BEFORE THE DIVISION OF CONSUMER PROTECTION OF THE UTAH DEPARTMENT OF COMMERCE

Expert Report of Sheila Weiss, Ph.D. FISPE

In The Matter of Purdue Pharma L.P. et al., DCP Case No. 107102 (Utah)

I. Qualifications

I hold a PhD in epidemiology and completed a post-doctoral fellowship in Pharmacoepidemiology and Regulatory Sciences at FDA. I was previously a tenured Professor at the University of Maryland Baltimore (Schools of Pharmacy and Medicine), where I also served as the founding director of the Center for Drug Safety. During that time, I held a number of appointments including Adjunct Professor at Johns Hopkins Bloomberg School of Public Health, Visiting Scientist at the National Cancer Institute, Research Associate at the Veterans Administration, and Special Government Employee at the Food and Drug Administration (FDA).

Prior to joining the faculty at the University of Maryland, I was an employee of FDA, where I worked on developing and testing methodologies and drafting guidance documents concerning the use and interpretation of epidemiologic data for regulatory decision making. I served as Principal Investigator on an FDA (sub)contract to evaluate the potential utilization of existing databases, including of PDMP data, for monitoring ER/LA opioid utilization within the context of a Risk Evaluation and Mitigation Strategy (REMS). I also worked with the State of Delaware Department of Public Health and Druglogic, Corp. to develop a platform to monitor and analyze trends in the prescribing and dispensing of scheduled prescription drugs upon launch of the Delaware PDMP. Prior to my doctorate, I managed the data collection and analyses for several large population-based surveys including the Massachusetts Women's Health Survey and the Normative Male Aging Study. In addition to writings and lectures, I have been a peer reviewer for various journals including the *Lancet*, *British Medical Journal*, *Journal of the American*

Medical Association, *Drug Safety*, and *Pharmacoepidemiology and Drug Safety*. A fuller statement of my qualifications is set forth in the attached CV.

I am expected to testify based on my background, training, knowledge and experience in epidemiology, and particularly pharmacoepidemiology and drug safety, as well as my knowledge and experience related to the regulatory approval and labeling process for prescription pharmaceuticals which, in turn, governs their marketing, and the process around the implementation and assessment of PDMP and REMS programs, and materials reviewed related to the subject matter at issue. The subject areas I am expected to address and the opinions I am expected to offer are discussed more fully below. At this time, I understand that there has been little to no discovery of Utah documents or witnesses and that no expert reports in support of Utah's allegations have been provided. I reserve my right to supplement and/or amend my opinions as a result of ongoing discovery and/or additional or different scientific information becomes available, and also as may be needed to respond to information or opinions asserted by Utah's fact and expert witnesses.

II. Epidemiological methods

Epidemiology is the study of the distribution and causes of disease in populations. Pharmacoepidemiology is a specialty area within epidemiology that focuses on the utilization and effects of pharmaceutical and other regulated medical products. Among other things, it seeks to understand whether there is a basis for finding a causal relationship between a drug and a medical outcome.[1]

[1] Weiss Smith S. *Pharmacoepidemiology.* In: Encyclopedia of Epidemiology. Editor: Boslaugh S. Sage Publications Inc. October 2007.

A. Study Designs

Scientists looking to answer questions regarding the relationship between a drug and a particular health effect may consider different types of studies, employing different designs and statistical methods. These include randomized, double-blind, placebo controlled clinical trials (RCTs), and both prospective and retrospective observational studies of various types (case-control, crossover, and cross-sectional), each of which has its own strengths but also limitations. Scientists generally first seek to determine whether a study result is statistically significant, meaning that it is unlikely to be due to chance (random error) based on a pre-specified threshold. After that, scientists consider the result to understand whether or not the study is internally valid; that it represents a true association rather than an artifact of the design or conduct of the study. Then it is necessary to consider the finding within a clinical or medical context, as small differences may be statistically significant but not clinically meaningful. Finally, scientists must consider whether the finding is externally valid; that the results may be extrapolated to a different population or can be generalized to a larger population from which the study population was identified.

Even when a finding produces a statistically significant result, it may not represent a causal association. Findings may be the result of bias(es) or unadjusted confounding.[2] This is particularly so if the relative risk is small, the confidence intervals around the statistical result is wide, and/or if the finding is for a non-primary endpoint of the study as designed.

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[2] There are many types of bias that may impact the reliability and interpretability of epidemiological data. Among these are sampling bias, recall bias, selection bias, confounding by indication and severity, reporting bias, and surveillance bias. Relatedly, there are many potential confounding factors including demographics, other physical or mental conditions, the use of concomitant medicines, the use of illicit drugs and other substances, socio-economic factors, and/or pre-existing exposure to the thing or problem being tested.

B. Totality of Evidence

When evaluating the potential that a statistical association represents an underlying cause-effect relationship, epidemiologists consider the "totality of evidence." Not all studies carry the same weight. Rather, there is a "hierarchy of evidence," such that data from different sources may be assessed differently.

RCTs are generally at the top of the hierarchy and deemed the gold standard for establishing cause and effect between a drug and a specific benefit or risk. Such trials, however, may be difficult or impractical in many situations – such as when the effect being studied occurs rarely, when long periods of observation are required and/or when it is either ethically or practically unacceptable to expect patients to be on placebo rather than receiving treatment.

Below RCTs are quasi-experimental studies and observational studies. Quasi-experimental studies involve manipulation of a study factor (experimental variable) but without randomization of study subjects. Observational studies involve measuring exposures and assessing what occurs among those with and without exposures without manipulation of the factor (exposure) of interest. Observational studies can be conducted by collecting data through surveys and interviews, or by repurposing existing data. Over the past three decades, epidemiological research has increasingly utilized large existing data-sets (public and private) that are collected for other purposes unrelated to that research. Using preexisting data can decrease the time and cost of research and make it easier to accumulate data on large numbers of patients. But the validity of the information extracted is subject to all of the internal limitations, restrictions and errors found in the underlying dataset.

In particular, one must be mindful of attributing a level of reliability or precision to the data that it was never meant to have given its original purpose. For example, datasets that track prescriptions written for insurance purposes provide an often imprecise proxy for actual

medication use in studies aimed at assessing the impact of exposure to a drug. This is particularly problematic in drug studies, where the reliability of the proxy measure (e.g., the probability a person fills a written prescription and then takes the medication) can vary by factors related to the outcome, resulting in a spurious association. While some observational data are generally given more weight than others, because of their design and data limitations, observational studies, at most, can determine if there is a statistical association between two things. Association and causation are not the same and observational studies typically cannot lead to a causal inference.

Ecological studies are observational studies at the group or population, rather than individual level. Ecological studies correlate group or population characteristics with outcome rates. Ecological studies may also be used to explore trends over time. However, findings at the group level may not represent what is occurring at the individual level. Ecological studies are useful for generating hypotheses rather than testing them.

Some research questions cannot be answered using existing databases and may instead require original data collection, such as surveys. Survey studies, like clinical trials, must be very carefully designed and conducted with strict adherence to data collection methods to prevent the introduction of bias within a single time period, and over time. Any changes made by design or inadvertently introduced at any stage of the study can impact the results and their interpretation. Even the method by which people are selected into the survey can introduce bias within time periods and also over time. Changes in survey methodology over time, whether an abrupt change that creates a break or a gradual implementation that produces a more subtle impact, limits the ability to analyze trends over time.

At the bottom of the evidentiary ladder are case reports and case series. These are anecdotal reports. They can be useful for formulating hypotheses, but not drawing a causal inference.

Irrespective of the type of study, the protocol design, study site, means of patient selection, determinations related to which factors are measured and how they are measured, what happens during the course of the study, and even the choice of statistics can have a marked impact on results. Depending on the degree of bias, and its direction, as well as unmeasured confounding, the results may be unreliable or false, leading to erroneous conclusions. Small effects, even when statistically significant, may be the results of residual or unrecognized confounding. In addition, chance (random error) can produce results that differ from the underlying truth. Finally, conclusions drawn from the results of a study need to take into account the study design itself. For example, sequential cross-sectional surveys provide snapshots in time while a longitudinally study which follows the same people measures changes over time. Scientists must consider the totality of evidence, including information external to the data set across scientific fields and medicine, before drawing a causal inference or attempting to apply results from a particular study to a broader or different population.

C. Bradford Hill

The Hill (or Bradford Hill) Criteria are a set of factors that are often used to guide the process of causal inference; whether a statistical association [between an exposure and outcome] represents an underlying case-effect or *causal* relationship.[3] The Bradford Hill Criteria are:

- Strength of Association: This refers to the magnitude of the effect (effect size). With a strong association, it is harder to implicate bias and/or uncontrolled confounding as alternative explanations. This criterion is less persuasive when the association is based on a very small numbers of exposed cases.

- Consistency: Observing similar findings among different populations, in studies of using different study designs, and at different times strengthens that argument for causality.

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[3] Hill. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine. 1965; 58(5): 295-300

- Specificity: The condition is clinically unique and is not seen in the absence of that particular exposure.

- Temporality: The exposure must precede the event (disease) in time. For diseases that are slow to manifest and/or require diagnostic testing to identify, it may be difficult to confirm the temporality.

- Dose-Response, or Biological Gradient: A dose-response, where the association increases with increasing dose (or cumulative dose), can be suggestive of a causal relationship.

- Biological Plausibility: There is an underlying biological mechanism that can potentially explain the relationship between exposure and event.

- Coherence: There the epidemiological findings are compatible with findings from other fields of science (i.e., laboratory research, animal studies, genetics, biology).

- Experimental Evidence: Experimental evidence, where it exists, can further support or refute a theory of causation.

- Analogy: In some circumstances, it is reasonable to compare to a newly observed association to a causally established relationship

These criteria remain relevant for purposes of this analysis for several reasons, including but not limited to: (1) the lack of specificity (non-medical use, misuse, abuse, addiction, "opioid use disorder" and death) in the outcomes allegedly caused by Purdue's (and their co-defendants) prescription opioids; (2) the lack of even a temporal connection between certain conduct alleged and the harms that Plaintiffs claim are causally related (as well as the fact that Plaintiffs appear to deliberately and inappropriately conflate temporality and causality); (3) lack of consistency in outcome across studies with different designs, as well as across population demographics and geographic locations; (4) changes in background rates of different drug exposures and addiction, as well as varying trends in patters of drug abuse and misuse involving multiple substances, such that findings are often not specific.

III. Publicly Available Data Sources

Much of the data related to drug abuse and misuse in general, and prescription opioid abuse and misuse in particular, comes from retrospective observational data, with limited ability to detect (let alone accurately assess causality regarding) the outcomes at issue. In addition, many of the observations made by Plaintiffs' experts as well as others discussing prescription opioid abuse and its consequences rely on large governmental datasets, which were designed to provide relatively high level data for population monitoring and/or law enforcement. They have certain strengths as well as limitations, including that they are not designed to prove or disprove the allegations raised. A brief summary of what they are as well as key features and limitations may be of use.

A. National Survey of Drug Use and Health (NSDUH)

NSDUH is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services. It measures the use of alcohol, tobacco, illegal drugs, and prescription drugs, and the prevalence and treatment of mental disorders, including co-occurring substance use. It surveys non-institutionalized U.S. civilians 12 years of age and older. Its chief methodology is in-person interviews. The years covered are 1971 to the present. Information is available at the national, state, and sub-state levels. The state and sub-state level estimates are more limited than the national data due to the sample size issues including sampling error, though this does vary over time as the survey methods have evolved to address this issue. State level estimates are calculated based on 2 years of results (e.g., 2014-2015) and sub-state level estimates are derived from 3 survey years (e.g., 2014-2016). The Survey underwent a substantial redesign in 2002 and then again in 2015, making results after the changes not comparable to results from previous years.[4] Even when particular questions remain the same,

[4] Substance Abuse & Mental Health Servs. Admin., National Survey on Drug Use and Health, https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health (last visited

other changes made to the survey may still impact them. Because of this and other changes, data on prescription drug misuse are generally presented in separate tranches, one 2002-2014 and one 2015 and beyond. The data are generally deemed not amendable to trend analysis across these time periods.[5]

B. CDC Wonder

CDC Wonder is an on line repository of publicly available database that are used extensively for epidemiological research and public policy. CDC Wonder is sponsored by the Centers for Disease Control.[6] These databases include vital statistics (mortality, births, fetal deaths) as well as measures and survey data on a wide range medical conditions and public health concerns. Some of the databases have limitations and/or restrictions in what is publicly available. Additionally, even when available cells may be suppressed due to small numbers.

C. Treatment Episode Data Sets

SAMHSA compiles annual data regarding publicly-funded substance abuse treatment, for those 12 years and older, that it receives from individual states into national-level research databases; Treatment Episode Data Set of Admissions (TEDS-A) and Treatment Episode Data Set of Discharges (TEDS-D).[7] TEDS-A data goes back as far as 1992, while TEDS-D database begins in 2000. Data include demographic information (e.g., age, sex, race/ethnicity), and substance abuse factors (e.g., substances used, age at first use, route and frequency of use). Substances used

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May 8, 2019). *See also* Substance Abuse & Mental Health Servs. Admin., 2015 National Survey on Drug Use and Health: Summary of the Effects of the 2015 NSDUH Questionnaire Redesign: Implications for Data Users (2016), http://www.samhsa.gov/data/sites/default/nsduh-trendbreak-2015.pdf.

5 Substance Abuse & Mental Health Servs. Admin., 2015 National Survey on Drug Use and Health: Summary of the Effects of the 2015 NSDUH Questionnaire Redesign: Implications for Data Users (2016), http://www.samhsa.gov/data/sites/default/nsduh-trendbreak-2015.pdf.

6 CDC Wonder Online Databases. https://wonder.cdc.gov (last visited July 8, 2019).

7 SAMHSA Treatment Episodes Data Set. https://www.datafiles.samhsa.gov/study/treatment-episode-data-set-admissions-teds-teds-2015-2017-nid18477 (last visited July 11, 2019).

are limited to the primary, secondary, and tertiary substances that led to the admission rather than an inventory of all substances used and/or abused. The sampling frame is an admission (or discharges for TEDS-D), rather than an individual person, so the same person may contribute multiple records. Also, there are state variations in defining the facilities and admissions for which data are reported.

D. Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS)

The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System was developed by Purdue as part of its efforts to understand and prevent abuse and misuse of prescription medications. In 2006, Purdue transferred the system to Denver Health and Hospital Authority, a political subdivision of the State of Colorado, and it has since run entirely independently. RADARS' Poison Center Program captures intentional and unintentional exposures reported to 50 of the 55 US regional poison centers, and documents information regarding patient demographics, drug exposure characteristics, products involved, route of administration, and medical outcome.[8]

E. The Drug Abuse Warning Network (DAWN)

DAWN is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services. "Legacy DAWN," for which data sets are available from 2004 to 2011, was a "nationally represented public health surveillance system that continuously monitor[ed] drug-related visits to hospital emergency departments (EDs)."[9] It was used to "monitor trends in drug misuse and abuse, identify the emergence of new substances and drug combinations, assess health hazards associated with drug abuse, and estimate

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[8] Poison Center, RADARS® System, https://www.radars.org/radars-system-programs/poison-center.html (last visited May 8, 2019).

[9] Drug Abuse Warning Network (DAWN), https://www.datafiles.samhsa.gov/study-series/drug-abuse-warning-network-dawn-nid13516 (last visited May 8, 2019).

the impact of drug misuse and abuse on the Nation's health care system."[10] Its methodology involved direct review of medical charts from "all non-federal, short-stay, general medical and surgical hospitals in the United States that operate one or more EDs 24 hours a day, 7 days a week."[11] In 2003, major changes to DAWN resulted in a new case definition for drug-related ED visits eligible for DAWN. As a result, comparisons cannot be made between DAWN data prior to 2002 and DAWN data from 2004 to 2011.[12]

F. Monitoring the Future Report

Monitoring the Future is sponsored by the University of Michigan Institute for Social Research. It is "an ongoing study of the behaviors, attitudes, and values of American secondary school students, college students, and young adults. Each year, a total of approximately 50,000 8th, 10th and 12th grade students are surveyed (12th graders since 1975, and 8th and 10th graders since 1991). In addition, annual follow-up questionnaires are mailed to a sample of each graduating class for a number of years after their initial participation. The Monitoring the Future Study has been funded under a series of investigator-initiated competing research grants from the National Institute on Drug Abuse, a part of the National Institutes of Health."[13]

G. DEA Drug Threat Assessment Reports

The National Drug Threat Assessment (NDTA) is an annual report produced by the U.S. Drug Enforcement Administration (DEA), U.S. Department of Justice (DOJ). (Publicly available archives show publication beginning in 2003; in 2011 and before, the report was published by the

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[10] *Id.*

[11] Drug Abuse Warning Network (DAWN-2011), https://www.datafiles.samhsa.gov/study/drug-abuse-warning-network-dawn-2011-nid13586 (last visited May 8, 2019).

[12] *Id.*

[13] Monitoring the Future (Mar. 4, 2019), http://www.monitoringthefuture.org/ (last visited May 8, 2019).

now-closed National Drug Intelligence Center, U.S. DOJ.[14]) The NDTA is "a comprehensive strategic assessment of the threat posed to the United States by domestic and international drug trafficking and the abuse of illicit drugs."[15] It relies on federal, state, local, and tribal law enforcement reporting; public health data; open source reporting; and intelligence from other government agencies.[16]

H. Utah's Public Health Indicator Based Information System (IBIS)

Sponsored by Utah's Department of Public Health, IBIS is an online resource for epidemiological data at the state and local levels. IBIS contains raw data, epidemiological statistics, and reports on health and disease, health care utilization and services, and environmental risks. Certain data are available for the state as a whole, while others are available at the level of the local health district or small area designation. Available IBIS resources include public health datasets, publications, and online reports. Among the key "health indicators" available on the IBIS portal are mental illness and substance use.

I. Utah Poison Control Center (University of Utah)

The Utah Poison Control Center (UPCC) provides 24-hour expert assistance on poisonings to the public and healthcare professionals. The Poison Center collects and reports information on the exposure/poison, patient age, type and location of treatment, and medical outcome, UPCC publishes a variety of reports on their website including annual and special-topic reports (e.g. common poisoning substances, e-cigarettes).[17] UPCC reports specific to opioid product poisoning

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[14] U.S Department of justice Archives: Publications, https://www.justice.gov/archive/ndic/topics/archived2.htm#NDTAs (last visited May 8, 2019).

[15] U.S. Department of Justice Archives: Publications, National Drug Threat Assessments, https://www.justice.gov/archive/ndic/topics/ndtas.htm (last visited May 10, 2019).

[16] U.S Drug Enforcement Administration, 2018 National Drug Threat Assessment (2018), https://www.dea.gov/sites/default/files/2018-11/DIR-032-18%202018%20NDTA%20final%20low%20resolution.pdf.

[17] https://poisoncontrol.utah.edu/toxictrends.php (last viewed July 11, 2019)

calls for the years 2015-17 are also posted online. The reports provide specific incident counts related to single and combination oxycodone and hydrocodone products, tramadol, heroin and buprenorphine, as well as information for other substances including methadone and fentanyl. In 2017, the majority of oxycodone (56%) and hydrocodone (85.6%) cases involved combination products.[18]

IV. Analytical Challenges Posed By Available Data

There are a substantial range of scientific limitations, resulting from both the diverse nature of compounds categorized as opioids, as well as inconsistency and variability in how the alleged harms at issue are described and analyzed, and including a number of biases and confounders, that preclude the sweeping conclusions that have been drawn from these data. A non-exhaustive list of these issues includes:

- Opioids refer to both prescription and even non-prescription medicines in extended release (ER/LA) and immediate release (IR) formulations, as well as transdermal patches and other delivery modes. Opioids also include illicit drugs for which there are no recognized legitimate medical uses.

- The term misuse, which only applies to prescription medicines, is broad and includes concepts independent of abuse and addiction. For example, taking a medicine holiday or skipping a dose meets the definition of misuse. There is no comparable concept for illicit opioids, where any use is categorized as abuse.

- Most prescription opioids are approved for the treatment of pain. However, opioids may also be prescribed as a treatment for opioid addiction. Methadone is indicated for both. Buprenorphine is available alone or in combination with naloxone as a treatment for opioid addiction.

- Data sets that report overdose deaths or that rely on Medical Examiner information typically provide identifying information by the therapeutic class (e.g., "prescription pain reliever") or compound ("opioid"). They are not able to distinguish among many products that contain the same active ingredient, let alone identify any specific brand.

- Data sets that report outcomes related to prescription opioids vs. illegal drugs that are opioid compounds (e.g. heroin) typically fail to differentiate between lawfully obtained

[18] Opioids. Data from the Utah Poison Control Center (UPCC). 2015. https://poisoncontrol.utah.edu/images/trend17_opioid.pdf (last viewed July 11, 2019)

prescription medicines used by patients and prescription medicines that have been diverted by non-patients for intentional misuse.

- Data sets that purport to look at use of prescription opioids as precursors to use of other drugs, like heroin and fentanyl, may not distinguish between prior users and prior misusers of the prescription medicine, or abuse of other substances. They also may not identify how proximate the prescription use was to the illicit use, thus preventing any clear understanding of how a "transition" occurred.

- There is widespread polysubstance abuse in the U.S. population and a lack of data on most individuals' complete substance and drug exposure history.

- There have historically been no uniform standards for how medical examiners assign cause of death, with wide variations at the state, county and even individual examiner level, and changes in methods and reporting practices over time, which impacts the reliability of these data in multiple ways including: (a) under-reporting of suicide; (b) under-reporting of certain classes of drugs not historically within the screening protocols (e.g., fentanyl); (c) under-reporting of polysubstance deaths; (d) inconsistency, inaccuracy and bias in drug selected as cause of death.

- Surveys may ask different questions when asking people about use of illicit drugs versus prescription medicines, preventing direct comparisons. Further, people may answer questions about illicit drug vs. prescription drug use differently.

- Definitional inconsistency limits the interpretability of data. Terms including "misuse," "dependence," "addiction," and "opioid use disorder (OUD)," are defined and used differently at different times, in different data sets, by different users.

- There are data gaps, especially below a national level of reporting and certainly at a county level. There are also limited data for early years and problems establishing trends across the full time period of interest due to changes in survey design.

- Even at the national level, sampling error and design effects impact the precision of the estimates and limit the ability to make valid comparisons within and across survey years. This is particularly important for less common (low frequency) exposures.

- Sampling bias, selection bias, recall bias, observer bias, and reporting bias[19] all potentially impact the dataset, as do confounding factors including population demographics, other physical or mental disease processes, the use of other drugs, socio-economic variables, and/or pre-existing exposures.

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[19] Publicity, for example, may impact patients, health care providers, and others (such as medical examiners) by stimulating both the reporting of certain adverse outcomes and attribution of those outcomes to a particular drug or class of drugs. It also may reduce the reporting of other events or reduce the number of events attributed to other causes, thus adding to the problem of making comparisons across different drugs or classes of drugs and over time.

V. Pain Is Common, Often Severe, and Increases with Age

An estimated 50 million Americans suffer from chronic pain, among which 19.6 million are categorized as having high impact pain.[20] The prevalence of chronic pain increases with increasing age from 7.0% among adults aged 18-24 to over 27% among adults aged 45-84, and 33.6% among adults aged 85 years and older. Among adults aged 65 years and older, 42.5% those insured with both Medicaid and Medicare reported chronic pain, including 24.3% with high impact pain. The prevalence of chronic pain also is associated with being unemployed (29.2% unemployed versus 14.5% working), living in rural areas (24.0% versus 18.4%), and being a veteran (26.0% versus 19.0%). Obesity and overweight also are associated with chronic low back pain and care-seeking for pain.[21] The estimated prevalence of obesity in the United States, which has increased significantly from 1999-2000 to 2015-2016, is 39.8% among adults, aged 20 and older, and 18.5% among youth (aged 2 to 19 years).[22]

Reported use of prescription pain medicines also increases with age, consistent with the prevalence of chronic pain.[23] In 2016, an estimated 34.1% of the population used a prescription pain reliever in the past year. The rate was 19.0% among children 12-17 years, 30.1% adults aged 18-28%, and 36.5% among adults 26 years and older. The highest prevalence was in the age group 55-59 years (40.9%). A recent cross-sectional study showed obesity and obesity-associated co-

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[20] Dahlhamer et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:1001–1006.

[21] Shiri et al. The Association Between Obesity and Low Back Pain: A Meta-Analysis. Am J Epidemiol.2010;171:135-154.

[22] Hales et al. Prevalence of Obesity Among Adults and Youth: United States, 2015–2016. NCHS data brief, no 288. Hyattsville, MD: National Center for Health Statistics. 2017. Data table available at: https://www.cdc.gov/nchs/data/databriefs/db288_table.pdf#2 Last accessed: July 8, 2019.

[23] SAMHSA. Results from the 2017 National Survey of Drug Use and Health: Detailed Tables. Table 1.23A – Any Use of Pain Relievers in Past Year and Misuse of Pain Relievers in Past Year and Past Month among Persons Aged 12 or Older, by Detailed Age Category: Numbers in Thousands, 2016 and 2017, https://www.samhsa.gov/data/report/2017-nsduh-detailed-tables.

morbidities (such as back and joint pain and diabetic neuropathy) also to be closely associated with an increased use of pain medications. Based on this association, an estimated 14% of prescription opioid use, representing 1.5 million users annually, may be attributed to obesity in the United States.[24]

VI. Substance Abuse Is Endemic In the U.S. Population

Substance abuse and misuse, including abuse of prescription pharmaceuticals, is not a new phenomenon created by prescription opioids. Rather, it is endemic in the U.S. population, with patterns of abuse varying by different demographic variables as well as regions of the country and changing over time.[25]

In 2017, over one-half (51.7%) of the US population aged 12 and older reported drinking alcohol, with almost a quarter (24.5%) reporting binge use and 6.1% reporting heavy use within the past 30 days. Tobacco use was 22.4%.[26] That same year, 11.2% of the US population, aged 12 and older, reported current use of any illicit drugs; 9.6% used marijuana within the past 30 days. Illicit drug use was highest among the 18-25 year age group; 24.2% reported using an illicit drug (any) and 22.1% reported recent use of marijuana.[27]

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[24] Stokes et al. The Contribution of Obesity to Prescription Opioid Use in the United States. Pain. 2019 May 29. doi: 10.1097/j.pain.0000000000001612. [Epub ahead of print]; *see also* Caraveti et al., Increase in poisoning deaths caused by non-illicit drugs – Utah, 1991-2003. MMWR 2005;54;33-36, which found higher rates among those who were overweight or obese.

[25] National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services. Nationwide Trends, https://www.drugabuse.gov/publications/drugfacts/nationwide- trends. See also Scholl et al. Drug and Opioid-Involved Overdose Deaths — United States, 2013–2017. MMWR. 2019;67:1419–1427; O'Donnell et al. Trends in Deaths Involving Heroin and Synthetic Opioids Excluding Methadone, and Law Enforcement Drug Product Reports, by Census Region — United States, 2006–2015. MMWR. 2017;66:897–903.

[26] Center for Behavioral Health Statistics and Quality. (2018). 2017 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD.

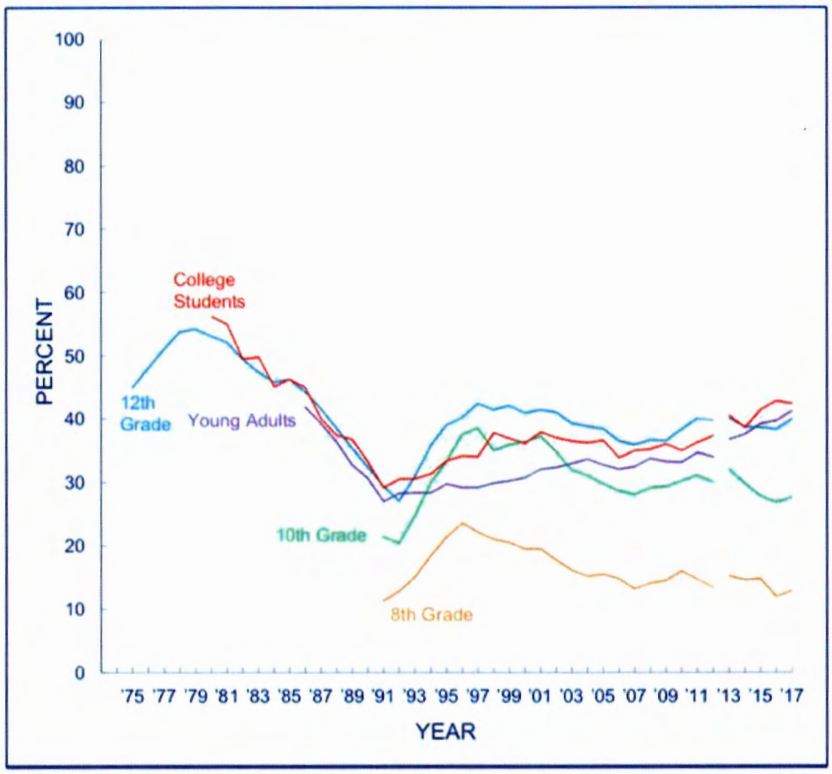
[27] Monitoring the Future, College Students & Adults Ages 19-55 – 2017, Volume II; Monitoring the Future, Highlights from Drug Use Among American High School Students, 1975-1977.

The Monitoring the Future survey shows an annual prevalence of illicit drug use over 10 percent for all ages and groups surveyed from 1975 through 2017 with wide variations over time and specific sub-populations. Overall, the historic rates are higher than those today with the annual prevalence having peaked at over 50% among 12th graders in the late 1970s (See figure below).[28] Prevalence remained over 50% for both 12th graders and college students until the mid-1980s.[29]

[28] Monitoring the Future, College Students & Adults Ages 19-55 – 2017, Volume II; Monitoring the Future, Highlights from Drug Use Among American High School Students, 1975-1977.

[29] *Id.*

FIGURE 2-1
Trends in Annual Prevalence of an Illicit Drug Use Index across 5 Populations



Source. The Monitoring the Future study, the University of Michigan.

Notes. Illicit drug use index includes any use of marijuana, LSD, other hallucinogens, crack, cocaine other than crack, or heroin; or any use of narcotics other than heroin which is not under a doctor's orders, stimulants, sedatives (barbiturates), methaqualone (excluded since 1990), or tranquilizers. Beginning in 1982, the question about stimulant use (i.e., amphetamines) was revised to get respondents to exclude the inappropriate reporting of nonprescription stimulants. The prevalence rate dropped slightly as a result of this methodological change. In 2013, the question on use of amphetamines was changed such that "Amphetamines" was replaced with "Amphetamines and other stimulant drugs." Data for any illicit drug were affected by this change.

DAWN Data, reporting emergency department (ED) visits related to substance misuse or abuse, reflect an increase in misuse of prescription drugs between 2004 and 2011 (the years of available data), from 626,470 to 1,428,145, but must be viewed with caution as they suffer from a host of

limitations as discussed above.[30] Of note is that in 2011, the last year of reporting, narcotic pain relievers were the *second* most reported class of drug, at 134.8 visits per 100,000 population. The most commonly involved drugs were anti-anxiety and insomnia medications (160.9 visits per 100,000 population).[31]

VII. Most Prescription Drug "Misusers" Are Seeking Relief from Pain

Between 2002 and 2014 NSDUH's survey of prescription opioid use asked whether respondents had, even once, used a prescription pain reliever solely for "the experience or feeling it caused?"[32] In 2015, NSDUH's revised its survey. It now asks a "screener" question to establish whether the person has, in the past year, used a prescription opioid. If yes, it then asks a follow-up question regarding whether the person had ever "misused" - i.e., "use[d] in any way not directed by a doctor, including use without a prescription of one's own medication; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor." As such, it captures common medication-taking behaviors including stopping or skipping doses of a medication, taking a medication more frequently than prescribed (using a Q12 dose on a Q8 basis), or taking a friend or family member's medicine for one's own medical need.

Importantly, NSDUH also asks *why* patients misuse opioids, and the data are revealing. Even when the use of pain relievers is characterized as "misuse" it is still primarily to relieve pain (63.6%).[33] Related but less commonly reported reasons are to relax or relieve tension (10.7%) and

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30 SAMHSA, The Dawn Report: Highlights of the 2011 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits (2013).

31 Crane, E.H. Highlights of the 2011 Drug Abuse Warning network (DAWN) Findings on Drug-Related Emergency Department Visits. The CBHSQ Report: February 22, 2013. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD.

32 NSDUH Questionnaires 2002-2017. Available at: http://datafiles.samhsa.gov/study-series/national-survey-drug-use-and-health-nsduh-nid13517.

33 SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2015 and 2016, Table 6.62B, 2016 estimates referenced.

to help with sleep (3.3%). Much smaller proportion of respondents who report misuse of pain relievers report that they are doing so to feel good or get high (12.4%), because they are hooked or had to have it (2.3%), or to experiment or see what it is like (2.5%).

These data point back to the varied and very broad understanding of misuse that is reported when surveyed persons taking prescription medications describe themselves as any time "misusers." They reveal that "misuse" of prescription opioids is not necessarily "abuse" as that term would be commonly understood, and may not even reflect any aberrant behavior.

Table 6.62B Main Reasons for Last Episode of Misuse of Prescription] of Prescription Psychotherapeutic: Percentages, 2015 and

Main Reason for Last Episode of Misuse	Past Year Pain Reliever Misuse[1] (2015)	Past Year Pain Reliever Misuse[1] (2016)
Relieve Physical Pain	63.4	63.6
Relax or Relieve Tension	10.9	10.7
Help with Sleep	4.5	3.3
Help with Feelings or Emotion	3.2	3.5
Experiment or See What It's Like	2.0	2.5
Feel Good or Get High	11.7	12.4
Increase or Decrease Effect of Other Drug	0.9	0.9
Because I Am Hooked or Have to Have It	2.5	2.3
Help Lose Weight	--	--
Help Concentrate	--	--
Help Be Alert or Stay Awake	--	--
Help Study	--	--
Some Other Reason	1.1	0.8

* = low precision; -- = not available; da = does not apply; nc = not comparable due t

VIII. The Available Data Support a Low Rate of Iatrogenic Addiction

There are no studies that definitively quantify the rate of iatrogenic addiction in properly managed pain patients. Still, the weight of the evidence and observational experience indicates that rates are low and not driving a crisis of opioid addiction or death. Indeed, as recently as 2019, FDA has recognized that "[a]ccording to the National Institutes of Health, studies have shown that properly managed medical use of opioid analgesic compounds (taken exactly as prescribed) is safe, can manage pain effectively, and rarely causes addiction."[34]

Noble et al. conducted a systematic review of 26 clinical studies limited to chronic pain patients who were using prescription opioids for at least 6 months. As such, it is a useful reference point evidencing that appropriately screened patients for whom an opioid like OxyContin would be indicated for chronic pain are not being driven into addiction and are not the reason for wide-spread opioid abuse. Based on the reported results of the 26 published studies, the combined rate of "addiction" was 0.27%.[35]

There also are a number of additional published studies addressing abuse/addiction rates, noted in my materials considered list. These studies focus on diverse populations and report a range of results. Some of the studies include those at high risk of addiction, and use various definitions of outcomes and methodologies. They do not necessarily inform the issue of abuse and addiction with chronic non-cancer pain patients treated with extended release/long-acting opioids.[36]

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[34] United States Food & Drug Administration, "A Guide to Safe Use of Pain Medicine" (Feb. 9, 2009), https://www.fda.gov/consumers/consumer-updates/guide-safe-use-pain-medicine.

[35] Noble et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD006605.

[36] Vowles et al., is another review article that is cited in the literature by those arguing that there exists a much higher level of risk. Vowles' literature review resulted in 38 evaluable studies reporting misuse, abuse and/or addiction. The range of populations, designs, and quality was broader than in Nobles and, not surprisingly, so were the results. Still, it again provides evidence that in those low risk patients who

Further, a recent epidemiological review conducted by FDA focused on "higher prescribed DD [daily dose]" of opioid medicines and found it was only "weakly associated with higher risks of abuse and addiction."[37] The reviewers noted that "reverse causation, and more rigorous screening in people with higher DDs, may have contributed to the observed associations."[38] Ultimately, the FDA reviewers concluded that "[l]imited epidemiologic evidence from published healthcare claims-based studies suggests an association" but that "due to the limitations of healthcare data, including the difficulty establishing temporal relationships, it remains unclear whether the higher dose plays a causal role in the development of opioid addiction."[39] The FDA based these conclusions on their evaluation of three retrospective claims-based studies. It deserves noting that all three suffer from an important limitation, which is that all defined the outcome "abuse and addiction" based on diagnostic codes for opioid dependence and abuse, and (in one study) overdose.[40] Yet, as FDA has recently reiterated, opioid dependence is not the same as abuse

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are carefully managed, the risk is low. See Vowles et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015 Apr;156(4):569-76.

37 For purposes of its briefing document, FDA stated that "because of widespread familiarity with the 2016 CDC guidelines, we used 90 MME/day as a benchmark for higher dosage strength product prescribing [....] "FDA Briefing Document. Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), at 36. June 11-12, 2019. https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-11-12-2019-joint-meeting-drug-safety-and-risk-management-advisory-committee-and-anesthetic-and#event-materials.

38 *Id.* at 59.

39 *Id.* at 63.

40 *See* Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. BMJ. 2018;360:j5790; Ciesielski T, Iyengar R, Bothra A, Tomala D, Cislo G, Gage BF. A Tool to Assess Risk of De Novo Opioid Abuse or Dependence. Am J Med. 2016;129(7):699-705.e694; Coutinho AD, Gandhi K, Fuldeore RM, Landsman-Blumberg PB, Gandhi S. Long-term opioid users with chronic noncancer pain: Assessment of opioid abuse risk and relationship with healthcare resource use. J Opioid Management. 2018;14(2):131-141.

or addiction.[41] Given the relative number of cases, dependence is driving the observed (weak) association of the study outcome with longer use and dependence is not abuse and addiction.[42]

IX. Epidemiological Evidence Does Not Support a Claim That Prescription Opioids Generally, or OxyContin Specifically, Act As "Gateway" Drugs for Heroin Abuse

To the extent that Plaintiff's Citation purports to link in any manner Utah's current issues with heroin and illicit fentanyl with allegedly improper past marketing of prescription opioids, particularly OxyContin, it bears stating that there is no reliable research which would allow for such a causal inference. There also is no reliable evidence that the specific introduction of Purdue's abuse deterrent formulation for OxyContin in 2010 – the first abuse deterrent opioid to receive FDA approval – either "tripped" people into heroin abuse or that it continues to fuel an epidemic of heroin, and illicit fentanyl abuse, almost a decade later.

Nationwide data on heroin and fentanyl use comports with past cycles of abuse in different drugs. A spike in heroin abuse in the 1960s and 1970s was followed by a spike in cocaine and crack cocaine in the 1980s and a rise in methamphetamines in the 1990s. Thus, heroin abuse is not a new phenomenon. Further, over 80% of the heroin-dependents in the 1960s reported heroin as their first opioid. This decreased to 8.7% among individuals entering substance abuse treatment in 2005, before rising sharply to 33.3% in 2015.[43] These data reflect that usage patterns may be independent of "transition" opioids and that heroin initiation is not a function of prior opioid use.[44]

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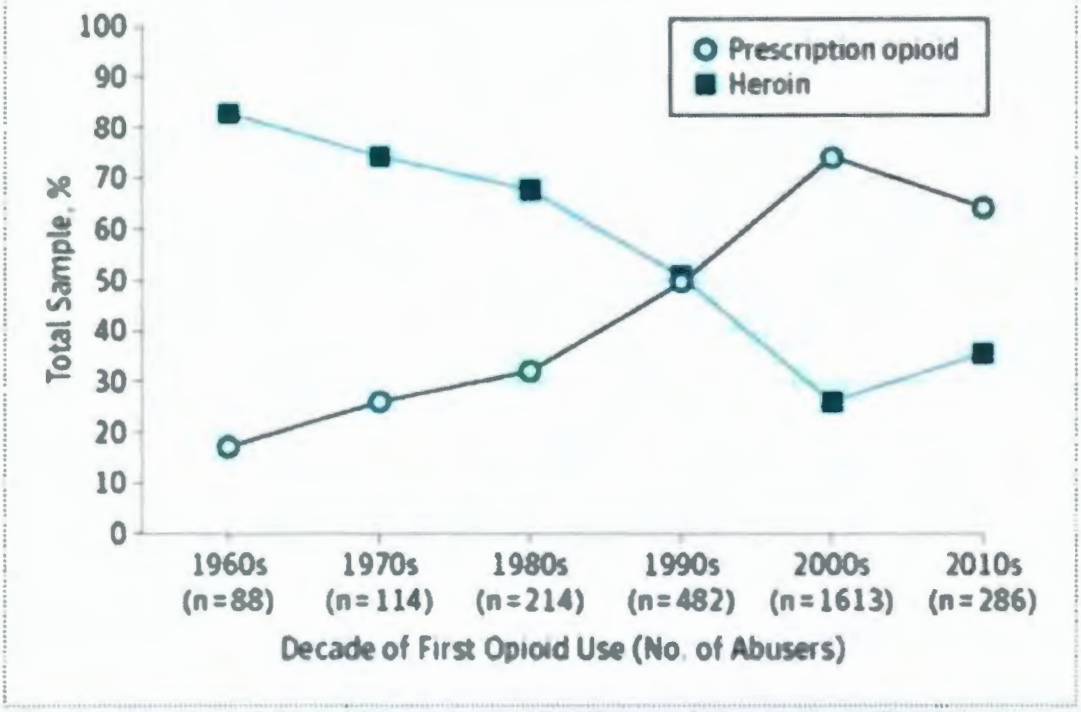
41 FDA Briefing Document at 12.

42 For example, in Brat et al (2018), only 626 of the 5906 patients (10.6%) meeting the outcome definition for "abuse and addiction" had diagnostic codes specific to opioid abuse. *See* FDA Briefing Document at 59, 81, Appendix E.

43 Cicero et al. Increased use of heroin as an initiating opioid of abuse. Addictive Behaviors 74 (2017) 63-66.

44 Cicero et al. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. *JAMA Psychiatry*. 2014;71(7):821-826.



Percentage of the total heroin-dependent sample that used heroin or a prescription opioid as their first opioid of abuse. Data are plotted as a function of the decade in which respondents initiated their opioid abuse. *Source: Cicero et al., 2014*

Heroin abuse has been increasing since at least 2007, several years before abuse deterrent formulations of prescription opioids were introduced to the market in 2010.[45] In the first few years of this rise in heroin abuse (2007-2010), nonmedical use of prescription opioids remained relatively stable. The introduction of abuse deterrent formulations of prescription opioids in 2010 contributed, over time, to a downward trend in the nonmedical use of prescription opioids, while

[45] Compton et al. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. N Engl J Med. 2016 Jan 14;374(2):154-63 (analyzing data from the Center for Behavioral Health Statistics and Quality, SAMHSA).

the increase in heroin abuse continued to rise unabated.[46] The lack of correlation between the two trend lines shows that the current rise in heroin abuse is not being driven by nonmedical prescription opioid use, but instead by factors more specific to heroin over this period such as greater availability (not withstanding significant regional and local variation), lower cost, and higher potency.[47]

Muhuri et al. investigated the pattern of drug use and predictors of heroin initiation among persons aged 12 to 49 years who were at risk of heroin abuse.[48] Because heroin use is rare, NSDUH data from 2002 to 2011 was combined. There were several important takeaways. First, only 3.6% of nonmedical pain reliever (NMPR) users reported initiating heroin within 5 years following NMPRs. This indicates that any alleged "transitioning" from prescription opioid abuse to heroin occurs, at most, in a very small subset of users. Second, the population described as having "transitioned" to heroin were not prescribed patients but rather non-medical or misusers of prescription opioids. In other words, that 79.5% of current heroin initiates reported previous NMPR use reflects movement among drug abusers from one opioid of abuse to another, rather than a transition from appropriate use of prescription medicines to heroin.

Regardless of whether or not there was NMPR use, most heroin initiates had prior illicit drug use (marijuana/hashish, cocaine (including crack), hallucinogens, and inhalants). Given the

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[46] Similarly, there is no epidemiological evidence supporting Plaintiffs' assertion that other efforts to prevent abuse and misuse, such as REMS programs, fueled further nonmedical use of opioids. These were important public health measures. Indeed, the FDA has announced that both ER and IR opioids will be subject to REMS requirements. FDA. Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to strengthen agency's safety requirements aimed at mitigating risks associated with transmucosal immediate-release fentanyl products. March 27, 2019.

[47] Compton et al. (2016).

[48] Muhuri et al. Substance Abuse and Mental Health Services Administration. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. *CBHSQ Data Review.* http://www.samhsa.gov/data/2k13/DataReview/DR006/nonmedical-pain-reliever-use-2013.pdf. Published August 2013.

low number of heroin initiates, rates were not adjusted and the rates of "no prior illicit drug use", was too low to be reported accurately. The available data do suggest a possible interaction (synergy) with those having both prior illicit drug use and NMPR, which merely suggests that heroin initiation may be highest among those who have a history of polysubstance abuse.

Secades-Villa et al. studies a similar question regarding progression of drugs of abuse, but among cannabis users.[49] Based on survey data from National Epidemiological Survey on Alcohol and Related Conditions (NESARC), 44.7% of persons with lifetime cannabis use progress to other illicit drugs. There were a number of factors that predicted progression: nicotine dependence, alcohol disorder, cannabis use disorder, personality disorder and demographics (age, race, and marital status). This does not mean that marijuana use "causes" or is a "gateway" for use of other drugs later in life.

In addition to the above, there is not any logical or fact-based explanation for a claim that years after Purdue reformulated OxyContin to make abuse and misuse more difficult (particularly through crushing, snorting, and injecting), and the use (and misuse by crushing, snorting, and injecting) declined, the reformulated product either remained an abuse-drug of choice or pushed abusers to "transition" to illicit drug use.

X. National Data Evidence Fentanyl And Poly-Substance Abuse Are The Current Drivers of Opioid Deaths

Substantial evidence supports the conclusion that abuse of heroin and illicit fentanyl are the drivers of the rapid increase in opioid-related deaths nationally, as confirmed by multiple sources. The National Vital Statistics System shows a sharp rise in deaths associated with synthetic

[49] Secades-Villa et al. R, Garcia-Rodríguez O, Jin CJ, Wang S, Blanco C. Probability and predictors of the cannabis gateway effect: a national study. *Int J Drug Policy*. 2014;26(2):135–142.

opioids other than methadone.[50] The rate of drug overdose deaths involving synthetic opioids (including fentanyl, fentanyl analogs, and tramadol) increased approximately 18% per year from 1999 through 2006, did not change from 2006 to 2013, and then increased by 71% annually from 2013 to 2017. In fact, the impact of illicit fentanyl and other synthetic opioids was likely to be greater than reflected, as, until recently, fentanyl had not been consistently and separately tracked. Rather, fentanyl was captured with all "synthetic opioids other than methadone."[51]

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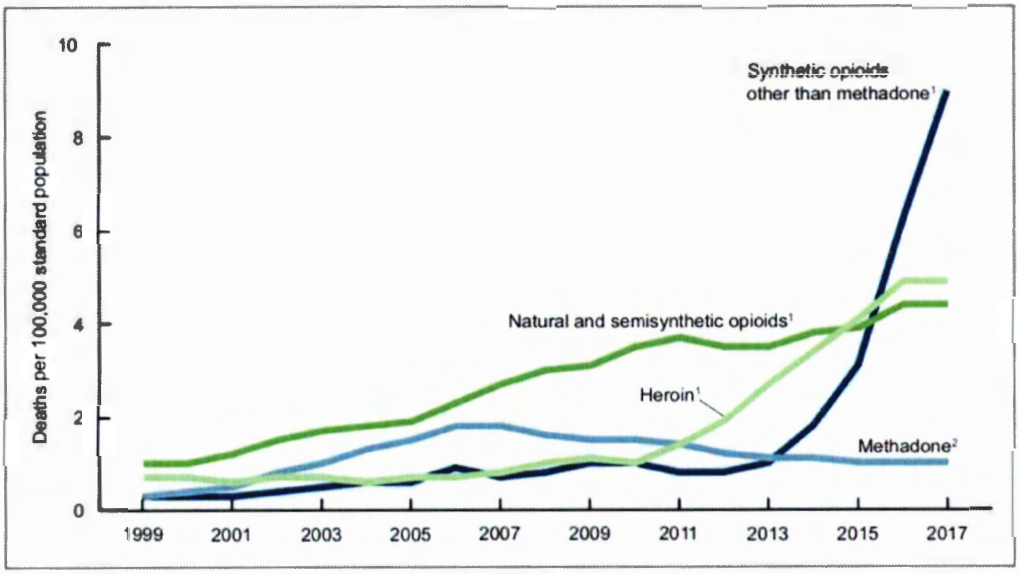
[50] Hedegaard et al. Drug overdose deaths in the United States, 1999–2017. NCHS Data Brief, no 329. Hyattsville, MD: National Center for Health Statistics. 2018. https://www.cdc.gov/nchs/data/databriefs/db329-h.pdf.

[51] It should be remembered that mortality statistics are derived from death certificates, which are known to vary in quality and completeness. Drug-related deaths do not always include information on the specific drug(s) and fentanyl and fentanyl analogs were not, particularly in the earlier years of the fentanyl crisis, uniformly assessed by medical examiners across the country. Adequate information on Utah's practices over time with regard to identifying fentanyl deaths is has not yet been provided and is needed for further analysis.

Figure 4. Age-adjusted drug overdose death rates, by opioid category: United States, 1999–2017



[1]Significant increasing trend from 1999 through 2017 with different rates of change over time, $p < 0.05$
[2]Significant increasing trend from 1999 through 2008, then decreasing trend from 2008 through 2017, $p < 0.05$.
NOTES: Deaths are classified using the *International Classification of Diseases, 10th Revision*. Drug-poisoning (overdose) deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Drug overdose deaths involving selected drug categories are identified by specific multiple-cause-of-death codes: heroin, T40.1; natural and semisynthetic opioids, T40.2; methadone, T40.3; and synthetic opioids other than methadone, T40.4. Deaths involving more than one opioid category (e.g., a death involving both methadone and a natural and semisynthetic opioid) are counted in both categories. The percentage of drug overdose deaths that identified the specific drugs involved varied by year, with ranges of 75%–79% from 1999 through 2013 and 81%–88% from 2014 through 2017. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db329_tables-508.pdf#4.
SOURCE: NCHS, National Vital Statistics System, Mortality.

In fact, Spencer et al.[52] using a text search protocol to identify deaths associated with fentanyl and fentanyl analogs, observed that the number of deaths in which fentanyl and fentanyl analogs were identified held relatively steady during 2011 and 2012, and then began increasing. Age-adjusted rate of drug overdose deaths involving fentanyl increased 113% annually from 2013

[52] Spencer MR, Warner M, Bastian BA, Trinidad JP, Hedegaard H. Drug overdose deaths involving fentanyl, 2011–2016. National Vital Statistics Reports; vol. 68 no 3. Hyattsville, MD: National Center for Health Statistics. 2019. https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_03-508.pdf.

to 2016. Age-adjusted death rates increased from 0.5 per 100,000 in 2011 and 2012 to 5.9 per 100,000 in 2016.

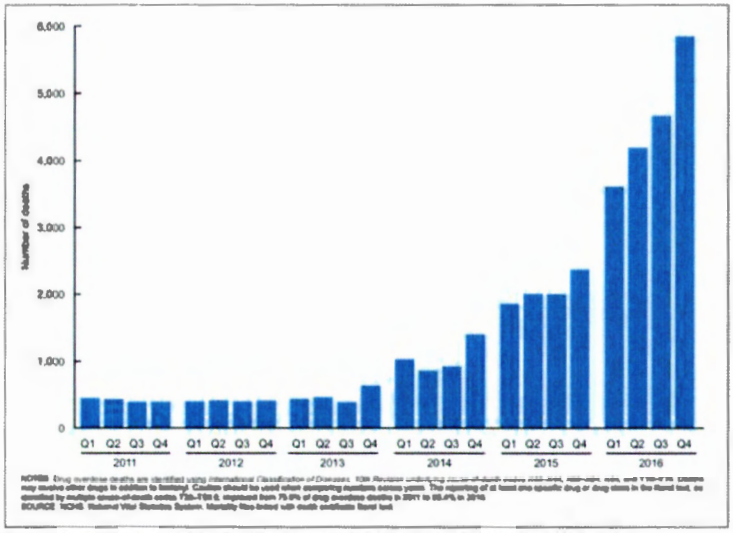


Figure 1. Number of drug overdose deaths involving fentanyl, by quarter: United States, 2011–2016

The lethality of fentanyl and analogs also distorts the death curves for other opioid products. In addition to being sold alone and mixed with other illicit drugs, the DEA has identified an increase in fentanyl in counterfeit prescription medicines.[53] When fentanyl-related deaths are excluded from the cocaine-, heroin-, or prescription pain medication-involved overdose deaths, the trends changed dramatically. The apparent increase in deaths from semi-synthetic prescription pain medicines, which include OxyContin and other prescription opioids, shrank from 32% with fentanyl-related deaths included to 7% after excluding known fentanyl-relate deaths, as the below graph reflects.

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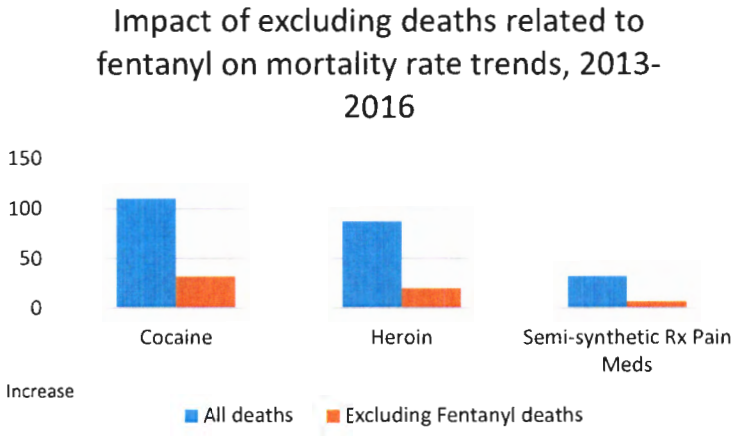
[53] Drug Enforcement Administration. 2018 National Drug Threat Assessment Summary. DEA-DCT-DIR-032-18. October 2018.https://www.dea.gov/sites/default/files/2018-11/DIR-032-18%202018%20NDTA%20final%20low%20resolution.pdf.



Before the spike in fentanyl deaths, use of benzodiazepines has increased 67% from 8.1 million persons in the US in 1996 to 13.5 million persons in 2013. More than 30% of overdoses involving opioids also involve benzodiazepines.[54] Again, this is important because it highlights the potential for misclassification of outcomes. Also, the increased risk of death when opioids are taken with benzodiazepines (as well as alcohol and other substances) has long been well-known, considered as part of their risk/benefit profile for opioid medicines including OxyContin and reflected in FDA-approved label.

XI. Utah's Own Data And Analysis of State-Specific Trends

In October 2005, Utah's Department of Health convened a working group in response to Utah's medical examiner's observation of an increasing number of deaths associated with prescription pain medications. A Summary of Findings followed, [55] along with a subsequent publication in 2011.[56] The objectives of the effort were:

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[54] Jones & McAninch. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. Am J Prev Med 2015;49:493-501.

[55] Sundwall DN, Rolfs RT. Prescription Medication Deaths in Utah. Workgroup Meeting. October 24-25, 2005. Summary of Findings.

[56] Utah Department of Health. 2011 Utah State Health Profile. https://ibis.health.utah.gov/ibisph-view/pdf/opha/publication/2011StateHealthProfile.pdf (Last accessed July 11, 2019.)

1. Define current understanding of the causes of the epidemic of deaths due to prescription medications in Utah.

2. Identify important unanswered questions that can guide investigations leading to interventions to prevent deaths.

3. Identify action steps that can be taken now to prevent deaths from prescription medications.

According to Utah's own analysis, methadone was responsible for one-third of deaths from prescription opioids and the death rate for methadone was disproportionate in relations to its relative use. The use was predominately for pain treatment.[57]

By 2015, the percent of prescription opioid deaths involving methadone dropped below 20%, despite having the highest risk of death.[58] The majority of prescription opioid involved deaths were associated with more commonly prescribed opioids, IR oxycodone and then hydrocodone, followed by methadone and then tramadol. Importantly, more than 90% of the deaths associated with prescription opioid involved additional drugs.

Prescription opioid deaths, as reported by the Utah medical examiner, reached a peak in 2007, and then declined until 2010 (consistent, it seems, with a brief state initiative to address prescription medication abuse) when they began to rise again. In 2014, they again reversed course and have been declining since.[59] But Utah has reported increased trafficking in methamphetamines, heroin, illicit fentanyl and cocaine, noting that drug traffickers were taking criminal advantage of its interstate highway system and rural areas.[60]

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57 Porucznik et al. Studying adverse events related to prescription opioids: The Utah Experience. Pain Med. 2011;12:S16-S25.

58 Utah Department of Health. Violence & Injury Prevention Program. Prescription Opioid Drugs. April 2017. http://health.utah.gov/vipp/pdf/RxDrugs/PDODeaths2015.pdf. Last accessed: July 9, 2019.

59 See https://ibis.health.utah.gov/ibisph-view/indicator/view/PoiDth.Opi.html Last accessed July 11 2019. It should be noted that these numbers include all drug poisoning deaths regardless of intent (e.g. unintentional suicide, homicide, and undetermined).

60 Drug Enforcement Agency: Utah meth-related deaths on the rise, Nov. 16, 2018.

XII. Other Trends Help Explain Opioid Prescription Use, Misuse & Death

Opioid use was rising before the approval of OxyContin. Long a Schedule III opioid, hydrocodone was only upregulated by DEA in 2014 to a Schedule II in response to diversion concerns. It was and remains one of the most commonly diverted opioids. Utah legislature added tramadol as a scheduled drug (Schedule V) in 2013, prior to it being listed as a Schedule IV drug nationally. As noted above, from 2015-17 Utah noted tramadol among the prescription opioids most frequently associated with overdose deaths, and in 2018 the State Controlled Substances Advisory Committee recommended upregulating tramadol to schedule IV to align with federal scheduling.[61]

Overall drug prescribing and drug use, and access to prescription drugs, also was changing during this time. The Centers for Disease Control (CDC) National Medical Care Ambulatory Survey contains provides national population- based estimates of outpatient care, including data related to drug prescribing, at physician office visits utilization by year. The total number of drugs mentioned during physician office visits increased from just under 983.7 million in 1996 to 3.658 Billion in 2015. Similarly, looking at physician office visits in which a drug was provided or prescribed (drug visits), in 1996, 64.3% of physician office visits were classified as drug visits. By 2015, the percentage of drug visits was 76.2%.

The U.S. mortality rate from unintentional drug overdoses has been increasing exponentially since 1979, decades before the introduction of a new generation of prescription opioids such as OxyContin. These data represent a composite of multiple substances of abuse,

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[61] State of Utah Controlled Substance Advisory Committee. Controlled Substances Advisory Committee—2019 Legislative Recommendations. October 12, 2018.

including cocaine, methamphetamines, heroin, fentanyl, and other drugs of abuse, as well as prescription opioid medications. As the authors of the study stated, "Individual drugs come and go, demographic risk groups vary, policies are implemented and enforced, while the overall overdose death curve grows inexorably." In other words, various substances may rise and fall in their rates of use and abuse, but there seem to be larger forces at work driving overdose mortality. The authors suggest powerful social factors are the true driving forces behind this rise in overdose mortality: "widening economic disparities, loss of a sense of purpose, and dissolution of communities." These data show that prescription opioids are a very small part of a much larger set of factors that have been the true driving force of the substance abuse crisis in the United States.[62]

Suicide is a major cause of death; it is among the top ten causes of death in the United States.[63] Suicide rates are also increasing.[64] In 2017, the age-adjusted suicide rate was 14.0 per 100,000 persons in the United States.[65] This represents a 35% increase from 2000, when the age-adjusted suicide rate was 10.4 per 100,000 persons. The female suicide rate increased 50% - from 4.0 in 2000 to 6.0 per 100,000 persons in 2016.[66] Poisonings (drug and nondrug) were the most frequent method among women 45 years and older. Utah has one of the highest suicide rates in the country. The age-adjusted suicide rate in Utah is 22 suicides per 100,000 with some counties

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62 Jalal *et al.*, "Changing dynamics of the drug overdose epidemic in the United States from 1979 through 2016," *Science*, volume 361, issue 6408 (Sept. 21, 2018); Jalal and Burke, "Why there's an overdose epidemic — in two graphs," *STAT* (Sept. 20, 2018).

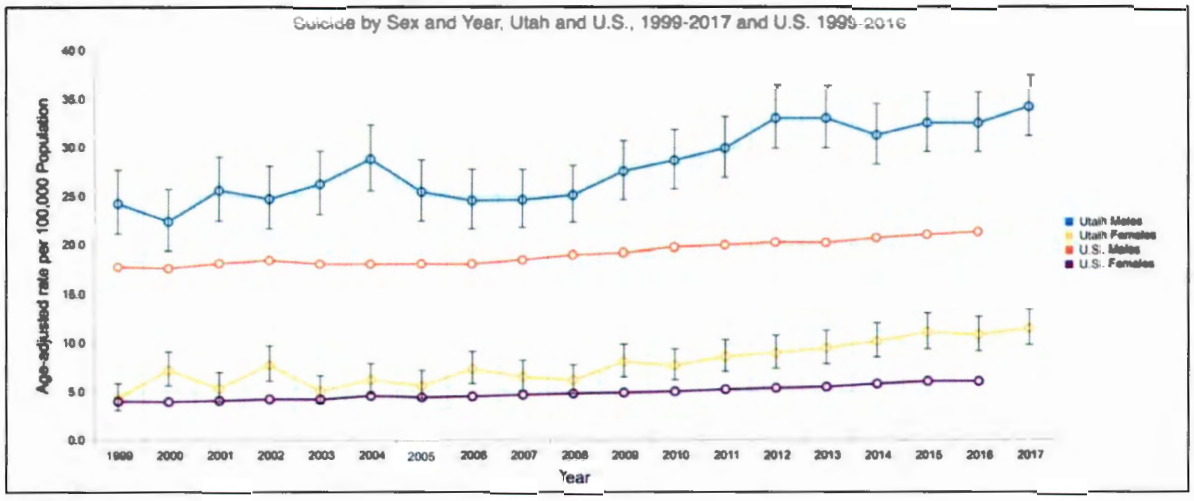
63 Murphy SL. Xu J. Kochanek KD. Mortality in the United States, NCHS Data Brief No.328. November 2018. https://www.cdc.gov/nchs/data/databriefs/db328-h.pdf.

64 Hedegaard H, Curtin SC, Warner M. Suicide rates in the United States continue to increase. NCHS Data Brief No. 309. June 2018. https://www.cdc.gov/nchs/data/databriefs/db309.pdf.

65 CDC Wonder Data. Available at https://www.cdc.gov/nchs/pressroom/sosmap/suicide-mortality/suicide.htm.

66 Hedegaard H, Curtin SC, Warner M. Suicide rates in the United States continue to increase. NCHS Data Brief No. 309. June 2018. https://www.cdc.gov/nchs/data/databriefs/db309.pdf.

reporting significantly higher rates; suicide is the leading cause of death in older children (age group 10-17 years) and young adults (age groups 18-24 years) and the second leading cause among adults aged 25-44 years. Suicide rates in Utah are consistently above the national rates for both genders. (See Figure Below).[67]



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[67] Public Health Indicator Based Information System (IBIS). Health Indicator Report of Suicide. Violence and Injury Prevention Program, Bureau of Health Promotion, Division of Disease Control and Prevention, Utah Department of Health. 11/27/2019. https://ibis.health.utah.gov/ibisph-view/indicator/view/SuicDth.html. Last accessed on: July 9, 2019.

XIII. Prescription Drug Monitoring Programs Can Substantially Impact Prescribing And Diversion of Prescription Opioids Within Utah If Effectively Implemented

Prescription Drug Monitoring Programs (PDMPs) are state operated systems that allow for the input, viewing, and analysis of prescribing and dispensing of controlled drugs and other products on a state-wide basis.[68] There is variation from state to state in the authorizing laws and regulations which restrict who can or is required to access the data and under what circumstances, the ability to track patients over time through identifiers, linkages with other health data, and whether or not the PDMP data can be used for secondary purposes. PDMP's have their origin in a tracking program for heroin, cocaine, morphine, opium, and codeine established by New York State in 1918.[69] California has the longest continuously running PDMP, which was authorized by law in 1939.

PDMPs are the only data system that can track the pathway of all controlled prescription drugs dispensed within a state; from the doctor who prescribed the medicine to the pharmacy that dispensed it, and the patient who received it. PDMPs provide states with a unique level of actionable data that can be used to identify potentially problematic prescription drug seeking behaviors, prescribing practices, and dispensing trends. All other databases of prescription drug prescribing or dispensing have limitations and gaps. For example, an insurance claim database is limited to eligible enrollees, not all drugs may be covered, and will not capture a prescription if they pay cash. Unlike the states, no manufacturer has access to such complete and detailed data nor the ability to intervene at all points within the drug distribution system.

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[68] SAMHSA. *Prescription drug monitoring programs: A guide for health professionals.* Published in: In Brief. 2017. HHS Publication No. (SMA) 16-4997.

[69] PDMP TTAC. Technical Assistance Guide. History of Prescription Drugs Monitoring Programs. 2018. Brandeis University. https://www.pdmpassist.org/pdf/PDMP_admin/TAG_History_PDMPs_final_20180314.pdf.

Utah established a PDMP, called its Controlled Substances Database (CSD) in 1995. Housed in the Utah Department of Commerce, Division of Professional Licensing, it originally received a one-time funding of $50,000. Twelve years later, in 2007, the Utah State Legislature authorized the UDOH to establish a Prescription Pain Medication Program (PPMP) to "coordinate statewide initiatives and receive access to the Controlled Substance Database (CSD) to reduce deaths and other harm from prescription opiates." Among other things, the legislature charged the Department of Health, along with others, to utilize the CSD to investigate the causes and risk factors for death and non-fatal complications of prescription opiate use in Utah for chronic pain. . . ." [70] However, based on available information it appears that legislative measures to meaningfully impact utilization of the CSD were not initiated until 2016 at which time a variety of measures were put in place.[71]

XIV. OxyContin Represented A Very Small Share of Prescription Opioids Nationally and In Utah And Since 2010 Has Had Abuse-Deterrent Properties

As noted elsewhere, the majority of prescriptions opioids nationally and in Utah are immediate release products. Further, most products have not included abuse deterrent properties, which OxyContin had incorporated from 2010.[72]

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[70] Opiate Prescribing Practices in Utah at Appendix A.

[71] According to Utah's own report, between 2007-2010, the PPMP received state funding and joined with several "community partners," to run a "Use Only As Directed" media campaign, developed the Utah Clinical Guidelines on Prescribing Opioids, launched a statewide provider education intervention where physicians had the opportunity to receive continuing medical education for participation in small and large group presentations, provided academic detailing, and produced analytic profiles for Utah drug overdose deaths. Drug overdose deaths decreased from 2007-2010, when the UDOH had state funding for the PPMP, but have since increased. But following budget cuts, the positive trends did not continue. Opiate Prescribing Practices in Utah, at 5.

[72] *See* Public Employees Health Program (PEHP) Report on Abuse Deterrent Opioid Analgesic Drug Products (Oct. 2015).

There is no epidemiological evidence nationally or in Utah of which I am aware evidencing that OxyContin, a product with a very limited share of the prescription pain reliever market and unique properties relative to other prescription opioids, drove a crisis of addiction or death.

XV. Sales Data And "Misuse" Data Cannot Be Reconciled

Also, there appears to be a significant error with the NSDUH estimates. As noted above, the revised questionnaire in 2015 for the first time allowed one to estimate the population of prescription opioid users (the gating question), as well as the population of prescription opioid "misusers" (the second question), and thus to subtract out the prescription opioid "non-misusing users." Further, it allowed one to estimate the number of survey participants who reported *misuse* of particular medicines, including OxyContin. Concerningly, the estimated number of total "non-misusing Oyxcontin users" reported by NSDUH based on its survey samples for 2015-2017 turns out to be between 9 and 15-fold greater (depending on the year) than the total number of OxyContin prescribed patients during the same time as reported by patient level IQVIA data. This wide disparity between the estimates of OxyContin users based on survey data compared to hard data from filled prescriptions, which does not appear in any comparable order of magnitude for any other branded prescription opioid reported out by NSDUH, at a minimum, casts doubt on the reliability of NSDUH to estimate misuse of OxyContin specifically.

It is likely that people do not know (or remember) exactly which medicine they took even when prompting with photographs of the medicine. Similarities in names, and common conflating of the active ingredient (e.g. oxycodone) and the brand name (i.e. OxyContin) – essentially a "Kleenex" effect -- can also be a source of confusion.

Dr. Weiss's Compensation

Dr. Weiss is being compensated at an hourly rate of $500.

Dr. Weiss's Prior Testimony

Dr. Weiss has testified in a deposition on June 18, 2019 in the matter of *In re: National Prescription Opiate Litigation*, MDL No. 2804.

Dated: July 12, 2019

/s/ Sheila Weiss

Sheila Weiss, PhD FISPE

EXHIBIT A

AVIGILAN

Regulatory – Safety – Strategy

Sheila Weiss, Ph.D., FISPE
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Potomac, MD 20859
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EDUCATION

The Johns Hopkins University	Ph.D., Epidemiology	*JUN 1996*
Northeastern University	M.S., Exercise Science	*MAY 1986*
University of Maine, Orono	B.S., Biology	*DEC 1981*

CURRENT POSITION

Avigilan, LLC, Potomac, MD, USA (Sheila Weiss Consulting, est. 1997) SEPT 2018 - PRESENT
President/Consulting Epidemiologist AUG 2013 – MAR 2017

- Consultations in complex safety issues
- Regulatory support pre and post-approval
- Protocols for REMS, registries, and Phase IV studies
- Expert witness/consulting for product liability cases

PROFESSIONAL EXPERIENCE

Evidera-PPD, Bethesda, MD
Senior Research Leader, Peri and Post Approval MAR 2017 – SEPT 2018

- Design and execute methodology and processes to elucidate, evaluate, and mitigate rare adverse events
- Consultations in regulatory sciences/regulatory strategies
- Provide leadership in pharmacoepidemiology within the company and to the profession

Johns Hopkins University, Baltimore, MD, USA JUL 2005 – JULY 2015
Bloomberg School of Public Health, Epidemiology & Biostatistics Graduate Summer Institute
Visiting Professor

- Designed and taught a 1 week course in Pharmacoepidemiology
- Attracted an average of 30 graduate students annually from across the globe
- Popular among Government (FDA, NIH, CDC) and Industry professionals

Optum (UnitedHealthcare), Waltham, MA, USA MAR 2013 – AUG 2013
Principal Epidemiologist

- Provide leadership in Pharmacoepidemiology
- Develop new offerings in Pharmacovigilance and Pharmacoepidemiology

University of Maryland, Baltimore, MD, USA APR 1997 – MAY 2013
Schools of Pharmacy and Medicine
Professor and Director of the Center for Drug Safety

- Developed a research and training program in epidemiology and pharmacoepidemiology
- Mentored graduate students and junior faculty many of whom have leadership positions

National Cancer Institute, National Institutes of Health, Rockville, MD, USA JAN 2008 – MAY 2012
Visiting Scientist

- Consulted in the development of the intra and intermural research program in pharmacoepidemology and pharmacogenomics
- Conducted cancer research as an intramural scientist, mentoring junior scientists
- Provided input into the annual research directions and strategy for the branch and division

US Food and Drug Administration, Rockville, MD, USA AUG1996 – APR1997
Center for Drug Evaluation and Research
Epidemiologist/Biostatistician (Postdoctoral fellow from 1994-1996)

- Design and conduct of research in pharmacoepidemiology
- Development of regulations and regulatory documents
- Developed new methodologies for study of birth defects

PROFESSIONAL AFFILIATIONS

International Society of Pharmacoepidemiolog
Editorial Board, Research in Social and Administrative Pharmacy

HONORS & AWARDS

Patricia Sokolove Outstanding Mentor Award, University of Maryland Graduate Student Association
Best Article (2010), Pharmacoepidemiology & Drug Safety Journal
Fellow, International Society of Pharmacoepidemiology
Kappa Delta Pi, International Honor Society in Education

PUBLICATIONS & PRESENTATIONS

RESEARCH

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Weiss Smith S, Sellers J. *Drug Safety.* In: A Pharmacist's Guide to Public Health. American Pharmacists Association Press. September 2010

Weiss Smith S. *Pharmacoepidemiology.* In: Encyclopedia of Epidemiology. Editor: Boslaugh S. Sage Publications Inc. October 2007.

PRESENTATIONS

Over 100 invited lectures and abstracts/presentations at professional meetings globally. Further information available upon request.

Rev. Oct 2018

EXHIBIT B

Materials Considered List – Dr. Sheila Weiss

Produced Documents:

- PDD1501603661-3669
- PDD1501610836-0844
- PDD1501710124-0126
- PDD7024303221-3257
- PDD1701603255
- PDD8901578396-8398
- PDD8901035967-6004
- PPLP003275296-5307
- PPLP004509518-0199
- PPLP004510200-0992
- PPLPC001000124576-4640
- PPLPC003000060503-0538
- PPLPC031000441510-1520
- PPLPC031000946522-6552
- PPLPC031001522632-2649
- PPLPC031000685835-5838
- PPLPC055000000232
- ALLERGAN_MDL_04449164
- ALLERGAN-NDL014(ALLERGAN_MDL_02485011).zip
- ALLERGAN-NDL021(ALLERGAN_MDL_03281086).zip
- IMS_Production001 (LOAD FILES).rar
- Password to IMS Production.docx
- NVSS Data

Utah Pleadings and Discovery Materials:

- Utah Administrative Citation, *In The Matter of Purdue Pharma L.P. et al.*, DCP Case No. 107102 (Utah)
- Plaintiff's Initial and Supplemental Disclosures, *In The Matter of Purdue Pharma L.P. et al.*, DCP Case No. 107102 (Utah)
- Defendants' Initial and Supplemental Disclosures, *In The Matter of Purdue Pharma L.P. et al.*, DCP Case No. 107102 (Utah)
- Division's Interview/Deposition Report (Utah)
- Purdue's Preliminary List of Interviews-Depositions

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- Monitoring the Future, 1979 Highlights: Drugs and the Nation's High School Students, Five-Year National Trends
- Monitoring the Future, Student Drug Use in America, 1975-1981 (1982)
- Monitoring the Future, Student Drug Use, Attitudes, And Beliefs: National Trends 1975-1982 (1983)
- Monitoring the Future, Highlights From Drugs And American High School Students 1975-1983 (1984)
- Monitoring the Future, Use Of Licit And Illicit Drugs By America's High School Students 1975-1984 (1985)
- Monitoring the Future, Drug Use Among American High School Students, College Students, And Other Young Adults: National Trends Through 1985 (1986)
- Monitoring the Future, National Trends In Drug Use And Related Factors Among American High School Students And Young Adults 1975-1986 (1987)
- Monitoring the Future, 1988 Illicit Drug Use, Smoking, And Drinking By America's High School Students, College Students, And Young Adults 1975-1987 (1988)
- Monitoring the Future, 1989 Drug Use, Drinking, And Smoking- National Survey Results From High School, College, And Young Adult Populations 1975-1988 (1989)
- Monitoring the Future, 1990 Trends In Drug Use And Associated Factors Among American High School Students, College Students, And Young Adults 1975-1989 (1990)
- Monitoring the Future, Drug Use Among American High School Seniors, College Students And Young Adults 1975-1990, Vol. I-II (1991)
- Monitoring the Future, Smoking, Drinking, And Illicit Drug Use Among American Secondary School Students, College Students, And Young Adults 1975-1991, Vol. I-II (1992)
- Monitoring the Future, National Results on Adolescent Drug Use: Overview of Key Findings 1975-79, 2000-2017
- Monitoring the Future, National Survey Results on Drug Use 1975-2017 - College Students and Adults 19-55 (2018)
- 2016-2017 National Survey on Drug Use and Health National Maps of Prevalence Estimates, by State
- Monitoring the Future, Highlights From Student Drug Use in America 1980-81
- National Survey Results on Drug Use From the Monitoring the Future Study, Vol. I Secondary School Students, 1993-96, 1998-2000
- National Survey Results on Drug Use From the Monitoring the Future Study, Vol. II College Students and Young Adults, 1993-2000
- National Ambulatory Medical Care Survey Summaries, 1996-2007.
- National Ambulatory Medical Care Survey Summary Tables, 2008-2016.
- Monitoring the Future Tables 1-3 (2018)
- Monitoring the Future Figures 1-10 (2018)
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- Drug Abuse Warning Network (DAWN) Highlights, July 2012, Jan. 2013
- Drug Abuse Warning Network (DAWN), A Day in the Life of American Adolescents - Substance Use Facts Update (Aug 2013)
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- Drug Abuse Warning Network (DAWN), BenzoCombos with Opioids (Dec. 2014)
- Drug Abuse Warning Network (DAWN), Benzodiazepines in Drug Abuse-Related Emergency Department Visits 1995-2002
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- Drug Abuse Warning Network (DAWN), Emergency Department Visits for Drug-Related Suicide Attempts Have Increased (Aug 2014)
- Drug Abuse Warning Network (DAWN), Emergency Department Visits Involving Methamphetamine 2007 to 2011 (June 2014)
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- Drug Abuse Warning Network (DAWN), Trends in Drug-Related Emergency Department Visits 1994-2001 (June 2003)
- Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health (NSDUH) (1979, 1982, 1985, 1988, 1990-91, 1993-2017)
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