Appendix 8 for *Overdose Data to Action (OD2A) (CDC-RFA-CE-19-1904)*: Draft Guidance for Implementation of Comprehensive Toxicology Testing of Suspected Drug Overdose Deaths for Opioids

1.0 Background

In 2017, over two-thirds of drug overdose deaths involve opioids, and increases in drug overdose deaths over the last decade are primarily driven by increases in opioid overdose deaths. Also, the sharp increases in drug overdose deaths involving opioids over the past five years, coupled with the introduction of new synthetic opioids into the illicit opioid market, especially fentanyl and fentanyl analogs, have made it more costly and difficult for medical examiners and coroners (ME/C) to conduct comprehensive toxicology panels. In response, the *OD2A* funding opportunity requires recipients to fund efforts to support and enhance comprehensive post-mortem toxicological testing of suspected drug overdose deaths for opioids.

2.0 Intended Use

This document provides guidance to applicants on what is meant by comprehensive toxicology testing of suspected drug overdose deaths for opioids. As applications are prepared, this document can help guide applicant discussions with laboratory facilities and ME/Cs involved in toxicology testing.

Testing parameters are stratified into escalating levels of comprehensiveness to allow jurisdictions to adapt the testing guidance to their context. This flexibility is necessary to address geographic variations in drug availability and usage, varying economic constraints of ME/C budgets, and different capacities of the laboratories used by anticipated recipients. **This guidance may be updated or revised before and during the funding period in response to changes in the opioid overdose epidemic, national toxicology standards, or new technologies.** Expected updates include ongoing identification of new fentanyl analogs or synthetic opioids detected in opioid overdose deaths as well as testing guidance for non-opioid novel psychoactive substances such as synthetic cannabinoids and cathinones that may co-occur with opioids.

Toxicological testing in medico-legal death investigations is based on an evaluation of clinical evidence, pathology findings at autopsy, and other potentially available information such as evidence at the death scene including drug paraphernalia. When drugs are suspected to contribute to a death, at minimum, a primary toxicology drug screen, described below, should be performed. When opioids are suspected as a contributing substance in a drug overdose death based on clinical symptoms consistent with the opioid toxidrome (i.e., pinpoint pupils, altered mental status, or respiratory depression), autopsy findings consistent with an opioid overdose (i.e., presence of a "foam cone" or pulmonary edema), findings from the death investigation (illegal drugs at the scene or witness reports of heroin use) or results from immunoassay drug screens, drug confirmatory/quantitative testing for opioids is indicated.

3.0 Forensic Toxicological Testing Parameters

3.1 Primary Toxicology Drug Screen

For purposes of this funding announcement, the minimum level of toxicological testing for suspected opioid overdose deaths should include screening and confirmatory/quantitative testing for commonly prescribed opioids, medications commonly co-prescribed with opioids such as benzodiazepines, illicit opioids such as fentanyl and heroin, and illicit drugs that commonly co-occur with prescription and illicit opioids, including cocaine and methamphetamine. Testing for commonly co-occurring substances is important because these substances may have contributed to the opioid overdose (e.g., benzodiazepine or cocaine) and may help identify high-risk drug use or prescribing patterns. Unconfirmed positive immunoassay screening test results alone offer only weak (potentially disputable) evidence of the presence of an opioid or other drugs, are potentially falsely positive or negative, and are not adequate for establishing a definitive medico-legal cause of death. These test results, however, can provide an overview of involvement of possible substances and inform drug confirmatory/quantitative testing.

Primary Toxicology Drug Screen
Immunoassay screen to include fentanyl, methadone, and methadone metabolite (EDDP) and a broad screen to detect any natural and semi-synthetic opioids (including oxycodone/oxymorphone). Substances commonly co-occurring with opioids should also be included such as amphetamines, benzodiazepines, cocaine and cocaine metabolites.
Drug identification and quantitation of:
– Amphetamine, Methamphetamine
– Alprazolam, Clonazepam, Diazepam, Nordiazepam, Oxazepam, Temazepam, Lorazepam
– Cocaine, Cocaethylene, Benzoylecgonine
– Methadone, EDDP
– Fentanyl*
– Codeine, Hydrocodone, Hydromorphone, Morphine, Oxycodone, Oxymorphone, 6-Acetylmorphine

*Fentanyl-only analysis is not adequate in regions where fentanyl analogs or other illicit synthetic opioids such as U-47700 are prevalent.

3.2 Enhanced Toxicology Drug Screen

When economically feasible, expanded testing should be conducted in order to obtain a more comprehensive assessment of potential drugs involved in suspected opioid overdose deaths.

Enhanced Toxicology Drug Screen
Immunoassay screen to include fentanyl, methadone, and methadone metabolite (EDDP) and a broad screen to detect any natural and semi-synthetic opioids (including oxycodone/oxymorphone). Substances commonly co-occurring with opioids should also be included such as amphetamines, benzodiazepines, cocaine and cocaine metabolites.
Comprehensive chromatographic-based screen and confirmatory analysis of common over-the-counter, prescription/therapeutic and illicit drugs; for example – antidepressants, antihistamines, antipsychotics, hallucinogens, sedatives and stimulants.
Fentanyl and fentanyl analog testing to include relevant analogs common to the region
Drug quantitation of all toxicologically-relevant drugs

3.3 Comprehensive Fentanyl Analog and other Illicit Synthetic Opioids Testing

Further expanded testing of suspected opioid overdose deaths may be necessary under circumstances in which a fentanyl analog or other illicit synthetic opioid is suspected. This may occur when:

1) An opioid overdose is highly suspected based on scene, clinical, and/or autopsy findings, but all opioid screening tests were either negative, or positive results were insufficient to support a toxicological cause of death.
2) A case of suspected opioid overdose death tests positive for fentanyl by immunoassay, but is negative for fentanyl upon confirmatory testing.

Utilization of specific fentanyl analog testing should take into account economic feasibility and availability of fentanyl, fentanyl analogs and other illicit synthetic opioids in the region, and the capabilities of the laboratory used by the ME/C. Due to the rapid shifts in the types of fentanyl analogs and illicit synthetic opioids such as U-47700 detected and involved in opioid overdose deaths, recipients when funded will receive an up-to-date list of what fentanyl analogs and illicit synthetic opioids should be considered when conducting comprehensive testing. The following drugs are recommended for inclusion in comprehensive testing for fentanyl analogs and other illicit synthetic opioids as of the summer of 2018.

Fentanyl Analog Testing*	
Fentanyl Analogs	**Fentanyl Analogs (Continued)**
Acetylfentanyl	para-Fluorofentanyl
Acrylfentanyl	Valerylfentanyl
Beta-hydroxythiofentanyl	4-Methoxybutyrylfentanyl
Butyrylfentanyl	4-Methylphenethyl Acetylfentanyl
Carfentanil	3-Methylfentanyl
Crotonylfentanyl	**Fentanyl Precursor**
Cyclopentylfentanyl	4-ANPP^
Cyclopropyfentanyl	**Other Illicit Synthetic Opioids**
Furanylfentanyl	AH-7921
Isobutyrylfentanyl	MT-45
Methoxyacetylfentanyl	U-47700
ortho-Fluorofentanyl	U-48800
para-Fluorobutyryl Fentanyl/FIBF	U-49900

*This list of fentanyl analogs and other illicit synthetic opioids will be updated as needed to reflect new identified fentanyl analogs or other synthetic opioids such as U-47700.

^Despropionylfentanyl, also known as 4-anilino-N-phenethylpiperidine (4-ANPP), is a fentanyl compound that can serve as a marker for illicitly manufactured fentanyl and fentanyl analogs because it is both a precursor and a metabolite of these illicit products (but not pharmaceutical fentanyl), while having low metabolic activity that does not contribute to overdose toxicity.

If results from the above comprehensive testing are negative and do not support the toxicological cause of death, further probative testing should be considered to assess whether a fentanyl analog/other synthetic opioid was involved. This may require discussion with the lab to clarify their capabilities beyond the range of fentanyl analogs/other synthetic opioids listed above.

3.4 Further Considerations for Comprehensive Fentanyl Analog and Synthetic Opioid Testing

If economically feasible, there are certain situations in which broader fentanyl analog and other synthetic opioid testing should be considered. These include:

- Suspected opioid overdose deaths that test positive for fentanyl immunoassay and confirmatory testing. Common co-mixing of fentanyl with fentanyl analogs indicates it is useful to test these overdose deaths, or
- Suspected opioid overdose deaths testing positive for 6-acetylmorphine and morphine. Common co-mixing of heroin with fentanyl analogs indicates it is useful to test these overdose deaths.

However, if economic constraints are a limiting factor, then the ME/C could consider testing only a subset of such overdoses.

If additional testing remains feasible after all above testing is completed, further testing to consider includes:

- Any suspected opioid overdose death where illicit drugs or injection drug use was involved. If this captures too many deaths, testing a sample of such deaths could be considered.
- Testing a random sample of all opioid overdose deaths.

Quick Card for SUDORS Testing Recommendations

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