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Prescription Drug Research Center

Special Report

Fentanyl Analogs in Street Drugs

Prepared for Center for Substance Abuse Treatment/JBS
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Note: All source materials used and cited in this report are in the public domain. In some cases, specific details about active cases were obtained from unsealed court filings and affidavits of law enforcement officers. Although containing sensitive information, these are public records. Nonetheless, readers of this report are requested to respect the sensitive nature of some of the information reported in this document.

Background

Fentanyl was developed in 1963 at the Janssen Research Laboratory in Belgium, and in 1968, was approved by the U.S. Food and Drug Administration (FDA) as an intravenous anesthetic under the trade name, Sublimaze™ (Taylor Pharmaceuticals, San Clemente, CA). Fentanyl and several of its analogs are approved in the U.S. for medical use and listed under the Controlled Substances Act (CSA) as C-II controlled substances because of their high abuse potential. There also are unapproved fentanyl analogs, such as 3-methylfentanyl, 3-methylthiofentanyl, alpha-methylfentanyl, alpha-methylthiofentanyl, beta-hydroxy-3-methylfentanyl, beta-hydroxyfentanyl, para-fluorofentanyl, and thiofentanyl. The unapproved versions of fentanyl are listed as C-I controlled substances and cannot be used lawfully for medical purposes in the U.S. (Drug Enforcement Administration, 2007)

Pharmaceutical Versions of Fentanyl in the U.S.

In 1990, the FDA approved a transdermal form of fentanyl called Duragesic® (Alza Corp, Mountain View, CA), the first outpatient form of fentanyl available in the U.S. Initially approved to treat moderate to severe malignant pain, it later was approved to treat moderate to severe non-malignant pain. In 1997, the FDA approved an oral transmucosal form of fentanyl, called Actiq™ (Cephalon, Salt Lake City, UT) for break-through cancer pain, and in January 2005, the FDA approved a generic version of the fentanyl transdermal system in a solid matrix patch (Mylan Laboratories, Pittsburgh, PA). (Wolters Kluwer Health Inc., 2005) On May 22, 2006, the FDA approved Ionsys® (Alza Corp, Mountain View, CA), a fentanyl iontophoretic transdermal system approved for in-patient-only acute postoperative pain. On February 7, 2007, the FDA approved Fentora® (Cephalon, Salt Lake City, UT), a fentanyl tablet designed for buccal administration and indicated for breakthrough cancer pain.

Emergence of Clandestinely Produced Fentanyl and Fentanyl Analogs

In the late 1970s, authorities in California discovered the presence of an unusual but potent substance that was being sold as heroin on the street. Called "China White[a]," this new substance was identified initially as 3-methylfentanyl, a known fentanyl analog. Additional forensic examination, however, showed it to be alpha-methylfentanyl, a substance having twice the potency of ordinary pharmaceutical-grade fentanyl. As a new chemical entity, statutes then in force did not cover it. It was not until 1981 that alpha-methylfentanyl was scheduled under the CSA as a C-I controlled substance. (Federal Register, 1981; Henderson GL, 1989)

In the intervening 25 years, clandestinely produced fentanyl analogs have appeared in the street drug trade and usually with predictable consequences. Emergency medical technicians are often the first to learn of street fentanyl's presence because of the sudden rise in drug overdose calls that invariably follows the arrival of fentanyl in an area.

[a] Also known as "synthetic heroin" or "synthetic morphine."

In February 2006, Chicago authorities identified fentanyl in connection with the drug overdose deaths of about a dozen heroin addicts. Since then, fentanyl-related overdose deaths have occurred in Philadelphia, Harrisburg (PA), Camden (NJ), New Castle County (DE), Detroit, and Baltimore. More recently, St. Louis has been added to this list.

According to a Drug Enforcement Administration (DEA) notice recently published in the Federal Register, the following jurisdictions have confirmed illicit fentanyl-related deaths in the numbers shown for the periods indicated:

Table 1. Confirmed Fentanyl Deaths

Jurisdiction	Dates	# of Deaths
Philadelphia , PA	4/13/06-9/27/06	179
Cook County, IL	4/18/05-11/9/06	314
Wayne County, MI	8/27/05-12/31/06	230
St Louis, MO	8/16/05-8/28/06	33
New Jersey	1/25/06-9/21/06	86
Wilmington, DE	4/20/06-9/2/06	19
Total		861

Source: Drug Enforcement Administration (FR Doc 07-2015, p. 20039)

In addition to these 861 fentanyl-related deaths, the DEA report includes an additional 111 confirmed fentanyl-related deaths reported by other jurisdictions, for a total of 972 confirmed fentanyl-related deaths, as of April 23, 2007. An additional 162 deaths are "suspected fentanyl-related deaths," according to the DEA report. (Federal Register, 2007)

Details

In February 2006, after fentanyl-laced heroin was implicated in a series of drug overdose deaths in Chicago and Detroit, local media at first speculated that pharmaceutical fentanyl was to blame and even provided excerpts from medical sources, such as the *Physicians' Desk Reference,* to describe the drug. (Schmitt B, Norris K, & Warikoo N, 2006; Sweeney A, 2006b) These press accounts caused patients undergoing medically supervised treatment with fentanyl to believe, incorrectly, that pharmaceutical fentanyl may have caused the reported deaths.

By May 2006, media stories, citing unnamed local and federal authorities, had begun to hint that the source of the deadly fentanyl being mixed with heroin and sold on the streets of Chicago, Detroit, Philadelphia, and elsewhere, might be "an illegal lab, possibly as far away as Mexico." (Sweeney A, 2006a)

Also in May 2006, the DEA's *Microgram Bulletin*, a forensic science newsletter sent to subscribers, issued a "Special Intelligence and Safety Alert" for "all law enforcement personnel, including forensic and crime laboratory personnel, along with medical emergency response

personnel, hospital emergency room personnel, toxicologists, pathologists, etc." to be aware of the emerging outbreak of fentanyl and fentanyl-heroin and to take appropriate and necessary steps to avoid exposure. The *Microgram Bulletin* provided several pages of scientific data about fentanyl intended to inform crime lab personnel and others of specific markers for fentanyl. The DEA document also requested readers to provide information on illicit fentanyl seizures, as well as overdoses and deaths attributed to illicit fentanyl. (Drug Enforcement Administration, Office of Forensic Sciences, 2006e)

By the end of May 2006, the Chicago Police Department had formed a special task force that included officers from other agencies, including the DEA. The goal was to find the source of the fentanyl as quickly as possible. On June 14 and 15, 2006, the DEA hosted a meeting in Chicago of over 125 law enforcement officials, scientists, public health officials, and emergency first responders from seven U.S. cities and Mexico. They had the same goal: locate and eliminate the source of the fentanyl. (Norris K, 2006)

A month later, a similar meeting in Philadelphia of law enforcement, medical, and health department officials also included the directors of the Office of National Drug Control Policy and the National Institute on Drug Abuse. At this meeting, the federal prosecutor told the group that, thus far, there were 170 deaths from fentanyl in the tristate area and another 300 nonfatal overdoses. (DiFilippo D, 2006)

Forensic Intelligence

As in other instances when a new and deadly drug trend emerges rapidly, the work of the forensic chemist is vital for deciphering the origin and spread of the substances involved. As previously stated, police and first responders are usually the first to discover the presence of a drug like fentanyl in the community. It is impossible to state precisely when the most recent outbreak of fentanyl-heroin began, although it appears likely from the sudden rise in recorded heroin overdose deaths that it began sometime in early to mid-2005, probably in Chicago.

The first victims were not opioid-naïve individuals but long-term "seasoned" heroin addicts. This provided the police with a valuable clue: either very powerful heroin was on the street or something else was in the package. Initial tests of seized heroin exhibits showed purity levels within normal ranges, thus indicating that something else was present. It was not long before forensic chemists and medical examiners were able to compare notes and discover the presence of fentanyl in the seized heroin exhibits and body fluids of the decedents.

The next challenge was to identify the specific form of fentanyl from a list of known fentanyl analogs and the original pharmaceutical-grade version. According to the DEA, there are two known routes of synthesis used to produce illicit fentanyl. The first of these is the original 1965 patented process used by the Janssen Pharmaceutica lab in Belgium. The Janssen route begins with a precursor substance called N-benzyl-4-piperidone and requires a complex process considered to be beyond the rudimentary skills of most clandestine laboratory operators. (Federal Register, 2007)

The second method was published in the scientific literature in the early 1980s and is referred to as the Siegfried route. This process begins with a different precursor, N-phenethyl-4-piperidone, known as NPP. Variations and modifications to the Siegfried route have been noted by the DEA in four of the five clandestine fentanyl labs seized in the U.S. since 2000.[b] (Federal Register, 2007)

By analyzing the finished product, forensic chemists can tell which method was use to make it and, as a result, know whether the fentanyl has a clandestine or legitimate origin. The Janssen route produces a substance called benzylfentanyl, an impurity that is present in detectable traces when the precursor starting material is N-benzyl-4-piperidone. The Siegfried route, however, produces a different impurity, called 4-anilino-N-phenethyl-4-piperidine, known as ANPP, and is detectable by the lab in the finished product. (Federal Register, 2007)

The cited report was published by DEA in the Federal Register, as required by law, to announce the agency's decision to control NPP, the precursor material for making fentanyl via the Siegfried route. Because of its importance, the DEA's Interim Rule took effect immediately and, as of April 23, 2007, the date of publication, NPP is a List I chemical, meaning that anyone manufacturing, distributing, importing, or exporting NPP must register each location where NPP is handled, maintain records of transactions involving NPP, and take steps to ensure that the chemical is securely stored. The DEA has identified 14 domestic chemical companies that handle NPP and that will be required to comply with the new rule. (Federal Register, 2007)

The DEA report notes that three of the five laboratories seized by law enforcement since 2000 were known to have obtained their NPP from domestic suppliers. The importance of this forensic intelligence is apparent in the following statement in the DEA's Interim Rule:

> From the information and data collected, there is a strong indication that the fentanyl in these confirmed and suspected fentanyl-related deaths is illicitly manufactured rather than diverted from legal pharmaceutical manufacturers…. The current forensic data suggests that most of these fentanyl-related deaths are from fentanyl illicitly manufactured by the Siegfried method using NPP. (Federal Register, 2007, p. 20042)

Clandestine Fentanyl Makers

As reported above, DEA forensic scientists have examined evidence from five illicit fentanyl labs seized by police authorities in the U.S. since 2000. Four of the five labs, according to the DEA, used the Siegfried method or a modified version of the Siegfried method to manufacture illicit fentanyl. In addition to these lab seizures, police and sheriff's departments throughout the country have made a number of seizures of illicit fentanyl in bulk, as well as in smaller packets, sometimes alone or in combination with heroin. These seizures, like the labs, help the authorities identify the sources, methods, and precursor substances used to manufacture the drug. It is worth taking a moment to review a representative sample of the data regarding

[b] Detailed recipes for making a fentanyl analog, "beta-hydroxy-alpha-methylfentanyl," have appeared on the Internet as far back as 1998. (See Appendix A for a sample)

seizures reported to, and by, the DEA's Office of Forensic Sciences. The descriptions presented here illustrate the complexity of the problem and the diversity of the fentanyl substances encountered by law enforcement throughout the nation.

Omaha, Nebraska (DEA report January 2006)

The Douglas County Sheriff's Department Laboratory was sent eleven (11) apparent OxyContin® tablets by the Cass County Sheriff's Department in Atlantic, Iowa. The tablets were part of a drug and currency seizure case made pursuant to a vehicle stop on westbound Interstate I-80 near Atlantic (about 40 miles east of Omaha, Nebraska). The tablets were light green and bore the logos of 80 mg OxyContin tablets. Using GC/MS, the Douglas County Sheriff's Department Laboratory determined that the tablets were counterfeit OxyContin and instead of oxycodone, each tablet contained fentanyl (not quantitated). This was the first fentanyl exhibit ever submitted to this laboratory. The DEA report adds that other drugs, including personal use amounts of methamphetamine, oxycodone tablets, hydrocodone tablets, and dietary supplement tablets were seized from the vehicle, along with $370,000 in cash. Authorities believe the driver was a currency courier en route from Minneapolis, Minnesota to San Francisco, California. The DEA report also states, "A seizure of similar fentanyl-containing OxyContin mimic tablets was recently made by the New York Police Department (no further details available)." (Drug Enforcement Administration, Office of Forensic Sciences, 2006d)

Figure 1. Fake 80s in IA

Azusa, California (DEA report April 2006)

One of the most significant seizures of illicit fentanyl occurred in November 2005, in Azusa, California, a suburb of Los Angeles, when officers from the Los Angeles Sheriff's Department executed a search warrant on what initially was believed to be clandestine MDMA ("Ecstasy") lab. Upon entering the location, officers found a very large-scale clandestine laboratory, complete with a variety of chemicals, drug manufacturing recipes, laboratory equipment, powders and tablets, and a commercial, full-sized pill punch. Visual examination of the site indicated that the operators were making counterfeit OxyContin® tablets. Thousands of finished tablets showing the "OC" and "80" logos typically found on authentic OxyContin 80 mg tablets were seized, along with a quantity of loose powder ready to be pressed into tablets.


Figure 2. Pill Press at Azusa Lab


Figure 3. Equipment at Azusa l Lab

Because of the unusual nature of the seized items, the authorities requested assistance from the DEA Southwest Laboratory. There, DEA forensic chemists analyzed the materials, consisting of some 80 separate exhibits, using GC, GC/MS, and IR to test the drug substances. The examination showed that the counterfeit OxyContin tablets contained no oxycodone, as might be expected by purchasers, but instead each tablet contained 1.5 mg of fentanyl HCL.

> *Tablets like these have been seized throughout the country, and it appears that this lab was a source or possibly the source…. There were many thousands of these tablets at the laboratory.*
>
> —DEA lab report

The DEA report advised that the fentanyl found at this laboratory "appeared to be synthesized using the Siegfried route, and was found in both tablet and powder form." The report indicated that counterfeit OxyContin tablets containing fentanyl were found throughout the country but their connection to this lab had not been determined by ballistic tests because the seizing authorities had not submitted the tablet press, punches, and dies. Tablets containing other substances, including MDA, TMA (2,4,5-trimethoxyamphetamine) also were seized. Some of the MDA tablets contained fentanyl and caffeine and, according to the DEA laboratory report, were the first ever submissions of "Ecstasy-type tablets" containing these ingredients. (Drug Enforcement Administration, Office of Forensic Sciences, 2006c)

Figure 4. Above: Real Oxy 80s Below: Fake Oxy 80s

Westmoreland, California (DEA report: June 2006)

U.S. Border Patrol Agents stopped a vehicle at a California Highway 86 checkpoint and seized several plastic-wrapped packages containing powder, originally believed to be cocaine and/or methamphetamine. Examination by the DEA Southwest Laboratory determined one of the exhibits consisted of 13.85 kgs of 95 percent d-methamphetamine HCL. The other exhibit, originally believed to be cocaine, upon examination turned out to be 945.1 gms of 83 percent fentanyl HCL. Identified also by GC, ATR, GC/MS, was the presence of 4-anilino-N-phenethylpiperdine (ANPP), a standard marker for illicit fentanyl. The DEA *Microgram Bulletin* reporting this analysis provided a note of caution that even though this large amount of fentanyl was clandestinely produced, it was found to have "extraordinarily high purity" indicating, among other things, that it was produced by an experienced laboratory operator. The report speculated that the source of this shipment might be "responsible for the ongoing epidemic of heroin/fentanyl-related overdoses and deaths in the northeastern and upper Midwestern United States." The report indicated that the source and laboratory might be located in Mexico. The Mexicali, MX, port of entry to Calexico, US, is about 30 miles south of where this event occurred. (Drug Enforcement Administration, Office of Forensic Sciences, 2006b)

Figure 5. Fentanyl Seized by USBP

Painesville, Ohio (DEA report June 2006)

Figure 6. Fentanyl in OH

The Lake County (Ohio) Crime Laboratory received a plastic baggie submitted by a Lake County Deputy Sheriff and retrieved from a gas station restroom where a male subject had been discovered unresponsive and struggling to breath. The subject later advised that he believed the substance was crushed Vicodin®. Examination, however, by the crime laboratory using GC/MS and FTIR determined the substance to be 23 percent fentanyl, 0.7 percent despropionyl fentanyl, trace (0.1 percent) cocaine, and 62 percent mannitol. The report notes that the presence of a trace amount of cocaine may have not been intended but, instead, was the result of contamination. The DEA report stated that this percent of fentanyl (23%) in a "street sample" was extraordinarily high and only because of the early discovery and response by the deputy sheriff and first responders was this subject able to survive. (Drug Enforcement Administration, Office of Forensic Sciences, 2006a)

Houston, Texas (DEA report August 2006)

The Houston Police Department Crime Laboratory received two drug exhibits containing white powder and a chunky white substance, both suspected to be cocaine. A third exhibit contained a brown granular powder, suspected of being heroin. The exhibits had been seized by police from a local residence. Analysis of the white powder (6.7 gms) by color testing and FTIR/ATR, and of the chunky white substance (4.3 gms) by color testing and GC/MS, confirmed cocaine in both cases. The brown powder (0.5 gm) had a distinct odor inconsistent with the usual vinegar odor (from acetic acid) associated with heroin. Further examination, using color testing (Marquis), UV/Vis, and GC/MS determined that the exhibit was not heroin but, instead, 54 percent fentanyl. Benzylfentanyl was also identified. This was the first submission in memory of a fentanyl exhibit to Houston Police Department Crime Laboratory. The DEA report notes the "extremely high" purity of this street level sample of illicit fentanyl.

Figure 7. Fentanyl Seizure in Houston, TX

Albuquerque, New Mexico (DEA report August 2006)

DEA agents in Albuquerque seized 44 green tablets bearing the logos and color of OxyContin 80 mg tablets. The tablets, according to the DEA laboratory report, were distinctly smaller than authentic OxyContin 80 mg tablets. In addition, the tablets were solid green whereas authentic OxyContin 80 mg tablets have a green outer coating but are white on the inside. Analysis by GC/MS, GC/FID, and HPLC indicated that, instead of oxycodone, each tablet contained 1.9 mg of fentanyl. This was the first submission of these types of tablets to the DEA South Central Laboratory.

Figure 8. Fake Oxy 80s in Albuquerque

Blyth, California (DEA report: April 2007)

The Riverside County Sheriff's Department seized 1,675 grams of compressed white powder contained in two "bricks." Examination by the DEA Southwest Laboratory showed that the powder was heavily packaged in several layers of vacuum-sealed plastic bags, plastic wrap, and further contained in a "zip-lock" plastic bag. Initial testing of the powder with a Marquis reagent solution resulted in a slow-developing orange color, consistent with fentanyl. Further analysis by GC, FTIR, GC/MS, and LC confirmed 9.8 percent fentanyl HCL, cut with lactose. A small amount of 4-anilino-N-phenethyppiperidine (ANPP) was also noted (indicating the Siegfried route and starter material NPP). (Drug Enforcement Administration, Office of Forensic Sciences, 2006e)

Figure 9. Fentanyl Seizure (inside ruler legs are 8 cm)

Finding the Source

Among seasoned narcotics detectives, the appearance of fentanyl in the street drug trade evokes a sense of urgency and alarm. All too often, fentanyl announces its presence in an area by causing a sudden increase in drug overdoses and deaths. Locating and eliminating the drug's source becomes a top priority for law enforcement. In May 2006, for example, within days of being told by the Cook County medical examiner that a series of drug deaths in Chicago were linked to fentanyl-laced heroin, the Chicago Police Department formed a task force of local and federal investigators to track down the source. At about the same time, authorities in Michigan formed the Detroit-Wayne County Fentanyl Work Group to pursue the same objective.

Over the course of the past 30 years or so, the appearance of fentanyl in the street drug trade has been infrequent. In the majority of cases, whenever it did appear, the resulting overdoses and deaths tended to cluster close to the source. Because of this, police were able to collect sufficient information from victims and neighborhood sources to identify the source and shut it down. One of the earliest accounts of this comes from a presentation by noted toxicologist and pharmacologist, Gary L. Henderson, PhD, of the School of Medicine, University of California. In 1987, Dr. Henderson was invited to address an international conference in Rabat, Morocco, sponsored by the World Health Organization and the DEA. The conference focused on the subject of controlled substance analogues. (Henderson GL, 1989)

Dr. Henderson told of two very unusual apparent drug overdose deaths that occurred to known heroin addicts in Orange County, California, during the last week of December 1979. While autopsy reports showed the usual signs of a drug overdose, e.g., pulmonary edema, visible "tracks" or needle marks on the limbs of the victims, toxicology screens showed that no drugs were present. Over the next few months, according to Henderson, there were six similar deaths in Orange County and by the end of 1980, there were ten such deaths.

During this same period, police in Orange County had seized a number of street samples of a new form of purported heroin being sold as "China White." The initial forensic examination

identified the substance as 3-methylfentanyl, but a subsequent analysis, according to Henderson, showed it to be a different fentanyl analog called alpha-methylfentanyl.

This solved the mystery but did not end the overdose deaths. Dr. Henderson reported that by 1987, the date of the conference, there had been at least 110 confirmed fentanyl-related deaths. All of these cases occurred in California with the exception of two that occurred in Portland, Oregon (1983), one in Tempe, Arizona (1980), and one in Reno, Nevada (1987).

Dr. Henderson noted that although these cases tended to cluster in California, there was no reason to think that future outbreaks of fentanyl might not be more geographically dispersed. To support this, Henderson discussed the recent (1986) arrests of "at least two, and possibly four, well-trained organic synthetic chemists" for manufacturing 3-methylfentanyl. Even more disturbing, he said, was the fact that these chemists were all working in legitimate chemical laboratories in the eastern United States, not in California.

In his presentation to the conferees, Dr. Henderson stated:

> Answers to this problem are not readily apparent. The literature abounds with synthetic routes and pharmacological properties of thousands of narcotics, stimulants, hallucinogens, and sedative-hypnotics. This information is readily accessible throughout the world and creative chemists will continue to exploit the pharmaceutical chemistry literature. Restricting access to the literature is not feasible and controlling access to the chemicals needed to make these drugs will be minimally effective.
>
> In the past, restricting chemicals has only stimulated clandestine chemists to assemble the drugs from more elementary precursors. Locating these laboratories will be a similarly difficult task. When very potent chemicals are produced, a clandestine laboratory need operate for only a few days to make a few hundred grams of a material. Today, the problem is compounded by a new trend in which legitimate chemists are synthesizing illicit drugs in commercial chemical laboratories. (Henderson GL, 1989, p. 18)

A year later, Dr. Henderson published a report in which he attributed more than a hundred overdose deaths to the fentanyl analogs. He indicated that at least 10 different analogs had been identified, some like 3-methyl-fentanyl and beta-hydroxy-fentanyl being perhaps one thousand times as potent as heroin. (Henderson GL, 1988)

One of the earliest fentanyl cases referred to by Dr. Henderson occurred in October 1979, when a Narcotics Task Force in San Diego raided a suspected laboratory operation in Borrego Springs. At the site, agents found four pounds of methamphetamine, laboratory equipment, $7,000 in cash, weapons, and a small quantity of "China White" mixed with lactose. The DEA laboratory chief, in describing the drug, called it the "methylanalog of fentanyl," adding that,

technically, the drug was not illegal to possess because, as an analog, it was not listed as a controlled substance under the Controlled Substances Act.[c](Vollmer T, 1980)

Prior to a 1986 law, individual fentanyl analogs – of which there was a growing number – had to be identified by their molecular structure and individually scheduled by the DEA, a process that could take a year or more to complete. Alpha-methylfentanyl, the analog identified in the 1979 San Diego "mystery deaths," was not an unlawful substance until 1981 when it was officially designated a Schedule-I drug by the DEA. (Federal Register, 1981)

In the few cases during this time when authorities successfully tracked the sources for the fentanyl, they found, as Henderson told his audience in Rabat, that most had professional and/or academic backgrounds in chemistry. In 1985, for example, two men were arrested in North Hollywood, California, after local and federal authorities seized what was described as an "operational laboratory" actively making fentanyl. Authorities confiscated enough chemicals to make "100 million doses of the drug," according to a local DEA representative. One of the two defendants, Luther Dickson, 46, reportedly had a PhD in chemistry. (Palermo D, 1986b)

The following year, 1986, federal authorities in Fresno, California, announced the indictment of seven persons for manufacturing and distributing 60 pounds of synthetic heroin over a three-year period. The ringleader and reported chemist, Kenneth Baker, 43, had been arrested by the DEA in July 1985, for operating a clandestine fentanyl laboratory but charges had to be dropped when authorities learned that the analog seized was not a controlled substance at the time. The subsequent indictment in 1986 included violations of the Food, Drug, and Cosmetic Act. Baker's fentanyl was suspected of causing several overdose deaths in the area and prosecutors were intent on closing down this deadly source, even if it required using the comparatively weak provisions of the Food, Drug, and Cosmetic Act. (Corwin M, 1986)

In the same year, 1986, police and federal agents in Los Angeles worked a case involving a chemical supply company, Chemical Shed, Inc., suspected of supplying equipment and chemical precursors to clandestine laboratories in the area. One of the labs supplied by this company was the Dickson laboratory, described above, that was seized by authorities in 1985 in North Hollywood. In April 1986, the owner of Chemical Shed, Burton W. "Bud" Farrell, 58, pled guilty in U.S. District Court to racketeering, tax evasion, and aiding and abetting the manufacture of illegal drugs.

In a press statement, the federal prosecutor described Farrell's business. He stated that during a two-month period in 1985, investigators had seized chemicals from more than 70 suspicious vehicles stopped during a stakeout of Chemical Shed. The chemicals were seized under the new civil provisions of the CSA. The owners, who were not arrested, could file for the return of their chemicals but there was no indication that any ever did this. Officers were able to acquire incriminating evidence through undercover chemical purchases and a court-authorized wiretap. The defendant ordered most of his chemicals from Mallinckrodt, Inc., of St. Louis, a

[c] In 1986, Congress amended the CSA to make all analogs of controlled substances intended for human consumption Schedule-I controlled substances. ("Federal Analog Act," 1986)

bulk supplier of pharmaceutical ingredients. The defendant had been employed as a distributor with this company from 1968 to 1975. (Palermo D, 1986a)

In December 1985, DEA agents in Wilmington, DE, arrested Michael A. Hovey, 31, a PhD chemist employed by E.I. du Pont de Nemours & Co. Hovey was charged with manufacturing fentanyl analogs, including 3-methyl-fentanyl, using chemicals and equipment at the du Pont laboratory where he worked. After an undercover purchase of an ounce of fentanyl, Hovey was arrested. Agents seized another four ounces of fentanyl and six ounces of methamphetamine. Hovey pled guilty and was sent to prison but after a year, the conviction was vacated because the fentanyl analog that he was charged with making was not unlawful at the time of his arrest. Subsequently, Hovey was re-arrested on state charges and, while attempting to escape police custody, was shot dead by a Delaware state trooper. (Anonymous, 1986; Browne MW, 1989)

In September 1986, DEA and military authorities arrested a research chemist attempting to make fentanyl in the Naval Research Laboratory in Washington, D.C. The defendant, Hillel Daniel Hodes, 38, worked at the lab for two years under what was described as a "postdoctoral contract." Hodes held a federal security clearance to work at the government laboratory used for weapons research. Hodes had previously sold 10 ounces of high-grade methamphetamine to undercover agents and was completing the synthesis of about 10 ounces of 3-methyl fentanyl when he was arrested. Court records indicated that Hodes stole the chemicals from the naval facility that he was using to make fentanyl. After his arrest, Hodes told court officials that he had been convicted previously in Massachusetts for making LSD but authorities were unable to confirm this. (Lewis N, 1986)

One of the more serious outbreaks of fentanyl on the East Coast occurred in 1988 in Allegheny County, Pennsylvania. Martin and colleagues (1991) reviewed medical charts from 85,246 patient visits to the emergency department of a 750-bed urban hospital, Allegheny General, located on the north side of Pittsburgh. The study period was 24 months, from January 1, 1987 to December 31, 1988. The researchers also reviewed data for drug overdose deaths reported by the Allegheny County coroner's office. In the course of 24 months, the team identified 59 cases that fit the clinical case definition of an unintentional narcotic overdose. Thirty-nine (66%) of the 59 cases occurred in a cluster period between September 1 and November 30, 1988. During the same "cluster" period, researchers noted an unusually high number of deaths – 18 – attributed to "China White," the name given to the family of illicit analogs of fentanyl. (Martin M et al., 1991)

By the end of 1988, police and DEA officials in Allegheny County had made a series of arrests of people that they believed were behind the manufacturing and distribution of the fentanyl that killed 18 people. Thomas L. Schaefers, 48, a research chemist employed by the Calgon Carbon Corporation, was suspected of being the source of the drug. Over the course of a two-month period, from November to December 1988, authorities arrested a dozen suspects involved in the fentanyl "epidemic" in Allegheny county. Four additional defendants were charged with having supplied the drug to victims who died from it. (Associated Press, 1988)

In 1988, the US Congress passed H.R. 5210, the Anti-drug Abuse Act. On November 18, 1988, as he signed the bill into law, President Ronald Reagan thanked the Congress for this bipartisan legislation that added many new provisions to combat the illicit drug trade. One of these created a new class of regulated substances called chemical precursors and essential chemicals. Henceforth, the DEA would have authority to regulate a dozen important chemicals, including some used to make fentanyl analogs.

Interviewed after passage of the act, Dr. Gary Henderson, one of the nation's leading experts on the fentanyl crisis, gave a prophetic word of caution in stating that restricting access to certain chemicals might force clandestine chemists to come up with alternatives and in the process find even more powerful and dangerous substances. To illustrate this, Henderson added, "Alcohol in the form of beer or wine probably did relatively little harm before we learned how to distill it." (Browne MW, 1989)

New York was the next location on the East Coast to experience an outbreak of fentanyl. It happened quickly and with typical consequences. On the first Friday night in February 1991, packets of heroin sold in the South Bronx were blamed for at least six overdose deaths and more than 100 overdose cases at local hospital emergency departments. The packets of purported heroin all bore the same imprint, "Tango and Cash," and this made the job of tracking overdoses and deaths a little easier for the police. However, with the ensuing publicity and efforts to warn addicts about the killer drug on the street, police found that instead of avoiding the areas where the drug appeared, addicts were drawn to them in hopes of acquiring some of the powerful substance. Overdoses occurred in New York, Hartford, Newark, and Paterson, NJ. Preliminary forensic tests showed that the packets of purported heroin contained "methylfentanyl." (Nieves E, 1991)

New York is recognized as a hub for drugs supplied to dealers located as far away as Chicago or as far south as Washington, D.C., and all points between. Thus, in 1992, when the Baltimore region of Maryland began experiencing the typical signs of a fentanyl outbreak in its addict community, it was not long before authorities looked to New York as the source. Between January 25 and March 13, authorities identified at least 23 overdose deaths attributed to the dreaded "China White." Seventeen of these deaths occurred in Baltimore, and one each in nearby counties of Montgomery and Prince George's. Working quickly, authorities were able to identify what was described as a "$6.5 million-a-week New York to Howard County [MD] drug distribution ring."

In May 1992, authorities arrested a dozen suspects, including the leader of the gang, Carlos Ortiz, 27, of the Bronx, NY. State, county, and FBI officers seized a pound of what was referred to as "fentanyl citrate." Subsequently, another 21 persons were arrested and prosecuted in state court. Ortiz and several of his criminal associates were sentenced in federal court to life in prison. These arrests put an end to the fentanyl outbreak that, by mid-1993, had cost at least 30 lives in Maryland. (Tapscott R, 1992; Valentine PW, 1993)

George Marquardt: Genius or Mad Scientist?

In August 1992, emergency medical technicians answered a 911 call involving a man named Joseph Martier who had collapsed inside a storage building located in an industrial park near Wichita, Kansas. Martier, a 42-year old businessperson from Pittsburgh, survived what turned out to be a drug overdose, thanks to his rescuers. Authorities viewed this as just a routine drug overdose case until the tox screen showed that the drug involved was fentanyl, a drug not previously known to be in the area. This case remained a mystery until DEA agents in Boston picked up a clue months later in one of their undercover cases.

Boston DEA Diversion Investigators were routinely checking purchase records of regulated chemicals when they came across suspicious purchases by a Boston resident named Christopher Moscatiello. A quick check showed that Moscatiello had been arrested along with five others by the FBI in April 1983 in connection with the seizure of 15 tons of marihuana in Boston. By late 1992, DEA agents had successfully engaged Moscatiello in an undercover case in which they were able to purchase fentanyl from him.

Agents knew that Moscatiello was connected to a lab operation but they were unable to piece it together until he remarked, off-handedly, to an undercover agent that his supplier had nearly died of a fentanyl overdose in Wichita. It was not long after this that agents were able to tie Martier's overdose to Moscatiello's remark. After getting the address from the Wichita EMTs for Martier's overdose, agents obtained a search warrant and raided the building on February 3, 1993. Inside, they found about 40 pounds of the drug, along with chemicals and equipment used to make it.

Later the same day, the agents arrested two middle-aged Wichita suburbanites believed responsible for operating the lab. One of the defendants, George Marquardt, 47, was known to friends as a "genius," having once won a state science fair award as a teenager. His career as a scientist came to an end in 1978 when he was arrested for trying to combine LSD with methamphetamine. His associate and co-defendant, Phillip "Sam" Houston, 45, was described by friends as "an eccentric oil geologist who had built an observatory in his home and unearthed meteorites for a university museum." Marquardt was charged with manufacturing the drug and Houston with distributing it.

Meanwhile agents in Boston sought to find and arrest co-defendant Moscatiello. The night before the raid on the lab in Wichita, Moscatiello was murdered and dumped at a construction site near Boston. Authorities said that he had been shot several times in the head and his death appeared to be an "assassination." The next day, DEA agents executed search warrants at two residences belonging to Moscatiello and sized cash, money counting machines, records, and drug paraphernalia. Moscatiello's murder has never been solved. (Associated Press, 1983; Dowdy ZR, 1993; Zucchino D, 1993)

DEA analysts, after studying the Marquardt-Houston investigation, believed that this remote laboratory operation in Wichita was responsible for making and supplying the bulk, if not all, of the fentanyl that took 126 lives on the East Coast during 1991-1992. A DEA chemist in New

York who examined samples from Wichita and two local overdose victims reported that they were "consistent." (Zucchino D, 1993)

Fentanyl: 2005-2006-2007

The start of the most recent outbreak of fentanyl is unknown but piecing together reports from Detroit, Chicago, Philadelphia, and elsewhere, it appears likely that the current wave of fentanyl-laced heroin hit the streets sometime in mid-2005. While there are some similarities between the current situation and the cases cited above, there are important differences. Almost all the major outbreaks of fentanyl between 1979 and 2005 were clustered in a single geographical area.

By contrast, in the recent situation, fentanyl mixed with heroin appeared simultaneously in several major cities. A second difference worth noting is that many of the early fentanyl cases involved sources who were professional chemists rather than professional drug traffickers, and their attempted entrée into the world of the latter often resulted in their capture. In the recent situation, the distribution of the fentanyl-laced heroin in places like Chicago, Detroit, and Philadelphia appears to have been more organized and managed by professional dealers known to, and protected by, the communities they served.

These differences may have made the response to the current situation more difficult, inasmuch as there was no single source or single path to the source that the authorities could track. Instead, they were required to spend a good deal of time and energy on traditional methods for collecting intelligence and working sources and leads. How this all played out and the willingness of agencies and departments to work together to address the situation probably saved lives.

On June 21, 2006, about 400 federal and local police descended upon a public housing project in Chicago where they arrested about two dozen suspects and seized 200 pounds of heroin. Additional arrests tied to this case occurred in Texas and Ohio. This case involved dozens of cooperating witnesses (confidential informants), undercover purchases of evidence, and ten court-authorized wiretaps on mobile and fixed lines.

James Austin, aka "Jaymo," the ringleader, was considered the "king" of the "Mickey Cobras," a notorious criminal gang in charge of all heroin sales in the massive housing project known as Dearborn Homes on the South Side of Chicago. Gang members sold "lines" of heroin identified by color-coded packets or "bags," and colorful names like "Reaper," "Drop Dead," "Lethal Injection," and "Undertaker." Dealers worked authorized shifts and locations and were expected to pay a commission or tax to Austin in return for the franchise.

Forty-seven defendants were named in the original 221-page complaint. On February 28, 2007, a superseding indictment was filed in this case against Austin and 12 others. Trial is set for October 29, 2007 in US District Court, Chicago, IL. (Davey M & Ferkenhoff E, 2006; U.S. District Court, Northern District of Illinois, 2006, 2007)

Several days after the Chicago raid, an FBI task force in Philadelphia raided two homes in Chester, a nearby suburb, and seized a large quantity of suspected fentanyl-laced heroin. Three suspects were arrested and are believed to have headed a drug distribution ring operating in the area. These arrests follow by about six weeks the arrest by the FBI and Philadelphia Police of eight men and the seizure of 25,000 packets of what the authorities believed was fentanyl-laced heroin.

In 2006, fentanyl returned to the streets of New York City after an absence of almost 15 years. In June, the nearby city of Newark, NJ, reported nine deaths from fentanyl overdoses. This prompted New York City to begin checking for the drug. After reviewing autopsy results, New York City health officials concluded that at least 17 people died from taking either heroin or cocaine laced with fentanyl in a four-month period between May and August. (Santora M, 2006)

Throughout the spring and summer of 2006, the numbers of fentanyl-related overdose deaths continued to climb in places like Wilmington, Delaware, Camden, New Jersey, Philadelphia, Detroit, and Chicago. According to recent press account, in May 2006, investigators in Chicago "caught a break" when they received a tip that the fentanyl was being made at a clandestine laboratory in a small town near Mexico City. The DEA passed this information along to the Mexican authorities who agreed to raid the location. On Sunday morning, May 21, 2006, ten Mexican police officers dressed in gas masks and protective suits raided a business, Distribuidora Talios, located in a nondescript sheet-metal structure in Lerma, an industrial area located about 45 minutes from Mexico City.

Caught inside the laboratory was Ricardo Valdez-Torres, 53, the company's owner and chief chemist. Police videotaped the raid and were able to capture an on-the-spot interview with Valdez:

> 'This stuff, what do you call it, this final product?' a voice from behind the camera asked.
> 'I call it heroin,' Valdez said softly. 'Synthetic heroin. It's formulated in the laboratory.'
> 'How much have you made?'
> 'Perhaps 5 kilos,' Valdez answered. (Schaefer J & Swickard J, 2007c)

Valdez's "laboratory" consisted of a large room with a lab table in the center, a sink, and a triple-neck flask of the type commonly found in clandestine laboratories. On the wall was hung a poster showing the periodic table of elements and on the floor were barrels of aniline and pyridine – the telltale signs of a clandestine fentanyl lab.[d] At a later time, according to U.S. authorities, Valdez confessed to having made 10 kg of fentanyl – estimated to be enough for 80 million street doses. No fentanyl was found at the lab when Valdez was arrested. Besides

[d] For synthesizing fentanyl via the Siegfried route, aniline and pyridine are used in intermediary chemical processes required to convert N-phenethyl-piperidone (NPP) to fentanyl. This is detailed in Appendix A of this paper, a verbatim description of the Siegfried route found on the Internet. (Anonymous, Unk.)

Valdez, three others found at the lab were arrested by Mexican police authorities. (Schaefer J & Swickard J, 2007a, 2007c)

Who is Ricardo Valdez-Torres?

Called *El Cerebro* – The Brain – by his police captors, Ricardo Valdez-Torres arrived in the U.S. in 1961 when he was 7-years old. Valdez and his large family, consisting of his mother, father, five siblings, and several nephews, settled in San Diego, California. Young Ricardo Valdez had his first brush with illicit drugs when his older sister began using them. (Schaefer J & Swickard J, 2007d)

In an interview recently given to reporters from his prison cell in Mexico, Valdez told of his attraction to chemistry while attending high school in San Diego. A fellow student named Robert "Bob" Giebink, introduced himself to Valdez one day in English class. Bob told Valdez that he knew about heroin and the "synthetic stuff." Valdez told his new found friend that if he could make it, Valdez "probably could get it on the market." (Schaefer J & Swickard J, 2007b)

In 1990, the DEA office in San Diego was conducting an extended investigation of a large drug trafficking group suspected of selling heroin and other drugs, including fentanyl. On April 14, 1990, agents executed a search warrant on a wooden shed located behind a residence in Bonita, California, a suburb of San Diego, located about eight miles from the border with Mexico. In the shed, agents found chemicals typically used in a clandestine drug lab operation.

Over the coming months, as agents continued the investigation, numerous undercover heroin purchases were made from members of the trafficking group. Ultimately, agents were successful in making small fentanyl purchases. The first undercover purchase of fentanyl occurred on May 4, 1991, when a confidential informant for the Carlsbad Police Department obtained a $20 sample of a brown powdery substance that turned out to be 20 mg of 0.2 percent fentanyl. (Drug Enforcement Administration, 1991b)

By September 1991, the pace of the investigation picked up as undercover purchases of ounce quantities of fentanyl were made on a regular basis. Finally, on October 16, 1991, a DEA undercover agent was able to meet directly with Ricardo Valdez, the purported head of this trafficking group, at a taco shop in San Diego. Up to this point, the undercover agent had spent thousands of dollars for quantities of fentanyl analyzed to be about 3 percent pure. After the meeting at the taco shop, Valdez took the undercover agent to his vehicle where he gave him a small glass vial containing a brown granular substance. Unlike previous exhibits, this sample turned out to be 26 percent pure fentanyl. (Drug Enforcement Administration, 1991a)

By now, the DEA investigation bore the program code, "Full Press/Alliance SEO 492," indicating the important status of the case. On November 14, 1991, detectives and agents interviewed a confidential source close to Valdez. The source advised that Valdez was apprehensive about taking the DEA undercover agent to his fentanyl lab, as previously promised during one of their meetings. The source, however, had pressed Valdez, stating that the undercover agent and his boss, an unnamed "Chinaman" had a million dollars to invest. Valdez told the source that he and his "lab assistant, Bob," [later identified as Robert Giebink, a high school friend and

chemistry buff] had located a secluded area for the lab and that they would begin production immediately. Valdez told the source to advise the undercover agent that he would have approximately one pound of finished fentanyl for him in about three weeks. (Drug Enforcement Administration, 1991c)

On December 31, 1991, Valdez was arrested after delivering a quantity of fentanyl to the DEA undercover agent. A search warrant was executed on Valdez's laboratory and agents seized lab equipment, chemicals, and quantities of drug and chemical residues. (U.S. District Court, Southern District of California, 1996)

Besides Valdez, authorities arrested six other individuals who had been implicated in the case. (U.S. District Court, Southern District of California, 1997) On November 16, 1992, Valdez pled guilty to several felony counts, including manufacturing and selling controlled substances. On March 23, 1993, Valdez was sentenced to 170 months in federal prison. Over the next ten years, until his release, he filed scores of motions and appeals on his own behalf, claiming that his sentence was unfair and that the government reneged on the plea agreement. In his filings, he exhibited a remarkable knowledge and understanding of the law, despite the fact that his claims were not accepted by the court. (U.S. District Court, Southern District of California, 1996)

Valdez was released from prison in 2003 and was immediately deported to his native Mexico where he opened what he now claims was an "honest chemical company." Last June, in an exclusive interview given to a team of American reporters at the Reclusorio Notre prison in Mexico, Ricardo Valdez, now 53 years of age, insisted that he ran his chemical company "within the law." When confronted with statements that he made last year in a recorded police videotape made at the time of his arrest on fentanyl manufacturing charges, Valdez claimed that the statements were false, that he was forced to say them: "I gave these fools over here something so they wouldn't whoop my ass." (Schaefer J & Swickard J, 2007d)

Epilogue

More than a year has passed since Valdez and his fentanyl laboratory were put out of business. The team of American reporters that spent months on this story and travelled to Mexico to interview Valdez recently posed this rhetorical question: "Has the epidemic of fentanyl finally played out?" In response to their own question, they offered several possibilities. Some experts, they said, believe that the dealers simply have gotten better at measuring and mixing the right amounts of fentanyl and heroin together, thus accounting for the drop in overdose deaths.

A bigger question they ask, according to the reporters, is, "if Ricardo Valdez really did create 10 kilos, where is the rest?"[e] The prevailing theory, they say, is that "drug mules" brought the

[e] In the absence of a "standard" street dose of fentanyl or its many analogs, it is difficult to give a precise estimate of the number of doses one could make from 10 kg of the drug. Moreover, it would depend heavily on the purity of the finished product and the specific fentanyl analog produced. For example, some fentanyl analogs are far more potent than the parent fentanyl itself. Ten kilograms of illicit 3-

Mexican fentanyl directly to Chicago where it was distributed to the Mickey Cobras gang and passed along to other dealers in Detroit and Philadelphia.

The reporters note that while fentanyl-related deaths in Chicago are "way down," police in Philadelphia report hearing that fentanyl is still on the street, sometimes combined with cocaine. In metro Detroit, after fentanyl vanished from other cities last year, there was a resurgence in November when it claimed another 29 victims. Detroit has made several important fentanyl-related arrests in the past year and this may be having a positive effect, according to the reporters. They cite a county medical examiner who has said that, since the New Year [2007], "fentanyl deaths have largely disappeared." (Schaefer J & Swickard J, 2007e)

Discussion

Although finding fentanyl analogs in the illicit drug trade is a relatively recent phenomenon compared to older drugs like heroin and cocaine, we may still learn valuable insights for dealing with this threat by examining the above sequence of key cases and developments. Until about fifteen years ago, most persons involved in the actual production of illicit fentanyl were corrupted professional chemists seeking to use their skills to make some fast money. Although they possessed unique scientific skills, they lacked experience in the netherworld of drug trafficking. This, in turn, required that they take chances by engaging strangers in their secret enterprises – a dangerous gambit when one is involved in high-stakes drug dealing.

From a law enforcement perspective, identifying the corrupt scientists was sometimes quite easy. Having not "grown up" in the criminal underworld, there was little allegiance formed between the corrupt scientists and the underlings they had to engage to distribute their wares. These underlings, because of their exposure in the trade, were likely to be caught first. Tracing the drug to its source by trading underlings for makers was, and will continue to be, a proven and time-tested strategy for quickly halting crimes of this nature. As noted at the beginning of this paper, the early fentanyl outbreaks tended to remain clustered close to the source. This was likely the result of a poorly developed distribution system or one confined to a small number of local confederates.

The recent outbreak of fentanyl and fentanyl-laced heroin in Chicago, Detroit, Philadelphia, and elsewhere, differs significantly from prior outbreaks in several important ways. The Valdez case is a good example of these differences. The vulnerability gap, discussed above, between the chemist and the criminal distribution networks was closed. In addition, moving the clandestine laboratory across the border to Mexico made early detection and confiscation more difficult. Finally, the organizational cohesion of the suppliers and distributors, already present for existing drug trafficking purposes, made penetrating one to get to the other more difficult in the Valdez case than in prior cases.

The "first" Valdez case in the early 1990s presents several examples of the "new" wave of fentanyl traffickers. From the public record, Valdez had a well-developed and functioning

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methyfentanyl, conceivably, could produce hundreds of millions of street doses, depending, of course, upon the strength of both the starting and ending materials.

heroin distribution network operating in the San Diego area when he decided to branch out into making "synthetic heroin." His "lab assistant, Bob" was a trusted friend from high school days and, along with Valdez, was able to set up and operate a clandestine fentanyl operation.

Despite having some advantages over his predecessors in the fentanyl trade, Valdez was vulnerable from the beginning because his heroin trade was very active at the retail level, leaving him exposed to low-level informants. Several of the latter helped undercover officers to penetrate the Valdez heroin organization.

When arrested, Valdez was intelligent enough to understand his mistakes. As noted in his lengthy court file, the potential charges that he faced under the federal sentencing guidelines could put him in jail for life unless he pled guilty. By electing to plead guilty, he reduced his exposure and received a sentence of 170 months. His co-defendants, including his lab assistant, Robert "Bob" Giebink, received lengthy sentences, too.

Not long after arriving at the federal correctional institution in Stafford, Arizona, Valdez filed a Freedom of Information request with the DEA to obtain his investigative file. Reading the reports, Valdez probably had little difficulty filling in the redacted blanks blocking the identity of informants who had introduced the undercover officers to him and his people over the course of the investigation.

While in prison, Valdez filed numerous appeals and motions, *in forma pauperis*, to vacate his sentence. Each showed skill and understanding of the law. Some of his arguments were technical, contesting, for example, the DEA laboratory's findings that the materials seized did not justify his status as a drug "manufacturer," as defined in the sentencing guidelines. Although his filings were rejected in every instance by the court, they presented reasoned, if somewhat disingenuous, claims.

When Valdez was released from prison in 2003, as stated above, he was immediately deported to Mexico. He later would complain about this to a reporter, stating that he had not been in Mexico since he was seven years old and had grown up and attended school in San Diego. Other than what he has told a team of reporters from the Detroit Free Press, nothing else has been published about Valdez's life in Mexico between the time he arrived there in 2003 and his arrest by Mexican authorities in May 2005.

Although Valdez took a number of precautions to protect his fentanyl operation in Mexico, he ultimately succumbed in traditional fashion when someone purportedly tipped off the authorities in Chicago.

The "second" Valdez case represents a victory for the authorities and no doubt reduced the availability of illicit fentanyl in the United States – at least for the time being. Since the passage of the Harrison Narcotic Act in 1914, drug traffickers have shown an uncanny ability to survive and thrive in the midst of the most formidable opposition from law enforcement. Adhering to a Darwinian-like theory of adaptation and survival, the fittest among them remain and expand, while the less fit are caught or driven out of the business. If we accept this hypothesis, then it probably makes sense to plan for the next outbreak of fentanyl analogs or, for that matter, any

of the thousands of other potential deadly substances about which we were warned by Dr. Henderson in 1987.

While it is helpful to analyze the Valdez case for historical reasons and to identify vulnerabilities to exploit elsewhere, it is but one case perhaps among many yet to be found and studied. The cases excerpted from the *Microgram Bulletins* presented earlier in this report reveal a diversity of evidence in form, purity, and routes of synthesis that may indicate the existence of multiple sources.

Lessons Learned & Recommendations

In this paper, for convenience, we have separated illicit fentanyl makers into two distinct types: corrupt scientists and, for lack of a better description, criminal entrepreneurs. Valdez represents the latter. While it is clear from the brief history presented here that illicit fentanyl makers have learned from their experiences over the last quarter century, it is not as clear that we have learned as much from our experiences. In the examination of the case histories presented above, we have attempted to highlight, at strategically important places, the importance of intelligence in the overall process.

Intelligence, *per se*, should not be thought of as being only information developed or learned from covert operations, such as undercover drug meetings and buys. To be sure, these are important activities and likely will continue to provide a good deal of tactical intelligence on drug movements. That said, there is another form of intelligence that can provide strategic information to maximize outcomes. As indicated elsewhere, the first to learn of a fentanyl outbreak in a community generally will be emergency medical technicians responding to 911 calls. Hospitals and coroners, likewise, get involved early in drug-related events, often within moments or hours of their occurrence.

As we learned from the recent outbreak of fentanyl cases in Chicago, Detroit, and Philadelphia, by the time the law enforcement community was informed and mobilized to track down the sources for the deadly drug, scores of people had already died in each of these cities. Their autopsies and toxicology screens may have indicated fentanyl intoxication.

At the Philadelphia meeting of federal and local officials in July 2007, experts proposed requiring automatic screening for fentanyl in the postmortems of all drug-related victims despite added costs and detection difficulties. While the City of Philadelphia is doing this now, attendees to the conference advised that this is not a requirement in other counties and states.

Recommendation #1: Improved systems to identify and to track fentanyl in postmortem examinations and to provide faster notification of law enforcement officials.

In each of the three major cities involved in the recent fentanyl outbreak, police and federal agencies quickly formed task forces to identify and eliminate the sources of supply. Of the three efforts, the Chicago example appears to have been the most effective. It is not the

purpose of this paper to critique a jurisdiction's response and any observations made about this are just that, observations, and are based solely on the published record.

Unlike "kingpin" drug traffickers and cartel leaders who come out of the shadows infrequently and only for a short while, low-level street dealers must ply their trade at all hours of the day, seven days a week. They must be accessible and visible to their customers with whom they may expect to have contact several times a day. These patterns provide vulnerabilities that can be exploited by law enforcement authorities. While recruiting informants and making undercover buys are the traditional means for attacking retail drug networks, they also are quite susceptible to the government's main weapon, reserved for major actors, the court-authorized wiretap.

Wiretaps placed on retail drug distribution rings often generate "too much" intelligence. At that level of the trade, wiretaps are not expected and so traffickers often talk openly or, as in the case of the Chicago investigation of the Mickey Cobras gang, they have to remind each other, while talking on the tapped line, of the codes to use and what they mean. As incriminating calls are made to and from the target phone in such an investigation, evidence is generated for "spin-off" wiretaps to the other phones in question.

Investigations of this sort aimed at this type of trafficking enterprise are usually frenetic but short, often lasting no more than a few weeks because of the enormous supply of evidence and intelligence that is typically gathered. To be sure, wiretap cases are not cheap and may require large commitments of language-qualified personnel and resources. They also are very labor-intensive for prosecutors who, by law, must supervise the investigation and prepare documents for periodic submission to the court. In short, the investigation in Chicago required a great deal of resources and cooperation among a number of departments, the prosecutors, and the court.

Recommendation #2: Establish a line item in the federal drug budget of DOJ to support extraordinary expenses incurred for pursuing wiretap investigations of groups suspected of trafficking in fentanyl.

To ensure the effectiveness of Recommendation #2, the Attorney General should encourage United States Attorneys to pursue fentanyl investigations by implementing wiretaps. The annual statistics of "Title IIIs" approved for drug cases by the Department of Justice suggest that some districts are more aggressive than others in the use of this technique. Inasmuch as the objective of every fentanyl investigation is to find and eliminate the source of the drug, there is an assumption, therefore, that federal venue will be present, even if the initial penetration via electronic surveillance is placed on a local intrastate distribution group.

Recommendation #3: The Attorney General should request the cooperation of all United States Attorneys to pursue wiretap authorizations in exceptional cases, such as those involving fentanyl, that may not otherwise meet locally established thresholds for such treatment.

As seen in the above description of cases, a vital participant in the response strategy is the forensic chemist. As in the case of the medical examiners and coroners, there was an excessive and, possibly, avoidable delay in the early forensic examination of street exhibits. For months after drug overdose deaths began mounting in Chicago, Detroit, and Philadelphia, "experts" were still speculating about the origin of the suspected fentanyl. Reporters, left to their own devices and not informed of forensic findings, frequently provided inaccurate descriptions of pharmaceutical fentanyl, leading some to conclude that prescription medications were involved.

Perhaps the most important weakness in the early response involved the DEA Southwest Laboratory's examination of the evidence seized by the Los Angeles Sheriff's Department at the clandestine lab site in Azusa, California. At this laboratory, authorities seized a large number of counterfeit OxyContin 80 mg tablets, loose powder, chemicals, equipment, other drugs, and a fully operational commercial pill punch. The deputy sheriff in charge of this case advised this author that this was one of the largest drug cases ever made by his office and that about 80 separate drug exhibits were submitted to the DEA Southwest Laboratory.

It was the DEA Southwest Laboratory that identified the fake OxyContin tablets as fentanyl. Moreover, according to the DEA *Microgram* article (April 2006):

> Tablets like these have been seized throughout the country, and it appears that this lab was a source or possibly the source (**could not be confirmed, because the tablet press, punches, and dies were not submitted**). There were many thousands of these tablets at the laboratory. [emphasis added] (Drug Enforcement Administration, Office of Forensic Sciences, 2006c)

The DEA Office of Forensic Sciences is credited with pioneering a number of innovative approaches to identifying drugs in terms of their origin or processing. For example, the *Heroin Signature Program* was "Developed by DEA as a means of classifying and determining the origin of a heroin sample based on its manufacturing process." (Drug Enforcement Administration, 1992, p. 85) Similarly, the DEA is credited with developing a sophisticated ballistics process for identifying pills manufactured from the same press. Just as bullets can be identified by the same microscopic marks produced when they are fired from the same weapon, tablets can be identified and compared by unique markings left by the same press or punch.

While no explanation is given in the DEA *Microgram* account for why the press, punches, and dies from the Azusa site were not submitted for ballistics testing, this is a detail that should not be overlooked in the future.

Recommendation #4: Encourage the DEA to establish appropriate liaison with state and local forensic and law enforcement authorities when it comes to fentanyl-related exhibits so that the amount of forensic intelligence is optimized and furnished immediately to law enforcement officials for use in pursuing investigations.

In Chicago, Detroit, and Philadelphia, cities hit the hardest by the latest outbreak of fentanyl, we found that each, within days or weeks of each other, formed working groups or task forces comprised of various officials. While this crisis, like any crisis, brought out the best in everyone seeking answers and solutions, there are some experts whose participation is crucial to such efforts. It is necessary to identify them and ensure their participation in a response strategy.

The Centers for Disease Control and Prevention (CDC) have established response plans for bioterrorism that might serve as a good model for a fentanyl response team. Upon identification of a threat, the CDC provides trained personnel, equipment, and resources to the affected area where their members work with local officials to remove or remediate the threat. To adapt this model for our use, specially trained investigators, familiar with all previous cases involving fentanyl drugs and knowledgeable in several areas should be identified and asked to respond to an area when fentanyl is detected in sufficient quantities to suggest an outbreak. Included should be a DEA forensic chemist, enforcement agents, and a medical pathologist or coroner from the US Public Health Service to work alongside local counterparts in identifying cases. The response team would not replace or supplant local resources but, instead, act in a temporary advisory capacity and have the authority and responsibility to recommend additional resources, as needed.

Recommendation #5: Establish a Rapid Response Team designed to travel on short notice to a location where fentanyl has been detected in street drug sales or from seizures or overdose cases.

Of all the fentanyl cases described in this report, not one was made by a single law enforcement agency. Almost all cases involved several local and federal agencies working together. This “task force” approach is a proven strategy for mobilizing resources, ensuring coordination and sharing of information and intelligence, and for maximizing outcomes. The cities of Chicago, Detroit, and Philadelphia are to be commended for moving swiftly to form various cross-jurisdictional *ad hoc* task forces. The institutional knowledge gained by officers and supervisors who participated in these combined operations should not be ignored until the next outbreak occurs but, instead, should be enshrined in a working document – an “after action report” – that describes the day-to-day operational details and highlights techniques or approaches that proved successful. This report, in turn, may become the “play book” for how to address the next fentanyl outbreak.

Recommendation #6: That an appropriate federal agency sponsor a two or three day “summit meeting” of key action officers and supervisors from the aforementioned cities and any others who wish to send representatives, for the purpose of putting together an “after action” report that may be used by departments and agencies in the future when and if faced with a similar challenge.

The work by Dr. Gary Henderson and others in the 1980s to identify and contain the first recorded outbreak of fentanyl in the U.S. was notable in that it demonstrated the value of good forensic science in an era when it was not always applied to the illicit drug trade. Henderson was one of the first experts on this subject to advise that recipes and routes of

synthesis were often obtained by clandestine chemists from the scientific literature and the U.S. Patent and Trademark Office.

The DEA Interim Rule published in the Federal Register on April 23, 2007 seeking the control of a chemical precursor, N-phenethyl-4-piperidone (NPP), notes that "In the early 1980s, an alternate fentanyl synthesis route was published in the scientific literature that uses NPP as the starting material." (Federal Register, 2007, p. 20040)

The DEA received legislative authority in 1988 to regulate precursor chemicals used to make illicit drugs:

> DEA chemical control was initiated in the United States with the passage of the Chemical Diversion and Trafficking Act of 1988 (CDTA) that became effective on August 1, 1989. The initial legislation was drafted in 1985. The CDTA regulated 12 precursor chemicals, eight essential chemicals, tableting machines, and encapsulating machines by imposing record keeping and import/export reporting requirements on transactions involving these materials. (Drug Enforcement Administration, 2005, p. 13)

Unlike the scheduling provisions of the Controlled Substances Act that require a recommendation by the FDA before a drug or other substance may be controlled, the 1988 CDTA gave the DEA administrator exclusive authority to act unilaterally:

> (c) The Administrator may add or delete a substance as a listed chemical by publishing a final rule in the Federal Register following a proposal which shall be published at least 30 days prior to the final rule. (Code of Federal Regulations, 1970, as amended)

The DEA Interim Rule, published April 23, 2007, that designated N-phenethyl-4-piperidone (NPP) a List I chemical, arguably, comes almost twenty years after this important fentanyl precursor chemical was identified in the literature, and after the DEA received statutory authority to regulate it. The irony here is that part of the impetus for passage of the CDTA in 1988 was the discovery that precursor and essential chemicals manufactured in the United States and exported to South America were aiding in the illicit production of heroin and cocaine for eventual sale on the streets of America.

Recommendation # 7: The DEA should establish a mechanism for monitoring the use of precursor and essential chemicals and propose them for regulatory control under the CDTA as soon as they are identified as essential for the manufacture of illicit drugs.

The more recent Valdez fentanyl case shows the vulnerability of the United States to illicit drug production abroad. In this instance, Mexican police officials acted appropriately and closed down Valdez's fentanyl laboratory but one is moved to ask if this would have been done if Valdez was considered a local resident rather than an American interloper, as he described himself to American reporters recently. Drug law enforcement in Mexico and South America often is viewed differently than in the United States, in part, because of the different legal

systems and traditions. The Napoleonic Code, in all its variations and regional differences, prevails south of the border, from Mexico to Tierra del Fuego.

Many Americans who do not understand the nuances of the Napoleonic Code system of jurisprudence tend to dismiss the enforcement of the law south of the border as discretionary and capricious. Moreover, the underdeveloped economic status of nations in this region very often encourages corruption among police and governmental officials.

Despite these regional weaknesses, international cooperation has been very successful in regulating illicit drugs and precursor/essential chemicals. The basis for this is the 1988 United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. In this international agreement, the United States and most nations of the world agreed, among other things, to control the international commerce in essential chemicals and precursor substances used to make illicit drugs. This United Nations treaty is credited with having prevented or stopped a good deal of illicit drug production in the world.

Unfortunately, despite having considerable influence as a "victim nation" in the deliberations of the United Nations drug conventions and boards, the United States failed to recommend inclusion of N-phenethyl-4-piperidone (NPP) in the control mechanisms of the 1988 Convention. Thus, as of now, this important fentanyl precursor substance remains unregulated in international commerce.

Recommendation #7: That the Department of State move immediately to propose to the United Nations that N-phenethyl-4-piperidone (NPP) be placed on the schedules of chemicals requiring international reporting of transactions, in accordance with the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

Evidence obtained by investigators in Chicago during the course of the Mickey Cobras case in the summer of 2006, according to court filings, shows that dealers were concerned and alarmed at the number of deaths being caused by the deadly mixture of fentanyl and heroin. It is not in the economic interest of a drug dealer to kill off his/her customers. Moreover, overdose deaths tend to attract police attention or reprisal by friends of the victim(s), neither of which is helpful for a dealer who must take to the street daily to supply an insatiable clientele.

The current lull in the rate of fentanyl-heroin overdose deaths may be the result of a successful learning curve by traffickers who have discovered how to mix and sell these drugs without killing their customers. This was one possibility posed by the team of American reporters that recently travelled to Mexico to interview Ricardo Valdez (see above). The other possibility that they offered was that the arrest of Valdez has shut down for the time being, at least, the supply of fentanyl.

Within the two preceding paragraphs reside inferred questions regarding the quality and potency of fentanyl and fentanyl analogs entering the illicit drug trade. The key to finding responses, as noted several time throughout this paper, is better and faster information from the forensic end of the business.

The DEA's Office of Forensic Sciences is to be commended for publication of its *Microgram Bulletin* and *Microgram Journal*, both excellent sources of important information. We devoted an entire section of this report to the findings and photographs on fentanyl reported in the *Bulletin*. These DEA publications are distributed by subscription-only to interested parties, including state and local forensic chemists, police departments, academic and research institutions, and members of the public. As might be expected, from time to time, details provided in these publications are cited by underground sources when discussing the production of chemicals and precursors. A recap of fentanyl data from the *Microgram Bulletins* appears in Table 2, below:

Table 2. Fentanyl seizures reported to/by DEA's *Microgram Bulletin*

Location	Date*	Amt.	Purity of Fentanyl
Omaha, NE	**Jan 2006**	**11 tabs**	**n/a**
Azusa, CA	**Apr 2006**	**>1000 tabs**	**1.5 mg/tab**
Westmoreland, CA	**Jun 2006**	**945.1 gm**	**83%**
Painesville, OH	**Jun 2006**	**1-2 gm (?)**	**23%**
Houston, TX	**Aug 2006**	**0.5 gm**	**54%**
Albuquerque, NM	**Aug 2006**	**44 tabs**	**1.9 mg/tab**
Blyth, CA	**Apr 2007**	**1,675 gm**	**9.8%**

*date of *Microgram* publication (Source: Drug Enforcement Administration)

While the above table provides some relevant data, it is more informative for what it does not show. It does not show, for example, any seizure data from Chicago, Detroit, or Philadelphia, three cities in which as many as one thousand deaths occurred from fentanyl-laced heroin in the past two years. The range of purity, 9.8% to 83%, appears remarkable although the description of the exhibit containing 9.8% purity, as given in the *Microgram* account, states that the drug was "cut with lactose," a common diluent.

Three of the seven cases reported by *Microgram* involved seizures of counterfeit OxyContin 80 mg tablets, suggesting, possibly, a common source. This hypothesis, however, is not supported by the apparent differences in size and shades of green of the seized tablets, as shown in the *Microgram* photographs. Ballistics tests on the tablets could prove or disprove the common source theory but there is no indication that ballistics examinations were ever performed by the DEA labs receiving the samples.

It is worth noting that the dramatic decrease in small toxic methamphetamine labs over the past year came about because of legislative controls on precursor substances used to make

methamphetamine. These legislative controls followed several years of close tracking of small toxic labs by state and federal law enforcement agencies that were encouraged to furnish information about seizures to the El Paso Intelligence Center. There, analysts worked diligently to collate the data and pull from them important variables that could be addressed from a regulatory perspective. The control of over-the-counter pseudoephedrine products soon became a compelling strategy for reducing the small toxic labs. Legislation and industry compliance followed on the heels of irrefutable forensic evidence. The very positive outcome, to date, confirms this.

The above brief account of the pseudoephedrine-methamphetamine situation provides a model and justification for a similar effort to curb fentanyl production. A similar coordinated compilation of cases and data involving fentanyl seizures needs to be undertaken immediately and analysts need to be assigned to collate the data and pull from them common variables that may provide successful strategies for addressing future outbreaks.

Recommendation #8: Create within the DEA Office of Forensic Sciences a new division devoted to forensic intelligence and liaison. Trained forensic chemists and analysts would maintain professional contacts with counterparts at the state and local level to ensure coordination of important cases involving fentanyl. A standard procedure for describing samples and measuring and quantitating samples should be developed between the DEA and a consortium of state forensic experts, perhaps under the auspices of the American Academy of Forensic Sciences. Formal agreements of the type currently in existence between DEA's Office of Diversion Control and State Medical Boards should be executed to provide an expanded level of federal-state cooperation.

Recommendation #9: The DEA's Office of Forensic Sciences' *Microgram* publications are valuable sources of information for the scientific and law enforcement communities and should be expanded. Individual cases involving fentanyl, for example, should be the subject of more thorough discussion and should include actual case histories of the exhibits, where and when seized or obtained, along with the demographics of the sources, when known. Telephone numbers or email addresses of the submitters of the information should be provided in the *Microgram* publications so that interested chemists, investigators, or others can contact the reporting source for additional information and coordination of cases and intelligence.

As discussed throughout this report, the role of the coroner or medical examiner in detecting the presence of fentanyl in postmortem examinations of overdose victims is a vital bellwether for spotting fentanyl outbreaks early. How quickly the medical examiner notifies the community and law enforcement that fentanyl is present in the street drug trade may be a function of how individual offices are structured and managed. In some counties, for example, full-time medical examiners are employed, along with appropriate facilities and staff. In smaller jurisdictions, the duties of the medical examiner may be "contracted out" to private physicians who perform their services, when needed, at local hospitals where arrangements for postmortem examinations have been made.

In some jurisdictions, the coroner is an elected official and may not even be a physician, although a physician or pathologist will conduct the actual examinations. Some states compile postmortem drug abuse data from individual medical examiners throughout the state but many states do not collect or publish these data on a regular basis. Clearly, there is a need for improved coordination of toxicology results from medical examiners throughout the country.

This may be accomplished by expanding the revised Drug Abuse Warning Network (DAWN) that is managed by the Substance Abuse and Mental Health Services Administration (SAMHSA) to include in its *DAWN-Live* component the collection of data from medical examiners. DAWN presently collects some of these data from medical examiners but often by the time the data are processed and published, two years or more have elapsed since the time of the event in question.

The current revised DAWN hospital emergency department component uses the Internet to collect and provide data on almost a real-time basis to track the mentions of manufactured and illicit drugs that are involved in acute drug-related emergencies. The design of this system took several years and appears to address the needs of the medical and scientific communities.

Questions have been raised, however, about the sufficiency of the sampling and the lack of cooperation by hospital emergency departments in large cities like Dallas, Los Angeles, Philadelphia, etc. In 2004, for example, less than 10 percent of the 4,438 eligible hospitals in the U.S. participated in DAWN. Of the 417 hospitals that participated in the network, there was less than a 50 percent response rate. (Substance Abuse and Mental Health Services Administration, Office of Applied Studies, 2006)

The DAWN sampling of medical examiners appears more robust and, according to a recent publication, the DAWN medical examiners database collects data from 6 states and 122 participating jurisdictions (counties), which is about 42 percent of the total eligible jurisdictions (122/289). As ambitious as the DAWN medical examiners database is, by the time that its data are published, they have little significance. The most recent report available shows data for CY2003 and fentanyl is not even mentioned in the document. (Substance Abuse and Mental Health Services Administration, 2003)

Recommendation #10: With respect to the DAWN hospital emergency department data that are now being compiled in the DAWN-Live component, SAMHSA should ask the contractor providing these services to program the central computer to highlight cases in which fentanyl is mentioned. These data need to be collated rapidly and furnished to SAMHSA officials for appropriate dissemination (see Recommendation #11).

In a document published by SAMHSA describing its new DAWN-Live system, it is stated that the FDA uses the new system “to assess the abuse potential of prescription drugs and assist in making decisions on scheduling and labeling.” (Substance Abuse and Mental Health Services Administration, 2007b, p. 1)

Only three federal agencies (SAMHSA, FDA, ONDCP) have access to DAWN-Live data. None is a law enforcement agency. When queried about this, DAWN officials advise that the statutory authority for DAWN, Section 505 of the Public Health Service Act (42 USC 290aa-4), requires that access to DAWN-Live "is restricted in accordance with Federal Laws governing the confidentiality of data. Only authorized users from eligible public health agencies may access DAWN LIVE!" (Substance Abuse and Mental Health Services Administration, 2005, 2007a)

The Federal Food, Drug, and Cosmetic Act and the Controlled Substances Act provide statutory authority for both the Secretary of the Department of Health and Human Services (DHSS) and the Attorney General (AG) to schedule drugs and other substances in accordance with criteria to be evaluated by each department. These responsibilities have been delegated by regulation to the FDA (by DHSS) and to the DEA (by the AG). (Controlled Substances Act, 1970)

SAMHSA's interpretation of the regulations governing access to DAWN data prohibits the DEA from having access despite the DEA's having co-equal responsibility with the FDA for scheduling drugs and other substances with abuse potential. The DAWN hospital emergency department database was originally established by the DEA in the 1970s, specifically to aid in the drug scheduling responsibilities of the agency. The DAWN system eventually was transferred from DEA to the National Institute on Drug Abuse (NIDA) and later transferred again to SAMHSA where it presently resides.

Prohibiting the DEA from having access to DAWN-Live information prevents the agency from having access to timely information needed for scheduling drugs and for focusing scarce resources to combat specific threats such as those posed by fentanyl.

SAMHSA currently permits public health authorities at the state and local level to become "designated users" of DAWN-Live data that SAMHSA advises will allow them to "monitor drug-related events in real time to: identify new drugs of concern; confirm recent patterns identified in other metropolitan areas, and run special inquiries on new public health priorities." (Substance Abuse and Mental Health Services Administration, 2005) It is not known whether DAWN-Live, as advertised, was able to alert state-level public health authorities to the recent fentanyl outbreak before or during its occurrence.

Recommendation #11: Either by administrative rule change or specific legislation, if necessary, allow direct and full online access to DAWN data (both ED and ME) to the Attorney General and his/her designated agencies, including the DEA and FBI.

Recommendation #12: DHSS, the parent organization of SAMHSA, already provides resources to all eligible hospitals in the DAWN sampling frame. Using this relationship as leverage, DHSS should request hospitals that presently do not participate in DAWN to become active and participating members of this vital sentinel network. DAWN already provides reimbursement for time and services for participating hospitals and, if necessary to increase participation, additional resources should be favorably considered.

Pharmaceutical Fentanyl:

About a year before fentanyl-laced heroin began appearing on the street, concerns were raised by drug epidemiologists and others about the increasing number of overdoses and deaths attributed to lawfully made fentanyl. The introduction in January 2005 of generic transdermal fentanyl patches expanded this market to segments previously closed because of restrictive formularies prohibiting the prescribing of the more expensive branded formulation, Duragesic. Although the number of Duragesic prescriptions in 2005 declined by 58.9 percent, there was an overall increase of 4.4 percent in the total number of prescriptions written for fentanyl patches (from 4.1 million Duragesic prescriptions in 2004, to 4.3 million prescriptions in 2005 for all forms of fentanyl patches). (Drug Topics, 2006)

In July 2005, the FDA issued a public health advisory calling attention to the increasing number of fentanyl patch-related overdoses and deaths, particularly among patients ignoring the product's boxed warnings and instructions for use. This advisory followed a June 2005 report by researchers at the University of Florida at Gainesville who found that the number of sudden deaths from fentanyl overdoses was growing nationwide. The study cited records of the Florida Department of Law Enforcement showing that, in 2004, the abuse of the fentanyl patch was the cause of 115 deaths in Florida. (Meadows M)

In an edition of the *FDA Consumer* magazine (March-April 2006), we find the following additional safety warnings about fentanyl patch misuse:

> There have been reports of people extracting fentanyl from the patches and abusing the drug. Uncontrolled delivery of this potent drug is very dangerous and raises the risk of overdose. The New York State Department of Health has investigated incidents in which fentanyl patches have been stolen from hospital ward stocks or have been removed from the skin of patients.
>
> As with other opiate drugs, there is a risk of becoming either addicted to the substance in the fentanyl patch or tolerant to the drug. The risk goes up for people who have a history of mental problems, or who have been addicted to other medicines, street drugs, or alcohol. According to Janssen, concerns about addiction and abuse shouldn't interfere with the management of chronic, long-term pain. The manufacturer encourages physicians to screen and monitor patients to reduce the risk of problems. (Meadows M)

Several years ago, at a national conference of drug diversion investigators, a medical director for a large drug company made an offhand remark that FDA warnings and cautions, while well-intentioned and meant to inform practitioners and patients of safety risks, frequently are used by abusers as "instructions for use."

Similarly, media reports intended to inform the public may attract abusers looking for new and improved ways to get high. Last year, the newspaper account of a Philadelphia case involving eight arrests and the seizure of 25,000 packets of "killer heroin" mentioned that police,

"declined to give specifics about the suspects or where the busts took place, saying that they might attract more users to those neighborhoods." (Stoiber J, 2006)

The attention paid by the FDA and the media to the abuse of fentanyl patches in the past several years, while no doubt of benefit to patients and their caregivers, may also have had the unintended consequence of attracting addicts to these products. In addition, the publicity about the outbreak of fentanyl-laced heroin in 2006 may have triggered an interest to try this drug in individuals having access to new or used fentanyl patches.

Besides the increased abuse of fentanyl patches, authorities have noticed an increase in the number of reports of abuse of Actiq, the fentanyl lozenge on a stick approved only for breakthrough cancer pain but believed to be widely prescribed off-label for other forms of severe pain. As discussed in the introduction of this report, a new buccal form of fentanyl in a tablet has recently been approved by the FDA.

Conclusions

From all of the available information and discussions with many well-informed law enforcement and forensic sources, it appears that two entirely separate but nominally related drug abuse phenomena occurred – and may still be occurring – simultaneously. That the abuse of prescription fentanyl, whether in oral (transmucosal) or transdermal form, has increased in the past several years is indisputable and well supported by available data. The reason for this is considerably less clear and simply may be a confluence of factors, some of which are discussed in this report.

The second phenomenon involves the sudden and catastrophic emergence of fentanyl mixed with street heroin in 2005 that, to date, has cost at least a thousand lives and countless injuries. Unlike many previous fentanyl appearances that tended to cluster close to the source, the recent appearances of this drug have occurred simultaneously in several large American cities, as well as smaller locations nearby. As discussed in this report, the capture of an important clandestine fentanyl laboratory operator in Mexico last year appears to have diminished the volume of fentanyl currently on the market. Reported fentanyl-related overdose deaths in 2007 have decreased over 2006 levels. Whether this is the result of a reduced supply of the drug or better quality control of the mixing and dosing by dealers remains to be seen.

Over the long term, we may expect to see more fentanyl analogs made within and outside the United States. The recent Valdez case provides a primer for both sides to study. Over the years, very few domestic drug cases have led to finding and dismantling the foreign source. Part of the reason for this, no doubt, is the enforced division of labor typically found in criminal organizations. The growers are separate from the producers who are separate from the shippers who are separate from the smugglers who are separate from the distributors who are separate from the dealers. Maintaining these separations is essential for security. As the clandestine fentanyl industry matures, it is likely to develop a similar approach to security, thus making a future Valdez-type case more unlikely.

Finally, a word about Homeland Security is in order. In October 2002, terrorist groups named the Islamic International Brigade, the Special Purpose Islamic Regiment, and the Riyadus-Aalikhin Battalion were directly involved in the seizure of over 800 hostages at Moscow's Dubrovka Theatre. The reaction by Russian security forces was to disable the terrorists by introducing a fast-acting toxic substance into the ventilation system of the theatre. This resulted in the deaths of 129 hostages and 41 terrorists. One of the dead hostages was a U.S. citizen. (Department of State, 2003)

Subsequently, it was learned that the toxic substance used in the failed rescue attempt was a vaporized form of fentanyl, likely an analog and possibly carfentanil, a substance having 10,000 times the potency of morphine and used to subdue large animals. The three groups mentioned above have been designated by the U.S. Department of State as "terrorists" pursuant to Executive Order 13224. They also have links to Al-Qaida. (Department of State, 2003)

While the objective of this paper is to catalogue the history of illicit fentanyl in the street drug trade and to propose recommendations for addressing future fentanyl outbreaks, the potential for even greater catastrophic use of fentanyl analogs should be obvious from the above brief discussion of the Moscow hostage situation. Some of the recommendations contained herein may require the allocation of new resources. The justification for the additional resources should not rest solely on a need to upgrade our capabilities to combat the threat of street fentanyl. While our efforts to do so are deserving of consideration on their own merits, the prospect of an even more insidious use of these potent substances cannot be ignored.

In the appendix to this paper we provide a verbatim recipe found on the Internet for making fentanyl. Besides this recipe, there are published books that provide detailed how-to instructions for making fentanyl and other illicit drugs. Some of these publications treat federal controls on chemicals and precursors as challenges for finding ways of devising alternative substances or for synthesizing starting materials from non-regulated chemicals and precursors. Entire chat rooms and websites are devoted to exchanging information and recipes for making potent substances like fentanyl. Often, this becomes a global contest of wits among highly skilled scientists not unlike some of the ones mentioned earlier in this report.

Even more ironic, perhaps, is that the United States Government, in the form of its Patent and Trademark Office, is often the source of information on how to make potent chemicals and drugs, including the fentanyl analogs. As *bona fide* scientists develop new molecular entities with potential industrial or medical uses, they usually file for a patent to protect their ownership interests should they or someone else wish to develop the substance commercially. The patent application must contain a detailed description of the "invention" so that the government and private patent attorneys can identify and confirm the uniqueness of the new item or process and its suitability for patent protection. Copies of these detailed patents are available, often online, for the asking and are sufficiently detailed to permit clandestine producers to replicate them. In the research for this report we came across a good example of this.

In November 1980, a deputy sheriff on patrol in San Diego County, California, saw a body being dumped from a car. The deputy followed the car to a secluded cabin some distance away. In the meantime, backup officers retrieved the dumped body and began an investigation. In the victim's pocket, deputies found a packet of white powder that did not field test for cocaine, methamphetamine, or heroin. The mystery powder eventually found its way to the DEA's Special Testing and Research Laboratory in McLean, Virginia, where it took forensic chemists more than a month to identify it.

After running the sample through their sophisticated machines, the DEA chemists believed that it was a variation of fentanyl, possibly a new analog. Combing the scientific literature for substances with a similar chemical structure, the DEA chemists finally found a reference to a patented version of their mystery powder.

It had been discovered and patented several years before by Dr. Tom Riley, a University of Mississippi pharmacologist. Dr. Riley was contacted by a DEA chemist and he obligingly sent a sample of his patented analog to the DEA lab where it matched up perfectly with the mystery powder from San Diego. DEA chemists speculated that someone had obtained a copy of Dr. Riley's patent and, based on the detailed step-by-step description of the synthesis route, they were able to recreate the analog using commonly available chemicals and precursors. (Wilford JN, 1980)

Given that the above example occurred three decades ago, there is good reason to believe that the same is being done today and with greater ease and anonymity, since the United States Patent and Trademark Office provides online access to patents. A recent search of the online database for U.S. patents using the search term "fentanyl" returned 1,920 individual full-text patents pertaining to some unique application involving this substance. Complete and detailed patents are available online from 1976 to the present, with page-image files available online from 1790 to 1975. In addition, patent applications, often a source for the most recent discoveries and inventions, are available online from March 15, 2001, to the present. (U.S. Patent and Trademark Office, 2007)

At the conclusion of his presentation in 1987 to the conferees meeting in Rabat, Dr. Gary Henderson gave a prophetic warning that is worth repeating here:

> Traditional responses to drug abuse problems seem to offer little promise. In fact, success in curtailing the distribution of natural products such as opium, coca and marijuana and preventing the diversion of pharmaceuticals is likely to be the stimulus for the development of potent synthetic substitutes. The challenge for toxicologists and forensic chemists is to keep pace technologically. Potent drugs of unusual chemical structure will require both broader screening techniques capable of detecting drugs and their metabolites present at the nanogram and pictogram levels. Simple answers to this problem are not readily apparent, but they are not likely to be found unless the problem is first recognized. (Henderson GL, 1989, p. 18)

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Appendix A

[Quote]

Synthesis of Fentanyl
by *Siegfried*
Introduction
I'm french speaking organic chemist so excuse my rusty english [*most things corrected by me - Rhodium*].

***Note: Full report available at: http://opioids.com/fentanyl/synthesis.html

Fentanyl and its analogs are among of the most powerful opiate agonists, but their synthesis are often hard. Here is a synthesis of Fentanyl which can be easily adapted for the other analogs (Para-Fluoro-Fentanyl, Alpha-Methyl- Fentanyl).
This procedure is not theoretic and have been tested and improved many times over. This synthesis is conducted at room temperature so you don't need any special apparatus.
Fentanyl is a very interesting component for underground chemistry because one gram of pure fentanyl is equivalent of 100gr of very good street heroin.

2. Principle
The precursor used is N-Phenethyl-Piperidone (NPP) which can be easily synthesized from Piperidone and Phenethyl-Tosylate or Phenethyl-Bromide through a simple SN2 mechanism.
The NPP is reacting with Aniline giving the Imine derivative which is reduced to the 4-Anilino-N-Phenethyl-Piperidine (4-ANPP).
The 4-ANPP is then reacted with Propionyl Chloride giving Fentanyl which is then purified.

3. Procedure
a) Synthesis of the Imine derivative of NPP
10 mmole of NPP is dissolved in a minimal volume of Aniline (about 5-6 ml), then 1 gr of 4A Molecular Sieves is added.
The mix is really gently stirred (so that the Molecular Sieves aren't destroyed by the agitation) with a magnetic stirrer for about 24 H at room temperature.
The conversion have repeatedly been calculated with MS and is more than 99%, so the next phase can be conducted without any purification.
b) Synthesis of the ANPP
The reaction mixture from (a) is filtered from the Molecular Sieves which are rinsed with 2*2ml THF, the filtrate and washings are poured into a 50 ml flask, whereupon 20 ml dry Methanol is added, and the mix is stirred.
About 1-1.5gr of Sodium Borohydride is very slowly added to the mixture at room temperature, and the mix is stirred for about 2 h. The conversion into ANPP is checked with any method and if not completely reduced, add slowly another 0.5gr NaBH4 and stir for one more hour.

When the conversion into ANPP is complete (more than 95%), evaporate the Methanol and the THF under vacuum.
After the evaporation there is a mass formed from the Aniline, the excess NaBH4 and the ANPP complexed with borane.
Pour 50 ml of water into the flask, then destroy the complex by the slow addition of a small quantity of concentrated HCl (35%) until the pH is about 1, then the mix is well stirred for another hour. Now 50ml of a saturated NaCl solution is added to the mixture, and after about 10 min, a solid mass precipitate.
Separate the solid from the liquid with a filtration and keep the solid (this is ANPP hydrochloride) after washing it with a little saturated NaCl solution.
Add another 50ml of saturated NaCl solution and place the mix in the fridge (at about 2 deg C) and wait 2-3 h. If there is more precipitate, filter the solution and add the solid to the first crop. The solid mass is ANPP which must be treated.
Dissolve the solid in about 60ml water and 2N NaOH until the pH reaches 12.5, then extract with 3*15ml CH2Cl2. Wash the CH2Cl2 phase with 5 ml water, and evaporate the solvent in vacuum. The residue is an oily yellow-orange liquid which spontaneously crystallizes, this is the ANPP which is pure enough for the next step.
The overall yield of ANPP is about 50-80%. The main loss of yield is during the purification process because the separation process between the excess of Aniline and ANPP is not optimized. There are perhaps some solutions to this, which will be discussed in the optimization and discussion section.
c) Conversion of ANPP to Fentanyl
10mmols of ANPP are dissolved in about 8 ml of Pyridine with stirring, and then 12 mmoles of Propionyl Chloride is added dropwise to the reaction mixture at room temperature. The reaction is exothermic and the Propionyl Chloride must be carefully added, so that the temperature doesn't rise over 60 deg C. You don't need a cooling bath, the temperature should be controlled with the addition rate of Propionyl Chloride and must stay between 30 and 60 deg C during the addition.
When all the Propionyl Chloride is added, the reaction mixture is stirred for about one hour at room temperature.
Check the conversion with any method and if not complete, add another 1 mmol of Propionyl Chloride. Normally the conversion should be complete after the first operation but if there is too much Aniline you need more Propionyl Chloride.
The reaction mix is then poured into 80 ml water with stirring, and conc HCl (about 35%) is added dropwise until the pH falls below 1.5. This operation can be done with another procedure as follows: Prepare 80 ml of 2N HCl and simply pour the reaction mix into this solution. This results in the pyridine and the fentanyl turns into their respective hydrochlorides. The solution is then leaved with stirring for about 30min. The Pyridine HCl is not soluble in CH2Cl2, while the nonpolar Fentanyl HCl is. Extract the solution with 3*20ml of CH2Cl2, then wash the organic phase with 2*10ml saturated NaCl solution.
The solvent is evaporated under vacuum, and a yellow mass is formed which consists of Fentanyl hydrochloride with a small quantity of Propionanilide as an impurity. 10-15ml Acetone is now added, and a white powder forms, which is Fentanyl HCl. Filter the solid and wash it with a small quantity (2*3ml) of acetone.
The Fentanyl HCl is now pure enough for use (>99.5%). The yield in this step is over 90%!

If not pure enough (it was never the case for me) you can purify it by recrystallisation from hot acetone.

d) Preparation of synthetic white Heroin for street use
The pure Fentanyl can not be used as is, because it's much, much too strong and MUST be diluted, else there will be a lot of overdoses!
The following procedure gives a white heroin which is the same as very good (30%) street heroin.
100mg of Fentanyl. HCl is dissolved in 2ml of Methanol. Weigh up 10g of Lactose and warm it at about 60-70 deg C into a large dish with a hotplate. Add the methanolic solution of Fentanyl dropwise at regular intervals into the warm Lactose for a good pre-mix . Wait until all the Methanol is evaporated and mix the Lactose-Fentanyl thoroughly. This is crucial because if this is not thoroughly mixed, there will be a part of the Lactose without Fentanyl and part of the Lactose with too much Fentanyl, possibly causing dramatic overdoses!
Now you have a very high quality of street white Heroin.
This type of Heroin was used and sold during a year, and the feedback of the consumers was very good. The consumers were very happy and didn't want the usual brown Heroin anymore. So be careful, some people (The Mafia and other dealers) will perhaps turn very jealous!
Remember that with 1gr of pure Fentanyl HCl you can make 100gr of very high quality Heroin!
DON'T USE and DON'T SELL pure Fentanyl HCl, this is a very toxic material which can cause many overdoses if not diluted!
e) Optimization and discussion
The overall yield of this synthesis is about 50-80% and the main loss of product is during the purification of ANPP in step (b).
There are perhaps other alternatives for the separation of Aniline and ANPP (recrystallisation, distillation). I think a good solution is extracting the Aniline and ANPP together and separate them with the evaporation of Aniline under vacuum, then recrystallize the ANPP in a suitable solvent.
Para-Fluoro-Fentanyl can be synthetised with this procedure using Para-Fluoro- Aniline instead of plain Aniline, but the purification process must be adapted.
The very powerful Alpha-Methyl-Fentanyl can also be synthetised with this method using N-(2-Phenylpropyl)-Piperidinone which can be synthetised from 1-Phenyl- 2-Bromopropane and Piperidinone or other methods. The 1-Phenyl-2-Bromopropane is used in the underground manufacture of Amphetamine, and the procedure of the synthesis of this compound can be easily adapted for the creation of N-(2-Phenylpropyl)-Piperidinone or the NPP (N-Phenethyl-Piperidinone).
Fentanyl is a very good and powerful opiate but there are some remarks:
- Fentanyl is very addicting , much more than simple Heroin, the regular users of this synthetic white Heroin I described was really strongly addicted.
- The risk of overdose is really large, even with the dilution I described before, so test your stuff before selling it!
- The duration of the effects is a little shorter than with normal Heroin.

Related texts:
N-Phenethyl-4-piperidone

N-alkylation of 4-piperidone can be done in PTC conditions - and no need to isolate your piperidone as free base. Add to one liter of acetonitrile 3 mole finely powdered potassium carbonate, then add 10 g of PTC catalyst - TBAB or TEBA, or just polyethylene glycol-400. Stir this suspension 15 min at 50-60°C, and then add in little portions your 4-piperidone hydrochloride, watching that the CO2 evolution wasn't too vigorous. Stir another hour at 50-60°C, and then add dropwise phenethylbromide, and stir 15-20 h at mild reflux. Then cool, and filter off inorganic salts - if filtration goes too slowly, add to suspension some (30-40 ml) saturated sodium sulphate solution, this makes the sticky precipitate granular and filterable. Yield almost quantitative (trust me), and no distillation needed - as result you have slightly yellow solid with mp 60°C.

[Unquote]

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