive statements;

- Sponsoring and assisting in the distribution of publications that promoted the deceptive concept of pseudoaddiction, even for high-risk patients, throughout the United States—including, upon information and belief, in Mississippi;

- Providing significant financial support to pro-opioid KOL doctors who made deceptive statements concerning the use of opioids to treat chronic non-cancer pain

and breakthrough chronic non-cancer pain that, upon information and belief, reached Mississippi doctors and prescribers; and

- Providing needed financial support to pro-opioid pain organizations that made deceptive statements, including in patient education materials, concerning the use of opioids to treat chronic non-cancer pain that, upon information and belief, reached Mississippi doctors and prescribers.

646. These false representations and concealments were reasonably calculated to deceive the State, were made with the intent to deceive, and did in fact deceive the State, which paid for prescription opioids for long-term chronic pain.

647. As a direct and proximate cause of Defendants' fraudulent conduct, the State has been injured.

COUNT III

NEGLIGENT MISREPRESENTATION

648. Plaintiff realleges and incorporates by reference all preceding paragraphs as if fully set forth herein.

649. Defendants made false representations and concealments of material fact regarding the use of opioids to treat chronic non-cancer pain.

650. Defendants failed to adequately and timely advise the State regarding the false representations and concealments of material fact regarding the use of opioids to treat chronic non-cancer pain.

651. The misrepresentations and omissions by the Defendants were material and significant.

652. Defendants failed to exercise reasonable care in making the misrepresentations and omissions.

653. Defendants and their employees and/or agents intended that the State would rely and act upon the misrepresentations and/or omissions.

654. The State was justified in relying upon the statements and/or actions of the Defendants. The State reasonably relied on the statements, representations, and acts of the Defendants.

655. The State has suffered damages as a direct and proximate result of the misrepresentations and omissions by the Defendants and their employees and/or agents.

COUNT IV

UNJUST ENRICHMENT

656. Plaintiff realleges and incorporates by reference all preceding paragraphs as if fully set forth herein.

657. As a direct and proximate result of the unlawful conduct described above, Defendants have been and will continue to be unjustly enriched.

658. Defendants have benefited from their unlawful acts by causing millions of opioid prescriptions to be written for the long-term treatment of chronic non-cancer pain, when those prescriptions were not supported by knowledge in the scientific or medical community. As alleged above, Defendants fraudulently and/or negligently marketed their opioids to increase their profits at the expense of the State. It would be inequitable and not in good conscience for Defendants to retain any ill-gotten gains earned as a result of the conduct alleged herein, which gains would not exist but for the overpayments made by the State and other payors.

COUNT V

PUBLIC NUISANCE

659. Plaintiff realleges and incorporates by reference all preceding paragraphs as if fully set forth herein.

660. This action is brought by the State to abate the public nuisance created by the Defendants.

661. Defendants, individually and in concert with each other, have contributed to, and/or assisted in creating and maintaining a condition that is harmful to the health of Mississippians or interferes with the comfortable enjoyment of life in violation of Mississippi common law.

662. The public nuisance created by Defendants' actions is substantial and unreasonable – it has caused and continues to cause significant harm to the community and the harm inflicted outweighs any offsetting benefit. The staggering rates of opioid use resulting from Defendants' marketing efforts have caused harm to the community that includes, but is not limited to:

a. Upwards of 30% of all adults have used them. These high rates of use have led to unnecessary opioid abuse, addiction, overdose, injuries, and deaths.

b. Children too have been harmed by opioids. They have been exposed to medications prescribed to family members or others, resulting in injury, addiction, and death. Easy access to prescription opioids has made opioids a recreational drug of choice among Mississippi teenagers; opioid use among teenagers is only outpaced by marijuana use. Even infants have been born addicted to opioids due to prenatal exposure, causing severe withdrawal symptoms and lasting developmental impacts.

c. Mississippians who have never taken opioids also have suffered the costs of Defendants' public nuisance. Many have endured both the emotional and financial costs of caring for loved ones addicted to or injured by opioids, and the loss of companionship, wages, or other support from

family members who have used, abused, become addicted to, overdosed on, or been killed by opioids.

d. More broadly, opioid use and misuse have driven Mississippians' health care costs higher.

e. Employers have lost the value of productive and healthy employees who suffered from adverse consequences from opioid use.

f. Defendants' success in extending the market for opioids to new patients and chronic conditions has also created an abundance of drugs available for criminal use and fueled a new wave of addiction, abuse, and injury. Defendants' scheme created both ends of a new secondary market for opioids – providing both the supply of narcotics to sell and the demand of addicts to buy them.

g. This demand also has created additional illicit markets in other opiates, particularly heroin. The low cost of heroin has led some of those who initially become addicted to prescription opioids to migrate to cheaper heroin, fueling a new heroin epidemic in the process.

h. The diversion of opioids into the secondary, criminal market and the increase in the number of individuals who abuse or are addicted to opioids has increased the demands on emergency services and law enforcement in the State.

i. All of this has caused significant harm to the community – in lives lost; addictions endured; the creation of an illicit drug market and all its concomitant crime and costs; unrealized economic productivity; and broken families and homes.

j. These harms have taxed the human, medical, public health, law enforcement, and financial resources of the State.

k. Defendants' interference with the comfortable enjoyment of life of a substantial number of people is entirely unreasonable because there is little social utility to opioid use and any potential value is outweighed by the gravity of the harm inflicted by Defendants' actions.

663. Defendants knew or should have known that their promotion of opioid use would create a public nuisance.

a. Defendants have engaged in massive production, promotion, and distribution of opioids for use by the citizens of the State.

b. Defendants' actions created and expanded the market for opioids, promoting its wide use for pain management.

c. Defendants misrepresented the benefits of opioids for chronic pain and fraudulently concealed, misrepresented, and omitted the serious adverse effects of opioids, including the addictive nature of the drugs.

d. Defendants knew or should have known that their promotion would lead to addiction and other adverse consequences and that the larger community would suffer as a result.

664. Defendants' actions were, at the least, a substantial factor in opioids becoming widely available and widely used. Defendants' actions were, at the least, a substantial factor in doctors and patients not accurately assessing and weighing the risks and benefits of opioids for chronic pain. Without Defendants' actions, opioid use would not have become so widespread, and the enormous public health hazard of opioid overuse, abuse, and addiction that now exists would have been averted.

665. The health and safety of the citizens of the State, including those who use, have used or will use opioids, as well as those affected by users of opioids, is a matter of great public interest and of legitimate concern to the State's citizens and residents.

666. The public nuisance created, perpetuated, and maintained by Defendants can be abated and further reoccurrence of such harm and inconvenience can be prevented.

667. Defendants' conduct has affected and continues to affect a considerable number of people within the State is likely to continue to cause significant harm to chronic pain patients who take opioids, their families, and the community at large.

668. Each Defendant created or assisted in the creation of the epidemic of opioid use and injury, and each Defendant is jointly and severally liable for abating it.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully prays:

A. That the acts alleged herein be adjudged and decreed to be unlawful in violation of State statutory and common law;

B. That Plaintiff recover all measures of damages allowable under the State statutes identified herein and the common law, and that judgment be entered against Defendants in favor of Plaintiff;

C. That Plaintiff recover the costs and expenses of suit, pre- and post-judgment interest, investigative costs, and reasonable attorneys' fees as provided by law;

D. That Defendants be ordered to pay restitution to Plaintiff;

E. That Defendants be ordered to pay civil penalties for violations of applicable statutes;

F. That Defendants be permanently enjoined from engaged in future unfair and deceptive trade practices;

G. That Defendants be ordered to abate the public nuisance that they created in in violation of State law; and

H. That the Court order such other and further relief as the Court deems just, necessary and appropriate.

DATED this 12th day of November, 2019.

Respectfully submitted,

STATE OF MISSISSIPPI
JIM HOOD, ATTORNEY GENERAL

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