

Fentanyl and Fentanyl Analogs

Ruth E. Winecker, Ph.D. F-ABFT
Director, Quality Assurance and
Proficiency Program

Project Director, National
Laboratory Certification
Program

Center for Forensic Sciences

RTI International

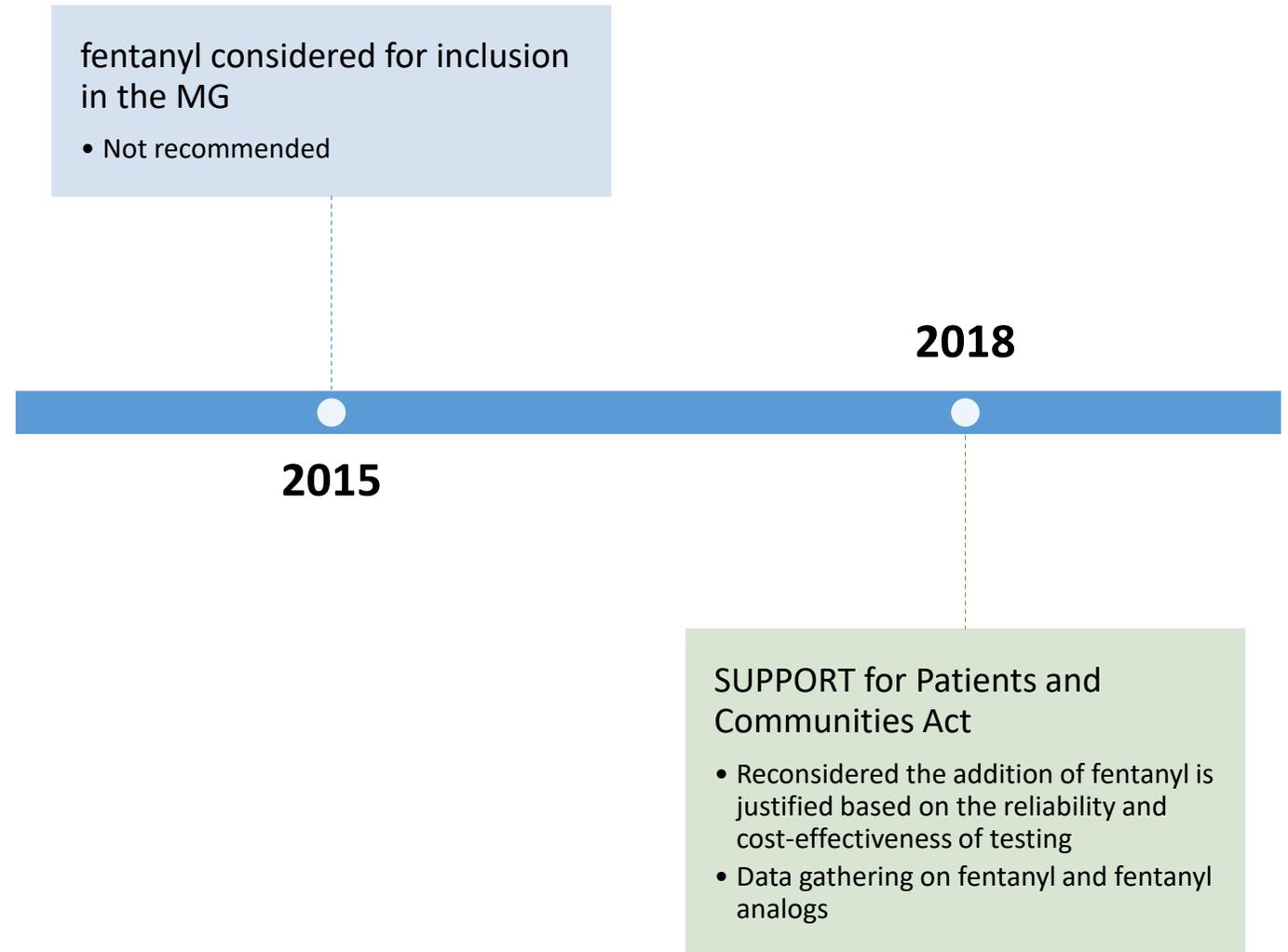
Outline

- SUPPORT for Patients and Communities Act
- Background and Definitions
- Fentanyl and Fentanyl Analogs
 - MDI and Crime Labs
 - Workplace Population
- Analysis
- Summary

SUPPORT for Patients and Communities Act required the Secretary of the Department of Health and Human Services (HHS) to determine whether it is justified based on the reliability and cost-effectiveness of testing to:

1. revise the Mandatory Guidelines for Federal Workplace Drug Testing Programs to include fentanyl and
2. to consider whether to include any other drugs or other substances listed in Schedules I and II of CSA Section 202.

Timeline of Fentanyl and MG



Background and Definitions

Fentanyl and Fentanyl Analogs

Fentanyl and Fentanyl Analogs

μ opioid receptor agonists

narcotic analgesics

new and novel psychoactive substances

- DEA CSA Schedule II
 - Legally prescribed narcotic analgesic
 - Pharmaceutical grade
 - Hospital setting-intraoperative anesthetic (1968-present)
 - Chronic pain (2005-present)
 - Can be illicitly diverted
 - Clandestinely manufactured illicit substance
 - Heroin “substitute”
 - Found in mixtures
 - Heroin/Fentanyl analogs
 - Cocaine/Methamphetamine
 - “Non-active” components
 - Found in counterfeit tablets

What is Fentanyl?

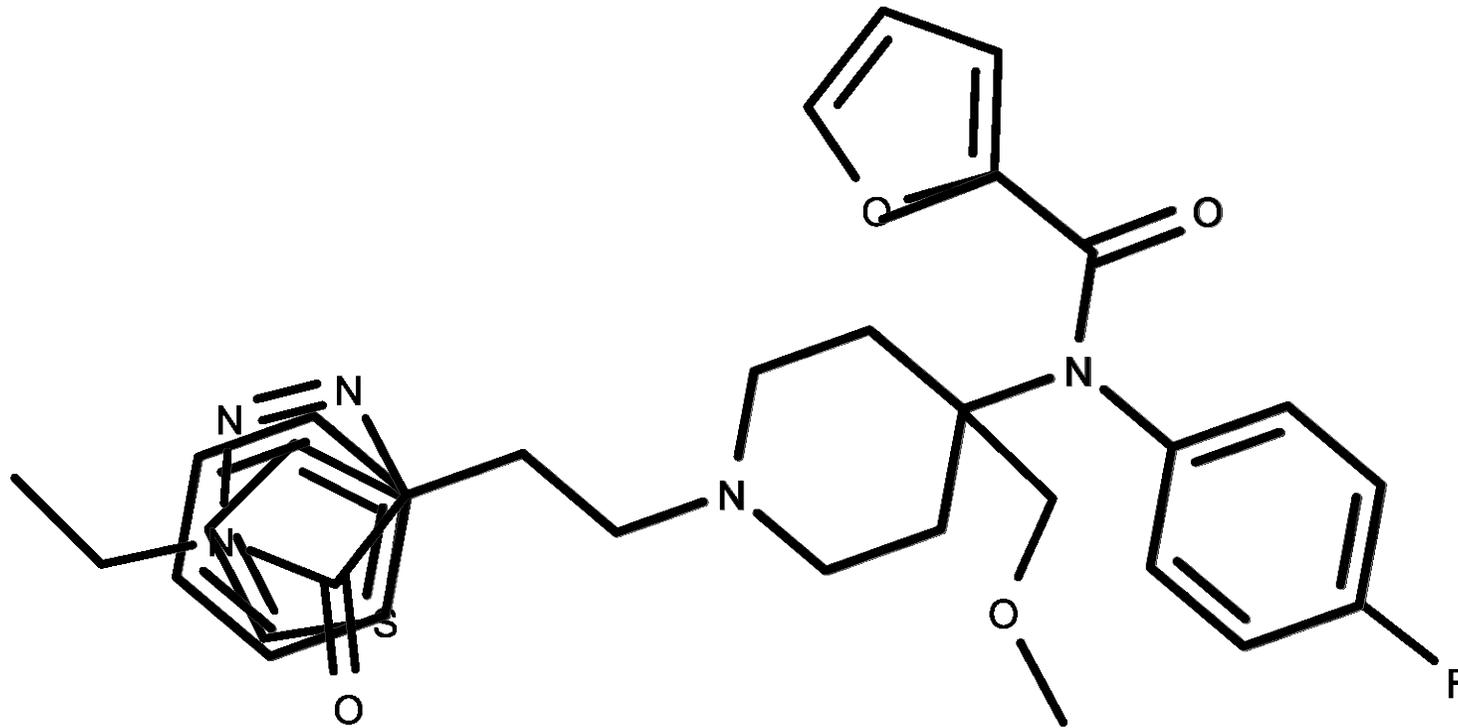
“Clandestine fentanyl is distributed in the United States in the same manner as heroin. It is sold in powder form in glassine bags or wax envelopes, often stamped with brand names. It is often sold as heroin, with many users not aware of the presence of fentanyl in the substance”.

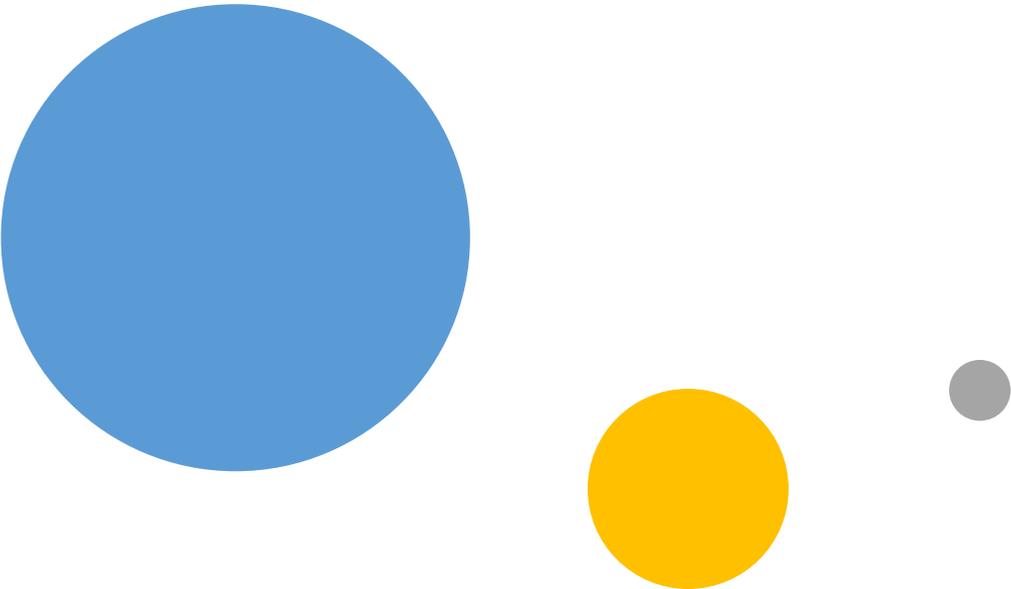
-DEA National Drug Threat Assessment 2016

What is a Fentanyl Analog?

- DEA CSA Schedule I and II
 - Schedule I
 - Before Feb 2018-emergency scheduling by DEA as they appeared/identified
 - Illicitly manufactured
 - Driven by quest to evade penalties associated with use, possession, distribution of controlled substances
 - Found in mixtures
 - Found in counterfeit tablets
 - After 2018-automatically Schedule I based on the substantial similarity between the chemical makeup and effects of fentanyl-relevant to any analog not already schedule II
 - Schedule II-analogs with a legitimate medical use
 - Sufentanil, Carfentanil, Remifentanil, etc.

What constitutes substantial similarity?





History

Outbreaks of Fentanyl
and Fentanyl analog
deaths in the US

History of Fentanyl Deaths

Fentanyl mixed with heroin

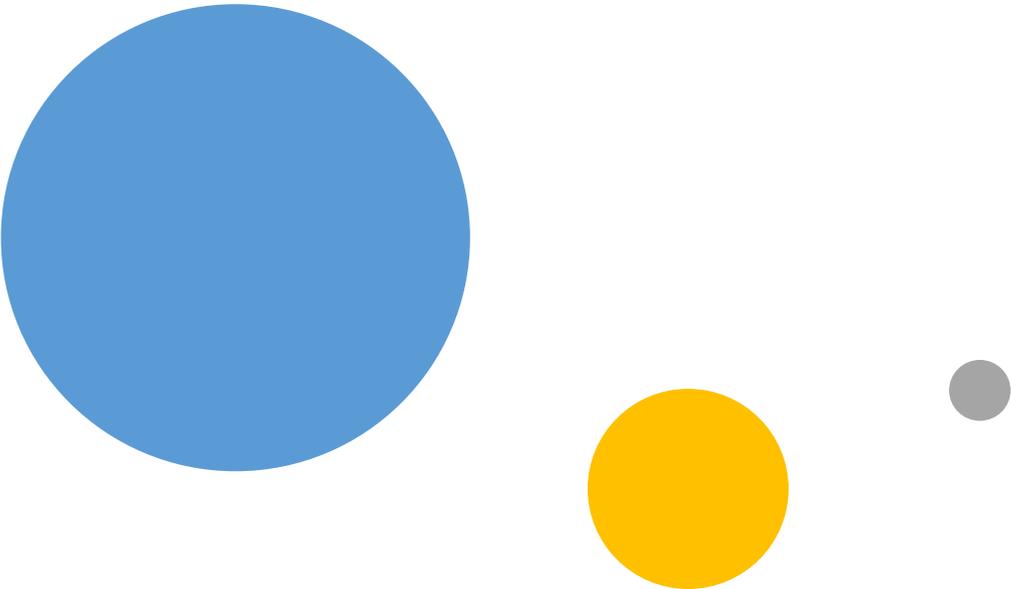
- 1993: “Tango and Cash” fentanyl produced in Wichita KS mixed with heroin
- 2005-2007: Midwestern states reported heroin mixed with fentanyl clandestinely produced in Mexico caused ~1,000 deaths
- 2014-present: Primarily produced in Mexico with precursor chemicals bought from China

Fentanyl

- 1960s-present: Diverted pharmaceutical fentanyl known to cause deaths in medical settings (hospitals, surgery centers)
- 2004-present: Larger numbers of deaths associated with the fentanyl after approval of Duragesic and other prescribed forms of fentanyl -higher diversion liability
- 2016-present: Increasingly sold without heroin

Fentanyl Analog Deaths

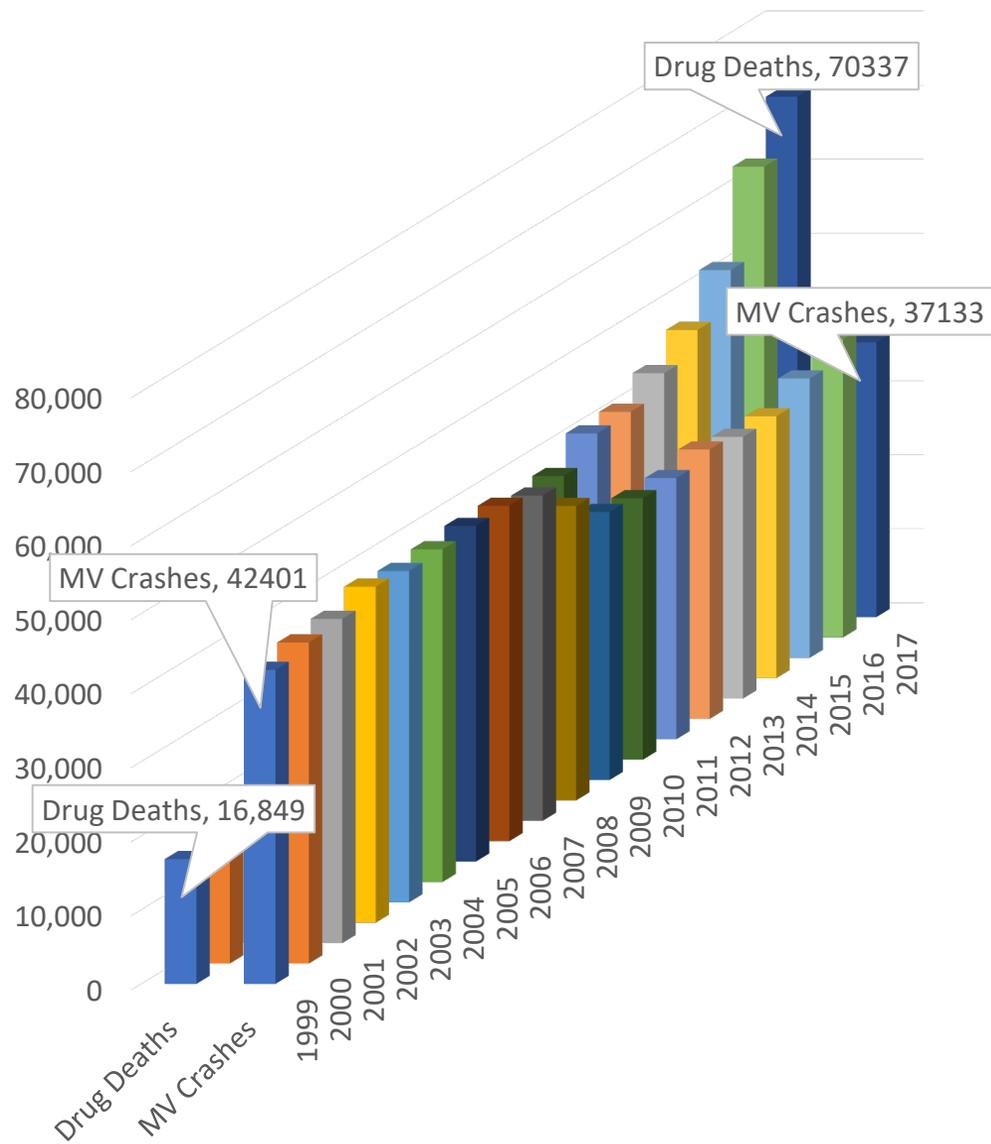
- Analogs-prior to 2015 limited outbreaks
 - 1976: Alpha-methyl-fentanyl mixed with heroin and sold as high purity heroin aka “china white”
 - 1984: 3-methylfentanyl supplied to heroin users
 - 2013-2014: Acetyl fentanyl- deaths in heroin users in RI
 - ~2017 remerged but largely in combination with fentanyl
 - manufacturing “artifact”
 - 2015- Furanylfentanyl first reported
 - 2016- 9 new analogs reported
 - 2017-10 new analogs reported
 - 2018- 4 new analogs reported*



Criminal Justice System

MDI and Crime Lab Data

Drug Deaths vs MV Deaths 1999-2017



NC: Top Five Drugs: Poisoning Deaths by Year

YEAR	1st	2nd	3rd	4th	5th
2000	Methadone	Cocaine	Morphine	Oxycodone	Ethanol
2001	Methadone	Cocaine	Oxycodone	Morphine	Heroin
2002	Methadone	Cocaine	Oxycodone	Morphine	Heroin
2003	Methadone	Cocaine	Morphine	Oxycodone	Heroin
2004	Methadone	Cocaine	Morphine	Oxycodone	Fentanyl
2005	Cocaine	Methadone	Hydrocodone	Oxycodone	Fentanyl
2006	Methadone	Cocaine	Oxycodone	Fentanyl	Morphine
2007	Methadone	Cocaine	Oxycodone	Fentanyl	Morphine
2008	Methadone	Oxycodone	Cocaine	Fentanyl	Morphine
2009	Methadone	Oxycodone	Cocaine	Fentanyl	Morphine
2010	Methadone	Oxycodone	Cocaine	Fentanyl	Morphine
2011	Methadone	Oxycodone	Cocaine	Oxymorphone	Fentanyl
2012	Cocaine	Oxycodone	Methadone	Heroin	Fentanyl
2013	Oxycodone	Methadone	Heroin	Cocaine	Oxymorphone
2014	Heroin	Cocaine	Oxycodone	Fentanyl	Methadone
2015	Heroin	Cocaine	Oxycodone	Fentanyl	Oxymorphone
2016	Cocaine	Fentanyl	Heroin	Oxycodone	Fentanyl Analogues
2017	Cocaine	Fentanyl	Fentanyl Analogues	Heroin	Ethanol

Emerging Threat Reports-DEA

- 2016: 1299 identifications of fentanyl and related substances

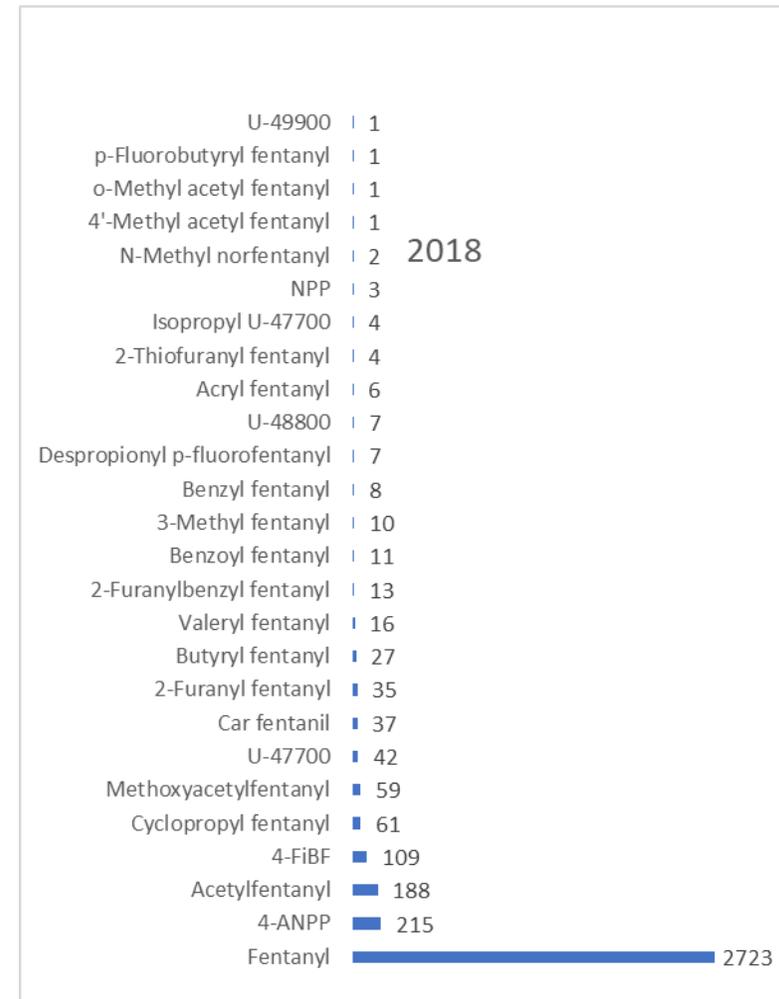
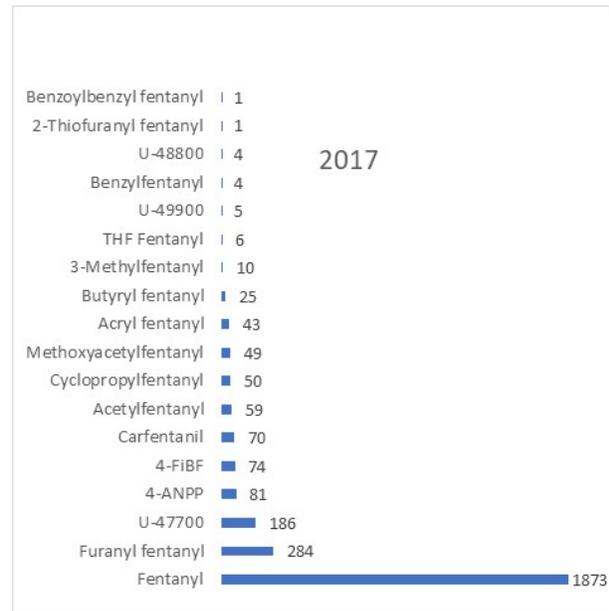
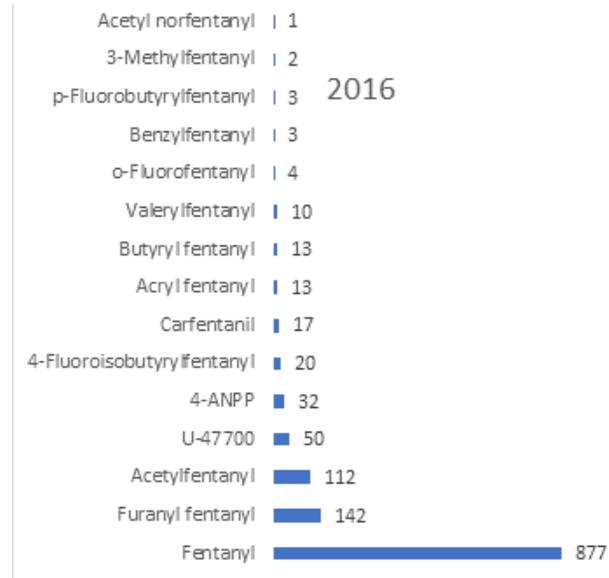
- 68% contained fentanyl
- 46.5% fentanyl was only substance identified
- 42% found with heroin
- 9 new analogs identified

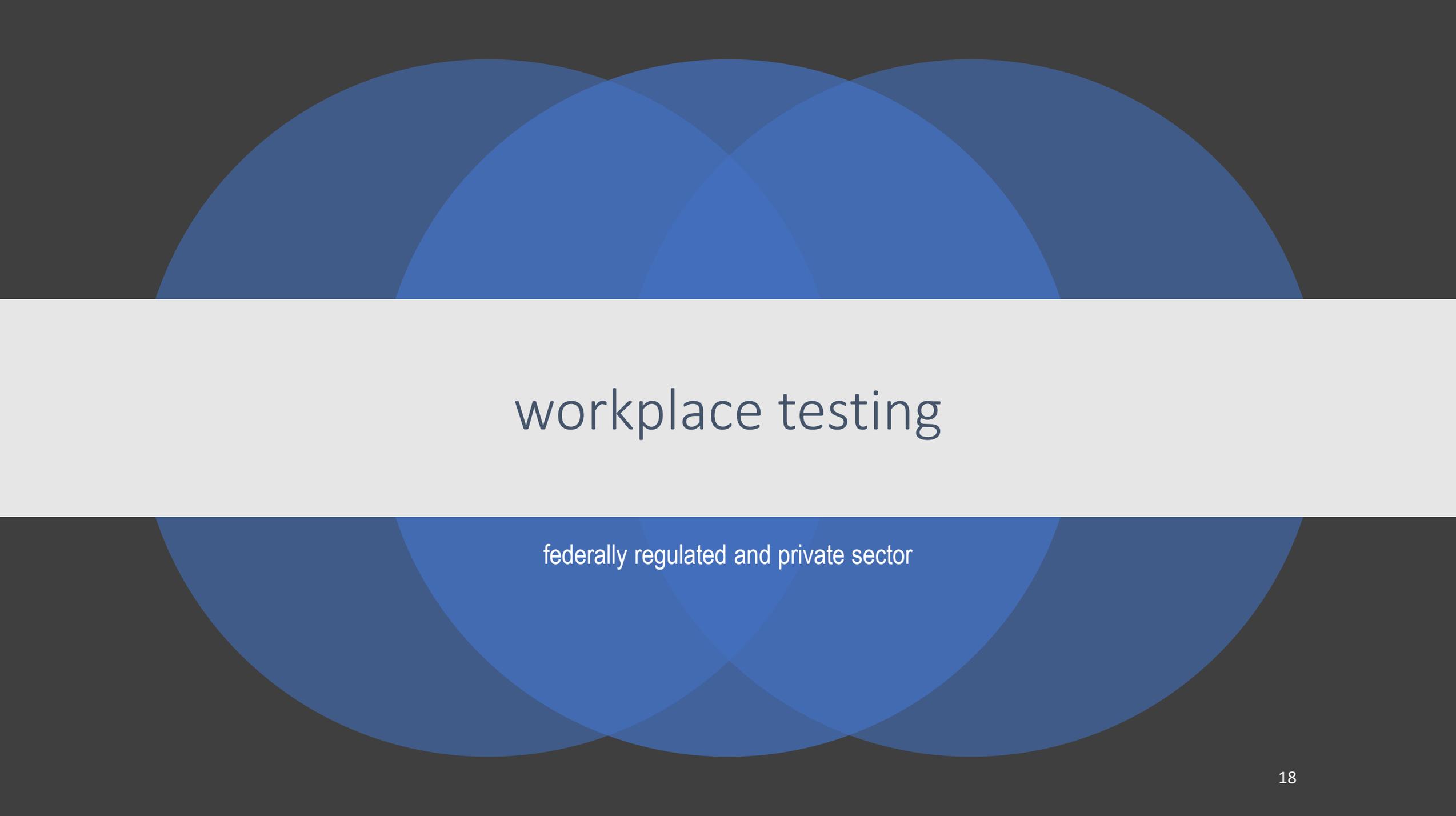
- 2017: 2825 identifications of fentanyl and related substances

- 66% contained fentanyl
- 43% fentanyl found as only substance identified*
- 47% found with heroin
- 10 new analogs identified

- 2018: 3591 identifications of fentanyl and related substances

- 76% contained fentanyl
- 39% fentanyl only substance found*
- 45% found with heroin
- 4 new analogs identified





workplace testing

federally regulated and private sector

Mandatory Guidelines

Fentanyl and Analog Testing by request of federal agency or MRO

2 HHS-certified labs currently offer fentanyl testing of federal agency specimens upon request.

- One additional lab discontinued offering fentanyl testing on 10/15/18.
- NLCP data for the period 1/1/17-12/31/17
 - 34 requests
 - 6 laboratory reported positives (hospital setting)
 - 3 multiple positive
 - 2 with THCA
 - 1 with HYC and HYM
- NLCP data for the period 1/1/18-12/31/18
 - 16 requests (hospital setting)
 - 1 laboratory reported positive
- NLCP data for the period 1/1/19-5/30/19
 - 1 request-negative result

Fentanyl in Workplace Testing

Not well studied

- HHS laboratories performing fentanyl testing for non-regulated testing estimate positivity at 0.2%

RTI pulse testing studies

- 2017: 2,139 regulated urine specimen aliquots were deidentified and screened for fentanyl
 - Confirmation testing for fentanyl and norfentanyl
- 2019: 2,158 regulated urine specimen aliquots were deidentified and screened for fentanyl
 - Confirmation testing for fentanyl, norfentanyl, and 11 analogs

Pulse Testing Results

Year	Assay	Total specimens	# specimens ≥ 1 ng/mL (%)	# confirmed by LCMSMS (%)
2017	EIA #1	1,083	3 (0.27)	2 (0.19)
	ELISA (cutoff = 0.75 ng/mL)	1,056	3 (0.27)	3 (0.27)
2019	EIA #2	2,158	8 (0.37)	2 (0.09)

- Specimens between 50% of cutoff and cutoff (n=31 in 2017 and n=39 in 2019) were also referred to confirmation testing, but none confirmed.
- No analogs were detected in 2019 study

Other Considerations

Initial test positivity rate in
pulse studies 0.27-0.37%

Overall low confirmation rate
for the two EIA's

- 66% for EIA #1 and 25% for EIA #2
- Consistent with a study of another EIA with a 32.6% confirmation rate
- Compare to THCA with > 95% confirmation rate

Confirmed positive test analytes in 9,646 specimens tested on the two pulse testing days

Analyte	COUNT	% Positive
MDA	1	0.01%
MDMA	1	0.01%
6AM	2	0.02%
Morphine	4	0.04%
Codeine	8	0.08%
Fentanyl*	2	0.09%
Oxycodone	17	0.17%
Oxymorphone	20	0.21%
Methamphetamine	24	0.24%
Benzoyllecgonine	30	0.31%
Hydromorphone	32	0.33%
Hydrocodone	35	0.36%
Amphetamine	77	0.80%
THCA	96	0.99%

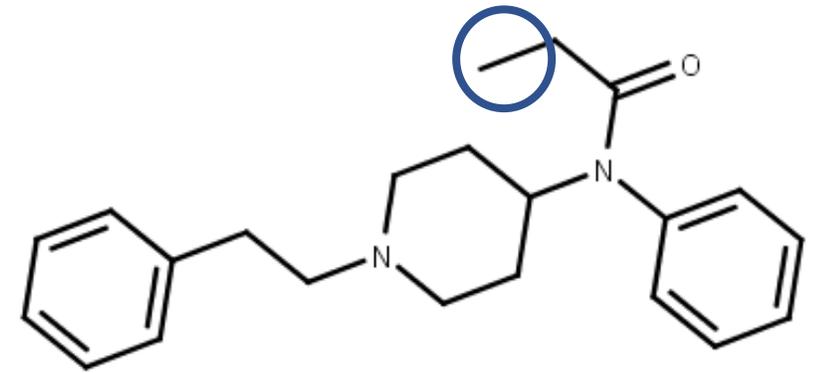
*fentanyl based on 2158 specimens

Current Technology

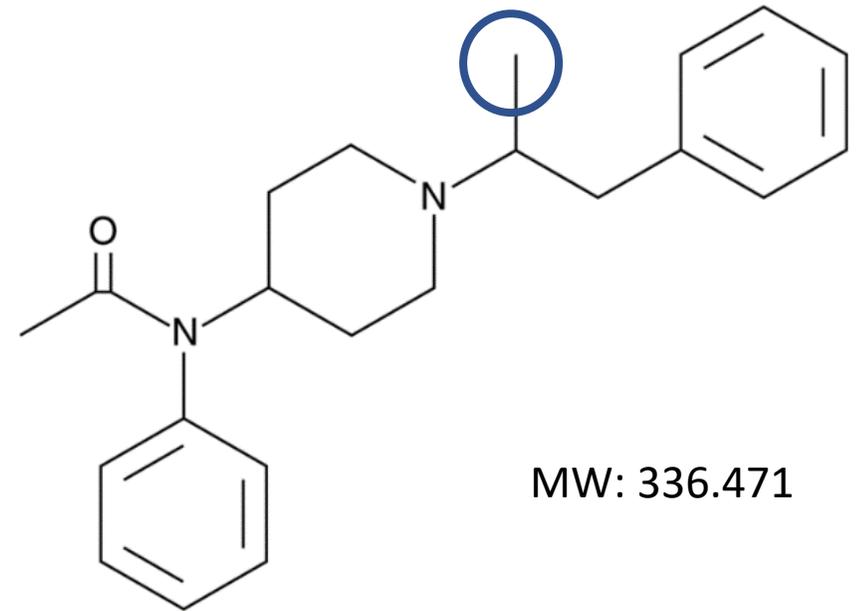
- 83% of HHS labs can test for fentanyl/norfentanyl in urine
 - Immunoassays currently in use are targeted towards fentanyl
 - Variable cross-reactivity to analogs
 - Unreliable for detection
 - Insensitive to norfentanyl
 - 30% of chronic pain patients treated with fentanyl were only positive for norfentanyl in urine. The remainder (70%) were positive for fentanyl (39%) or fentanyl and norfentanyl (31%)
 - Labs use LC-MS/MS or GC-MS for confirmation

Current Technology

- Confirmation Testing
 - GCMS and LCMSMS
 - appropriate for fentanyl and norfentanyl
 - GCMS may not be sensitive enough for some analogs
 - LCMSMS problem of isomers
 - Fentanyl
 - α -Methyl-acetylfentanyl



MW: 336.471



MW: 336.471

Further Considerations

Fentanyl as an initial test analyte

- Current EIA's are amenable to high volume environment
 - Confirmation positivity rates vary
 - Confirmation testing is expensive

Norfentanyl as an initial test analyte

- No current EIA for this analyte

Fentanyl Analogs as initial test analytes

- Which ones? Is this a moving target?
- No comprehensive high-throughput solution
- Prevalence-low



summary

Summary

- Areas of agreement (pros):
 - Fentanyl Deaths are increasing
 - Fentanyl is readily accessible
 - Safety issue in regulated testing
 - Federal Agency's could be authorized
 - HHS Certified Labs currently test for fentanyl

Summary

- Areas of concern (cons):
 - EIA's low specificity for target analytes
 - Prevalence
 - May be moving target
 - Cost

Caveat- Prior to DEA actions, fentanyl analogs were considered “legal highs” and a decreased risk of legal consequences may have played a role in their distribution and use. Scheduling of fentanyl analogs appeared to foster a decrease in the incidence of these dangerous compounds.