UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE: NATIONAL PRESCRIPTION OPIATE LITIGATION

MDL No. 2804

This document relates to:

Master Docket No. 1:17-MD-02804-DAP

Hon. Judge Dan A. Polster

AMANDA HANLON, INDIVIDUALLY AND ON BEHALF OF ALL OTHERS SIMILARLY SITUATED;

AMY GARDNER, INDIVIDUALLY AND ON BEHALF OF HER MINOR DAUGHTER A.L.D. AND ALL OTHERS SIMILARLY SITUATED,

Plaintiffs,

v.

PURDUE PHARMA L.P.;
PURDUE PHARMA, INC.;
THE PURDUE FREDERICK COMPANY, INC.;
TEVA PHARMACEUTICAL INDUSTRIES, LTD.;
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;
WATSON PHARMACEUTICALS, INC. n/k/a ACTAVIS, INC.;
WATSON LABORATORIES, INC.; ACTAVIS LLC; and
ACTAVIS PHARMA, INC. f/k/a WATSON PHARMA, INC.;

Defendants.

Case No. 1:19-op-45206

UNDISPUTED MATERIAL FACTS SUPPORTING
MOTION FOR PRELIMINARY INJUNCTION

1. Except for ancient history, for which there is no evidence, mankind has used opium.[1] For centuries, mankind has understood the addictive nature of opium.[2]

2. Addiction is defined as a chronic, relapsing disorder characterized by compulsive drug seeking, continued use despite harmful consequences, and long-lasting changes in the brain. It is considered both a complex brain disorder and a mental illness. Addiction is the most severe form of a full spectrum of substance use disorders, and is a medical illness caused by repeated misuse of a substance or substances. An addicted person is willing to sacrifice themselves, their families, and society in general to gain access to a harmful substance.[3]

3. Addiction is a complex chronic psychiatric illness with a high relapse rate.[4] The costs associated with addiction include medical costs, police costs, jail and prison costs, work-related accidents, other accidents caused by impairment, to name a few.[5] In all users, long-term opioid use leads to decreased brain volume, for example, in the emotional centers of the brain (amygdala).[6]

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[1] **Exhibit 1**: Nencici P. The rules of drug taking wine and poppy derivatives in the Ancient World. IX. Conclusions. Subst Use Misuse 1997; 32 :2111-9.; **Exhibit 2:** Nencini P. The Rules of drug taking wine and poppy derivatives in the Ancient World. VIII. Lack of evidence of opium addiction. Subst Use Misuse 1997; 32:1581-6.; **Exhibit 3:** Nencini P. The rules of drug taking: wine and poppy derivatives in the ancient world. VII. A ritual use of poppy derivatives? Subst Use Misuse 1997; 32:1405-15.

[2] **Exhibit 4:** Kocherlakota, P. (2014). Neonatal Abstinence Syndrome. Pediatrics, 134(2). doi:10.1542/peds.2013-3524, Retrieved from https://pediatrics.aappublications.org/content/134/2/e547; **Exhibit 5:** Rosenblum, A., Marsch, L. A., Joseph, H., & Portenoy, R. K. (2008). Opioids and the treatment of chronic pain: Controversies, current status, and future directions. Experimental and Clinical Psychopharmacology, 16(5), 405-416. doi:` 10.1037/a0013628, Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2711509/; **Exhibit 6:** Brownstein, M. J. (1993). A brief history of opiates, opioid peptides, and opioid receptors. Proceedings of the National Academy of Sciences, 90(12), 5391-5393. doi:10.1073/pnas.90.12.5391, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC46725/; **Exhibit 7:** Gomez-Pomar, E., & Finnegan, L. P. (2018). The Epidemic of Neonatal Abstinence Syndrome, Historical References of Its' Origins, Assessment, and Management. Frontiers in Pediatrics, 6. doi:10.3389/fped.2018.00033; retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5827164/.

[3] **Exhibit 8**: Media Guide. *National Institute on Drug Abuse*, (2 Jul. 2018) Retrieved from https://www.drugabuse.gov/publications/media-guide.; **Exhibit 9:** Parekh, R. What is Addition. *American Psychiatric Association* (2017, January) Retrieved from https://www.psychiatry.org/patients-families/addiction/what-is-addiction.

[4] **Exhibit 8**

[5] **Exhibit 8**

[6] **Exhibit 10**: Upadhyay J, Maleki N, Potter J, et al. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. Brain 2010; 133:2098-114.

4. Short of addiction, drug abuse, impacts critical brain regions resulting in reward – seeking and crediting, drug dependence, withdrawal, and alterations in both anxiety, learning, and memory.[7]

5. In December 1995, the FDA approved the manufacturing and dispensing of time-released synthetic opioids, namely Oxycontin.[8] Others soon followed.

6. The American Pain Society was sponsored by the opioid manufacturers. In 1996 it trademarked the slogan "Pain: The Fifth Vital Sign". In 1998, the Veterans Health Administration and the Joint Commission for Accreditation of Healthcare Organizations made pain the fifth vital sign.[9]

7. The Federation of State Medical Boards in 1998 released a recommended policy reassuring physicians they would not face regulatory action for prescribing large amounts of narcotics (opioids).[10]

8. In 2001, the JCAHO issued new standards requiring hospital to ask patients about pain and to make treating pain a priority. It also published a Purdue Pharma sponsored guide that stated that some physicians exaggerated concerns about addiction, tolerance, and risk of death. It stated there was no evidence that addiction was a significant issue when persons are given opioids for pain control.[11]

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[7] **Exhibit 11**: Sinha, Rajita. "Chronic stress, drug use, and vulnerability to addiction" *Annals of the New York Academy of Sciences* vol. 1141 92008): 105-30.

[8] **Exhibit 12**: FDA. "Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse." Federal Drug Administration. 13 Feb. 2019. https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm

[9] **EXHIBIT 13:** Retrieved from: Terplan, M. (2017). Women and the opioid crisis: Historical context and public health solutions. Fertility and Sterility, 108(2), 195-199. doi :10.1016/j.fertnstert.2017.06.007.

[10] **EXHIBIT 14:** Kolodny, A. (2013, March 29). [Letter to State Medical Board]. Physicians for Responsible Opioid Prescribing, Brooklyn, NY, Retrieved from: https://www.supportprop.org/wp-content/uploads/2014/12/PA_3_29_13_FSMB.pdf.

[11] **EXHIBIT 15:** Silverman, E. (2019, January 19). Drug maker payments to doctors linked to higher opioid overdose deaths. Retrieved from https://www.statnews.com/pharmalot/2019/01/18/opioids-payments-doctors-overdose-deaths/

9. The need for pain medication for chronic or acute pain needs did not increase from 1995 to present. Stated another way, major increases in opioid prescriptions cannot be explained by the underlying health-related trends for the U.S. population, although some studies point to the past prevalence of untreated pain.[12]

10. Recent studies published in JAMA concluded that physicians were greatly influenced to write more opioid prescriptions when they were the beneficiary/recipient of industry "freebies", such as meals. According to the study, physicians who had greater interactions with industry marketing efforts were more likely to write opioid prescriptions.[13]

11. In 2007, Purdue Pharma and three of its executives pleaded guilty to "misbranding" opioids as less addictive and less subject to abuse than other pain medications. The fine was $635 million. Purdue agreed that these facts were true, even though the individual defendants did not agree they had knowledge of their salesforce saying these things to physicians:[14]

> The information in this case charges, among other things, that
>
> [b]eginning on or about December 12, 1995, and continuing until on or about June 30, 2001, certain PURDUE supervisors and employees, with the intent to defraud or mislead, marketed and promoted OxyContin as less addictive, less subject to abuse and diversion, and less likely to cause tolerance and withdrawal than other pain medications as follows:
>
> a. Trained PURDUE sales representatives and told some health care providers that it was more difficult to extract the oxycodone from an OxyContin tablet for the purpose of intravenous abuse, although PURDUE's own study showed that a drug abuser could extract approximately 68% of the oxycodone from a single 10mg OxyContin tablet by crushing the tablet, stirring it in water, and drawing the solution through cotton into a syringe;

[12] **EXHIBIT 16:** Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1-49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1; **EXHIBIT 17:** Portenoy RK. Cancer pain. Epidemiology and syndromes. Cancer 1989;63;2298-307.; Pain in nursing-home cancer patients often goes untreated. Am J Health Syst Pharm 1998:55;1544, 8.

[13] **EXHIBIT 15**

[14] **EXHIBIT 18:** *USA v The Purdue Frederick Company,* 1:07-cr-00029, pp. 2-3

b. Told PURDUE sales representatives they could tell health care providers that OxyContin potentially creates less chance for addiction than immediate-release opioids;
c. Sponsored training that taught PURDUE sales supervisors that OxyContin had fewer "peak and trough" blood level effects than immediate-release opioids resulting in less euphoria and less potential for abuse than short-acting opioids;
d. Told certain health care providers that patients could stop therapy abruptly without experiencing withdrawal symptoms and that patients who took OxyContin would not develop tolerance to the drug; and
e. Told certain health care providers that OxyContin did not cause a "buzz" or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids, and could be used to "weed out" addicts and drug seekers.

12. Synthetic opioids, like natural opioids, are highly addictive.[15]

13. "Prescription drug abuse is rampant in all areas of our country, particularly among young people, causing untold misery and harm. The White House Drug Policy Office estimates that such abuse rose seventeen percent from 2001 to 2005. That office reports that currently there are more new abusers of prescription drugs than new users of any illicit drug…. Young people mistakenly believe prescription drugs are safer than street drugs…. There are more than 6.4 million prescription drug abusers in the United States.[16]

14. Since 1996, the incidence of opioid-based addiction in the United States of America has risen to the point of a national epidemic.[17]

15. In the late 1990s and early 2000s, a correlation was found between escalating crime and opioid addiction. The problem was traced to the increased use of time-released opioids like Oxycontin. At that time, the issue was prevalent in only a handful of states; those states had high

[15] **EXHIBIT 12**
[16] **EXHIBIT 18**
[17] **EXHIBITS 12, 18** and **EXHIBIT 20:** Ending America's Opioid Crisis. (n.d.). Retrieved from https://www.whitehouse.gov/opioids/

populations of chronic pain sufferers and higher rates of work-related accidents.[18] Criminals seized on the money-making potential and the illicit-drug market dramatically increased. Addicts were committing crimes and disrupting their families and communities. Both the House and Senate held hearings and programs were initiated to reverse the course of addiction resulting from Oxycontin and drugs like it. In addition to the federal government, states and professional organizations also participated in identifying the causes and plans to resolve the increasing addiction rates. Notwithstanding those efforts, the opioid epidemic spread to where it is now a national problem, crossing every population, rich poor, coastal interior, industrial rural, every race, every religion. In sum, any person is subject to potential injury by the opioid epidemic.[19]

16. Dispensing of synthetic opioids requires a written prescription under federal and state laws.[20]

17. In 2012, the number of opioid prescriptions written in the U.S. was 259 million resulting in sales of more than $9 billion.[21]

18. Several of the defendants have made settlements with government agencies related to opioids.[22]

19. Women are more likely than men to be prescribed opioids for conditions such as headache.[23]

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[18] **EXHIBIT 19:** 2002 Hearing before a subcommittee on appropriations; **EXHIBIT 20:** U.S. Senate, Committee on the Health, Education, Labor, And Pensions. (2002). Oxycontin: Balancing Risks and Benefits [S. Rept. from 107th Cong., Second sess.]. Washington, DC: US Government Printing Office.

[19] **EXHIBIT 21**

[20] 21 CFR §1306.11 2010.;

[21] **EXHIBIT 22:** Schirle, L., & McCabe, B. E. (2016). State Variation in Opioid and Benzodiazepine Prescriptions between Independent and Non-Independent APRN Prescribing States. Nursing Outlook, 64(1), 86-93. Retrieved from https://www.nursingoutlook.org/article/S0029-6554(15)00277-8/pdf.; **EXHIBIT 23:**To require the Food and drug Administration to Revoke the Approval of One Opioid Pain Medication for Each New Pain Medication Approved, S. 419, 116th Cong. (2019).

[22] F.R.E. Rule 201. The Court may take judicial notice of other judicial proceedings.

[23] **EXHIBIT 24:** Darnall, Beth D and Brett R Stacey. "Sex differences in long-term opioid use: cautionary notes for prescribing in women" Archives of internal medicine vol. 172,5 (2012): 431-2.

20. Female subjects, on average, have plasma of oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.[24]

21. It is estimated that one third of all opioid users are female and that two thirds of these women are of childbearing age; Almost 40% of women aged 15-44 years report receiving at least one opioid prescription in 2015.[25]

22. Among women in the U.S. who use opioids, an estimated 86% of their pregnancies are unintended.[26] Many women do not realize that they are pregnant.

23. Opiate drugs easily transfer cross the placenta to the fetus.[27] The placenta is an organ created by the embryo that allows the transfer of nutrients and oxygenated blood from the mother to the baby. Waste from the fetus transfers via the placenta to the mother. This is a symbiotic relationship that allows fetal growth and development.[28] Anything the mother ingests, or inhales is eligible to cross the placenta to the fetus.[29] Opioids are lipid (fat) based and easily transfer from mother to the baby. The developing fetal brain has a high lipid content and easily combines with the opioids circulating in blood.[30]

24. The transmission of opioids across the placenta is increased as gestation increases.[31]

25. Synthetic opioids cross the placenta more easily compared with semi-synthetic opiates.[32]

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[24] **EXHIBIT 25:** OXYCONTIN. Purdue Pharma LP; 2018, Http://app.purduepharma.com/xmlpublishing/pi.aspx?id=o

[25] **EXHIBIT 26:** Terplan, Mishka. "Women and the Opioid Crisis: Historical Context and Public Health Solutions." Fertility and Sterility, Volume 108, Issue 2, 195 – 199. https://www.fertstert.org/article/S0015-0282(17)30431-4/fulltext?rss=yes. 05 Mar. 2019.

[26] **EXHIBIT 27:** Ko, J. Y., Wolicki, S., & Barfield, W. (2017, March 10). Morbidity and Mortality Weekly Report (MMWR) 66(9); 242-245. Retrieved from https://www.cdc.gov/mmwr/volumes/66/wr/mm6609a2.htm.

[27] **EXHIBIT 28:** Kocherlakota, P. (2014). Neonatal Abstinence Syndrome. Pediatrics, 134(2). doi:10.1542/peds.2013-3524

[28] **EXHIBIT 29 -** Anand Declaration

[29] **EXHIBIT 29**

[30] **EXHIBIT 28**

[31] **EXHIBIT 28**

[32] **EXHIBIT 28**

26. The ease with which synthetic opioids can cross the blood-brain barrier of the fetus and the prolonged half-life of these drugs in the fetus may increase the risks of abnormal brain development[33] and worsen opioid withdrawal in infants after birth (NAS).[34]

27. The addictive nature of synthetic opioids can transmit to a fetus in utero during gestation. [35]

28. Prescription opioid use in pregnancy is strongly associated with neonatal complications.[36]

29. Opioid use can disrupt fetal brain development at any stage during pregnancy, except the first 10-14 days after conception.[37]

30. The prevalence of opioid abuse or dependence among pregnant women in the United States has increased from 1.7 per 1000 delivery admissions in 1998 to 3.9 per 100 delivery admissions in 2011.[38]

31. Recent figures demonstrated almost a 40-fold increase in the number of infants presenting with opioid withdrawal or neonatal abstinence syndrome (NAS) at birth.[39]

32. Neonatal abstinence syndrome is a constellation of symptoms suffered by newborn infants exposed to opioids in utero. Clinically significant NAS most commonly results from prolonged exposure to opioids, but symptoms of neonatal withdrawal have also been noted after short-term therapy.[40]

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[33] **EXHIBIT 30:** Hu S, Sheng WS, Lokensgard JR, Peterson PK. Morphine Induces Apoptosis of Human Microglia and Neurons. *Neuropharmacology* 2002; 42:829-36.
[34] **EXHIBIT 29**
[35] **EXHIBIT 29**
[36] **EXHIBIT 29**
[37] **EXHIBIT 29**
[38] **EXHIBIT 27**
[39] **EXHIBIT 31:** Yuan, Q., Rubic, M., Seah, J., Rae, C., Wright, I. M., Kaltenbach, K., Oei, J. L. (2014). Do Maternal Opioids Reduce Neonatal Regional Brain Volumes? A Pilot Study. *Journal of Perinatology*, 34(12), 909-913. doi:10.1038/jp.2014.111
[40] **EXHIBIT 32:** Hill, Timothy B. CMS. Neonatal Abstinence Syndrome: A Critical Role for Medicaid in the Care of Infants. Jun. 11, 2018. https://www.medicaid.gov/federal-policy-guidance/downloads/cib060818.pdf

33. By 2012, on average, one NAS-affected infant was born every 25 minutes in the United States.[41] In 2019, one NAS-affected baby is born every 15 minutes.[42]

34. Opioid-exposed infants are typically born with small head circumference, low birth weight, respiratory and feeding difficulties, seizures, neural tube defects, cleft palate, and visual disturbances which, are recognized as a complication of gestational opioid exposure.[43] Long-term outcomes beyond the initial NAS diagnosis are concerning. A substantial number of these children demonstrated neurodevelopmental, behavioral, and attention problems.[44]

35. Both long-term and short-term in utero exposure to opioids presents dangers to the developing child.[45]

36. NAS and OUD can occur with both long-term and short-term use of opioid use by the mother. Brain damage resulting from human opioid exposure[46] (duration and dose) is not well known. This means that a high dose short-term course could be more harmful than a long-term low dose opioid course. Science is unlikely to resolve this issue without required fetal testing. This is why preventing in utero exposure is the key to abatement.[47]

37. Prenatal exposure to opioids may decrease full brain and basal ganglia volumes in otherwise healthy newborn infants.[48]

38. Risks of sudden infant death syndrome (SIDS) in preterm infants with prenatal opioid exposure are increased because of the changes in normal infant sleeping patterns, depressed respiration or responses to hypoxia (low oxygen levels).[49]

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[41] **EXHIBIT 33:** GAO. Newborn Health: Federal Action Needed to Address Neonatal Abstinence Syndrome. GAO-18-32. Oct. 2017.
[42] National Institute on Drug Abuse. (2019, January 22). Dramatic Increases in Maternal Opioid Use and Neonatal Abstinence Syndrome. Retrieved from https://www.drugabuse.gov/related-topics/trends-statistics/infographics/dramatic-increases-in-maternal-opioid-use-neonatal-abstinence-syndrome
[43] **EXHIBIT 31**
[44] *Id.*
[45] **EXHIBIT 29**
[46] **EXHIBIT 30**
[47] **EXHIBIT 29**
[48] **EXHIBIT 31**

39. Preschool aged children, exposed to opiates, are known to the experience one or more of the following symptoms: mental and motor deficits, cognitive delays, hyperactivity, impulsivity, attention deficit disorder, behavior disorder, aggressiveness, poor social engagement, failure to thrive (socially), and short stature.[50]

40. School-age children exposed to opiates may experience one or more of the following cognitive/behavioral deficits: verbal impaired performance, impaired reading and arithmetic skills, for mental and motor development, memory and perception problems, attention deficit hyperactivity disorder, developmental delays, speech problems, language disorders, impaired self – regulation, school absence, reduced executive functions and behavioral regulation, for responses to stressful stimulations situations, poorly developed confidence or efficacy, impaired task performance, depressive disorder, and substance abuse disorder.[51]

41. Compared with nonexposed children, the children of drug-using parents are more than twice as likely to develop an alcohol and/or drug abuse disorders themselves as an adult.[52]

42. There is a continuous negative effect on infants/children related to prenatal-opioid exposure over time.[53]

43. Methadone has become the standard of care for pregnant women with opioid addiction.[54]

44. Methadone treatment is related to the increase incidence of NAS.[55]

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[49] **EXHIBIT 34:** Ratliff, Brittany V., "Prevalence of Communication Disorders in Children with Neonatal Abstinence Syndrome on School Speech-Language Pathology Caseloads: A National Survey" (2017). *Electronic Theses and Dissertations.* Paper 3204. http://dc.etsu.edu/etd/3204.
[50] **EXHIBIT 34**
[51] **EXHIBIT 34**
[52] **EXHIBIT 34**
[53] **EXHIBIT 35:** Nygaard, E., Moe, V., Slinning, K., & Walhovd, K. B. (2015). Longitudinal cognitive development of children born to mothers with opioid and polysubstance use. Pediatric Research, 78(3), 330-335. doi:10.1038/pr.2015.95
[54] **EXHIBIT 29**
[55] **EXHIBIT 29**

45. Gaps in medical knowledge still exists with NAS, including a lack of clarity and consistency in how the syndrome is defined, measured, and managed.[56]

46. NAS and OUD remain poorly understood.[57]

47. In the United States of America, between 2000 and 2012, NICU admissions increased more than fivefold, resulting in annual costs from $61 million and 67,869 hospital days (2003) to nearly $316 million and 291,168 hospital days (2012).[58] According to the CDC, once discharged from the NICU, first year Medicaid costs of opioid exposed babies in utero in 2015, ranged from $159,000 to $238,000.[59]

48. A recent study concluded that the opioid exposure to a developing animal brain may cause epigenetic modifications that makes addiction in that individual more likely. This modification, no matter the sex of the exposed fetus, is thought to pass on in their genetic material to their offspring.[60]

49. The number of NAS/OUD children in the U.S. is estimated by the CDC to be hundreds of thousands.[61] But when mothers stop taking opioids during pregnancy the fetus may go through in utero withdrawal, so those babies cannot be counted.[62] Only 28 states report NAS/OUD births.[63]

50. It is thought that in utero opioid exposures occurring between 3 weeks and 12 weeks after conception carry the highest risks for congenital defects.[64] The long-term risks of opioid

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[56] **EXHIBIT 29**
[57] **EXHIBIT 36:** Newborn Health Federal Action Needed to Address Neonatal Abstinence Syndrome. USGAO. Oct. 2017
[58] **EXHIBIT 32**
[59] **EXHIBIT 37:** Mihali, R. Medical Costs of Addicted Newborns: Neonatal Abstinence Syndrome." NC Drug Court. http://www.ncdrugtreatmentcourts.com/NAS.html
[60] **EXHIBIT 38:** Yohn, N. L., Bartolomei, M. S., & Blendy, J. A. (2015). Multigenerational and transgenerational inheritance of drug exposure: The effects of alcohol, opiates, cocaine, marijuana, and nicotine. Progress in Biophysics and Molecular Biology, 118(1-2), 21-33. doi: 10.1016/j.pbiomolbio.2015.03.002
[61] **EXHIBIT 39:** Ko JY, Patrick SW, Tong VT, Patel R, Lind JN, Barfield WD. Incidence of Neonatal Abstinence Syndrome — 28 States, 1999–2013. MMWR Morb Mortal Wkly Rep 2016; 65:799–802. DOI: http://dx.doi.org/10.15585/mmwr.mm6531a2
[62] **EXHIBIT 39**
[63] **EXHIBIT 39**

exposure during the 14-day period following conception are currently unknown, although the limited data available suggests that opioid will not result in fetal injury from in utero opioid exposure.[65]

51. Urine pregnancy tests are reliable and relatively inexpensive.[66] They provide an immediate test result. Blood pregnancy tests are more expensive and require lab analysis, and the test results are not immediately available.[67]

52. The closer a pregnancy test is taken from the completion of the menstrual cycle, the less likely it is to be accurate.[68]

53. If a woman has a negative urine pregnancy test and she is in fact pregnant, it is reasonable to conclude the pregnancy is very early, less than a few days. By limiting the opioid prescription to seven days, putative risks to such a fetus would be minimal. If the woman needs more opioids, she would return to her physician for a pain discussion and a second pregnancy test. If negative, it can be safely concluded the woman is not pregnant. If pregnant, a medication change to non- opioid analgesics can be made to deal with the pain issue.[69]

54. The standard of care for prescribing opioids changed as a result of the defendant manufacturers marketing campaigns which promoted pain resolution and created pain as a 5th vital

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[64] **EXHIBIT 30, EXHIBIT 40:** Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol* 2011; 204:314 e1-11.; **EXHIBIT 41:** Rayburn WF, Brennan MC. Periconception warnings about prescribing opioids. *Am J Obstet Gynecol* 2011; 204:281-2.; **EXHIBIT 42:** Kallen B, Reis M. Use of tramadol in early pregnancy and congenital malformation risk. *Reprod Toxicol* 2015; 58:246-51.; **EXHIBIT 43:** Interrante JD, Ailes EC, Lind JN, et al. Risk comparison for prenatal use of analgesics and selected birth defects, National Birth Defects Prevention Study 1997-2011. *Ann Epidemiol* 2017; 27:645-53 e2.; **EXHIBIT 44:** Lind JN, Interrante JD, Ailes EC, et al. Maternal Use of Opioids During Pregnancy and Congenital Malformations: A Systematic Review. Pediatrics 2017; 139;

[65] **EXHIBIT 45:** Gallego MJ, Porayette P, Kaltcheva MM, Meethal SV, Atwood CS. Opioid and progesterone signaling is obligatory for early human embryogenesis. Stem Cells Dev 2009; 18:737-40.; **EXHIBIT 46:** Brennan MC, Rayburn WF. Counseling about risks of congenital anomalies from prescription opioids. Birth Defects Res A Clin Mol Teratol 2012; 94:620-5.; **EXHIBIT 47:** Dehghani L, Sahraei H, Meamar R, Kazemi M. Time-dependent effect of oral morphine consumption on the development of cytotrophoblast and syncytiotrophoblast cells of the placental layers during the three different periods of pregnancy in Wistar rats. *Clin Dev Immunol* 2013; 2013:974205.

[66] **EXHIBIT 48:** Werntz Declaration

[67] **EXHIBIT 48**

[68] **EXHIBIT 48**;

[69] **EXHIBIT 29**

sign. The marketing campaigns were successful in the sense that prescriptions for opioids increased tremendously and prescriptions were given for conditions not typically requiring opioids.[70]

55. The CDC has also issued guidelines to limit/control prescribing opioids for chronic pain.[71]

56. Professional medical societies devoted to the healthcare of women and children have recently issued guidelines on prescribing opioids to women and children.[72]

57. A teratogen is an agent that can disturb the development of the embryo or fetus. Teratogens halt the pregnancy or produce a congenital malformation (a birth defect). Classes of teratogens include radiation, maternal infections, chemicals, and drugs.[73]

58. The iPledge Program was established in Oct. 2010 and closely monitors women prescribed isoretinoin (Accutane) because of its teratogenic effects.[74] It was developed by the isoretinoin pharmaceutical manufacturers group under the guidance of the FDA.[75] It protects women from causing fetal injuries when taking this prescription medication. It is an established and successful program.[76]

59. The 2013 National Drug Control strategy focuses on four main pillars, each designed to intervene at a critical juncture in the process of diversion and abuse: education for prescribers,

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[70] **EXHIBIT 49:** Dept. of Veterans Affairs. *Pain as the 5th Vital Sign Toolkit*. Oct. 2000.
[71] **EXHIBIT 50:** Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49. DOI: http://dx.doi.org/10.15585/mmwr.rr6501e1
[72] **EXHIBIT 51:** Patrick, S. W., & Schiff, D. M. (2017). A Public Health Response to Opioid Use in Pregnancy. Pediatrics, 139(3). doi:10.1542/peds.2016-4070. Retrieved from https://pediatrics.aappublications.org/content/139/3/e20164070; **EXHIBIT 52:** The American College of Obstetricians and Gynecologists. (2017). Opioid Use and Opioid Use Disorder in Pregnancy. ASAM. Number 711. Aug. 2017.
[73] **EXHIBIT 53:** *(2005). Stedman's medical dictionary for the health professions and nursing. Philadelphia :Lippincott Williams & Wilkins,*
[74]Risk evaluation and Mitigation Strategy (REMS). The iPledge Program. https://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm234639.pdf; **EXHIBIT 54:** iPledge Patient Introductory Brochure. Nov. 2016.
[75] **EXHIBIT 54**
[76] **EXHIBIT 54**

patients, and parents; prescription drug monitoring programs; proper medication disposal; and effective enforcement.[77]

60. There are many pain-relieving medications other than opioids.[78]

Respectfully submitted,

/s/ Celeste Brustowicz
COOPER LAW FIRM
Celeste Brustowicz
Stephen Wussow
1525 Religious Street
New Orleans, Louisiana 70130
Telephone: 504-399-0009
Facsimile: 504-309-6989
Email: cbrustowicz@sch-llc.com

CREADORE LAW FIRM
Donald E. Creadore
450 Seventh Avenue, Suite 1408
New York, New York 10123
Telephone: 212-355-7200
Email: donald@creadorelawfirm.com

THOMPSON BARNEY LAW FIRM
Kevin W. Thompson
David R. Barney, Jr.
2030 Kanawha Boulevard, East
Charleston, WV 25311
Telephone: 304-343-4401
Facsimile: 304-343-4405
Email: kwthompson@gmail.com

MARTZELL, BICKFORD & CENTOLA
Scott R. Bickford

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Spencer R. Doody
338 Lafayette Street
New Orleans, Louisiana 70130
Telephone: 504-581-9065
Facsimile: 504-581-7635
Email: srb@mbfirm.com

THE LAW OFFICES OF KENT HARRISON ROBBINS, P.A.
Kent Harrison Robbins
242 Northeast 27th Street
Miami, Florida 33137
Telephone: (305) 532-0500
Facsimile: (305) 531-0150
Email: khr@khrlawoffices.com
Secondary: ereyes@khrlawoffices.com
Tertiary: assistant@khrlawoffices.com

CERTIFICATE OF SERVICE

Service of the foregoing was accomplished through the Court's Electronic Filing System this 28th day of March, 2019,

/s/ *Celeste Brustowicz*
Celeste Brustowicz