STATEMENT OF

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1. Introduction

This statement focuses on three factors as related to fentanyl and its analogues:

- Pharmacological potency of fentanyl and its analogues relative to other opioids
- Toxicity of fentanyl and its analogues relative to other opioids
- Public health impact of abuse of fentanyl and its analogues relative to other opioids

Other relevant information is also presented. Where feasible, I have identified quantifiable differences between fentanyl and its analogues *versus* heroin and prescription opioids in relation to these three factors. This statement also identifies, where feasible, quantifiable temporal changes in the diversion, abuse and adverse health impact of prescription opioids, pharmaceutical fentanyl, illicitly manufactured fentanyl and its analogues.

2. Background

2.1. Prescription opioid analgesics

Prescription opioid analgesics are mainly used for the management of pain associated with various clinical conditions. Starting in the 1990s, prescriptions for opioid analgesics gradually escalated in the United States, reaching a peak around 2010-2011.[1] [2] Although in the last few years there has been a small reduction in the prescriptions for opioids, these numbers for 2016 continue to be high. In parallel to these increases in prescriptions for opioid analgesics, abuse of these pharmaceutical products and its adverse impact on the public health have gradually increased. Details regarding diversion and abuse of prescription opioid analgesics and their adverse impact on public health are presented later in the document.

2.2. Fentanyl and its analogues

Fentanyl is a prescription opioid analgesic. Fentanyl was first synthesized in Belgium in the late 1950s. Fentanyl analogues have chemical structures that are similar to that of fentanyl; the chemical structure of fentanyl has been modified in specific locations to produce fentanyl analogues. Law enforcement encounters of illicitly produced fentanyl and its numerous analogues markedly escalated in the last few years, as has the abuse of these substances and deaths associated with such abuse.

2.3. FDA approval of fentanyl and its analogues for medical use

Fentanyl was first introduced into medical practice as an injectable formulation in the early 1960s in Europe. In the United States, fentanyl was first approved by the Food and Drug Administration (FDA) as an injectable combination product (mixed with droperidol) in 1968. Four years later, a single-entity injectable formulation of fentanyl was approved for clinical use. Subsequently, FDA approved various other formulations of fentanyl such as buccal tablets, transmucosal lozenges, transdermal films, sublingual spray and tablets, nasal spray, and

[1] Guy Jr. GP, Zhang K, Bohn MK, Losby J, Lewis B, Young R, Murphy LB, Dowell D (2017) Vital signs: Changes in opioid prescribing in the United States, 2006 – 2015. Morbidity and Mortality Weekly Report, 66(26): 697-704.

[2] Data source: the National Prescription Audit database of the IMS Health America.

transdermal iontophoresis. A few analogues of fentanyl also have been developed and approved for medical use in humans (remifentanil, alfentanil, and sufentanil) and in animals (carfentanil and thiafentanil) in the United States. These analogues of fentanyl and fentanyl itself are controlled as Schedule II substances under the Controlled Substances Act (CSA) due to their high potential for abuse and dependence, as well as their approved medical use.

Because of the risk for misuse, abuse, addiction, and overdose, marketing and clinical use of fentanyl pharmaceutical products are currently subject to FDA-designated restricted program called Risk Evaluation and Mitigation Strategy (REMS). Currently, there are three different REMS programs that apply to fentanyl pharmaceutical products. Transmucosal fentanyl pharmaceutical products are only available through an FDA-designed restricted program called Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS). Fentanyl transdermal formulations are subject to a program called Extended Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS). Fentanyl iontophoretic transdermal system (IONSYS®) formulations are available through a program called IONSYS® Risk Evaluation and Mitigation Strategy (REMS) program to mitigate the risks of respiratory depression resulting from accidental exposure.

2.4. Current public health crisis related to opioid abuse

The United States is in the midst of unprecedented public health crisis involving overdoses and overdose deaths related to abuse of heroin, prescription opioid analgesics, and illicitly produced fentanyl and its analogues. Over the past 20 years, the public health threat related to prescription opioid analgesic abuse has escalated to epidemic levels, impacting significant portions of the United States.[3] According to the National Survey on Drug Use and Health (NSDUH),[4] in 2015, an estimated 12.5 (4.7%) million people aged 12 or older "misused"[5] pain relievers (opioid analgesics) in the past year, and 2.1 million people "misused" pain relievers for the first time. About 2 million people aged 12 or older had "pain reliever use disorder" in 2015.

Since the early 2000s, overdose deaths related to prescription opioid analgesics have escalated in the United States and have consistently exceeded those for cocaine and heroin combined. Data from the Centers for Disease Control and Prevention (CDC) also show that deaths related to synthetic opioids (e.g., fentanyl, tramadol etc.) excluding methadone exceeded the deaths associated with natural and semisynthetic opioids and methadone combined in recent years.[6] Data from the CDC also indicate that illegally manufactured fentanyl, its analogues and heroin are the main factors driving the marked increase in opioid overdose deaths in the last few years.

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[3] Drug Enforcement Administration, 2017 National Drug Threat Assessment summary, U.S. Department of Justice (2017).

[4] Arthur Hughes, Matthew R. Williams, Rachel N. Lipari, Jonaki Bose, Elizabeth A.P. Copello & Larry A. Kroutil, *Prescription Drug Use and Misuse in the United States: Results from the 2015 National Survey on Drug Use and Health*, National Survey on Drug Use and Health, Sept. 2016.

[5] Key Substance Use and Mental Health Indicators in the United States: Results from the 2016 National Survey on Drug Use and Health, defines misuse of substances as: "in any way that a doctor did not direct you to use them, " including (1) use without a prescription of the respondent's own; (2) use in greater amounts, more often, or longer than the respondent was told to take them; or (3) use in any way a doctor did not direct the respondent to use them. https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.htm.

[6] Provisional synthetic opioid death overdose counts are based on CDC data available for analysis as of August 6, 2017, based on the 12-month reporting period ending January 2017. See https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates.pdf accessed 09-06-2017.

According to the more recent data from CDC, fentanyl and its analogs may be emerging as a unique class of its own for abuse without mixing with other illicit opioids.[7] In recognition of an unprecedented, dramatic and continuing escalation in opioid related overdoses and overdose deaths, on October 26, 2017, the President of the United States has declared the opioid crisis as a national public health emergency.

3. Pharmacology and potency considerations

3.1. Pharmacological class

Pharmacologically, fentanyl falls into a class of drugs known as "opioid analgesics." Based on the method of manufacturing, opioid analgesics can be further subdivided into three different categories such as natural, semisynthetic and synthetic opioids: (1) Natural opioids are those that are obtained from natural sources (e.g., morphine and codeine from opium poppy); (2) Semisynthetic opioids (e.g., oxycodone, hydrocodone, hydromorphone, oxymorphone etc.) are manufactured by chemical modification of natural opioids; (3) Synthetic opioids (e.g., fentanyl, methadone, meperidine, tramadol etc.) are not present in nature and are man made chemical substances produced in laboratories through chemical synthesis. These opioid analgesics are mainly used to manage pain associated with various clinical conditions.

3.2. Pharmacological and pharmacodynamic effects of opioid analgesics

Scientific investigations have shown that opioid analgesics such as morphine, hydrocodone and oxycodone produce pharmacological effects including euphoria, analgesia, sedation, constipation, respiratory depression, and dependence. These effects are produced primarily through activation of μ-opioid receptors and these analgesics act as agonists at these receptors.[8] Fentanyl and fentanyl analogues that are used in clinical medicine (e.g., sufentanil, alfentanil, remifentanil) and in veterinary medicine (carfentanil and thiafentanil) are similar in their pharmacological effects to other prescription opioid analgesics (e.g., oxycodone, hydrocodone, morphine etc.) and heroin. These opioid analgesics activate the reward pathways in the brain to produce intense euphoria and are a highly addictive class of drugs.

3.3. Analgesic potency of fentanyl and its analogues relative to morphine

Fentanyl and fentanyl analogues used in medical settings (e.g., sufentanil, alfentanil, remifentanil) and in veterinary medicine (carfentanil and thiafentanil) are high potency μ-opioid

[7] Julie K. O'Donnell, John Halpin, Christine L. Mattson, Bruce A. Goldberger & R. Matthew Gladden, *Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 — 10 States, July–December 2016*, 66 Morbidity and Mortality Weekly Report, 1197-1202 (Nov. 3, 2017), *available at* https://www.cdc.gov/mmwr/volumes/66/wr/mm6643e1.htm.

[8] H.B. GUTSTEIN & H. AKIN, GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, ch. 21 OPIOID ANALGESICS, (McGraw-Hill 11th ed., 2006) (2005).

receptor agonists with rapid onset, and short duration of action.[9] [10] [11] They are highly lipophilic and are rapidly distributed across the blood-brain barrier. Fentanyl is about 50 to 80 times more potent that heroin[12] and about 100 times more potent than morphine[13] as an analgesic. Alfentanil[14] and carfentanil[15] are 600 and 10,000 times more potent than morphine, respectively, while thiafentanil is slightly less potent than carfentanil.[16] Sufentanil is 1000 times more potent than morphine while remifentanil is equipotent to fentanyl (Table 1).[17] The pharmacological and physicochemical properties of fentanyl and its analogues in combination with their potential to cause respiratory depression are likely to enhance their risk of causing life-threatening adverse effects when misused or abused. [18]

Table 1. Analgesic potencies of fentanyl and FDA approved fentanyl analogues

Drug	*Potency relative to morphine*
Fentanyl	100
Remifentanil	100
Alfentanil	600
Sufentanil	1000
Carfentanil	10000
Thiafentanil	Slightly less potent than carfentanil

3.4. Abuse and addiction potential of fentanyl and it analogues and other opioids

Prescription opioid analgesics (e.g., hydrocodone, oxycodone, morphine and fentanyl etc.) and heroin bind to and activate μ-opioid receptors and produce positive subjective and strong reinforcing effects. Such effects are thought to be responsible for their high potential for abuse and addiction. Novel fentanyl analogues that have been encountered by law enforcement in recent years in the United States also have been shown to bind to and to activate μ-opioid

[9] H.B. GUTSTEIN & H. AKIL, *Opioid Analgesics, in* GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS ch. 21 (Laurence L. Brunton, John S. Lazo & Keith L. Parker, McGraw-Hill 11th ed., 2006).

[10] Department of Health and Human Services (HHS) Review (2011) Basis for the Recommendation to Place Thiafentanil and Its Salts in Schedule II of the Controlled Substances Act (CSA).

[11] W.F.M. Van Bever, C.J.E. Niemegeers, K.H.L. Schellekens & P.A.J. Janssen, *N-4-Substituted 1-(2-Arylethyl)-4-Piperidinyl-N-Phenylpropanamides, a Novel Series of Extremely Potent Analgesics With Unusually High Safety Margin*, 26 Arzneimittel-Forschung, 1548-1551 (1976).

[12] C.W. Reichle, G.M. Smith, J.S. Gravenstein, S.G. Macris & H.K. Beecher, *Comparative Analgesic Potency of Heroin and Morphine in Postoperative Patients*, 136 J Pharmacol Exp Ther., 43-6 (1962).

[13] T.L. YAKSH & M.S. WALLACE, *Opioids, Analgesia, and Pain Management, in* GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (Laurence L. Brunton, John S. Lazo & Keith L. Parker, McGraw-Hill 12th ed., 2011).

[14] T. REISINE & G. PASTERNAK, *Opioid analgesics and antagonists, in* GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS ch. 23 (Laurence L. Brunton, John S. Lazo & Keith L. Parker, McGraw-Hill 9th ed., 1996).

[15] P.G. Van Daele, M.F. De Bruyn, J.M. Boey, S. Sanczuk, J.T. Agten & P.A. Janssen, *Synthetic Analgesics: N-(1-[2-Arylethyl]-4-Substituted 4-Piperidinyl) N-Arylalkanamides,* 26 Arzneimittenforschung, 1521-31 (1976).

[16] Department of Health and Human Services (HHS) Review, Basis for the Recommendation to Place Thiafentanil and Its Salts in Schedule II of the Controlled Substances Act (CSA), at 2 (2011).

[17] T.L. YAKSH & M.S. WALLACE, *Opioids, Analgesia and Pain Management, in* GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (Laurence L. Brunton, John S. Lazo & Keith L. Parker, McGraw-Hill 12th ed., 2011).

[18] H.B. GUTSTEIN & H. AKIL, *Opioid Analgesics, in* GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (Laurence L. Brunton, John S. Lazo & Keith L. Parker, McGraw-Hill 11th ed., 2006).

receptors and act as opioid agonists.[19] These preliminary findings suggest these novel fentanyl analogues are likely to have high abuse and addictive potential similar to fentanyl and other clinically used opioid analgesics (e.g., hydrocodone, oxycodone, morphine, etc.) and heroin. This is further supported by marked increase in the law enforcement encounters and in deaths associated with the illicitly produced fentanyl analogues in recent years. [20] [21] [22]

It is worth noting that drugs with similar abuse and addictive potential may actually be abused at different rates. This is true because there are many other factors that contribute to the rate at which a particular drug is actually abused. For example, such factors may include ease of drug availability, ease of drug manipulation such as extraction of active drug from pharmaceutical products, cost, profit margins, relative ease of clandestine synthesis and trafficking, and the availability of precursor and other chemicals for synthesis. The public health data as discussed later in this document show that harms associated with fentanyl abuse far exceed those associated with other opioid analgesics (e.g., hydrocodone, oxycodone, morphine, etc.).

The DEA has been tracking the increase in and evolution of fentanyl analogues that are being encountered in the recreational drug market in the United States. Since July of 2015, the DEA has issued six temporary scheduling orders to control nine fentanyl analogues as Schedule I substances under the CSA. These actions have been issued every few months in response to the appearance of new fentanyl analogues in the illicit drug market.[23] Currently, there are a total of 17 fentanyl-related substances controlled in Schedule I.

3.5. Potency differences in the abuse liability of fentanyl relative to heroin

Abuse potential of opioid analgesics in humans is typically evaluated by recording the positive subjective effects following drug administration. There are published scientific studies addressing the subjective effects of fentanyl in both drug-naive healthy individuals and in heroin

[19] *In vitro* pharmacological studies are conducted by the United States Veterans Affairs Administration under an interagency agreement with the DEA; *In vivo* studies are conducted by academic and research institutions under contracts with the DEA and by the National Center for Toxicological Research of the FDA under an interagency agreement with the DEA.
[20] A.B. Peterson, R.M. Gladden, C. Delcher, E. Spies, A. Garcia-Williams, Y. Wang, J. Halpin, J. Zibbell, C.L. McCarty, J. DeFiore-Hyrmer, M. DiOrio & B.A. Goldberger, *Increases in Fentanyl-Related Overdose Deaths – Florida and Ohio, 2013-2015*, 65 Morbidity and Mortality Weekly Report, 844-849 (2016), *available at* https://www.cdc.gov/mmwr/volumes/65/wr/mm6533a3.htm.
[21] J.K. O'Donnell, J. Halpin, C.L. Mattson, B.A. Goldberger & R.M. Gladden, *Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 — 10 States, July–December 2016*, 66 Morbidity and Mortality Weekly Report, 1197-1202 (Nov. 3, 2017), *available at* https://www.cdc.gov/mmwr/volumes/66/wr/mm6643e1.htm.
[22] J.K. O'Donnell, R.M. Gladden & P. Seth, *Trends in deaths involving heroin and synthetic opioids excluding methadone, and law enforcement drug product reports, by census region – United States, 2006-2015*, 66 Morbidity and Mortality Weekly Report, 1197-1202, 897-903 (Sept. 1, 2017), *available at* https://www.cdc.gov/mmwr/volumes/66/wr/pdfs/mm6634.pdf.
[23] July 17, 2015, 80 Fed. Reg. 42381; May 12, 2016, 81 Fed. Reg. 29492; November 29, 2016, 81 Fed. Reg. 85873; May 3, 2017, 82 Fed. Reg. 20544; July 14, 2017, 82 Fed. Reg. 32453; October 26, 2017, 82 Fed. Reg. 49504.

abusers. Based on review of several published studies,[24] [25] [26] [27] the lowest dose of fentanyl that produced significant subjective effects in drug-naïve volunteers appeared to be 50 micrograms.

Comer et al., (2008) conducted a double-blind, placebo-controlled inpatient study investigating the subjective effects of intravenously administered fentanyl (0.0625, 0.125, 0.187 and 0.25 mg), heroin (3.125, 6.25, 12.5 and 25 mg), morphine (6.25, 12.5, 25 and 50 mg), buprenorphine (0.125, 0.5, 2 and 8 mg) and oxycodone (6.25, 12.5, 25 and 50 mg) in individuals with past history of heroin abuse. All drugs produced dose-dependent increases in positive subjective effects such as "I feel a good drug effect" and "I like the drug." The lowest doses of fentanyl, heroin, morphine and oxycodone that produced significant increases in both of these subjective effects are summarized in Table 2. Fentanyl was found to be the most potent, while oxycodone and morphine were the least potent in producing these effects. The threshold dose of fentanyl that produced significant increases in these two positive subjective effects in individuals with history of heroin abuse was 0.187 mg, while the corresponding doses for heroin and morphine were 6.25 and 12.5 mg, respectively. These data suggest that fentanyl is about 33 and 67 times more potent than heroin and morphine, respectively in producing the above mentioned positive subjective effects.

Table 2. Threshold dose of fentanyl to produce positive subjective effects in human subjects with past history of heroin abuse*

Drug	*Threshold dose (mg)**	*Potency relative to morphine*
Morphine	12.5	1
Oxycodone	9.4**	1.3
Heroin	6.25	2
Fentanyl	0.187	67

*The lowest dose that produced significant increases in positive subjective effects namely, "I feel a good drug effect" and "I like the drug."

**For oxycodone, the lowest dose that produced significant increases in "I feel a good drug effect" was 6.25 mg while its lowest dose to produce significant increases in "I like the drug" was 12.5 mg. The mean of these two doses was presented as the threshold dose for oxycodone.

4. Toxicity of fentanyl and its analogues *versus* other opioids

4.1. Acute lethal dose in humans

[24] J.P. Zacny, J.L. Lichtor, J.G. Zaragoza & H. de Wit, *Subjective and behavioral responses to intravenous fentanyl in healthy volunteers*, 107 Psychopharmacology, 319-326 (1992).

[25] J.P. Zacny, M.A. McKay, A.Y. Toledano, S. Marks, C.J. Young, P.A. Klock & J.L. Apfelbaum, *The effects of a cold-water immersion stressor on the reinforcing and subjective effects of fentanyl in healthy volunteers*, 42 Drug and Alcohol Dependence, 133-142 (1996).

[26] M.M. Ghoneim, S.P. Mewaldt & J.W. Thatcher, *The Effect of Diazepam and Fentanyl on Mental, Psychomotor and Electroencephalographic Functions and Their Rate of Recovery*, 44 Psychopharmacologia, 61-66 (1975).

[27] M. Heohe, T. Duka & A. Doenicke, *Human Studies on the Mu opiate Receptor Agonist Fentanyl: Neuroendocrine and Behavioral Responses*, 13 Psychoneuroendocrinology, 397-408 (1988).

Acute lethal doses of fentanyl and other prescription opioid analgesics are difficult to estimate in a precise manner. Several variables such as differences in individual sensitivity, degree of tolerance to opioids, concomitant use of central nervous depressants and drugs that alter opioid metabolism, preexisting medical conditions etc., further complicate the assessment of lethal doses of opioids. Despite these limitations, some information exists in the published scientific literature data regarding acute lethal doses of opioids. For example, Gable (2004)[28] searched the Biosis, Science Citation Index, and the National Library of Medicine databases using several search criteria (e.g., fatal overdose, lethal dose 50, etc.) and retrieved 3000 records related to acute toxicity of various psychoactive substances. For heroin, this author found a total of 178 fatal human cases. Upon reviewing these cases, this author concluded that the usual lethal dose of heroin reportedly administered by decedents was 50 mg with a range of 12 to 180 mg.

Studies determining acute lethal dose of fentanyl in humans using the similar criteria mentioned above for heroin have not been found in the scientific literature. One published report[29] mentions an acute lethal dose for fentanyl as 2 mg. Salem and Katz (2014)[30] using lethal dose of fentanyl in monkeys extrapolated it to humans and reported the lethal dose of fentanyl as 2 mg in humans. Thus based on this limited information, fentanyl appears to be about 25 times more potent than heroin in producing acute lethality in humans. Acute lethal doses of fentanyl analogues in humans have not been reported.

4.2. Acute lethal doses in animals

The intravenous doses of morphine, heroin, fentanyl and its analogues that are expected to cause death of 50 percent of an entire defined population of experimental animals (LD50) in a given study are shown in Table 3. These data show that unlike the large potency differences in analgesic effects of morphine versus fentanyl and its analogues such as carfentanil, alfentanil and sufentanil (Table 1), the corresponding potency differences in producing acute lethality are smaller in magnitude. Fentanyl, carfentanil, alfentanil, sufentanil and heroin when administered intravenously in rats are 73, 65.8, 4.4 - 5.2, 12.5 and 9.9 fold more potent in producing acute lethality as compared to morphine, respectively.

Table 3. LD50 doses of selected prescription opioids administered intravenously in mice and rats

Drug	*Mouse*		*Rat*	
	LD50 (mg/kg)	*Potency Relative to morphine*	*LD50 (mg/kg)*	*Potency Relative to morphine*
*Morphine Sulfate**	156	1	223	1
*Heroin ***	21.8	7.16	22.5	9.9
*Fentanyl citrate****	10.1	15.4	3.05	73.1
Carfentanil§	Not tested	Not tested	3.39	65.8

[28] R.S. Gable, *Comparison and Acute Lethal Toxicity of Commonly Abused Psychoactive Substances*, 99 Addiction, 686-96 (2004).
[29] See Pharmacology, Fentanyl Drug Profile, European Monitoring Centre for Drugs and Drug Addiction (Jan. 8, 2015), http://www.emcdda.europa.eu/publications/drug-profiles/fentanyl.
[30] H. SALEM & S.A. KATZ, INHALATION TOXICOLOGY 252 (CRC Press, 3rd ed., 2014). ISBN-10: 1466552735.

Alfentanil hydrochloride§§	72-74	2.1-2.2	43-51	4.4-5.2
*Sufentanil citrate**	18.7	8.3	17.9	12.5

*Data are taken from the manufacturer's safety data sheets of Akorn. **Data are taken from the manufacturers safety data sheet of Cayman. ***Data are taken from the manufacturer's safety data sheet of Pfizer. §Van Bever WFM et al., (1976) Arzneimittel-Forschung, 26: 1548-1551. §§Data are taken from the manufacturer's safety data sheet of Hospira.

4.3. Toxicity associated with chronic use and abuse of fentanyl and its analogues

Chronic use and abuse of fentanyl and its analogues, similar to other prescription opioid analgesics and heroin, can lead to opioid use disorder (also referred as "addiction" or "abuse" or "dependence") manifested as unsuccessful attempts to cut down the opioid use and failure to fulfill the social obligations at school, home and employment. Development of opioid use disorder increases the risk of opioid related overdose deaths.[31] Additionally, individuals abusing drugs through parenteral route of administration are at higher risk of developing blood-borne infections such as HIV, and viral hepatitis B and C.[32]

5. Public health impact of abuse of fentanyl and its analogues relative to prescription opioid analgesics

5.1. Pharmacological considerations

Two main pharmacological effects of opioid analgesics (e.g., oxycodone, hydrocodone, morphine etc.) play a central role in their adverse impact on the public health: (1) Opioid analgesics activate the reward pathways in the brain to produce intense euphoria and are a highly addictive class of drugs; and (2) in high doses, opioid analgesics consistently depress the respiratory center in brain. Deaths resulting from overdoses with these substances are most often due to respiratory depression leading to complete failure of breathing. Another important overdose risk factor is an individual's opioid tolerance. Those who have little or no tolerance are at a higher risk of opioid analgesic overdose and death.

Additionally, the concomitant use of other central nervous system depressant drugs such as other opioids, sedative or hypnotics, general anesthetics, phenothiazines (antipsychotics), tranquilizers, skeletal muscle relaxants, sedating antihistamines or alcohol beverages may enhance depressant effects of opioid analgesics including fentanyl and its analogues. Concomitant use of drugs that inhibit fentanyl metabolism and discontinuation of drugs that enhance fentanyl metabolism can also result in a fatal overdose of fentanyl.

[31] Kaplovitch E, Gomes T, Camacho X, Dhalla IA, Mamdani MM, Juurlink DN (2015) Sex Differences in Dose Escalation and Overdose Death during Chronic Opioid Therapy: A Population-Based Cohort Study. PLoS one 10:e0134550. http://dx.doi.org/10.1371/journal. Pone. 0134550

[32] E. Shapatava, K.E. Nelson, T. Tsertsvadze & C. Del Rio, *Risk Behaviors and HIV, Hepatitis B, and Hepatitis C Seroprevalence Among Injection Drug Users in Georgia*, 82 Drug Alcohol Depend, S35-S38 (2014); V. Allread & S. Paul, The Misuse and Abuse of Prescription Medications: Part 1 Current Trends, 7 MD Advis, 12-20 (2014).

5.2. Public health impact of abuse of prescription opioid analgesics and pharmaceutical fentanyl

Since the 1990s, a major shift comprising of a gradual and marked increase in the clinical use of prescription opioid analgesics for the management of pain has taken place in the United States. Total annual prescriptions for opioid analgesics increased gradually peaking around 2010-2011.[33] [34] In 2011, there were 303 million prescriptions for all opioid analgesics combined.[35] [36] In parallel to these increases in prescriptions for opioid analgesics, diversion (forensic drug exhibits), emergency department (ED) visits, inpatient hospital admissions, admissions for addiction treatments and deaths related to these opioid analgesics also gradually and markedly escalated (Table 4). For example, the DEA's National Forensic Laboratory System (NFLIS) annual reports mentioned 7,680 and 137,670 forensic drug exhibits for all prescription opioid analgesics in 2000 and 2010, respectively. There were 17,545 inpatient hospitalizations in 2006 for prescription opioid analgesics excluding methadone.[37] In 2011, there were 366,181 ED visits related to nonmedical use of narcotic pain relievers (opioid analgesics).[38] According to the CDC, there were 16,651 deaths related to opioid analgesics in 2010.[39]

Table 4. Increases in annual prescriptions (or kilograms) and adverse health impact (emergency department admissions, inpatient hospitalizations, addiction treatment admissions and deaths) related to prescription opioid analgesics as compared to fentanyl or synthetic opioids

Drugs	*Increase in opioid prescriptions from 1998 to 2011*[40] [41] (Increase in kilograms sold from 1999 to 2010)	*Increase in Emergency Department visits*[42] *from 2004 to 2011*	*Increase in impatient hospitalizations from 1999 to 2006*	*Increase in admissions for addiction treatment from 1999 to 2009*	*Increase in deaths from 1999 to 2010*[43]

[33] G.P. Jr. Guy, K. Zhang, M.K. Bohn, J. Losby, B. Lewis, R. Young, L.B. Murphy & D. Dowell, *Vital signs: Changes in opioid prescribing in the United States, 2006 – 2015*, 66 Morbidity and Mortality Weekly Report, 697-704 (2017).

[34] Data source: the National Prescription Audit database of the IMS Health America.

[35] These data do not include data for propoxyphene as this opioid was taken off the market in late 2000.

[36] Data are obtained from the National Prescription Audit database of the IMS Health America.

[37] J.H. Coben, S.M. Davis, P.M. Furbee, R.D. Sikora, R.D. Tillotson & R.M. Bossarte, *Hospitalizations for Poisoning by Prescription Opioids, Sedatives, and Tranquilizers*, 38 Am J Preventive Med., 517-24 (2010).

[38] E.H. Crane, *Emergency Department Visits Involving Narcotic Pain Relievers*, The CBHSQ Report, The Substance Abuse and Mental Health Services Administration (Nov. 5, 2015).

[39] L.H. Chen, H. Hedegaard & M. Warner, *Drug Poisoning Deaths Involving Opioid Analgesics: United States, 1990-2011*, 166 National Center for Health Statistics Data Brief, Centers for Disease Control and Prevention (2014), *available at* https://www.cdc.gov/nchs/products/databriefs/db166.htm.

[40] These data for prescription opioid analgesics do not include data for propoxyphene as this opioid was taken off the market in late 2000.

[41] Data are obtained from the National Prescription Audit database of the IMS Health America.

[42] E.H. Crane, *The CBHSQ Report: Emergency Department Visits Involving Narcotic Pain Relievers*, The Substance Abuse and Mental Health Services Administration, (Nov. 5, 2015).

[43] L.H. Chen, H. Hedegaard & M. Warner, *Drug Poisoning Deaths Involving Opioid Analgesics: United States, 1990-2011*, 166 National Center for Health Statistics Data Brief, Centers for Disease Control and Prevention (2014).

All Prescription Opioid analgesics	2.0-fold (4.0-fold)[44]	2.5-fold	2.6-fold[45]	6-fold[46]	4.1-fold
Fentanyl (or) Synthetic opioids	4.4-fold	2.0-fold			4.1-fold[47]

Increases in prescriptions, forensic drug exhibits and emergency room visits involving fentanyl and deaths involving synthetic opioids excluding methadone (e.g., fentanyl, tramadol etc.) also paralleled increases for all prescription opioid analgesics combined. NFLIS annual reports mentioned 23 and 579 forensic drug exhibits for fentanyl in 2000 and 2010, respectively. According to the CDC, deaths related to synthetic opioids excluding methadone increased from 730 in 1999 to 3,007 in 2010. From 2013 to 2016, deaths related to synthetic opioids excluding methadone markedly escalated. As discussed later in the document, these recent increases in deaths related to this opioid category of drugs are in major part driven by illicitly produced fentanyl and in minor part by illicitly produced fentanyl analogues.

Unlike fentanyl, DEA is currently not aware of diversion and abuse of pharmaceutical products containing fentanyl analogues (alfentanil, remifentanil, sufentanil, carfentanil, and thiafentanil) that are approved by FDA for medical use. Although recently carfentanil appeared on the illicit market, the law enforcement evidence suggests that the carfentanil encountered so far by the law enforcement is of illicit origin and is produced in clandestine labs.

5.3. Public health impact of abuse of illicitly manufactured fentanyl and its analogues

Law enforcement and public health evidence indicate that in the last few years, illicitly manufactured fentanyl and its analogues have been the major contributors to the current opioid public health crisis. Following the peak increase around 2010-2011, total annual prescriptions for opioid analgesics showed a small decline especially from 2014 through 2016. Prescriptions for fentanyl also showed a similar trend with a peak increase occurring in 2008, followed by some decline from 2014 through 2016. In contrast to this decline in fentanyl prescriptions, the number of law enforcement encounters for fentanyl markedly escalated in recent years (Table 5). According to NFLIS database, forensic drug exhibits containing fentanyl increased from 978 in 2013 to 36,134 in 2016 (database queried on October 30, 2017). As of October 30, 2017, NFLIS reports for January - June 2017 for fentanyl were 21,872 and the corresponding data for fentanyl analogues were 6,808, respectively. Similar to the increases in law enforcement encounters for fentanyl, deaths related to synthetic opioids excluding methadone (e.g., fentanyl, tramadol etc.)

[44] L.J. Palouzi, C.M. Jones, K.A. Mack & R.A. Rudd, *Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999—2008*, 60 Morbidity and Mortality Weekly Report, 1487-1492 (Nov. 4, 2011), available at **https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm**.

[45] This change refers to the combined data for methadone and other narcotics.

[46] L.J. Palouzi, C.M. Jones, K.A. Mack & R.A. Rudd, Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999—2008, 60 Morbidity and Mortality Weekly Report, 1487-1492 (Nov. 4, 2011), available at https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm.

[47] Because death data specific for fentanyl is not reported by CDC, death data presented is for category called "synthetic opioid analgesics excluding methadone" which in major part involves fentanyl in recent years.

also increased markedly in recent years (Table 5). Evidence indicates that deaths in this opioid drug category are primarily driven by illicitly manufactured fentanyl. [48] [49]

According to the CDC, drug overdose deaths involving synthetic opioids (e.g., fentanyl and tramadol, etc.) excluding methadone increased from 3,105 in 2013 to 9,580 in 2015. According to provisional data released in August 2017 by the CDC, National Center for Health Statistics, drug overdose deaths involving synthetic opioids excluding methadone for the 12-month period ending in January of 2017 (20,145 deaths) approximately doubled from the corresponding data for the period ending in January of 2016 (9,945 deaths). An estimated 55 Americans are dying *every day* from overdoses of synthetic opioids excluding methadone.[50] Deaths related to synthetic opioids excluding methadone exceeded the deaths associated with natural and semisynthetic opioids and methadone combined.[51] Several recently published reports attributed the majority of these synthetic opioid (excluding methadone) related deaths mainly to illicitly manufactured fentanyl and to a minor extent to illicitly manufactured fentanyl analogues,[52] [53] [54] [55] [56] [57] [58] [59] but not due to pharmaceutical fentanyl. Illicitly manufactured

[48] R.M. Gladden, P. Martinez & P. Seth, *Fentanyl Law Enforcement Submissions and Increases in Synthetic Opioid–Involved Overdose Deaths — 27 States, 2013–2014*, 65 Morbidity and Mortality Weekly Report, 837-843 (2016), *available at* https://www.cdc.gov/mmwr/volumes/65/wr/mm6533a2.htm.

[49] J.K. O'Donnell, R.M. Gladden & P. Seth, *Trends in Deaths Involving Heroin and Synthetic Opioids Excluding Methadone, and Law Enforcement Drug Product Reports, by Census Region – United States, 2006-2015*, 66 Morbidity and Mortality Weekly Report, 1197-1202, 897-903 (Sept. 1, 2017), *available at* https://www.cdc.gov/mmwr/volumes/66/wr/pdfs/mm6634.pdf.

[50] Provisional synthetic opioid death overdose counts are based on CDC data available for analysis as of August 6, 2017, based on the 12-month reporting period ending January 2017. See https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates.pdf accessed 09-06-2017.

[51] Provisional synthetic opioid death overdose counts are based on CDC data available for analysis as of August 6, 2017, based on the 12-month reporting period ending January 2017. See https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates.pdf accessed 09-06-2017.

[52] DEA. DEA Issues Nationwide Alert on Fentanyl as Threat to Health and Public Safety, March 8, 2015, https://www.dea.gov/divisions/hq/2015/hq031815.shtml.

[53] CDC. Increases in fentanyl drug confiscations and fentanyl related overdose fatalities. HAN Health Advisory, 2015, https://emergency.cdc.gov/han/han00384.asp.

[54] A.B. Peterson, R.M. Gladden, C. Delcher, E. Spies, A. Garcia-Williams, Y. Wang, J. Halpin, J. Zibbell, C.L. McCarty, J. DeFiore-Hyrmer, M. DiOrio & B.A. Goldberger*, Increases in Fentanyl-Related Overdose Deaths – Florida and Ohio, 2013-2015*, 65 Morbidity and Mortality Weekly Report, 844-849 (Aug. 26, 2016), *available at* https://www.cdc.gov/mmwr/volumes/65/wr/mm6533a3.htm.

[55] R.M. Gladden, P. Martinez & P. Seth, *Fentanyl Law Enforcement Submissions and Increases in Synthetic Opioid–Involved Overdose Deaths — 27 States, 2013–2014*, 65 Morbidity and Mortality Weekly Report, 837-843 (Aug. 26, 2016), *available at* https://www.cdc.gov/mmwr/volumes/65/wr/mm6533a2.htm.

[56] , N.J. Somerville, J. O'Donnell, R.M. Gladden, J.E. Zibbell, T.C. Green, M. Younkin, S. Ruiz, H. Babakhanlou-Chase, M. Chan, B.P. Callis, J. Kuramoto-Crawford, H.M. Neilds & A.Y. Walley, *Characteristics of Fentanyl Overdose — Massachusetts, 2014–2016*, 66 Morbidity and Mortality Weekly Report, 382-386 (Apr. 14, 2017), *available at* https://www.cdc.gov/mmwr/volumes/66/wr/mm6614a2.htm.

[57] J.K. O'Donnell, J. Halpin, C.L. Mattson, B.A. Goldberger & R.M. Gladden, *Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 — 10 States, July – December 2016*, 66 Morbidity and Mortality Weekly Report, 1197-1202 (Nov. 3, 2017), *available at* https://www.cdc.gov/mmwr/volumes/66/wr/mm6643e1.htm.

[58] R. Daniulaityte, Matthew P. Juhascik, Kraig E. Strayer, Ioana E. Sizemore, Kent E. Harshbarger, Heather M. Antonides & Robert R. Carlson*, Overdose Deaths Related to Fentanyl and Its Analogs — Ohio, January–February 2017*, 66 Morbidity and Mortality Weekly Report, 904-908 (Sept. 1, 2017), available at https://www.cdc.gov/mmwr/volumes/66/wr/mm6634a3.htm.

[59] D. Dowell, R.K. Noonan & D. Houry, *Underlying Factors in Drug Overdose Deaths*, The Journal of the American Association, E1-E2 (Oct. 11, 2017).

fentanyl and its analogues have caused a recent spike in overdose deaths, whereas deaths from prescription opioid analgesics have stabilized.[60] [61]

Table 5. Changes in annual prescriptions and increases in forensic drug exhibits for fentanyl and deaths related to synthetic opioids excluding methadone

Change in fentanyl prescriptions[62] from 2013 to 2016	*Change in forensic drug exhibits[63] for fentanyl from 2013 to 2016*	*Change in deaths related to synthetic opioids excluding methadone from 2013 to 2016*	*Change in deaths related to synthetic opioids excluding methadone from 1999 to 2016*
13.8% decline	37-fold increase	6.5-fold increase[64]	27.6-fold increase

The CDC data also indicate that the deaths related to synthetic opioids excluding methadone (e.g., fentanyl, tramadol, etc.) increased by 27.6-fold from 730 deaths in 1999 to 20,145 in 2016.

The population likely to consume fentanyl analogues overlaps with the population consuming heroin, fentanyl and other prescription opioid analgesics. Just as with heroin and prescription opioid analgesics, once an individual consumes a fentanyl analogue he or she is at risk for developing a substance use disorder,[65] overdose, and death. Because illicitly produced fentanyl and its analogues are obtained through unregulated sources, the identity, purity, and quantity of such drugs are uncertain and inconsistent, thus posing significant adverse health risks to the end user. Harms associated with the abuse of these substances are further heightened by the fact that users may unknowingly consume unknown amounts of fentanyl and/or its analogues in products marketed as heroin or in counterfeit prescription pills. Recent CDC data demonstrated that injection is the most common route of administration in deaths related to fentanyl and its analogues.[66] This route of administration combined with high potencies of fentanyl and its analogues further increase the risk of overdoses and overdose deaths associated with these drugs.

I appreciate the opportunity to provide the Commission with my views and comments, and on behalf of the DEA I thank the Commission for taking up this important issue.

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[60] M.P. Prekupec, P.A. Mansky & M.H. Baumann, *Misuse of Novel Synthetic Opioids: A Deadly New Trend*, 11 J Addict Med., 256-265 (2017).

[61] R.A. Rudd, P. Seth, F. David & L. Scholl, *Increases in Drug and Opioid-Involved Overdose Deaths – United States, 2010-2015*, 65 Morbidity and Mortality Weekly Report, 1445-1452 (Dec. 30, 2016).

[62] Data are obtained from the National Prescription Audit database of the IMS Health America.

[63] Data are obtained from the DEA's National Forensic Laboratory Information System.

[64] According to the medical examiner reports published by the Florida Department of Law Enforcement, deaths related to fentanyl increased by 5.6-fold from 292 in 2013 to 1644 in 2016 in Florida. In 2016, there were 1,026 deaths related to fentanyl analogues. Available at http://www.fdle.state.fl.us/MEC/Publications-and-Forms.aspx.

[65] For a definition of the term substance use disorder, s*ee* DSM-IV – Reference: American Psychiatric Association (1994) Statistical Manual of Mental Disorders (DSM-IV) (4th ed.), Washington DC.

[66] J.K. O'Donnell, J. Halpin, C.L. Mattson, B.A. Goldberger & R.M. Gladden, *Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 — 10 States, July–December 2016*, 66 Morbidity and Mortality Weekly Report, 1197-1202 (Nov. 3, 2017), available at https://www.cdc.gov/mmwr/volumes/66/wr/mm6643e1.htm.