Testimony of Barry K Logan PhD, F-ABFT to the United States Sentencing Commission
Public Hearing on Fentanyl, Fentanyl Analogues, and Synthetic Cannabinoids

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Introduction

Mr. Chairman, Commissioners; thank you for the opportunity to present to you today on issues related to forensic laboratory challenges concerning the detectability and interpretation of forensic evidence involving the manufacture, distribution, and possession of fentanyl, and its role in intoxication and deaths.

I am chief scientist at NMS Labs, Inc., a private independent forensic laboratory providing testing for over 2500 law enforcement agencies; federal, state, county, and municipal forensic laboratories; coroner and medical examiners offices, and prosecuting attorneys offices throughout the United States and Canada. Our scientists perform seized drug testing, impaired driving, and death investigation toxicology testing, and provide testimony in federal, state and local courts. In 2016 our laboratories tested more than 68,000 exhibits in seized drug casework, and biological samples in over 50,000 death investigation cases. Many of these submissions came from major metropolitan centers with high rates of drug use, including Detroit and Chicago.

Our laboratories in Pennsylvania, Texas, North Carolina and Florida, specialize in the rapid identification of novel emerging drugs, and our scientists have authored over 25 publications and made dozens of professional presentations in the field of designer drug toxicology and chemistry over the last few years.

We have extensive first-hand experience of the impact of the burgeoning opioid crisis on forensic laboratories and medical examiners offices, and the challenges of identifying these substances in the laboratory, then interpreting the findings in court – challenges all forensic laboratories face.

<u>Frequently asked questions about Fentanyl and its Analogues</u>

Q: What has been the impact of the opioid crisis on your laboratory in Toxicology casework?

A: Based on state level data, the New York Times[1] estimated in September of 2017 that there were over 64,000 drug overdose deaths in 2016, mostly opioid drugs. This is an increase of 540% over three years since 2013. They reported that fentanyl and its analogues accounted for over 20,000 of those deaths – surpassing heroin related deaths for the first time ever.

[1] The First Count of Fentanyl Deaths in 2016: Up 540% in Three Years. By Josh Katz. New York Times, Sept. 2, 2017. https://www.nytimes.com/interactive/2017/09/02/upshot/fentanyl-drug-overdose-deaths.html

In the eighteen months between January 2016 and September 2017, NMS labs identified fentanyl in over 15,600 cases from medical examiners offices throughout the United States. In addition illicit analogues including acetylfentanyl (1813 cases), furanylfentanyl (1234 cases), carfentanil (678 cases), p-fluoroisobutyrylfentanyl (555 cases), were encountered along with another nine analogues representing an additional 500 cases. The positivity rates from January 2016 through September 2017 are more than double the rate for the prior 18 months. Keeping up with the rapidly changing menu of possible analogues has required five updates to the analytical procedure, additional R&D efforts in identifying new substances (approximately 1-2 new fentanyl related compounds per month), validating methods for forensic use, additional time answering questions from medical examiners and pathologists about the interpretation of results.

Q: Is fentanyl a drug class or a drug substance?
A: "Fentanyl" itself is a unique chemical compound, that was patented and marketed by the Janssen Pharmacutica Company in the 1960's. Chemical modifications to the core structure of fentanyl create the fentanyl drug class, of which there are at least hundreds if not thousands of potential variants or analogs. For example, changing the carbon chain length or conformation on the propanamide portion of the drug, results in the series: acetylfentanyl, fentanyl, butyrylfentanyl, isoburtyrylfentanyl, valerylfentanyl, furanylfentanyl, cyclopropylfentanyl, acrylfentanyl, crotonylfentanyl, and numerous other, purely illicit, fentanyl analogues. Similarly, modifications can be made to other sites on the molecule to create yet more potent variants, and combining these modifications creates an exponentially greater number of possible drugs.

Q: Do fentanyl analogues constitute a "class" of drugs subject to core structure scheduling?
A: Yes. Fentanyl was described in a patent issued to the Janssen Pharmaceutical company in 1960. The prototypical compound fentanyl contains three core elements, each of which can be modified to create large numbers of variants or analogues while retaining the core underlying structure[2]. They can be described for example in the following manner:

"The term "fentanyl related substance" includes any compound structurally derived from fentanyl by virtue of one or more of the following modifications, and not currently controlled in any schedule:
(A) replacement of the phenyl portion of the phenethyl group by any aromatic group, whether or not further substituted in or on the aromatic group;
(B) substitution on the phenyl portion of the phenethyl group with alkyl, alkenyl, alkoxyl, hydroxyl, halo, haloalkyl, amino or nitro groups, and/or substitution of or on the ethyl portion of the phenethyl group with alkyl (C2 or greater), alkenyl, alkoxyl, hydroxyl, halo, haloalkyl, amino or nitro groups;

[2] Logan BK, Mohr ALA, Papsun D. Recommended methods for the Identification and Analysis of Fentanyl and its Analogues in Biological Specimens United Nations Office on Drugs and Crime (UNODC), Vienna, Austria, November 2017

(C) substitution in or on the piperidine ring with alkyl, alkenyl, alkoxyl, ester, ether, hydroxyl, halo, haloalkyl, amino or nitro groups;
(D) replacement of the ring of the aniline group with any aromatic group whether or not further substituted in or on the aromatic group; and/or
(E) replacement of the N-propionyl group by an acyl, alkyl, alkenyl, alkoxyl, hydroxyl, haloalkyl, or amino group. Drugs containing these core elements can be considered to be members of the fentanyl class." [3]

Over 600 fentanyl analogues have been described in peer reviewed literature and patents, although many of today's emerging illicit analogues have not previously been so described. The vast majority of these however, and many other possible variants, are captured under core structure scheduling language similar to the example above.

Q: Do drug users know when they are taking fentanyl versus heroin?
A: Typically, no. Recent studies have demonstrated that drug users cannot reliably differentiate between the effects of fentanyl and other opioids such as heroin. Since doses used by drug users are either unknown to them, or outside of their control, differences in intensity of effects can equally well be dose related as opposed to substance related.[4] There is evidence that once drug users become aware of the availability of a particular high potency batch such as one cut with a fentanyl analog, they may actively seek it out.

Q: Do forensic laboratories report the presence of non-controlled substances such as currently uncontrolled new fentanyl analogs in seized drug cases?
A: Practices vary from laboratory to laboratory. Typically, crime laboratories performing seized drug testing do not have the time, resources or mandate to confirm and report the presence of non-controlled substances in their case reports, especially where they do not have available standard references materials. This practice has led to the under-reporting of prevalence of new novel psychoactive substances (NPS) including new fentanyl analogues.

Q: Can laboratories distinguish between illicit fentanyl and diverted pharmaceutical fentanyl?
A: Most diverted pharmaceutical fentanyl is either in solution, transdermal patch or buccal/transmucosal formulations. Illicit fentanyl is typically in powder form, usually cut with an inert material like glucose, acetaminophen, dipyrone, microcrystalline cellulose, levamisole or other non-controlled substances. Frequently illicit fentanyl at the individual dosage level may contain greater or lesser amounts, sometimes trace amounts, of other controlled substances including heroin, cocaine, ketamine, and methamphetamine. Illicit fentanyl may contain residual amounts of precursor chemicals such as 4-ANPP, or other by products of synthesis. Crime laboratories typically do not test for or report these trace chemicals. The DEA special testing laboratory may test for them under some circumstances, but rarely make public

[3] Logan BK, *Modelled after* 115th Congress, 1st Session; A Bill to amend the controlled substances Act to list fentanyl analogues as schedule I controlled substances, Sponsor Senator Ron Johnson (WI): https://www.ronjohnson.senate.gov/public/_cache/files/be56bfcf-24b1-4d28-be03-ef6def0ba89f/sofa-act.pdf
[4] Griswold MK, Chai PR, Krotulski AJ, Friscia M, Chapman B, Boyer EW, Logan BK, Babu KM. Self-identification of nonpharmaceutical fentanyl exposure following heroin overdose. Clin Toxicol (Phila). 2017 Jul 6:1-6.

these findings. There are only five fentanyl related compounds that are licit controlled substances (fentanyl, sufentanil, alfentanil, remifentanil, and for veterinary applications, carfentanil, and thiafentanyl). Any other fentanyl analogues are by definition illicit. In practice there are no reported seizures of significant diverted amounts of scheduled sufentanil, alfentanil, remifentanil, or thiafentanyl.

After ingestion, it is virtually impossible to distinguish between illicit and diverted pharmaceutical fentanyl based on analysis of biological specimens (blood, urine, tissue). Some of the precursor chemicals used for illicit fentanyl production, are also metabolites of fentanyl, so their origin cannot be determined.

Q: Can we forensically differentiate the fentanyl analogues from one another?
A: With the combined use of currently available technology, including infrared spectrophotometry (FTIR), Electron Impact/Gas Chromatography Mass Spectrometry (EI/GCMS), quadrupole time of flight mass spectrometry (QTOF), and nuclear magnetic resonance spectroscopy (NMR), it is possible to differentiate between most analogues of fentanyl in seized drug samples. Closely related chemical isomers (e.g. "o"- versus "m-" isomers) may be very challenging for most laboratories to differentiate. Arguably these cases can be prosecuted under the more cumbersome, and more heavily litigated, analogue laws.

In practice, most forensic laboratories doing seized drug testing do not have access to all of the above technologies and do not have the time or resources in any individual case to track down the subtle differences between some of these chemical forms or isomers. The instruments needed to perform this testing cost in the region of $500K to $750K each, so equipping every laboratory with this technology is not feasible.

Q: Can we recognize something as being fentanyl-related even if we don't know its absolute identity?
A: In most cases, yes, but not in every case. There are characteristic analytical and chemical features of some of the fentanyl analogues that they have in common with other known fentanyl analogues or derivatives, such that they can be readily identified as being derived from fentanyl, and consequently members of the fentanyl class. Compounds derived from fentanyl but with multiple chemical modifications may not demonstrate some of these tell-tale analytical properties, and would require additional complex analytical work to determine their absolute identity.

Q: What do we know about the relative toxicities of the fentanyl analogues?
A: We currently know very little about this as it relates to toxicity in humans. A series of patents and peer-reviewed articles reported the relative analgesic potency of approximately 300 fentanyl analogues discovered in the 1960's through the 1980's. These studies are done using mouse or rat models for assessment of the analgesic effects of the drug, using the animal's response to standing on a hot plate, placing its tail in hot water, or response to a chemical irritant, as an end-point. Since the different reports use different animals and different stimuli, comparisons between studies are difficult to make, and estimates of relative

potency can vary widely. Also, the end-point of these studies is analgesia or nociception (pain relief), not the toxic respiratory and central nervous system depression effects of fentanyl and its analogues, and the two are not always correlated. While it is likely that analgesic efficacy and toxicity are inter-related, there are not data to support the quantitative relationship between the two, and certainly not in humans.

Consequently, popular estimates of potency based on these studies (e.g. "carfentanil is 10,000 times more potent than morphine") should be, at best, considered general approximations. The ratio depends on the species and pain stimulus used, and the corresponding effective dose for morphine, which also varies from study to study. Different studies support a range of relative potencies for carfentanil of between 5,000 and 43,000 compared to morphine, and in animal sedation, the dose of carfentanil used is typically only 100 to 1000 times less than the corresponding dose of morphine. Even this rudimentary animal study data does not exist for most of the currently popular and emerging illicit fentanyl analogues.

Since the available studies and data relate neither to toxicity, nor to humans, it is not possible to opine quantitatively with any accuracy regarding the relative respiratory toxicity of the currently popular fentanyl analogues in humans, compared to say morphine.

Q: What factors influence the dangerousness of a fentanyl analogue?
A: The major considerations are whether the analogue will bind to the receptors in the central nervous system that cause the characteristic constellation of effects of opioids, including analgesia, sedation, respiratory and central nervous system depression, cough suppression, inhibition of gastric motility, pinpoint pupils, histamine release, and other minor signs. The degree to which the compound binds to the receptor is one indicator of potency. However not all compounds that bind to the receptor produce the same effects. For example, Naloxone, the popular opioid overdose reversal agent, binds strongly to the opioid receptors but does not produce the effects described above.

The second factor influencing whether a compound is potent or toxic relates to its functionality at the receptor; in other words does it initiate the cascade of biochemical reactions that result in the classic opioid intoxication described above. Unfortunately, in practice this determination has not been made for most of the emerging novel psychoactive opioid analogues, or if it exists has not been published or made public.

Consequently, while it is possible to make some educated guesses about the likely potency of a novel compound based on its structure, its receptor binding, and animal analgesia studies, these are not definitive in quantitatively establishing its toxicity in humans.

Q: How are drug concentrations interpreted in deaths that are suspected of being drug related?
A: Interpretation of drug concentrations needs to be approached on a case-by-case basis. Determination of cause and manner of death is made by the coroner, medical examiner or forensic pathologist, based on consideration of the history, scene and circumstances, autopsy,

and laboratory studies including toxicology and histology. Toxicology results are interpreted by the pathologist ideally in consultation with a forensic toxicologist, based on previously reported therapeutic, toxic and fatal concentrations from publications and other reports, where they exist[5]. For many fentanyl analogues, these reference data are not available, especially around the period when the substance is identified for the first time. Additional factors considered include drug tolerance, pharmacokinetics, prescription or drug use history, central versus peripheral blood, survival interval, postmortem redistribution, and other factors to the extent they are known. These factors are considered along with autopsy findings of trauma, disease, indicia of recent drug use, and other anatomic and physiological factors. Ultimately the pathologist based on his or her professional experience determines the most likely cause or causes contributing to the death.

Q: When multiple drugs are present with a fentanyl analogue can we answer the question as to whether a death would have occurred in the absence of one of the drugs in the mixture?
A: In cases where multiple drugs are present the same process applies, however an additional consideration of the concentrations and effects of the other substances must be taken into account. If the other substances are benign, or present at therapeutic or typical recreational concentrations, and other anatomical causes of death have been discounted, it increases the likelihood that death was caused by addition of the fentanyl analogue, even when little is known about its toxicity in man. When other drugs are present at concentrations previously known to have resulted in death, it reduces the likelihood that the fentanyl analogue was the causative factor. If the fentanyl analogue is present in amounts known to have contributed to previously reported deaths, it would undoubtedly have contributed in some measure to causation of the death, irrespective of the nature and amounts of the other substances.

Q: Are carfentanil or other analogue ingestions always fatal?
A: No, in our casework we frequently see very elevated carfentanil and other analogue concentrations in presumably tolerant, living drug users, such as arrestees in drug impaired driving investigations. The blood carfentanil concentrations in these subjects are frequently many times those concentrations which have caused death in less tolerant users, underscoring the difficulty in establishing a lethal dose, or minimum blood concentration that will always independently result in death.

Q: How have the medical examiners offices and forensic laboratories been affected by the increase in opioid related deaths?
A: Medical examiner's office are reporting being overwhelmed by the increase in autopsies in drug overdose deaths[6]. In some jurisdictions it is putting their accreditations at risk, due to pathologists being limited with respect to workload to maintain quality. Other conditions, (non-competitive salaries, workload, stressful nature of the work, etc.) have led to fewer

[5] Logan BK, Mohr ALA, Friscia M, Krotulski AJ, Papsun DM, Kacinko SL, Ropero-Miller JD, Huestis MA. Reports of Adverse Events Associated with Use of Novel Psychoactive Substances, 2013-2016: A Review. J Anal Toxicol. 2017 Sep 1;41(7):573-610.
[6] Andrew TA, Duval JV. Confronting an Upsurge in Opiate Deaths With Limited Resources. Academic Forensic Pathology, 7:1;7-18, March 2017.

physicians entering the field, making vacancies hard to fill. Medical examiner offices are frequently not budgeted for the additional costs of toxicology testing in these cases, resulting in incomplete drug testing, and failing to identify deaths attributable to newly emerging fentanyl analogs. This results in delays in scheduling the compounds and educating drug users about the emergence of more dangerous and potent drugs.

Forensic laboratories have encountered greater testing volumes, and greater demands for research and development and validation to keep their methods current and forensically defensible. They have to invest in large libraries of new drug standard reference materials, and pay for the costs of new more sensitive equipment, or for outsourcing more challenging and hard to identify drugs to reference laboratories. Advanced expertise in drug chemistry and toxicology is needed to identify newly emerging drugs, and in research and development to create and validate methods for them, which many laboratories cannot afford. These considerations result in backlogs and delays in reporting results, which slows the process of issuing death certificates, impacting families' abilities to settle estates, make insurance claims, and reach closure around the death of a loved one.

Due to the complexity of the testing process, and the limitations of laboratories resources, many of these deaths related to novel fentanyl analogues go undetected and uncounted.

Q: What considerations might apply in considering the community, public health and public safety impact of fentanyl and its analogues?

A: The class of drugs derived from fentanyl with the common structural elements described above are an extremely potent new class of drugs made all the more dangerous by that fact that they are distributed and used outside of a regulated market, with often little to no data to indicate their potential toxicity, increasing the risk of overdoses. Users do not have any idea about what drugs are actually in the product they are buying. With increasing frequency, the street drug supply contains mixtures of fentanyl analogues with one another or with other street drugs, creating unpredictable drug interactions with potentially lethal consequences. Although quantitative comparisons between the toxicity of individual drugs are not well understood, as a class they are more dangerous and more potent than prototypical narcotic drugs like morphine and codeine. While these fentanyl analogues are the latest in a series of novel drug classes, following synthetic cannabinoids, and hallucinogens/stimulants, they are involved in far more deaths.

Thank you for the opportunity to present this testimony.

Biography:

Dr. Barry Logan, is Vice President of Forensic Science Initiatives at NMS Labs, and Executive Director of the non-profit Center for Forensic Science Research and Education (CFSRE) at the Fredric Rieders Family Foundation, in Willow Grove PA

Dr. Logan is a Fellow of the American Board of Forensic Toxicologists and has over 120 publications in toxicology and analytical chemistry, including work on the effects of drugs on driving impairment, and cause and manner of death for a wide range of drugs and toxins. His recent work has focused on the analytical and interpretive toxicology of emerging recreational and designer drugs.

His other appointments include Executive Director of the Robert F Borkenstein course at Indiana University. He holds academic appointments at Indiana University, Arcadia University, Thomas Jefferson University and Temple University, and he oversees a variety of research initiatives with other academic institutions and medical examiners offices. He has served as a consultant to the National Highway Traffic Safety Administration (NHTSA), and the United Nations Office on Drugs and Crime (UNODC), and various other government agencies, and testified over 200 times in criminal and civil cases involving forensic toxicology.

In recognition of his work and contributions, Dr. Logan has received numerous national and International awards including the AAFS Rola Harger Award, the ICADTS Widmark Award, the National Safety Council's Robert F Borkenstein Award, and in 2013-14 served as President of the American Academy of Forensic Sciences.

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