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NPS DISCOVERY

Examining the Evidence on Fluorofentanyl – Multidisciplinary Evaluation of this Emerging Drug with a Focus on Forensic Toxicology Investigations

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Society of Forensic Toxicologists (SOFT) Annual Meeting – Nashville, Tennessee

Disclosures

- I have no conflicts of interest to disclose.
- I am a scientist and employee of FRFF / CFSRE, a 501(c)(3) non-profit research and educational facility.
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  - The opinions, findings, conclusions and/or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect those of the Department of Justice

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NIJ | National Institute of Justice
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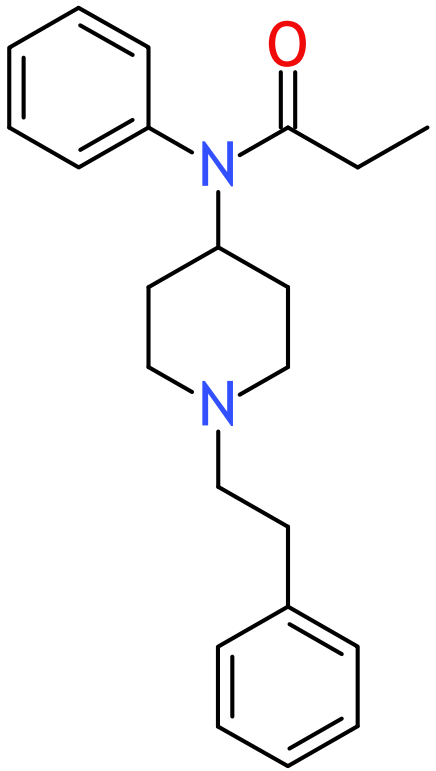
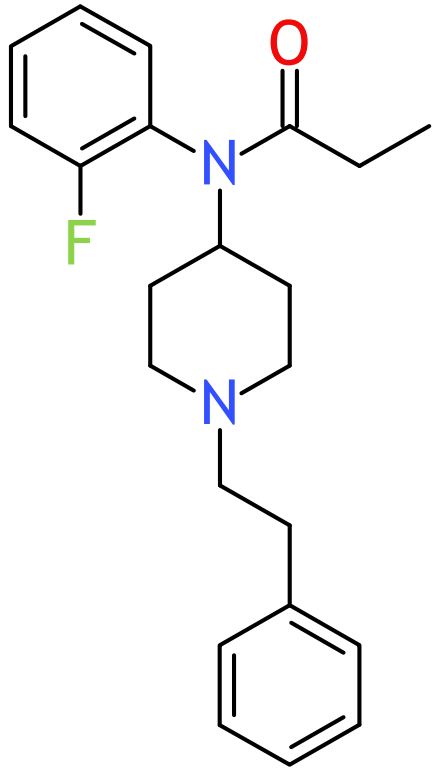
Fluorofentanyl (FF) Isomers

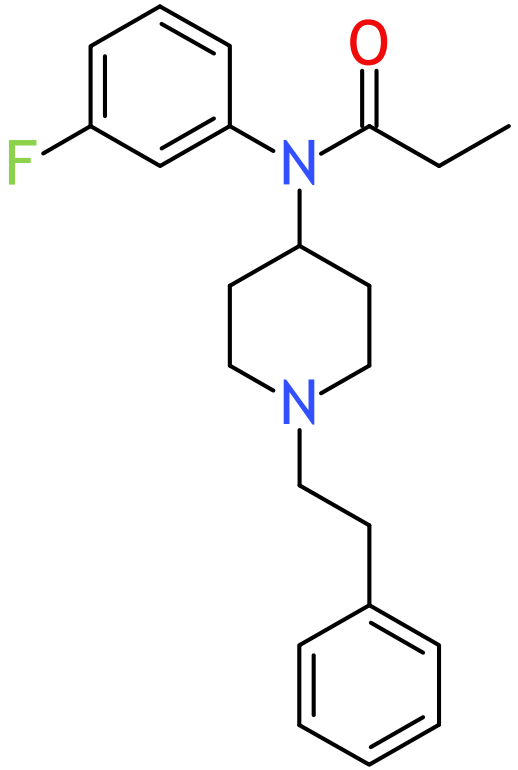
Fentanyl



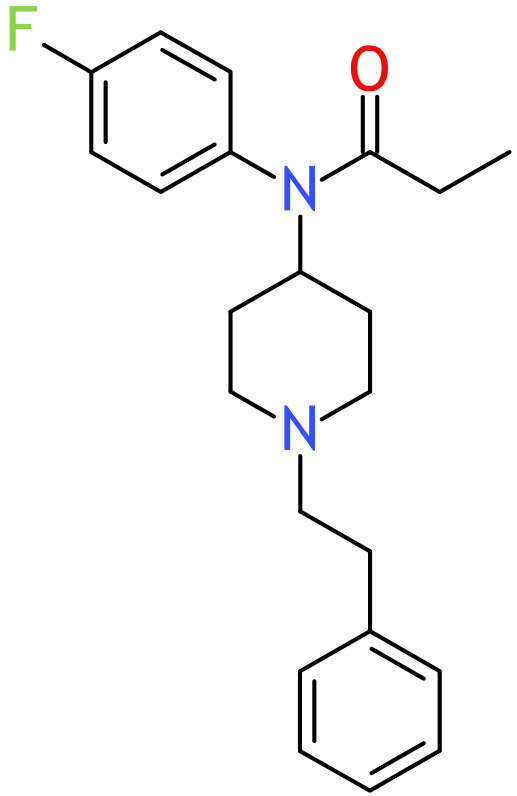
***ortho*-FF**



***meta*-FF**



***para*-FF ***



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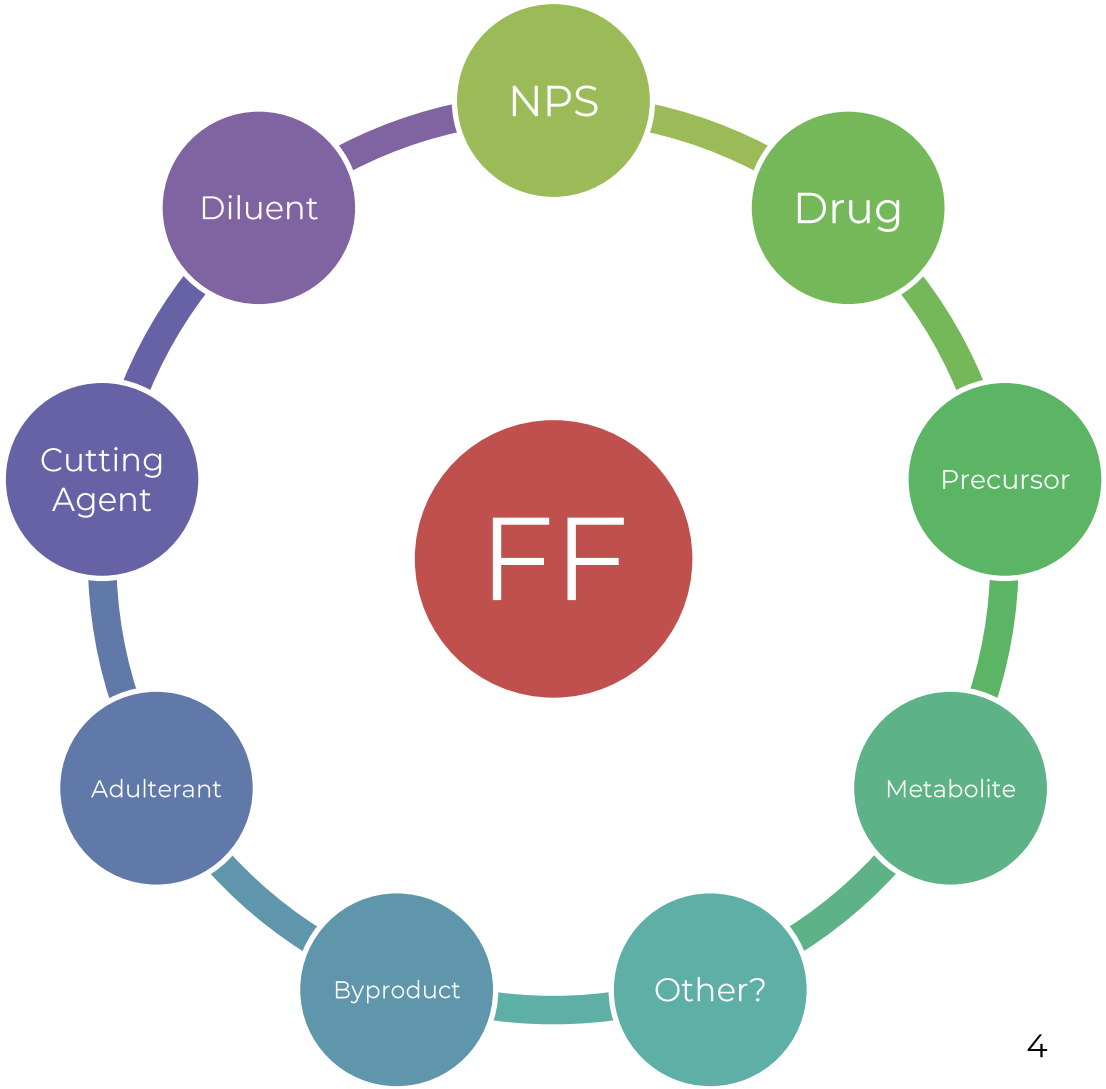
What is Fluorofentanyl (FF)?

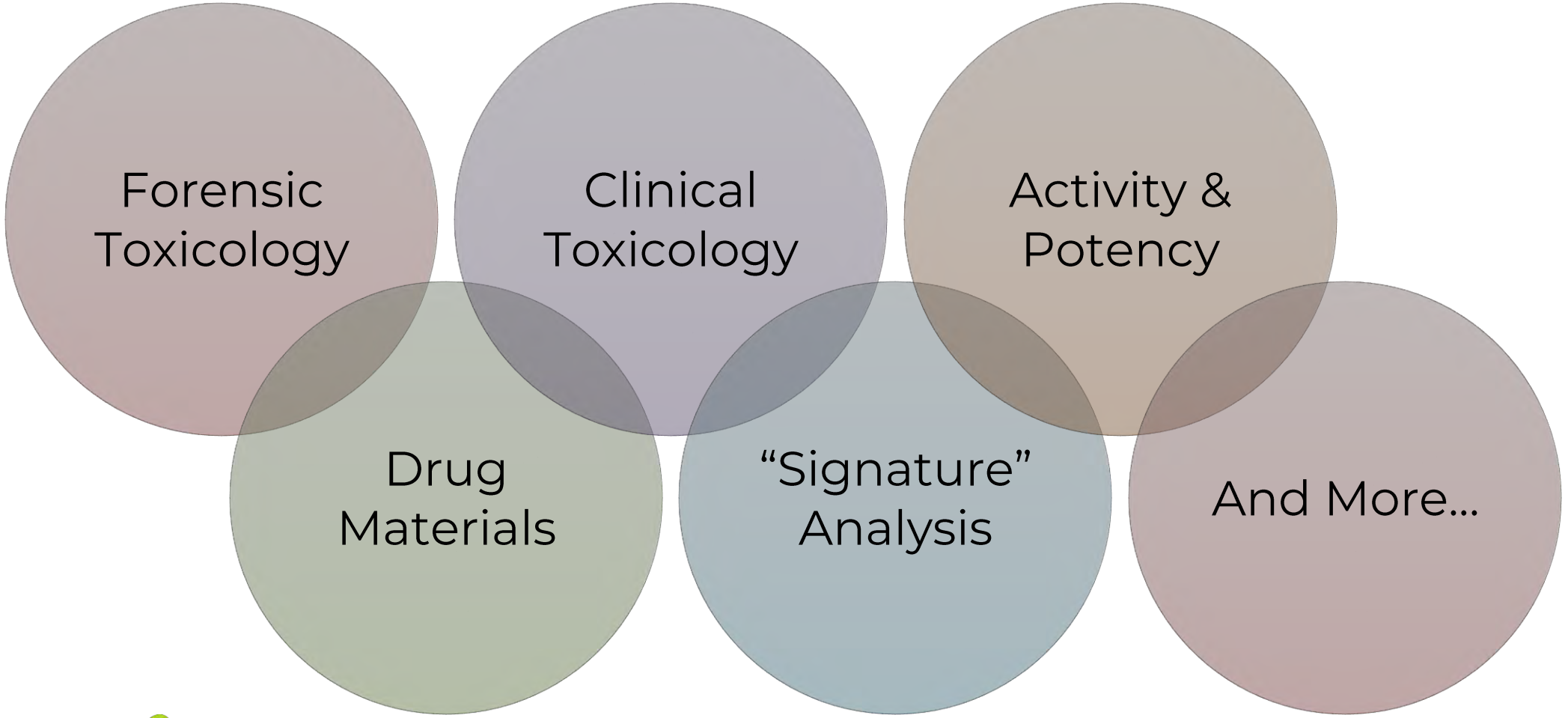
- Developed in 1960s by Janssen Pharma.
- FF is a fentanyl analogue
- *o*-FF and *p*-FF are explicitly Schedule I
- Reported potencies vary *(to fentanyl)*:
  - *o*-FF → approx. 4x more potent
    - Similar to cis-3-methylfentanyl
  - *m*-FF → approx. 6x less potent
  - *p*-FF → approx. 3x less potent
- Confusion regarding classification →



Examining the Evidence – Important Questions

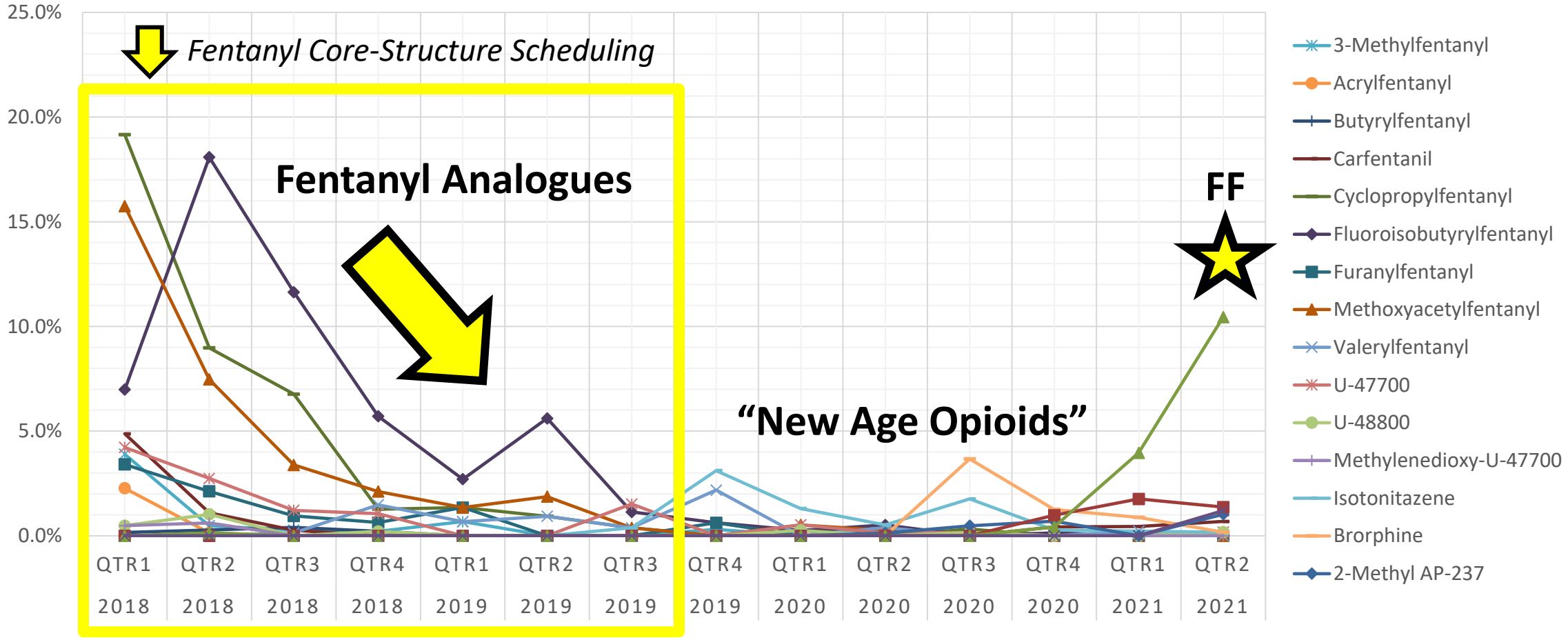
- Are fentanyl analogues back?
- Is fluorofentanyl a “typical” fentanyl analogue?
- Does fluorofentanyl *behave* like an NPS?
  - Legal status, positivity, distribution, drug materials, drug combinations
- Should fluorofentanyl be considered an NPS?
- How should toxicologists handle cases involving fluorofentanyl?

What **evidence** do we have?



Toxicology Trends

NPS Opioid Trends in the United States



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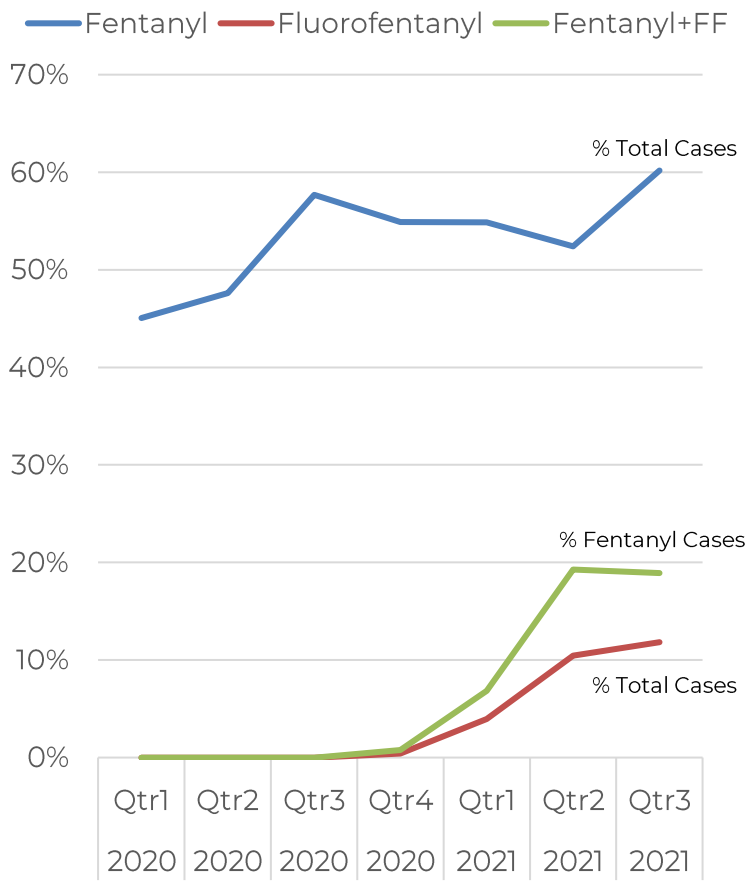
Fentanyl vs. Fluorofentanyl Positivity

Year	Quarter	Fentanyl	Fluorofentanyl	Fentanyl + Fluorofentanyl
2018	Qtr1	153	0	0
2018	Qtr2	576	2	2
2018	Qtr3	329	0	0
2018	Qtr4	116	0	0
2019	Qtr1	55	0	0
2019	Qtr2	39	0	0
2019	Qtr3	115	0	0
2019	Qtr4	151	0	0
2020	Qtr1	173	0	0
2020	Qtr2	369	0	0
2020	Qtr3	361	0	0
2020	Qtr4	392	3	3
2021	Qtr1	249	18	17
2021	Qtr2	306	61	59
2021*	Qtr3*	402*	79*	76*



*Quarter not complete

→ **FF detected without Fentanyl in 6 cases (4%) in 2021**

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Drug Material Testing

Drug Checking and Signature Analysis

- Vital datasets that provide important information
  - Drug checking → study of active ingredients (drug or adulterants)
  - Signature analysis → study of what's left behind during synthesis
- Both needed to accurately assess fluorofentanyl

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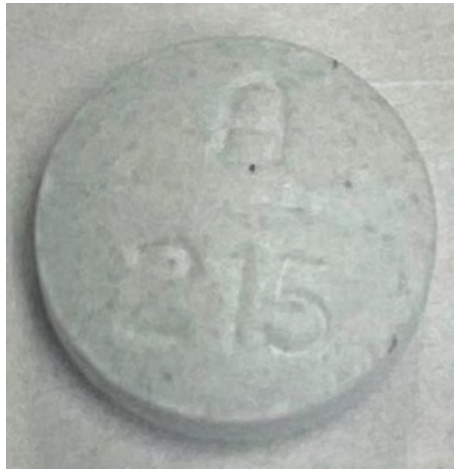
Drug Checking Collaboration

- Philadelphia, PA
  - September 2020 to Present
  - 157 “dope” samples analyzed
  - Primary component:
    - Fentanyl: 137
    - p-FF: 8
    - Heroin: 7
    - Other: 5

  - Fentanyl + *para*-Fluorofentanyl
    - Together: 57 (38%)
    - **Ratio: 0.1 to 10x**

- Counterfeit Oxycodone Pill
  - November 2020



  - **Results:** *para*-Fluorofentanyl, Gabapentin, Acetaminophen, trace amount of Fentanyl, *and more…*

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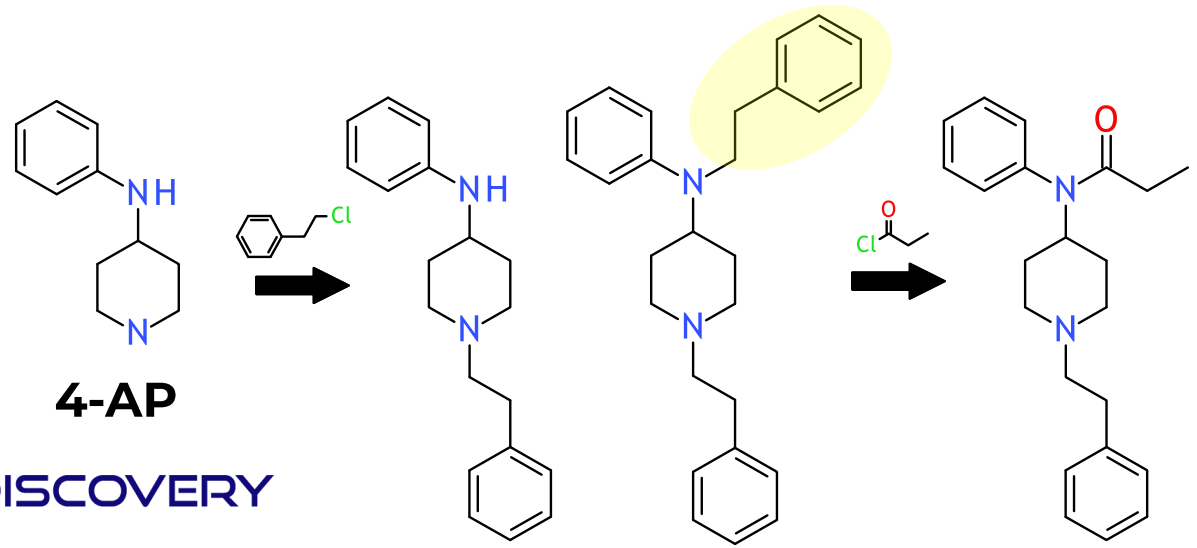
Signature Analysis

- Fentanyl has been synthesized in various ways historically
  - **"Janssen Route"** → 4-ANBP and benzylfentanyl as precursors/intermediates
  - **"Siegfried Route"** → NPP and 4-ANPP as precursors/intermediates
  - **"Gupta Route"** → 4-AP as precursor/intermediate, 4-ANPP as intermediate, and *phenethyl-4-ANPP* as byproduct *(More next from Christophe Stove!)*



4-AP

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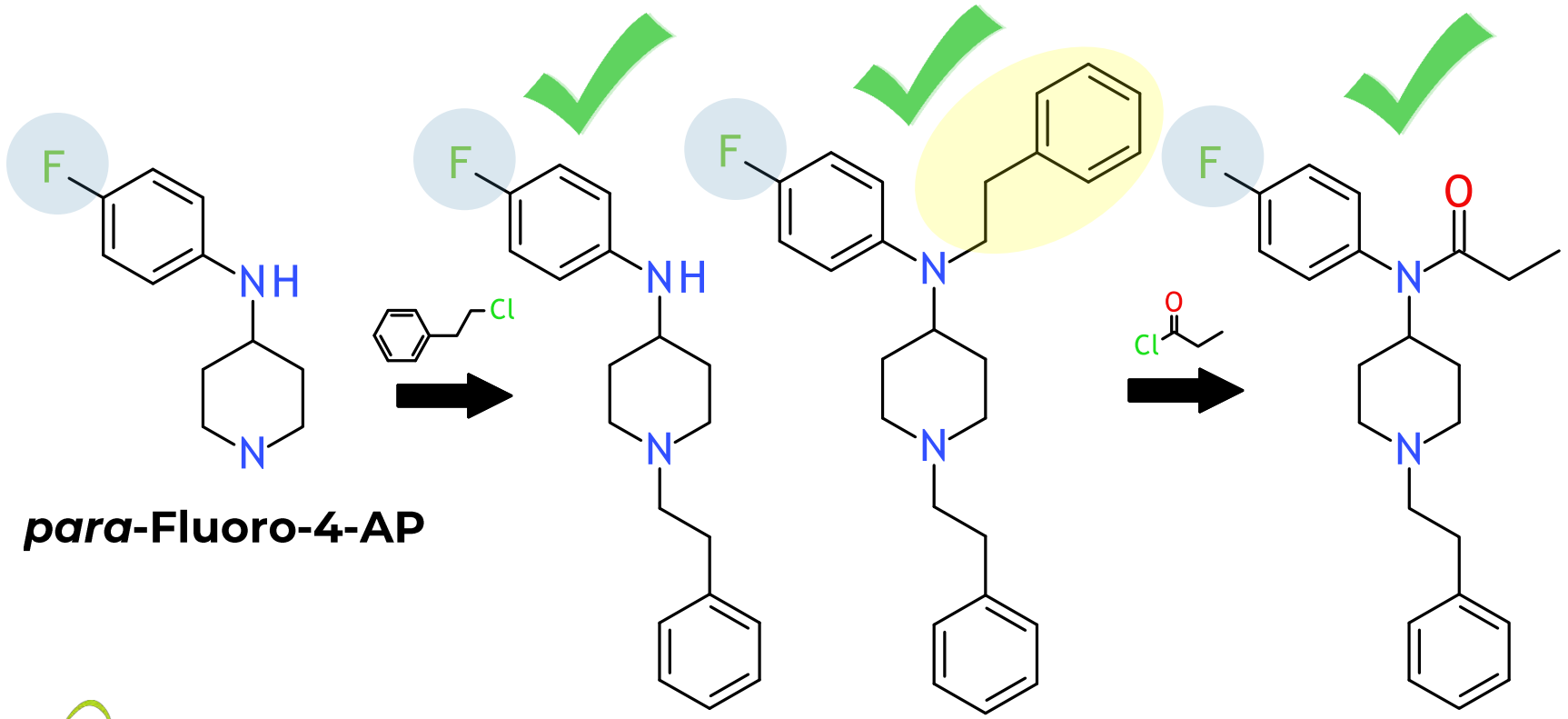
Signature Analysis

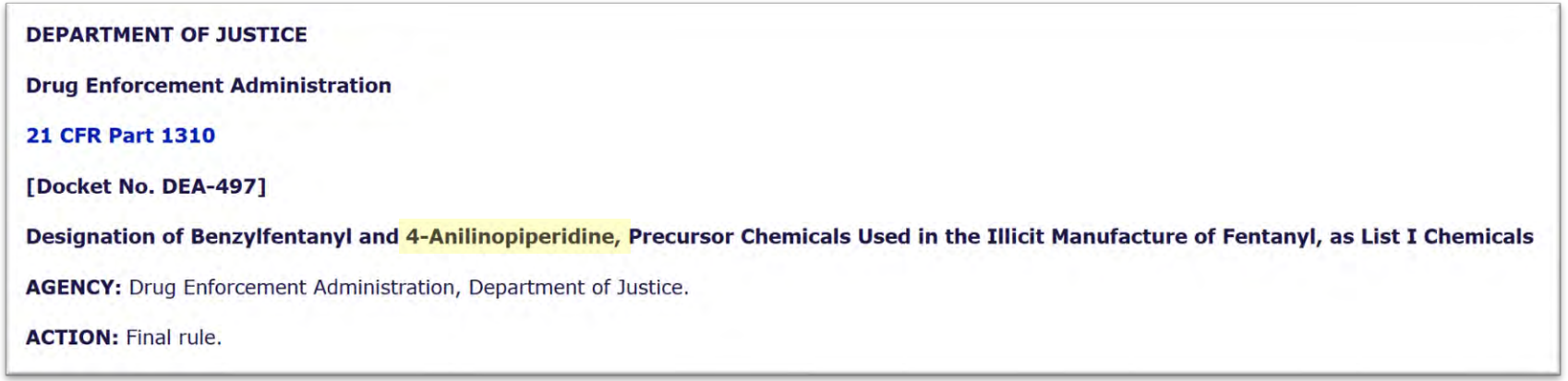
- Fluorofentanyl can follow same synthesis routes
  - Varying position of fluorine atom on the aniline ring (*o/m/p-*)



✓ = *Detected in Drug Material*

Significance of 4-AP and Fluoro-4-AP

- DEA moved to control 4-AP in April 2020



DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1310

[Docket No. DEA-497]

Designation of Benzylfentanyl and 4-Anilinopiperidine, Precursor Chemicals Used in the Illicit Manufacture of Fentanyl, as List I Chemicals

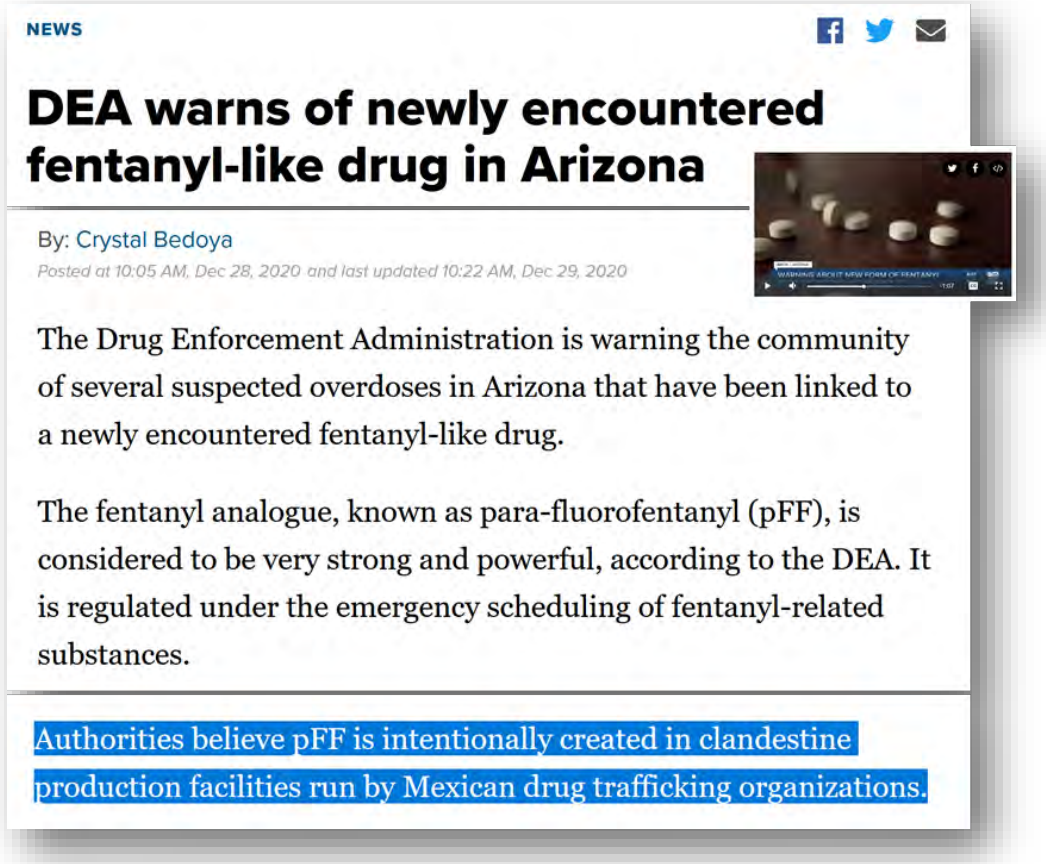
AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

- Fluoro-4-AP available as “legal” alternative precursor
  - *Note: This is opposite of what we see with most other drugs*

Culmination of Intelligence

- Origin of pFF ? →
- FF ***is not*** an adulterant, cutting agent, diluent, etc.
- FF ***is not*** a byproduct like 4-ANPP or acetylfentanyl
- FF ***is*** an intentional final drug product



NEWS

DEA warns of newly encountered fentanyl-like drug in Arizona

By: Crystal Bedoya

Posted at 10:05 AM, Dec 28, 2020 and last updated 10:22 AM, Dec 29, 2020

The Drug Enforcement Administration is warning the community of several suspected overdoses in Arizona that have been linked to a newly encountered fentanyl-like drug.

The fentanyl analogue, known as para-fluorofentanyl (pFF), is considered to be very strong and powerful, according to the DEA. It is regulated under the emergency scheduling of fentanyl-related substances.

Authorities believe pFF is intentionally created in clandestine production facilities run by Mexican drug trafficking organizations.

https://www.abc15.com/news/dea-warns-of-newly-encountered-fentanyl-like-drug-in-arizona

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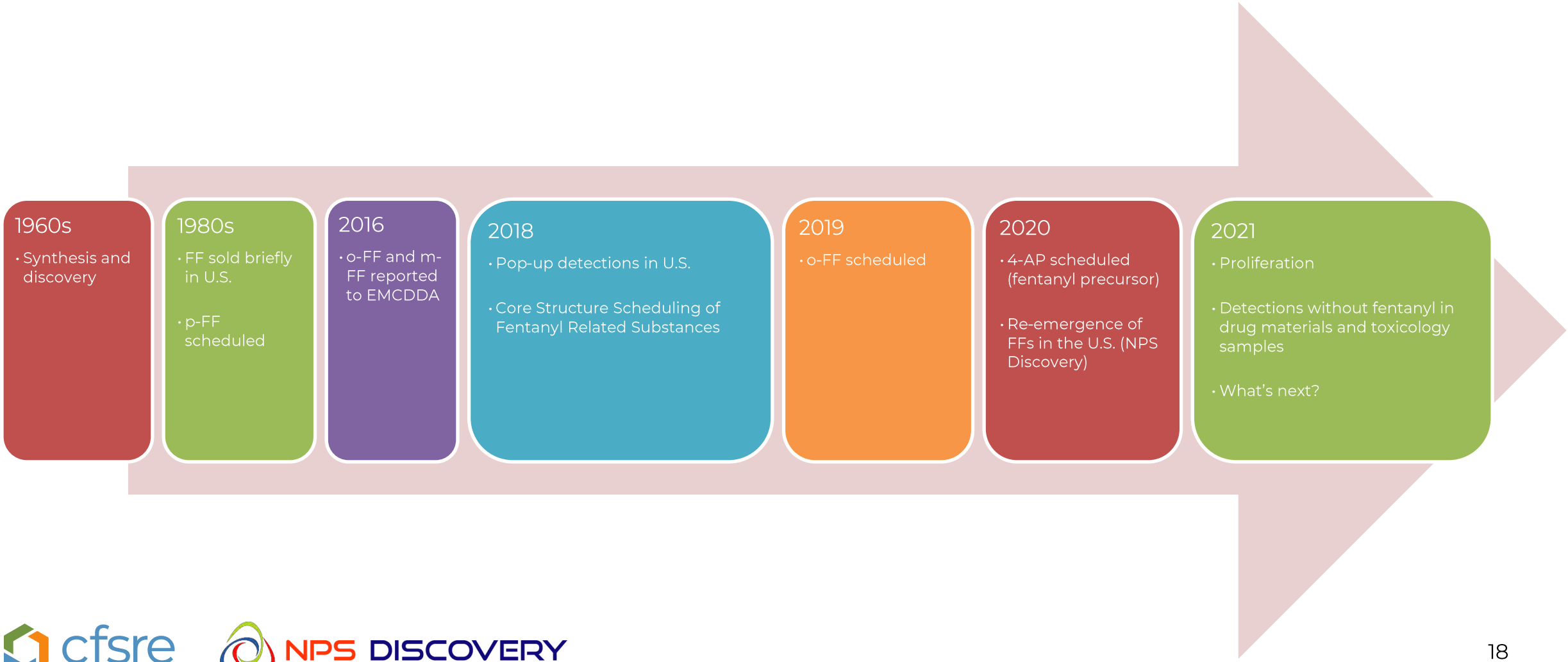
Summary and Discussion

Timeline of Fluorofentanyl



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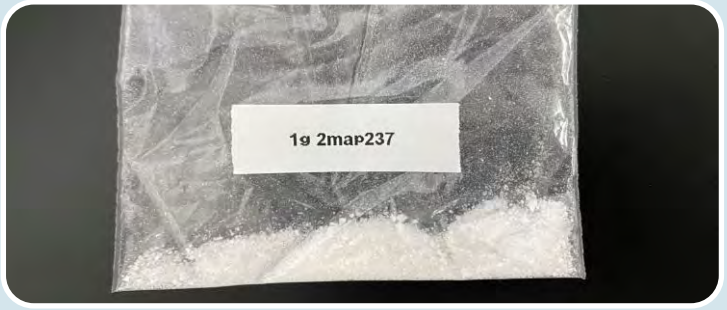
Not All NPS Opioids Are Created Equal



Gray Market Vendors & Research Chemicals

E.g., 2-Methyl AP-237

Fogarty → Today @ 9:15 am

Sold Recreational as "Heroin/Fentanyl"

E.g., Metonitazene (Midwest)

Logan → Today @ 8:45 am

Combined With The Larger Drug Supply*

E.g., para-Fluorofentanyl with Fentanyl (Widespread)

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*Excluding cases where drug found alone

Toxicological Interpretation – Not All The Same

- *Case 1:*
  - Suspected opioid OD
- *Toxicology Blood Results:*
  - **Fentanyl – 32 ng/mL**
  - ***p*-FF – 0.38 ng/mL**
  - 4-ANPP
  - Norfentanyl

- *Case 2:*
  - Suspected opioid OD
- *Toxicology Blood Results:*
  - ***p*-FF – 39 ng/mL**
  - **Fentanyl – 0.39 ng/mL**
  - Etizolam – 2.5 ng/mL

- *Case 3:*
  - Suspected opioid OD
- *Toxicology Blood Results:*
  - ***p*-FF – 55 ng/mL**
  - Cocaine – 150 ng/mL
    - BZE
  - Delta-9 THC – 2.4 ng/mL
    - Metabolites

Interpretation ???

Classification ???

Conclusions and Recommendations

- Fluorofentanyl marks a shift in illicitly manufactured fentanyl(s)
- Fluorofentanyl must be evaluated on a case-by-case basis
  - Cannot be treated as a byproduct or adulterant
- What is the future of fluorofentanyl and fentanyl analogues?
  - There are other (halogenated) fentanyl analogues that could be of concern
- *Use caution when categorizing and communicate about FF*
- **But… why are fentanyl and fluorofentanyl being found together?**

Acknowledgements

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